e-ISSN:2602-2079

Volume 4
Issue 11
2020

JOURNAL of Surgery and Medicine

International Medical Journal

Volume: 4 - Issue: 11

417 | 780

Contents

Case report

ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

ULAKBİM Dergi Sistemleri (//dergipark.org.tr/en/)

J Surg Med. 2020;4(11):915-919.
DOI: 10.28982/josam.747306

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of patients receiving hemodialysis in an emergency service

Acil serviste hemodiyaliz alan hastaların değerlendirilmesi

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Ethics Committee Approval: Ethical approval was obtained From Bursa Yuksek Ihtisas Trainig and Research Hospital Ethics Committee before the beginning of the study (2011-KAEK-25 2020/03-07). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma öncesi Bursa Yüksek İhtisas Eğitim ve Araştırma Hastanesi Etik Kurulundan etik onay alındı (2011-KAEK-25 2020/03-07). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/9/2020
Yayın Tarihi: 09.11.2020

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Abstract

Aim: Acute kidney injury (ARH) is an important emergency with high mortality and morbidity depending on patient characteristics, comorbidity and clinical situation. Rapid recognition of acute renal failure (ARF) and initiation of renal replacement therapy (RRT) is one of the most important factors determining the survival of these patients. The initiation of RTT in the emergency department depends on the correct indications in the critical patient, the correct use of resources and effective nephrological follow-up. This study aims to determine the hemodialysis indications of patients undergoing hemodialysis for the first time in the emergency service and to investigate the effect of this application on routine hemodialysis and survival.

Methods: We carried out a retrospective cohort study with patients who underwent hemodialysis for the first time by central venous catheterization in the emergency service between January 01, 2019 and December 31, 2019. Age, gender, presence of chronic disease, symptoms and laboratory values of the patients were recorded from the patient files in the hospital automation system. Data regarding the hospitalization or discharge of the patients after emergency hemodialysis were collected. Patient follow-up was carried out from the patient records, and the nephrology follow-ups were examined for 3 months after emergency hemodialysis. Their routine hemodialysis and 28-day mortality were evaluated.

Results: A total of 185 patients were included in the study. 55.1% of the patients (n=102) were male and the mean age was 65.63 (15.92) years. While 49.2% (n=91) of the patients were included in the routine hemodialysis program, mortality developed in 22.7% (n=42) on the 28th day. No statistically significant relationship was found between the current systemic diseases, hemodialysis indications and undergoing routine hemodialysis program (P=0.327, P=0.45).

Conclusion: Although there was no statistically significant relationship between the dialysis indications of the patients and their inclusion in the routine dialysis program, emergency hemodialysis is an important procedure. The clinical condition and laboratory values of the patients should be evaluated synchronously. Physicians should not be late in initiating hemodialysis in the follow-up and treatment of electrolyte disorders and intoxications; the treatment of the patient should be decided as quickly as possible.

Keywords: Emergency departments, Dialysis, Acute kidney injuries, Hyperkalemia

Öz

Amaç: Akut renal hasar(ARH) hasta karakteristiklerine, komorbiditesine ve klinik durumuna bağlı olarak yüksek mortalite ve morbiditeye sahip önemli bir acildir Akut böbrek yetmezliğinin (ABY) hızla tanınıp, renal replasman tedavisinin (RRT) başlanması, bu hastaların hayatta kalımını belirleyen en önemli unsurlardan biridir. RTT'nin acil serviste başlanması ise kritik hastada doğru endikasyonların konulmasına, kaynakların doğru kullanımına ve nefrolojik takibin etkin şekilde sağlanmasna bağlıdır. Bu çalışmanın amacı acil serviste ilk kez hemodiyaliz alan hastaların hemodiyaliz endikasyonlarını belirlemek ve bu uygulamanın hastaların rutin hemodiyalize alınması ve sağ kalımları üzerine etkisini araştırmaktır.

Yöntemler: 01 Ocak 2019- 31 Aralık 2019 tarihleri arasında acil serviste santral kateterizasyon işlemi yapılan ve hemodiyaliz uygulanan hastalar retrospektif olarak incelendi. Hastalara ait yaş, cinsiyet, kronik hastalık varlığı, acile geliş semptomları, laboratuvar değerleri hastane otomasyon sisteminde kayıtlı hasta dosyaları üzerinden kaydedildi. Hastaların acil hemodiyaliz sonrası hastaneye yatış ya da taburculuklarına ait veriler toplandı. Hasta kayıtlarından hasta takibi gerçekleştirilerek hastaların acil diyaliz alımı sonrası 3 aylık sürede nefroloji poliklinik takipleri incelenerek rutin hemodiyaliz programına alınımları ve 28 günlük mortaliteleri değerlendirildi. 18 yaş üzerinde olup acil serviste kateterizasyonu sağlanarak ilk diyalizi acilde serviste alan hastalar çalışmaya dahil edildi.

Bulgular: Çalışmaya toplam 185 hasta dahil edildi. Hastaların %55,1'i (n=102) erkek olup ortalama yaş 65,63 (15,92) olarak saptandı. Hastaların %49,2' si (n=91) sonrasında rutin hemodiyaliz programına alınırken, %22,7'sinde ise (n=42) 28. günde mortalite geliştiği gözlendi. Hastaların mevcut sistemik hastalıkları ve hastaların diyalize alınma endikasyonları ile rutin hemodiyaliz programına alınması arasında da istatistiksel olarak anlamlı bir ilişki saptanmadı (P=0,327, P=0,45).

Sonuç: Bu çalışmada her ne kadar hastaların diyalize alınma endikasyonları ile rutin diyaliz programına alınmaları arasında istatistiksel olarak anlamlı bir ilişki çıkmamasına rağmen acil hemodiyaliz önemli bir prosedürdür ve hastanın klinik tablosu ve laboratuvar değerleri eş zamanlı değerlendirilmelidir. Özellikle elektrolit bozuklukları ve intoksikasyonların takip ve tedavisinde hemodializ için geç kalınmamalı ve hastanın tedavisine hızla karar verilmelidir.

Anahtar kelimeler: Acil servis, Diyaliz, Akut böbrek hasarı, Hiperkalemi

How to cite/Atıf için: Eraybar S, Yüksel M. Evaluation of patients receiving hemodialysis in an emergency service. J Surg Med. 2020;4(11):915-919.

Introduction

Acute renal injury (ARI) is an important emergency with high mortality and morbidity depending on patient characteristics, comorbidity and clinical status [1]. These patients may be admitted to emergency services with different specific or nonspecific symptoms. A quick diagnosis of acute renal failure (ARF) and the initiation of renal replacement therapy (RRT) are important in determining the survival of these patients. While the RIFLE classification is frequently used in the definition of ARI, the KDIGO (Kidney Disease; Improving Global Outcomes) classification that regulates all the classifications was published in 2012 [2].

According to KDIGO, if any of the following criteria is fulfilled, it is defined as ARI.

1. At least 0.3 mg / dl decrease in absolute serum creatinine (SCr) level within the last 48 hours
2. 1.5 and above decrease in absolute serum creatinine level in the last 7 days compared to basal value
3. Having urine output below 0.5ml / kg / hour for 6 hours

The start time of the RRT is controversial. The results of studies conducted in terms of the effects of early and late RRT on patients' mortality are contradictory [3, 4]. There are data about early RRT application being effective in relieving inflammatory factors that play an important role in ARI development. This can stop renal damage and reduce mortality. Simultaneously, it can remove foreign bodies that aggravate renal damage [5].

Starting RTT in the emergency service depends on the correct indications in the critical patient, the correct use of the resources and the effective provision of nephrology follow-up [6]. In determining the need for emergency hemodialysis in patients diagnosed with ARI in the emergency room, the presence of uremic symptoms is very important. Although the indications for starting RRT are quite controversial, the currently accepted indications are hypervolemia not responding to conservative treatment, hyperkalemia (potassium [K]> 6.5 mg / dl), metabolic acidosis, the presence of uremic symptoms (uremic pericarditis, uremic encephalopathy, bleeding disorders, nausea, vomiting and itching), and having blood urea nitrogen (BUN) > 100 mg / dl [7]. Hemodialysis in the emergency room is an important treatment option in patient management in poisoning with lipid-soluble drugs such as salicylate, methanol, theophylline, phenobarbital, carbamazepine, which are highly bound to proteins and have a high dispersion volume [8,9].

It is possible to encounter prerenal azotemia, which often develops because of volume loss, in the emergency room. Increased arterial pressure secondary to intravascular volume loading, especially as in cardiorenal syndrome, in patients with congestive heart failure, may result also in ARI [10]. In the presence of this loading, emergency hemodialysis remains viable as a vital treatment modality.

The aim of our study is to determine the demographic features and hemodialysis indications of patients who received hemodialysis for the first time in the emergency room and to investigate the effect of this application on routine hemodialysis and survival of patients.

Materials and methods

Patients who underwent central catheterization and hemodialysis for the first time in our emergency service between January 01, 2019 and December 31, 2019 were examined in this retrospective cohort study. Ethical approval was obtained From Bursa Yuksek Ihtisas Trainig and Research Hospital Ethics Committee before the study (2011-KAEK-25 2020/03-07). Patients' age, gender, presence of chronic illness and emergency symptoms were recorded via the patient automation system. Potassium, calcium, BUN, creatinine values were recorded in the biochemical tests while PH, lactate, base and anion deficit values were recorded in the blood gas analysis of the patients in the emergency department. The reasons for emergency dialysis were grouped based on clinical findings, vital signs, and laboratory values. Data regarding the hospitalization or discharge of the patients after emergency hemodialysis were collected. Patient follow-up was carried out from the patient records. Examining nephrology follow-up for 3 months after emergency dialysis, routine hemodialysis and 28-day mortality of the patients were evaluated. Patients over 18 years of age who received the first dialysis by catheterization in the emergency room were included in the study. The presence of ARI was evaluated based on the KDIG classification. Chronic renal failure (CRF) cases, patients under 18 years of age, those who received routine hemodialysis and needed additional dialysis in the emergency room and pregnant women were excluded from the study. Emergency hemodialysis was performed on 1126 patients in one year. A total of 907 patients were excluded from the study because they were followed-up with the diagnosis of CRF, which included former nephrology follow-up, and had a history of peritoneum or hemodialysis. Of the remaining 219 patients, 34 others were excluded from the study for various other reasons (Figure 1).

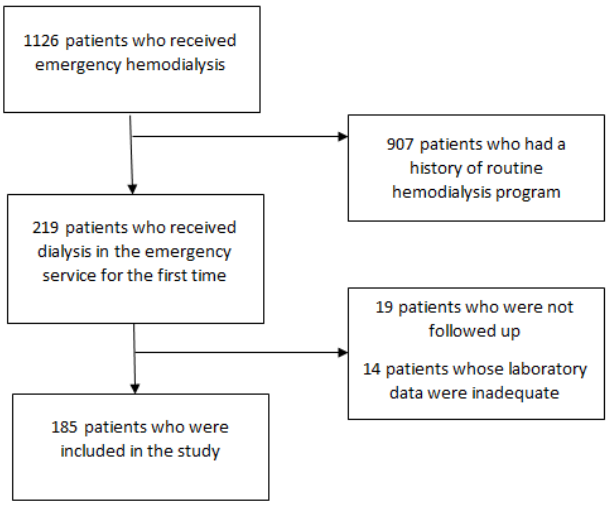

Figure 1: Identifying the cohort

Statistical analysis

The data of the study were analyzed using SPSS for Windows (22.0) software. All values were shown as the mean and standard deviation (SD). Kolmogorov-Smirnov test was used for the normality of data. Independent sample t-test was used to test whether there was a statistically significant difference between the two independent groups by examining the means. The one-way ANOVA test was used to investigate whether there were any significant differences compared to the mean of more than two independent groups. Chi-square and Fisher's exact tests

were used to analyze whether there was a relationship between categorical variables. Parametric variables were analyzed with Pearson test; non-parametric variables were analyzed with Spearman test. *P*-values <0.05 were considered statistically significant.

Results

A total of 185 patients were included in the study. Among them, 55.1% (n=102) of the patients were male while 44.9% (n=83) were female, and the mean age was 65.63 (15.92) years. The mean BUN was 79.99 (0.30) mg / dL, and the mean serum potassium level was 5.31(1.35) mEq / L (Table 1). The most common comorbidities in patients were hypertension (25.4%) and heart failure (16.2%). The most common indication of dialysis was hypervolemia (29.7%) and metabolic acidosis (22.2%) (Table 2).

While 49.2% (n=91) of patients were included in the routine hemodialysis program, mortality developed in 22.7% (n=42) on 28th day (Table 3).

No statistically significant relationship was found in the chi-square analysis performed to analyze the relationship between the gender of patients and their inclusion in the routine hemodialysis program (*P*=0.153). Similarly, no statistically significant relationship was found between the current systemic diseases of patients and the indications for dialysis, and their inclusion in routine hemodialysis program (*P*=0.327, *P*=0.45) (Table 4).

There was no statistically significant relationship between the patients' inclusion in the routine hemodialysis program and 28-day mortality (*P*=0.905).

In the independent sample t test performed to analyze the difference between 28-day mortality and the mean laboratory values, a statistically significant difference was found between 28-day mortality and BUN values (Table 5).

Table 1: Distribution of variables

n=185	Minimum	Maximum	Mean (SD)
Age	23	93	65.63(15.92)
BUN	195	236.4	79.9 (40.30)
GFR	1.17	129	13.47(16.81)
Potassium	2.4	9.4	5.31(1.35)
Creatinine	0.31	25.71	6.51(3:82)
Calcium	4.25	15.93	8.27(1.34)
PH	6.91	7.56	7.28(0.12)
Lactate	0.2	14.1	2.51(2.43)
BE	-25.3	9.3	-7.67(7.26)
Anion gap	-9.8	29.11	7.25(5.77)

BUN: Blood urea nitrogen, GFR: Glomerular filtration rate

Table 2: Systemic disease and dialysis indication data of patients

Comorbid diseases	Frequency	Percent
No	24	13
Hypertension	47	25.4
Diabetes Mellitus	21	11.4
Malignancy	19	10.3
Coronary artery diseases	14	7.6
Heart failure	30	16.2
COPD	11	5.9
Cerebrovascular Disease	6	3.2
Other	13	7
Total	185	100
Dialysis indications	Frequency	Percent
Metabolic acidosis	41	22.2
Hyperkalemia	34	18.4
Uremic encephalopathy	31	16.8
Hypervolemia	55	29.7
Pericardial effusion	4	2.2
Hypercalcemia	6	3.2
Intoxication	2	1.1
Contrast nephropathy	12	6.5
Total	185	100

Table 3: Data regarding the status of patients

Variables	Yes		No	
	n	%	n	%
Routine hemodialysis program inclusion	91	49.20%	94	50.80%
28-day mortality	42	22.70%	143	77.30%

Table 4: Relationship between current systemic disease, hemodialysis indication and inclusion of routine dialysis program

			Routine dialysis program inclusion		Total	Chi-Square Analysis
			Yes	No		
Systemic Disease	No	n	15	9	24	
		%	16.50%	9.60%	13.00%	
	HT	n	20	27	47	
		%	22.00%	28.70%	25.40%	
	DM	n	12	9	21	
		%	13.20%	9.60%	11.40%	X^2=9.184
	Malignancy	n	8	11	19	*P*=0.327
		%	8.80%	11.70%	10.30%	
	Coronary artery diseases	n	10	4	14	
		%	11.00%	4.30%	7.60%	
	Heart failure	n	13	17	30	
		%	14.30%	18.10%	16.20%	
	COPH	n	5	6	11	
		%	5.50%	6.40%	5.90%	
	CVD	n	4	2	6	
		%	4.40%	2.10%	3.20%	
	Other	n	4	9	13	
		%	4.40%	9.60%	7.00%	
hemodialysis indication	Metabolic acidosis	n	22	19	41	
		%	24.20%	20.20%	22.20%	
	Hyperkalemia	n	13	21	34	
		%	14.30%	22.30%	18.40%	
	Uremic encephalopathy	n	14	17	31	
		%	15.40%	18.10%	16.80%	X^2=6.800
	Hypervolemia	n	30	25	55	*P*=0.450
		%	33.00%	26.60%	29.70%	
	Pericardial effusion	n	1	3	4	
		%	1.10%	3.20%	2.20%	
	Hypercalcemia	n	4	2	6	
		%	4.40%	2.10%	3.20%	
	Intoxication	n	0	2	2	
		%	0.00%	2.10%	1.10%	
	Contrast nephropathy	n	7	5	12	
		%	7.70%	5.30%	6.50%	
Total		n	91	94	185	
		%	100.00%	100.00%	100.00%	

Table 5: Analysis of the data regarding 28-day mortality and laboratory values

	mortality	n	Mean (SD)	*P*-value
Creatinine	yes	42	6.31(4.23)	0.699
	no	143	6.57(3.71)	
BUN	yes	42	93.64(48.27)	0.033
	no	143	75.98(36.88)	
GFR	yes	42	11.33(8.28)	0.351
	no	143	14.09(18.56)	
Potassium	yes	42	5.39(1.41)	0.637
	no	143	5.28(1.34)	
Calcium	yes	42	8.56(1.69)	0.110
	no	143	8.18(1.21)	
PH	yes	42	7.26(0.13)	0.175
	no	143	7.29(0.11)	
Lactate	yes	42	3.18(3.01)	0.090
	no	143	2.31(2.20)	
BE	yes	42	-8.99(7.68)	0.181
	no	143	-7.28(7.11)	
Anion gap	yes	42	8.76(6.26)	0.054
	no	143	6.81(5.56)	

*independent sample t test

Discussion

Investigating the age, gender and concomitant diseases of the patients who were diagnosed with ARI in the emergency department and who were taken to emergency hemodialysis are crucial. In a study conducted by Bektaş et al. [7], the mean age of patients diagnosed with ARF in the emergency service was 63.7 (15.9) years and 57% were male. In another study by Golestaneh et al. [11], the mean age of patients who received hemodialysis in the emergency room was 61.6 (15.0) years and 56.8% were male. In our study, age and gender data were consistent with the literature. Race and geography play a role in comorbid diseases associated with renal failure. In a study conducted in our country, the most common comorbid disease associated with renal failure was hypertension [12]. Similarly, in the studies conducted in Africa, the most common comorbid disease was hypertension

[13,14]. In a study conducted in Canada, the most common comorbid diseases in patients receiving hemodialysis were diabetes mellitus (DM) and coronary artery disease [15]. In another study in the United States, it was found that hemodialysis inclusion was more common in black and Hispanic people, and the most common comorbidities in this population were DM and heart failure [11]. In our study, hypertension was the most frequent, followed by heart failure, which is consistent with the literature.

There are studies showing that early hemodialysis decreases mortality especially in the presence of septic table in patients with ARF. Carl et al. [16] used BUN level in early hemodialysis decision in their study. They evaluated patients undergoing hemodialysis with a BUN value below 100 mg/dL in the early dialysis class and found a significant difference in mortality compared to late dialysis. In our study, a significant correlation was found between 28-day mortality and BUN values.

In patients with cardiac insufficiency, shortness of breath that develops secondary to hypervolemia is a frequent reason for emergency admittance. Emergency hemodialysis in these patients provides significant relief in patients' symptoms, but often causes routine dialysis needs. In a study carried out jointly in 24 hemodialysis centers in Spain using cardiac loading for the treatment, it was reported that early hemodialysis had an important effect on intensive care hospitalization and survival [17]. In addition, in another study with 2308 patients, 185 ARF cases were examined and late dialysis was found to extend the length of stay in intensive care units [18]. In this study, in the patients who underwent hemodialysis due to hypervolemia, 54.5% needed to be included in the routine hemodialysis program, however, no significant decrease was obtained in data regarding mortality. To exclude renal dysfunction in the emergency department, a single blood sample is not always sufficient; the need for hemodialysis appears to be independent of creatinine, especially in electrolyte disorders according to the clinical condition of the patient. In patients with cardiac involvement and resistant hyperpotassemia, there is an urgent need for hemodialysis in the treatment of high potassium, regardless of the creatinine values [19,20]

In our study, hyperkalemia is an important indication of hemodialysis and 34 patients underwent hemodialysis for K^+ lowering therapy. The need for routine hemodialysis did not develop in the follow-up of 61.7% of these patients. Hyperpotassemia, an emergency with high mortality, was effectively treated. Similarly, in hypercalcemia and hypermagnesemia, emergency hemodialysis should be kept in mind in treatment-resistant cases [21,22]. In our study, 6 patients underwent emergency hemodialysis due to hypercalcemia.

Another important indication of emergency hemodialysis is intoxications. Treatment in poisoned patients includes the steps of vital support, dealing with organ dysfunction and removal of suspected toxins. In addition to enteric decontamination, lipid therapy after the use of antidotes is also on the agenda. Hemodialysis, on the other hand, is an important mechanism for extracorporeal drug removal, which is common in the world. It has been used successfully in medications, as well as metals such as arsenic and mercury [23,24]. In our study, although we only have 2 cases of intoxication, we think that effective and regular hemodialysis use is important in patient survival regardless of starting routine hemodialysis.

Contrast nephropathy is an important cause of ARF that develops as a result of contrast-containing procedures. In studies conducted, contrast nephropathy appears due to basal values of patients and comorbid diseases, and the need for urgent hemodialysis develops in 9.9% [12,23]. In our study, a total of 12 patients underwent hemodialysis with a pre-diagnosis of contrast nephropathy, and seven were included in the routine hemodialysis program. It is significant in terms of showing that contrast nephropathy may play a role in irreversible renal damage and the patient should be closely monitored after contrasting procedures.

Limitations

There are some limitations in this study. As our patients were retrospectively examined, we had data loss. As a result of the central catheterization of our patients, we did not have the opportunity to follow the dialysis activities. In routine nephrology follow-ups, changes in the indications for dialysis and underlying pathologies for existing renal damage could not be followed.

Conclusion

Emergency hemodialysis is an important procedure and the patient's clinical condition and laboratory values should be evaluated simultaneously. The physicians should not be late for initiating hemodialysis in the follow-up and treatment of electrolyte disorders and intoxications. Treatment of the current clinical condition and providing nephrology follow-up may prevent morbidity in patients and constitute a major step for renal replacement treatments.

Consequently, although there was no statistically significant relationship between the indications for dialysis inclusion and routine dialysis program, more than half of the patients were not included in the routine hemodialysis program. This issue should be studied in further prospective multicenter studies.

References

1. Challiner R, Ritchie JP, Fullwood C, Loughnan P, Hutchison AJ. Incidence and consequence of acute kidney injury in unselected emergency admissions to a large acute UK hospital trust. BMC nephrology. 2014;15:84. Epub 2014/06/03. doi: 10.1186/1471-2369-15-84. PubMed PMID: 24885247; PubMed Central PMCID: PMCPMC4046061.
2. Kellum JA, Lameire N. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical care (London, England). 2013;17(1):204. Epub 2013/02/12. doi: 10.1186/cc11454. PubMed PMID: 23394211; PubMed Central PMCID: PMCPMC4057151.
3. Bouman CS, Oudemans-Van Straaten HM, Tijssen JG, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. Critical care medicine. 2002;30(10):2205-11. Epub 2002/10/24. doi: 10.1097/00003246-200210000-00005. PubMed PMID: 12394945.
4. Sugahara S, Suzuki H. Early start on continuous hemodialysis therapy improves survival rate in patients with acute renal failure following coronary bypass surgery. Hemodialysis international International Symposium on Home Hemodialysis. 2004;8(4):320-5. Epub 2004/10/01. doi: 10.1111/j.1492-7535.2004.80404.x. PubMed PMID: 19379436.
5. Wang X, Jie Yuan W. Timing of initiation of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Renal failure. 2012;34(3):396-402. Epub 2012/01/21. doi: 10.3109/0886022x.2011.647371. PubMed PMID: 22260302.
6. Ricci Z, Ronco C, D'Amico G, De Felice R, Rossi S, Bolgan I, et al. Practice patterns in the management of acute renal failure in the critically ill patient: an international survey. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2006;21(3):690-6. Epub 2005/12/06. doi: 10.1093/ndt/gfi296. PubMed PMID: 16326743.
7. Bektas F, Nokay A, Güngör F, Söyüncü S. Demographic features of the patients with acute renal failure in the emergency department. Turk J Emerg Med. 2008;8(4):170-4.
8. Liakoni E, Berger F, Klukowska-Rötzler J, Kupferschmidt H, Haschke M, Exadaktylos AK. Characteristics of emergency department presentations requiring consultation of the national Poisons Information Centre. Swiss medical weekly. 2019;149:w20164. Epub 2019/12/18. doi: 10.4414/smw.2019.20164. PubMed PMID: 31846508.

9. Sidlak AM, Abesamis MG, Shulman JA, Marino RT. Feasibility of Intermittent Hemodialysis in Metformin Toxicity With Shock. The Journal of emergency medicine. 2020;58(5):749-55. Epub 2020/04/25. doi: 10.1016/j.jemermed.2020.02.018. PubMed PMID: 32327212.
10. Co I, Gunnerson K. Emergency Department Management of Acute Kidney Injury, Electrolyte Abnormalities, and Renal Replacement Therapy in the Critically Ill. Emergency medicine clinics of North America. 2019;37(3):459-71. Epub 2019/07/03. doi: 10.1016/j.emc.2019.04.006. PubMed PMID: 31262415.
11. Golestaneh L, Bellin E, Neugarten J, Lo Y. Avoidable visits to the emergency department(ED) and their association with sex, age and race in a cohort of low socio-economic status patients on hemodialysis in the Bronx. PloS one. 2018;13(8):e0202697. Epub 2018/08/25. doi: 10.1371/journal.pone.0202697. PubMed PMID: 30142175; PubMed Central PMCID: PMCPMC6108498.
12. Rencuzogullari I, Çağdaş M, Karakoyun S, Karabağ Y, Yesin M, Gürsoy MO, et al. Association of Syntax Score II with Contrast-induced Nephropathy and Hemodialysis Requirement in Patients with ST Segment Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. Korean Circ J. 2018;48(1):59-70. Epub 2017/11/25. doi: 10.4070/kcj.2017.0058. PubMed PMID: 29171203; PubMed Central PMCID: PMCPMC5764871.
13. Samuel D, Rafiu M, Akanbi O, Oluwamayowa D. Clinical and demographic characteristics of patients with kidney disease presenting at a tertiary hospital for expert care in south-west Nigeria. Journal of Surgery and Medicine. 2019;3(4):311-5. doi: 10.28982/josam.552956.
14. Madala ND, Thusi GP, Assounga AG, Naicker S. Characteristics of South African patients presenting with kidney disease in rural KwaZulu-Natal: a cross sectional study. BMC nephrology. 2014;15:61. Epub 2014/04/16. doi: 10.1186/1471-2369-15-61. PubMed PMID: 24731300; PubMed Central PMCID: PMCPMC4003519.
15. Vinson AJ, Bartolacci J, Goldstein J, Swain J, Clark D, Kiberd B, et al. Optimizing Ambulance Transport of Hemodialysis Patients to the Emergency Department: A Cohort Study. Canadian journal of kidney health and disease. 2019;6:2054358119848127. Epub 2019/06/28. doi: 10.1177/2054358119848127. PubMed PMID: 31245018; PubMed Central PMCID: PMCPMC6582295.
16. Carl DE, Grossman C, Behnke M, Sessler CN, Gehr TW. Effect of timing of dialysis on mortality in critically ill, septic patients with acute renal failure. Hemodialysis international International Symposium on Home Hemodialysis. 2010;14(1):11-7. Epub 2010/04/10. doi: 10.1111/j.1542-4758.2009.00407.x. PubMed PMID: 20377649.
17. García-Fernández N, Pérez-Valdivieso JR, Bes-Rastrollo M, Vives M, Lavilla J, Herreros J, et al. Timing of renal replacement therapy after cardiac surgery: a retrospective multicenter Spanish cohort study. Blood purification. 2011;32(2):104-11. Epub 2011/03/05. doi: 10.1159/000324195. PubMed PMID: 21372568.
18. Iyem H, Tavli M, Akcicek F, Büket S. Importance of early dialysis for acute renal failure after an open-heart surgery. Hemodialysis international International Symposium on Home Hemodialysis. 2009;13(1):55-61. Epub 2009/02/13. doi: 10.1111/j.1542-4758.2009.00347.x. PubMed PMID: 19210279.
19. Montford JR, Linas S. How Dangerous Is Hyperkalemia? Journal of the American Society of Nephrology: JASN. 2017;28(11):3155-65. Epub 2017/08/06. doi: 10.1681/asn.2016121344. PubMed PMID: 28778861; PubMed Central PMCID: PMCPMC5661285.
20. Peacock WF, Rafique Z, Clark CL, Singer AJ, Turner S, Miller J, et al. Real World Evidence for Treatment of Hyperkalemia in the Emergency Department (REVEAL-ED): A Multicenter, Prospective, Observational Study. The Journal of emergency medicine. 2018;55(6):741-50. Epub 2018/11/06. doi: 10.1016/j.jemermed.2018.09.007. PubMed PMID: 30391144.
21. Bajwa R, Amin A, Gandhi B, Mansur S, Amirpour A, Karawadia T, et al. A Simplified Approach to the Management of Hypercalcemia. The Open Urology & Nephrology Journal. 2018;11(1). doi: 10.2174/1874303X01811010022.
22. Nishikawa M, Shimada N, Kanzaki M, Ikegami T, Fukuoka T, Fukushima M, et al. The characteristics of patients with hypermagnesemia who underwent emergency hemodialysis. Acute medicine & surgery. 2018;5(3):222-9. Epub 2018/07/11. doi: 10.1002/ams2.334. PubMed PMID: 29988705; PubMed Central PMCID: PMCPMC6028801.
23. Oyamada N, Hamanaka I, Fujioka A, Iwasaku T, Minami T, Fujie H, et al. Effectiveness of high flow-volume intermittent hemodiafiltration during and after intervention to prevent contrast-induced nephropathy in patients with advanced chronic kidney disease: A pilot study. Catheterization and cardiovascular interventions: official journal of the Society for Cardiac Angiography & Interventions. 2019. Epub 2019/12/06. doi: 10.1002/ccd.28640. PubMed PMID: 31802610.
24. Chibishev A, Petkovska L, Tozija L, Zdravkovska M, Shikole E. The role of hemodialysis in treatment of acute acetic acid poisonings. Int J Artif Organs. 2017;40(5):219-23. Epub 2017/05/13. doi: 10.5301/ijao.5000588. PubMed PMID: 28497450.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):920-924.
DOI: 10.28982/josam.803731

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Assessment of anxiety and depression levels in parents of children presenting to the orthopedics outpatient clinic with the complaint of in-toeing

İçe basma yakınması ile ortopedi polikliniğine başvuran çocukların ailelerinin anksiyete ve depresyon düzeyinin değerlendirilmesi

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Ethics Committee Approval: For the present study, the approval of Başkent University Research and Ethics Committee was obtained (Project Number: KA17/209). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma için Başkent Üniversitesi Araştırma ve Etik Kurul onayı alınmıştır (Proje No: KA17/209). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The study was supported by Başkent University Research Fund.
Finansal Destek: Çalışma Başkent Üniversitesi Araştırma Fonu tarafından desteklenmiştir.

Published: 11/9/2020
Yayın Tarihi: 09.11.2020

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Abstract

Aim: In-toeing, a variant of normal growth and development of children, is an important reason of referral to the orthopedics outpatient clinics. The aim of the present study is to determine the anxiety, depression, and trait anxiety levels in parents of children presenting to orthopedics and traumatology outpatient clinic with the complaint of in-toeing. In addition, the study aims to investigate the conditions that might be associated with the anxiety level of parents.

Methods: This cross-sectional study included parents of 58 children who presented with the complaint of in-toeing (study group) and those of 40 healthy children (control group). The parents were required to fill in the sociodemographic data collection form, State-Trait Anxiety Inventory (STAI-II), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). The scale scores were compared statistically.

Results: The Beck Anxiety Inventory and STAI-II scores of parents of children presenting with in-toeing were statistically significantly higher compared to the control group (P=0.002, P=0.046, respectively). Spearman's correlation analysis revealed a strong correlation between BDI and BAI, STAI-II and BDI, BAI and STAI-II in the study group (r=0.518, P=0.001; r=0.546, P=0.001; r=0.566, P=0.001; respectively). In the control group, there was a weak correlation between BDI and BAI (r=0.346, P=0.029). An analysis of anxiety levels of the mothers in the study group revealed significantly higher scores of BAI and STAI-II compared to the fathers (P=0.025, P=0.001, respectively). The BAI, BDI and STAI-II scores of parents taking the child to the physician more than once a month, the BDI scores of parents having a history of psychiatric treatment and the BAI scores of parents aged between 20-40 were significantly higher in the study group (P=0.001, P=0.001, P=0.001, P=0.001, P=0.033, respectively).

Conclusion: The present study determined that anxiety levels were high in parents, especially mothers, who take their children to the physician frequently despite the absence of physical impairment. In addition, anxiety levels of parents were associated with taking the child to the physician more than once a month, having a history of psychiatric treatment and being aged between 20-40 years.

Keywords: In-toeing, Anxiety, Parents, Depression

Öz

Amaç: Normal büyüme ve gelişmenin varyantlarından olan içe basma, ortopedi polikliniklerine önemli bir başvuru nedenidir. Çalışmamızın amacı içe basma yakınması ile ortopedi ve travmatoloji polikliniğine getirilen çocukların ebeveynlerindeki anksiyete, depresyon ve durumsal kaygı düzeyini belirlemektir. Ayrıca ebeveynlerin kaygı düzeyi ile ilişkili olabilecek durumların gözden geçirilmesi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışmaya içe basma yakınması ile anne ve babası ile birlikte başvuran 58 çocuğun (çalışma grubu olarak) ve sağlık problemi olmayan 40 çocuğun (kontrol grubu olarak) ebeveyni dahil edilmiştir. Ailelerden sosyo-demografik veri formu, Süreklilik Kaygı Ölçeği (STAI II), Beck Depresyon Ölçeği (BDÖ) ve Beck Anksiyete Ölçeği (BAÖ) formlarını doldurmaları istendi. Ölçek puanları istatistiksel olarak karşılaştırıldı.

Bulgular: Beck Anksiyete Ölçeği ve STAI II ölçek puanları içe basma yakınması ile başvuran çocukların ebeveynlerinde kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek olarak saptandı (P=0,002, P=0,046, sırasıyla). Spearman korelasyon analizine göre içe basma yakınması olan grupta BDÖ ile BAÖ, STAI II ile BDÖ, BAÖ ile STAI II arasında güçlü korelasyon olduğu bulundu (r=0,518, P=0,001; r=0,546, P=0,001; r=0,566, P=0,001; sırasıyla). Kontrol grubunda ise BDÖ ve BAÖ arasında zayıf korelasyon saptandı (r=0,346, P=0,029). Annelerin kaygı düzeylerini belirleyen BAI ve STAI-II skorlarının babalara göre anlamlı oranda yüksek olduğu belirlenmiştir (P=0,025, P=0,001, sırasıyla). Çocuklarını ayda bir kezden fazla doktora götüren ebeveynlerin BAI, BDI ve STAI-II skorlarının, psikiyatrik tedavi öyküsü olanların BDI skorunun ve 20-40 yaş arasındaki ebeveynlerin BAI skorunun anlamlı olarak yüksek olduğu belirlenmiştir (P=0,001, P=0,001, P=0,001, P=0,001, P=0.033, sırasıyla).

Sonuç: Bu çalışmada fiziksel herhangi bir bozukluk olmamasına karşın çocuklarını sık doktora götüren ebeveynlerin özelliklede annelerin kaygı düzeylerinin yüksek olduğu belirlenmiştir. Ayrıca çocuğunu ayda birden fazla defa doktora götürme, psikiyatrik tedavi öyküsünün olması, yaş aralığının 20-40 arasında olması ile ebeveynlerin anksiyete düzeyi ilişkili bulundu.

Anahtar kelimeler: İçe basma, Anksiyete, Ebeveyn, Depresyon

How to cite/Atıf için: Haberal B, Altıntaş E, Beyaz S. Assessment of anxiety and depression levels in parents of children presenting to the orthopedics outpatient clinic with the complaint of in-toeing. J Surg Med. 2020;4(11):920-924.

Introduction

Parents often seek medical advice regarding their child's gait or posture [1,2]. Families visit orthopedics clinics, before the child starts to walk, for conditions that require treatment, such as talipes eqinovarus and metatarsus adductus. Plaster casts, pediatric boots and surgical methods are used in the treatment of these impairments. As with many diseases, children diagnosed early can be treated rather successfully with plaster casts and boots, but late diagnosis decreases the possibility of benefit from nonsurgical treatment methods [3].

Normal variants of the lower extremities in children are caused by rotational problems such as in-toeing and out-toeing, and angular problems such as genu varum (bowleg) and genu valgum (knock knee). In-toeing in childhood often occurs due to femoral anteversion and/or, less commonly, tibial torsion [4]. In fact, most of these conditions, which may cause parental concern, are variants of normal growth and development and have no effect on everyday physical function of the child in later years [2,5]. Gait disturbances, especially in-toeing, developing after the age of 1, are reasons for presenting to orthopedic outpatient clinics [6]. A study by Blackmur et al. [6] has revealed that none of the children who were brought to the hospital by their parents with the complaint of in-toeing needed surgery, 86% did not require a second visit and 14% did not have any significant pathology.

Anxiety in parents with children having chronic disease has been a particular subject of interest in various studies [7-9]. However, to the best of our knowledge, there are no studies in the literature assessing the anxiety levels in parents of children presenting to the hospital with the complaint of in-toeing, and the factors that may be linked to it. The aim of the present study is to determine the anxiety, depression, and trait anxiety levels in parents of children in this patient group.

Materials and methods

For the present study, the approval of Başkent University Research and Ethics Committee was obtained (Project Number: KA17/209) in accordance with the Declaration of Helsinki. The study was supported by Başkent University Research Fund.

Power analysis was performed before the initiation of the study to determine the minimum number of subjects that should be included in the patient and control groups. In this study, the required minimum sample numbers were determined as 30 study group patients and 30 control group patients (using Cohen criteria), alpha=0.05 and power=0.80.

Parents of 66 children who presented to Başkent University Faculty of Medicine Adana Dr. Turgut Noyan Application and Research Center Orthopedic Outpatient Clinic in 2017 with the complaint of in-toeing and whose examination revealed no orthopedic pathology were included in the study. Five children with chronic diseases and 2 children with histories of prior surgery were excluded. The parents of all 59 patients (the study group) were informed about the study. The parents of 1 patient stated their reluctance to enroll and were excluded. Both parents of the remaining 58 patients were administered the sociodemographic data collection form, State-Trait Anxiety Inventory (STAI-II), Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI). Forty healthy children with their parents visiting the pediatric outpatient clinic, who met the inclusion criteria and agreed to enroll in the study, were included as the control group, and completed the same scales.

Scales

Sociodemographic data collection form

This is a personal information form developed by the investigators to collect data related to the independent variables of the study. It inquires age, gender and birth rank of the child, mean number of hospital visits per month, presence of orthopedic disability in the family, presence or absence of family social support, parents' history of being ridiculed by peers and psychiatric treatment, and age and education level.

Beck Depression Inventory (BDI)

BDI is a multiple-choice self-report inventory created by Dr. Aaron T. Beck [10]. It consists of 21 questions, each having a set of 4 answers. Each answer is scored on a scale value of 0 to 3, and the total score ranges between 0 and 63. The total score is graded as follows: 0-4 no/minimal depression, 10-16 mild depression, 17-29 moderate depression, 30-63 severe depression. The reliability and validity study of the Turkish version of the inventory was conducted by Dr. Nesrin Hisli [11]. In the Turkish version, a score of 17 and above is considered major depression.

Beck Anxiety Inventory (BAI)

BAI is a 21-item Likert-type scale developed by Beck et al [12]. It is used to measure the severity of general anxiety. Each item is scored on a scale of 0 to 3 in order of increasing severity. The reliability and validity study of the Turkish version of the inventory was conducted by Dr. Ulusoy [13]. In the present study, the total scores were obtained through psychological assessment.

State-Trait Anxiety Inventory (STAI-II)

STAI is a paper-and-pencil test, developed by Spielberger, that can be administered to subjects aged 14 years and above with reading comprehension ability [14]. STAI-II aims to assess how a person feels in general, regardless of the situation. The validity and reliability study of the Turkish version of both were conducted by Öner and Le Compte [15].

Statistical analysis

Normal distribution of continuous variables was assessed using the Shapiro-Wilk test. Mann-Whitney U test was used to compare the two independent groups and the data were then compared with Kruskal-Wallis test. Two-way multiple comparison test was used to compare non-normally distributed data for more than two independent groups. Chi-square test was used to investigate the relationship between two categorical variables. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 24.0. A *P*-value <0.05 was considered statistically significant.

Results

Sociodemographic data

The comparison between the groups revealed no statistically significant difference regarding the genders of the children, ages of the parents, number of children in the family, history of prior surgery, continuous medication use, history of

psychiatric treatment, orthopedic disability in the family, and frequency of visit to the physician (P>0.05 for each). A statistically significant difference was found between the groups in terms of education level, occupation, presence of social support, history of being ridiculed by peers, birth rank of the child, history of problems in pregnancy and of in-toeing in either parent (P<0.05 for each) (Table 1).

Table 1: Demographic Characteristics of parents in the case and control groups

Variable	Case		Control		
	n	%	n	%	*P*-value
Child's gender					
-Male	36	62.1	26	65	0.741
-Female	22	37.9	14	35	
Age of parents					
-20-30	12	10.3	8	10	0.115
-30-40	47	40.5	16	20	
-40-50	49	42.2	48	60	
-50+	8	6.9	4	10	
Education level					
-Secondary school	16	13.8	0	0	0.019*
-High school	20	17.2	24	30	
-University	80	69	56	70	
Occupation					
-Unemployed	29	25	0	0	0.001*
-Worker	34	29.3	48	60	
-Civil servant	32	27.6	24	30	
-Self-employed	18	15.5	8	10	
-Physician	3	2.6	0	0	
Number of children					
-1	23	39.7	14	35	0.056
-2	25	43.1	12	30	
-3	10	17.2	14	35	
Prior surgery					
-Yes	51	44	24	30	0.121
-No	65	56	56	70	
Continuous medication use					
-Yes	11	9.5	10	12.5	0.588
-No	105	90.5	70	87.5	
Social support					
-Yes	27	23.3	40	50	0.001*
-No	89	76.7	40	50	
History of psychiatric treatment					
-Yes	10	8.6	8	10	0.792
-No	106	91.4	72	90	
History of being ridiculed by peers					
-Yes	12	10.3	20	25	0.022*
-No	104	89.7	60	75	
Birth rank of the child					
-1	59	50.9	24	30	0.016*
-2	35	30.2	24	30	
-3	22	19	32	40	
Health problems in pregnancy					
-Yes	8	13.8	0	0	0.013*
-No	50	86.2	40	100	
Chronic disease in the child					
-Yes	3	5.2	0	0	0.142
-No	55	94.8	40	100	
History of in-toeing in childhood					
-Yes	14	12	0	0	0.027*
-No	102	88	80	100	
Orthopedic disability in the family					
-Yes	4	3.4	8	10	0.105
-No	112	96.6	72	90	
Visit to the physician per month					
-1	73	62.9	48	60	0.124
-2	22	19	8	10	
-3	18	15.5	24	30	
-4+	3	2.6	0	0	

** Statistical significance P=0.05; Chi-squared test

Comparison of Inventory Scores

BAI and STAI-II scores were statistically significantly higher in the parents of children presenting with the complaint of in-toeing than in the control group (P=0.002, P=0.046, respectively). Spearman's correlation analysis revealed a strong correlation between BDI and BAI, STAI-II and BDI, BAI and STAI-II in the study group (r=0.518, P=0.001; r=0.546, P=0.001; r=0.566, P=0.001; respectively). In the control group, there was a weak correlation between BDI and BAI (r=0.346, P=0.029). The BAI, BDI and STAI-II scores according to study groups were given detail in Table 2.

An analysis of anxiety and depression levels of the mothers in the study group revealed significantly higher scores of BAI and STAI-II compared to the fathers (P=0.025, P=0.001, respectively). The scores did not vary significantly between the study and the control groups in terms of the gender of the children (P=0.561, P=0.984, P=0.546, P=0.834, P=0.318, P=0.547, respectively). The anxiety scores of parents between the ages of 30 and 40 years were higher compared to other age groups, while BAI and STAI-II scores were lower in parents above the age of 50 (P=0.033, P=0.001, respectively).

In the study group, BDI scores were higher in parents with history of psychiatric treatment (P=0.001). BAI scores were highest in parents bringing their 2nd child for examination in the study group (P=0.017). However, in the control group, BAI and STAI-II scores were higher for the 1st child compared to the 2nd and 3rd (P=0.001, P=0.001, respectively).

BDI and BAI scores of parents who took their children to the physician more than once per month for any reason were higher in the case group, while no significant difference was observed in the control group (P=0.001, P=0.001, P=0.858, P=0.316, respectively). BAI, BDI and STAI-II scores of the case and control groups are given in Table 3.

Table 2: Comparison of groups regarding scale scores

Variables	Case (n = 116)	Control (n = 80)	*P*-value
BDI, mean (SD)	7.45 (5.66)	5.8 (2.11)	0.283
BAI, mean (SD)	8.24 (8.4)	3.8 (2.16)	0.002*
STAI-II, mean (SD)	40.1 (8.39)	37.4 (9.68)	0.046*

* Statistical significance P=0.05; Mann-Whitney U test

Table 3: BDI, BAI and STAI-II scores in the case and control groups regarding each variable

Variable	Case				Control			
	n	BDI, mean (SD)	BAI, mean (SD)	STAI-II, mean (SD)	n	BDI, mean (SD)	BAI, mean (SD)	STAI-II, mean (SD)
-Mother	58	7.95 (5.44)	9.66 (9.68)	43.31 (8.25)	40	6 (1.95)	3.8 (2.71)	41.8 (10.09)
-Father	58	6.93 (5.89)	6.77 (6.59)	36.79 (7.23)	40	5.6 (2.3)	3.8 (1.51)	33 (7.06)
P-value		0.065	0.025*	0.001*		0.658	0.661	0.011*
-Female	36	7.29 (5.1)	8.43 (8.4)	40.21 (8.32)	26	5.73 (2.24)	3.54 (2.1)	36.42 (9.41)
-Male	22	7.7 (6.53)	7.93 (8.48)	39.93 (8.6)	14	5.93 (1.94)	4.29 (2.27)	39.21 (10.27)
P-value		0.561	0.984	0.546		0.834	0.318	0.547
Visit to the physician per month								
-0-1	37	6.03 (4.44)	6.68 (7.67)	39.18 (9.34)	24	5.83 (2.73)	3.83 (2.73)	37.58 (12.29)
-1-2	11	9.95 (6.67)	14.36 (9.39)	45.64 (5.25)	4	6 (0)	5 (0)	42.75 (1.26)
-2-3	9	9.89 (7.41)	7.11 (7.68)	36.28 (3.14)	12	5.67 (0.49)	3.33 (0.49)	35.25 (0.87)
-3+	1	9 (0)	8 (0)	45 (0)	0			
P-value		0.001*	0.001*	0.001*		0.858	0.316	0.129
History of psychiatric treatment								
-Yes	10	12.2 (5.01)	12 (17.01)	42.6 (6.79)	8	8 (0)	1 (0)	42 (0)
-No	106	7 (5.53)	7.89 (7.14)	39.89 (8.52)	72	5.56 (2.09)	4.11 (2.05)	36.89 (10.09)
P-value		0.001*	0.333	0.472		0.028*	0.001*	0.161
History of being ridiculed by peers								
-Yes	12	6.08 (1.93)	6.42 (3.42)	40.25 (8.75)	20	5.5 (1.51)	5.1 (1.66)	41.5 (9.12)
-No	104	7.61 (5.93)	8.45 (8.78)	40.09 (8.39)	60	5.9 (2.29)	3.37 (2.16)	36.03 (9.62)
P-value		0.694	0.613	0.835		0.548	0.014*	0.598
History of in-toeing in childhood								
-Yes	13	7.46 (9.92)	8.69 (11.71)	40.38 (11.79)	0	0	0	0
-No	103	7.45 (4.96)	8.18 (7.96)	40.07 (7.94)	80	5.8 (2.11)	3.82 (2.16)	37.4 (9.68)
P-value		0.083	0.27	0.756				
Age of parents								
-20-30	12	8.83 (2.98)	8.5 (3.66)	47.08 (4.17)	8	6 (0)	5 (0)	42.75 (1.26)
-30-40	47	8.3 (7.51)	9.85 (10.48)	42.4 (9.16)	16	6.5 (1.6)	7 (1.07)	50.88 (8.72)
-40-50	49	6.2 (3.25)	6.84 (6.58)	37.55 (5.73)	48	6.17 (1.99)	2.83 (1.49)	34.58 (4.23)
-50+	8	8 (7.09)	7 (9.26)	31.75 (10.4)	8	2 (0)	2 (0)	22 (0)
P-value		0.113	0.033*	0.001*		0.012*	0.001*	0.001*

* Statistical significance: P=0.05; Kruskal-Wallis test

Discussion

To the best of our knowledge, there are no studies in the literature assessing the anxiety levels in parents of children presenting to the hospital with the complaint of in-toeing, and the factors that may be linked to it. The present study aimed to determine the variance of depression and anxiety levels in parents of children with suspected in-toeing, compared to the general population.

BAI and STAI-II scores of parents in the case group of the present study were higher compared to the general population. These parents were in fact subjects who took their children to the physician more frequently, had higher levels of

depression and history of health problems in pregnancy and of being ridiculed by peers in childhood. In addition, anxiety levels were higher in parents visiting the physician with their 2nd child. Especially those between the ages of 30-40 years had elevated levels of anxiety concerning their children, whereas anxiety was lower in the older age group. This suggests that anxiety level decreases depending on the parents' life experience. Studies on parental roles have revealed results in favor of the positive effects of having a child. It has been shown that individuals with children have better physical and psychological health than those without: Mothers had lower life stress, health problems and depression, and higher life satisfaction and self-esteem; and fathers had better psychological health [16-19]. This is possibly related to feeling obliged to act more responsibly as parents. With fatherhood, men are generally more mature and responsible, taking less risk [20]. Most fathers restrain from risky behaviors, such as smoking, excessive alcohol consumption, or doing dangerous sports, both before and after the birth of their child, and become even more cautious thereafter [20,21].

The anxiety level of the parents in the case group of the present study was higher, which is consistent with the literature. The fact that the baby's physical and psychological needs are met by the mother during pre and postnatal periods leads to a strong bond between both. This may result in the mother's feeling of liability for any physical or mental impairment that may occur in the child. Some studies have shown that anxiety levels are higher in mothers with disabled children than in those with healthy children, whereas other studies reported no such difference, regardless of the disability level of the child [7,8].

Similarly, while some studies reported high levels of depression in parents with disabled children, others reported moderate levels of depression [8]. In the present study, no significant difference was observed between the case group and the control group with regards to depression scale scores, which was in line with the findings of Sajedi et al. [7]. However, the present study revealed higher anxiety and depression levels in parents who felt obliged to take their children to hospital more than once per month. The main reason for frequent visit to the physician may be the desire to achieve early management of any suspected deformity and, thus, to prevent chronic disability.

The correlation analysis in the present study revealed a statistically significant relationship between BAI and frequent visit to the physician, history of psychiatric treatment, and being between 20-40 years of age. Studies have shown that mothers of younger age tend more to have babies with difficult temperament, cognitive developmental delay, behavioral problems and inadequate language development [22-25]. In line with that, lower levels of depression and anxiety and higher marital satisfaction and well-being were reported in individuals who thought that they assumed parental role in due course [26,27]. However, this may be linked to better living conditions, as mentioned earlier. Individuals who become parents later in life are more likely to have better economic circumstances than those doing so earlier [28]. Older parents also have higher education levels and better career achievements, as well as lower fertility rates [29].

The present study determined lower levels of social support in the study group. This fact may have caused parents to spend more time with their children and exhibit more protective behaviors. It has elsewhere been reported that parents of children with congenital disabilities adapt to that condition easier in families with strong social ties [30]. Stronger social support partially relieves the burden on the mother, resulting in reduced stress and, in turn, decreased proneness to depression and anxiety.

Limitations

The present study has some limitations. First, it is a single-center study with a small sample size, which may be inadequate to give a picture of the general population. Similar future studies with multi-center design may promote the reliability of results for the general population. Second, self-reported sociodemographic data were used in the present study, meaning that their verification may be necessary to improve the reliability of results.

Conclusions

The present study determined that anxiety levels were higher in parents, especially mothers, of children who were taken to the physician with the complaint of in-toeing but who were found to be healthy upon examination. It is thus possible to conclude that parental anxiety may cause unnecessary examination and treatment of the child. Moreover, depression or anxiety symptoms in the mother, especially in the first 2 years of the child's life, may later lead to emotional and behavioral problems in childhood and prominent levels of depressive symptoms in adolescence. Therefore, it is of utmost importance to keep track of parental attitudes and mental states in the first years of the child's life. This requires a multidisciplinary approach, involving psychiatric support when necessary.

References

1. Hsu EY, Schwend RM, Julia L. How many referrals to a pediatric orthopaedic hospital specialty clinic are primary care problems? J Pediatr Orthop. 2012;32(7):732-6.
2. Molony D, Hefferman G, Dodds M, McCormack D. Normal variants in the paediatric orthopaedic population. Ir Med J. 2006;99(1):13-4.
3. Digge V, Desai J, Das S. Expanded Age Indication for Ponseti Method for Correction of Congenital Idiopathic Talipes Equinovarus: A Systematic Review. J Foot Ankle Surg. 2018;57(1):155-8.
4. Dietz FR. Intoeing--fact, fiction and opinion. Am Fam Physician. 1994;50(6):1249-59, 62-4.
5. Kong M, Jo H, Lee CH, Chun SW, Yoon C, Shin H. Change of Femoral Anteversion Angle in Children With Intoeing Gait Measured by Three-Dimensional Computed Tomography Reconstruction: One-Year Follow-Up Study. Ann Rehabil Med. 2018;42(1):137-44.
6. Blackmur JP, Murray AW. Do children who in-toe need to be referred to an orthopaedic clinic? J Pediatr Orthop B. 2010;19(5):415-7.
7. Sajedi F, Alizad V, Malekkhosravi G, Karimlou M, Vameghi R. Depression in mothers of children with cerebral palsy and its relation to severity and type of cerebral palsy. Acta Med Iran. 2010;48(4):250-4.
8. Yilmaz H, Erkin G, Nalbant L. Depression and anxiety levels in mothers of children with cerebral palsy: a controlled study. Eur J Phys Rehabil Med. 2013;49(6):823-7.
9. Anıl H, Sahbudak B. Parental anxiety and depression levels associated with challenge tests in children with suspected drug and food allergies. Journal of Surgery and Medicine. 2020;4(8):669-73.
10. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-71.
11. Hisli N. Beck Depresyon Envanterinin gecerliligi uzerine bit calisma (A study on the validity of Beck Depression Inventory.). Psikoloji Dergisi. 1988;6:118-22.
12. Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56(6):893-7.
13. Ulusoy M. Beck anksiyete ölçeğinin psikometrik özellikleri. Uzmanlık Tezi, Bakırköy Ruh ve Sinir Hastalıkları Hastanesi, İstanbul. 1993.
14. Spielberger C, Gorsuch RL, Lushene R. STAI manual for the State-Trait Inventory. Palo Alto. 1970.
15. Öner N, Le Compte A. Durumluk ve sürekli kaygi envanteri el kitabi. Bogaziçi Üniversitesi Yayınları, İstanbul. 1983.
16. Helbig S, Lampert T, Klose M, Jacobi F. Is parenthood associated with mental health? Findings from an epidemiological community survey. Soc Psychiatry Psychiatr Epidemiol. 2006;41(11):889-96.
17. Koropeckyj-Cox T. Beyond parental status: Psychological well-being in middle and old age. Journal of Marriage and Family. 2002;64(4):957-71.
18. McDonough P, Walters V, Strohschein L. Chronic stress and the social patterning of women's health in Canada. Soc Sci Med. 2002;54(5):767-82.
19. McQuillan J, Torres Stone RA, Greil AL. Infertility and life satisfaction among women. Journal of Family Issues. 2007;28(7):955-81.
20. Settersten Jr RA, Cancel-Tirado D. Fatherhood as a hidden variable in men's development and life courses. Research in human development. 2010;7(2):83-102.
21. Goldberg W. Father time: The social clock and the timing of fatherhood: Springer; 2014.
22. Furstenberg FF, Jr., Brooks-Gunn J, Chase-Lansdale L. Teenaged pregnancy and childbearing. Am Psychol. 1989;44(2):313-20.

23. Keown LJ, Woodward LJ, Field J. Language development of pre-school children born to teenage mothers. Infant and Child Development: An International Journal of Research and Practice. 2001;10(3):129-45.
24. Secco ML, Moffatt ME. Situational, maternal, and infant influences on parenting stress among adolescent mothers. Issues Compr Pediatr Nurs. 2003;26(2):103-22.
25. Sommer KS, Whitman TL, Borkowski JG, Gondoli DM, Burke J, Maxwell SE, et al. Prenatal maternal predictors of cognitive and emotional delays in children of adolescent mothers. Adolescence. 2000;35(137):87-112.
26. Carlson DL. Explaining the curvilinear relationship between age at first birth and depression among women. Soc Sci Med. 2011;72(4):494-503.
27. Helms-Erikson H. Marital quality ten years after the transition to parenthood: Implications of the timing of parenthood and the division of housework. Journal of Marriage and Family. 2001;63(4):1099-110.
28. Benzies K, Tough S, Tofflemire K, Frick C, Faber A, Newburn-Cook C. Factors influencing women's decisions about timing of motherhood. J Obstet Gynecol Neonatal Nurs. 2006;35(5):625-33.
29. Amuedo-Dorantes C, Kimmel J. The motherhood wage gap for women in the United States: The importance of college and fertility delay. Review of Economics of the Household. 2005;3(1):17-48.
30. Trute B, Hiebert-Murphy D. Family adjustment to childhood developmental disability: a measure of parent appraisal of family impacts. J Pediatr Psychol. 2002;27(3):271-80.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):925-929.
DOI: 10.28982/josam.780806

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Management of a radiation oncology clinic in a clean oncology hospital during the COVID-19 outbreak

COVID-19 salgını sırasında temiz bir onkoloji hastanesinde radyasyon onkolojisi kliniği yönetimi

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Ethics Committee Approval: This study was approved by the Medical Specialty Training Board of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval ID: 5/5/2020-92). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Dr. Abdurrahman Yurtaslan Ankara Onkoloji Eğitim ve Araştırma Hastanesi Tıpta Uzmanlık Eğitim Kurulu tarafından onaylanmıştır (Onay No: 05.05.2020-92). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/10/2020
Yayın Tarihi: 10.11.2020

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Abstract

Aim: COVID-19 is a disease that was declared a pandemic by the World Health Organization (WHO) in 2020. The first case in Turkey was confirmed on 11 March 2020. Since patients with cancer were reported to have a higher risk for COVID-19 infection, as an oncology hospital, we created a mini science board within our hospital. By following the advice of this science board and the permissions of the local administrators our hospital, which is the only training and research hospital that specialized in oncology in Turkey, undertook the clean hospital mission to continue cancer treatments uninterruptedly. Radiotherapy has an essential role in cancer treatment and our radiotherapy department is the biggest one in Turkey. This retrospective study aimed to constitute ideas for special issues such as pandemics by examining the workflow of our hospital's radiation oncology clinic.

Methods: The workflow of the clinic, the precautions taken, the number of treated patients and the COVID-19 positive cases were evaluated. The records of the radiation oncology clinic were used for evaluation.

Results: Two-hundred forty-seven patients in March 2020 and 164 patients in April 2020 were treated in our department. None of our staff and only 3 of our patients were COVID-19 positive.

Conclusion: For emergent situations like this pandemic that may occur in the future, the existence of clean hospitals is essential to continue cancer treatments uninterruptedly.

Keywords: COVID-19, Pandemics, Radiation oncology

Öz

Amaç: COVID-19 2020 yılında DSÖ tarafından pandemi olarak ilan edilmiş bir hastalıktır. Türkiye'de ilk vaka 11 Mart 2020'de tespit edilmiştir. Kanser tanısı olan hastaların COVID-19 enfeksiyonu açısından daha riskli olduğu bildirildiğinden onkoloji hastanesi olarak hastanemizde mini bilim kurulu oluşturuldu. Bu bilim kurulunun tavsiyeleri ve yerel yöneticilerin izinleri ile Türkiye'de kanser konusunda uzmanlaşmış tek eğitim ve araştırma hastanesi olan hastanemiz, kanser tedavilerine kesintisiz devam edebilmek için temiz hastane görevini üstlenmiştir. Radyoterapi kanser tedavisinde önemli bir role sahiptir ve hastanemizin radyoterapi kliniği Türkiye'nin en büyük radyoterapi kliniklerinden birisidir. Bu çalışmada, Türkiye'deki temiz bir onkoloji hastanesindeki radyasyon onkolojisi kliniğinin iş akışı incelenerek pandemi gibi özel durumlar için fikir oluşturulması amaçlanmıştır.

Yöntemler: Kliniğin iş akışı, alınan önlemler, radyoterapi uygulanan ve radyoterapi sürecinde COVID-19 pozitif tespit edilen hasta sayısı değerlendirilmiştir. Değerlendirme için radyasyon onkolojisi kliniği verileri kullanılmıştır.

Bulgular: Bölümümüzde Mart 2020'de 287 hasta, Nisan 2020'de 164 hastaya radyoterapi uygulanmış; bu hastalardan sadece 3 tanesinde COVID-19 pozitifliği tespit edilmiştir. Hiçbir personelimizde COVID-19 pozitifliği saptanmamıştır.

Sonuç: Gelecekte ortaya çıkabilecek bu pandemi gibi acil durumlarda kanser tedavilerinin kesintisiz devam edebilmesi için temiz hastanelerin varlığı önemlidir.

Anahtar kelimeler: COVID-19, Pandemi, Radyasyon onkolojisi

How to cite/Atıf için: Göksel F, Adaş YG. Management of a radiation oncology clinic in a clean oncology hospital during the COVID-19 outbreak. J Surg Med. 2020;4(11):925-929.

Introduction

In December 2019, many patients were admitted to hospitals with pneumonia in Wuhan, China. The etiology was unknown at the beginning. A coronavirus named 2019-nCoV was isolated by Chinese scientists on 7 January 2020 [1].

In January 2020, 7734 cases of COVID-19 were reported from China and 90 other cases were reported in various countries. The mortality rate was reported as 2.2% and the World Health Organization (WHO) declared COVID-19 as an international health emergency. On March 2020, COVID-19 was announced as a pandemic by the WHO [2].

As reported recently, COVID-19 is transmitted through close contact and respiratory droplets. The incubation period has been estimated as 3-7 days but extend up to 14 days. Asymptomatic cases within the incubation period and mildly infected children were declared as the main transmission routes. The illness was severe and more fatal in the elderly and those with underlying chronic disease [3]. So, precautions were taken in Turkey based on these observations. Firstly, in January 2020, the COVID-19 science board was established within the Ministry of Health. In line with the science board's recommendations, travel restrictions were introduced, primarily to China and Italy. Quarantine application was brought to citizens coming from abroad for fourteen days. The first COVID-19 case in Turkey was confirmed on 10 March 2020 by the Ministry of Health. Two days after the detection of the first case, education was interrupted in all schools and universities across the country. In the following days, the centers, such as theatre, cinema, show centres, shopping malls, cafes, restaurants and gym centers where people can be found collectively were all closed. A curfew was imposed to citizens who were over 65 and under 20 years of age.

During this process, all hospitals, including private ones, were declared as pandemic hospitals. An in-hospital science board was established at our hospital. It was reported to the Provincial Health Directorate with the suggestions of our science board that our hospital was a cancer hospital, the majority of the patients we serve were cancer patients and that these patients were in the group where COVID-19 infection may be severe. With the recommendation of the Provincial Directorate of Health, our hospital started to serve as a clean oncology hospital as of 16 March 2020. Clean hospital term means that the hospital where COVID-19 positive cases were not accepted and treated.

It was an important issue to stay as a clean hospital to continue the treatments of cancer patients without any interruptions. As the clean hospital, COVID-19 (+) cases were not allowed in our hospital. However, a pandemic polyclinic was opened for the cancer patients treated in our hospital. Suspicious cases were referred to this polyclinic and when these cases were confirmed as COVID-19 (+) they were transported to other pandemic hospitals.

As recently reported by Liang et al., cancer patients had a higher risk of contracting COVID-19 than otherwise healthy people. Besides, cancer patients with COVID-19 had poorer prognosis [4]. Our hospital is the only hospital in Ankara that specializes in oncology. Therefore, it was important to stay as a clean hospital for the protection of our patients from COVID-19. Radiotherapy has an essential role in cancer treatment. Over 50-60% of all cancer patients are treated with RT at some point in their treatment [5].

The COVID-19 outbreak is a health emergency, but cancer treatments are also important and cannot be omitted or interrupted because of this outbreak. This study aimed to evaluate the management and working flow of the radiation oncology clinic of a clean oncology hospital in this pandemic period.

Materials and methods

In this study, it was aimed to evaluate the personnel working order, the number of patients, management of patient treatments and treatment devices working time and order, as well as the regulations of radiotherapy indications and doses within the scope of the pandemic along with the precautions taken in the radiation oncology clinic of our hospital, which has served as a clean oncology hospital after the detection of first the COVID-19 positive case in Turkey.

As the biggest radiation oncology clinic in Turkey, many patients have been treated in our clinic. The number of patients treated during and before the pandemic period was compared to evaluate the effect of this emergent period to the number of treated patients. Treatment interruptions due to COVID-19 positivity were also evaluated.

1. General precautions in hospital

The training started throughout our hospital before the pandemic was announced. The first training was given on 11 February 2020. A training program was prepared in accordance with the pandemic action plan. The training was provided and continues to be delivered. All staff was trained about the use of PPE (personal protective equipment) and written documents were sent to the clinics. The PPE request of all personnel with the possibility of contact with COVID-19 (+) patients was met. Surgical masks were distributed to all staff in connection with the patients 5 days after the detection of the first case. Starting from the second week, protective eyewear, long-sleeved disposable gowns, shoe covers, gloves and surgical caps were distributed to those who had direct contact with the patient. Transparent protective barriers were placed in front of the data processing and patient registry units. Workflow charts and guidelines for patients suspected of COVID-19 were created in clinics. These guides have been added to the training documents on the desktop of the hospital computers and the remote education system.

To prevent the disruption of follow-up and treatment of cancer patients, the internal medicine intensive care unit and radiotherapy services were evacuated. Cancer patients suspected of COVID-19 were hospitalized and followed-up in these evacuated services, within the scope of the clean hospital, the positive results of PCR were sent to pandemic hospitals by ambulances. A polyclinic was opened for personnel screening. Until the 20 May 2020, 1565 personnel were scanned for COVID-19 by PCR and of these, 480 also by rapid antibody tests. Personnel screening is still on- going. All staff was questioned daily for COVID-19. In case of suspicious contact

with COVID-19 patients in his family or in his environment, he/she was asked to report to his/her administrators.

A flexible working schedule was set up for the staff. The hospital information management system was fully opened to remote access to doctors. In this way, remote consultations were possible if necessary. Council meetings were held online whenever possible; and with minimum participation, if not possible. Online patient information line was made more active to prevent patients from coming to the hospital except in very urgent and necessary situations. Attention was paid to ensure that the working areas were large and adequately ventilated by windows.

Triage was established in all clinical entrances. By the opening of local triages, the in-hospital entries were reduced to just one. The other two entrances to the radiation oncology clinic were closed, and the only access was provided from the main entrance. One security guard and one nurse commissioned in the triages. All PPE was given to these security guards and nurses. Importance was given to maintaining social distance at the entrances. The fever of every person, including personnel, who entered the clinic, was measured and queries suggested in the COVID-19 guidelines of the ministry of health were made. Suspicious cases were referred to the pandemic polyclinic, and the polyclinic was informed by phone about the patient. The department where the patients were treated, and their doctors were also informed. Patients were taken to the clinic alone, if possible, with one accompanying person if needed. Hand sanitizers were provided at the entrances. Patients who came with gloves were asked to remove their gloves; their hands were disinfected. Beginning from the third week, all patients were given a surgical mask in triage. With the recommendation of the radiation oncology clinic, since the valve mask has a high risk of spreading viruses to the environment, patients with a valve mask were asked to remove these masks and wear a surgical mask or use them together with the surgical mask.

2. Special precautions in the radiation oncology clinic

2-a) Devices

Necessary precautions were taken for 6 treatment devices and 3 planning CTs available in our clinic. While 8-10 patients were taken into treatment per hour before the pandemic, this number was reduced to 4-6 patients during the pandemic period. Due to the reduction of the number of patients by the hour, additional shifts were worked until all daily treatment patients were treated. After each patient, the cleaning staff dressed in appropriate PPE cleaned the devices with medical device disinfectants. Seats in the waiting rooms were removed. The patients were taken to the waiting areas one by one.

2-b) Staff

All radiation oncology clinic staff switched to flexible working hours. The work plans of the staff were made following patient flow. Thirty-five doctors working in our clinic came to work alternately. Every day, 10 doctors were arranged to be in the clinic. Attention was paid to only to have one doctor in each doctor's room.

Eighteen radiotherapy physicists were divided into 6 groups of 3 people. Arrangements were made so that one person from each of these 6 groups was brought to the clinic every day.

Forty-eight radiotherapy technicians were divided into groups of 4 people and these groups worked in shifts for a week. Each team was given one week off, they were asked to stay at home and follow social distancing rules when they were on leave.

Daily PPEs were given to the staff by the department officers. After the announcement of the first case, it was observed that all staff started wearing uniforms and surgical caps voluntarily.

Patients on treatment were questioned every day according to the Turkish Ministry of Health's pandemic guide. If any of these questions were answered 'yes', the patient was referred to the pandemic polyclinic.

2-c) Radiotherapy indications and treatment schedules

Radiation oncology communities published guidelines for both indications and radiotherapy schedules to be used during this outbreak. These guidelines and recommendations were shared online with our doctors [6-8].The decisions about the indications and treatment schedules were left to doctors 'interpretations.

Results

During the pandemic process, our hospital continued to serve oncology patients with the role of a clean hospital.

In January, February, and March 2020, the numbers of treated patients were 259, 257 and 247, respectively. When these numbers were compared to October, November, and December 2019 (n=286, 255, and 257, respectively), no difference was observed. The number 247 in March 2020 decreased to 164 in April 2020.

Although there was no decrease in the number of oncology patients compared to the same months of 2019, a severe decline was observed in our other polyclinics other than oncology due to the refusal of the elective cases and the shutdown of the central patient appointment system to maintain the role of the clean hospital. After the pandemic announcement, our outpatient clinic occupancy rates were 10% in the second half of March and 25% in April. Although there was a partial increase in the number of outpatients in April upon hearing that we are a clean hospital, these figures were lower than those in April 2019.

When 16 of the patients who were being treated in our clinic, answered 'yes' to the questions asked in the Ministry's guide, they were referred to the pandemic polyclinic with the suspicion of COVID-19. Three of these patients were COVID-19 positive. Radiotherapy was interrupted for these patients. One of the patients who underwent COVID-19 treatment continued radiotherapy after the PCR test was negative after the treatments. The COVID-19 treatments of the other 2 patients were ongoing during the writing process of this article. Radiotherapy technicians who treated these 3 patients were also referred to the staff pandemic clinic and recommended to stay at home until the test results came. After the test results were negative, they continued to work in accordance with the algorithm, using the necessary PPE.

All our staff was referred to personnel pandemic clinic and the test results of COVID-19 were negative for all of them.

Discussion

The COVID-19 outbreak is an international health emergency. As a result of our scientific board's attempts and the approval of the provincial health directorate, our hospital served as a clean oncology hospital in the pandemic process. If these attempts were not made, our hospital would have served as a pandemic hospital and cancer patients who were being treated in our hospital would have been at greater risk of being infected with COVID 19.

Our patient population had a higher risk in terms of contracting COVID-19 and having poorer outcomes because of their cancer[4]. Naturally, cancer was not the only risk factor for our patients. There were of course elderly patients and patients with other chronic diseases besides cancer. So, we had to take special precautions to protect both our patients and our staff.

The protection of the personnel was essential both in terms of infecting patients and continuing their treatment. Radiotherapy is a very specialized area and cannot be performed by uneducated and unqualified staff. With this in mind, our Ministry of Health published an instruction on 14 April 2020 in order not to hire oncology staff at pandemic clinics. As a clean hospital, our directors did not employ any oncology staff at our pandemic polyclinic even before this instruction.

In a recently published paper from the radiation oncology department of Istanbul Dr. Lutfi Kırdar Training and Research Hospital, 13 radiation oncologists of 18, one technician and one nurse were reported as COVID-19 positive because of small sized polyclinic rooms and not giving importance to social distance. So they reported that their hospital management committee decided not to accept new cancer patients and refer them to nearby centers [9]. In our clinic, strict precautions were taken from the announcement of the first case in Turkey. Social distancing was the most important issue for us. All the tumor boards and education programs were canceled in our clinic. Both tumor boards and education programs were made online as much as possible. No COVID-19 positivity was reported in the staff of our radiation oncology clinic so all new cancer cases were accepted and treated at our center. This supports both the importance of the early precautions and the clean oncology hospital concept. As a clean oncology hospital COVID-19 positive cases were not accepted to our hospital.

In German and Italian studies, institute sanitation, triage implantations and dividing staff into groups are reported as important precautions for radiation oncology departments [5, 10]. Institute disinfection, and triage implantation were the first precautions of our department. We also agreed on confidential working hours and the staff was divided into groups to prevent potential contamination. The division of radiotherapy technicians was nearly ideal. They were divided into groups as one week on and one week off. The off group did not come to hospital for 7 days, which is the average incubation period of COVID-19. They also did not contact each other. But a study of Shen et al. reported that the incubation period of COVID 19 may extend up to 14 days [3]. For this reason, it would have been more appropriate to set the working interval of the teams as 14-day-on-off periods instead of one-week, but this could not have been provided in the first periods. Our studies were continuing to increase this period to 14 days in the writing stage of this article. The doctors, radiotherapy physicists, nurses and cleaning staff were also divided into groups but this one week on one week off system could not have been provided for these groups due to the workload. In this process, the staff, who could not be interrupted for 7 days, could cause infection in our clinic. Nevertheless; none of our staff was COVID-19 positive. We think that is due to our other strict precautions like triage, sanitization, staff education, respecting social distancing.

PPE is another important issue in this outbreak. In Italy, for example, where the COVID-19 mortality rate was one of the highest in the World (about 9.8%), shortage of PPE was reported as one of the most critical problems. Because of this shortage, 10 % of the people infected by COVID-19 were health professionals [11]. In our clinic, surgical masks were provided for our staff from the date that the first case was announced in our country. All other necessary PPE (protective eye wear, long-sleeved disposable gowns, shoe covers, gloves, and surgical caps) were provided one week later. Moreover, our staff started to wear uniforms and surgical caps voluntarily. This was considered as an indication that the awareness of the staff in our clinic is high.

In recent studies, adapting the radiation therapy indications and durations were suggested in this pandemic period [6-8]. In our clinic these suggestions were shared with our doctors but the decision about this was left to the doctor. When the number of patients treated in March and April 2020 was compared, we observed that the patient number in April 2020 is nearly half the number of patients treated in March. This supports that our doctors have limited the indications of radiotherapy in line with the recommendations.

Radiotherapy should be administrated in a planned time. Interruptions in the treatment time may cause tumor cell repopulation. For head and neck cancers a 1-day interruption resulted of a 1.4% decrease in local control rates.so it is recommended to finish radiotherapy in planned time [12]. Only three of our patients were reported as COVID-19 positive in this period and radiotherapy was interrupted for only these three patients because of the COVID-19 outbreak. This emphasizes the importance of working as a clean oncology hospital in this pandemic period.

Conclusions

The establishment of a cancer science board in our hospital and our clean hospital status with the recommendation of the science board have been one of the most important steps in the protection of the hospital staff and cancer patients from infection during this period. In this process, we believe that the general measures are taken in our hospital, and the special precautions taken in our clinic have set an example for other hospitals and radiation oncology clinics in possible future emergencies.

References

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun. 2020;109:102433. Epub 2020/03/03. doi: 10.1016/j.jaut.2020.102433. PubMed PMID: 32113704; PubMed Central PMCID: PMCPMC7127067.
2. Bassetti M, Vena A, Giacobbe DR. The novel Chinese coronavirus (2019-nCoV) infections: Challenges for fighting the storm. Eur J Clin Invest. 2020;50(3):e13209. Epub 2020/02/01. doi: 10.1111/eci.13209. PubMed PMID: 32003000; PubMed Central PMCID: PMCPMC7163647.
3. Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020;16(3):223-31. Epub 2020/02/09. doi: 10.1007/s12519-020-00343-7. PubMed PMID: 32034659; PubMed Central PMCID: PMCPMC7090771.

4. Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol. 2020;21(3):335-7. Epub 2020/02/19. doi: 10.1016/S1470-2045(20)30096-6. PubMed PMID: 32066541; PubMed Central PMCID: PMCPMC7159000.
5. Combs SE, Belka C, Niyazi M, Corradini S, Pigorsch S, Wilkens J, et al. First statement on preparation for the COVID-19 pandemic in large German Speaking University-based radiation oncology departments. Radiat Oncol. 2020;15(1):74. Epub 2020/04/09. doi: 10.1186/s13014-020-01527-1. PubMed PMID: 32264908; PubMed Central PMCID: PMCPMC7136995.
6. Achard V, Tsoutsou P, Zilli T. Letter from Switzerland. Int J Radiat Oncol Biol Phys. 2020;107(3):600-1. Epub 2020/03/23. doi: 10.1016/j.ijrobp.2020.03.008. PubMed PMID: 32199942; PubMed Central PMCID: PMCPMC7269705.
7. Thomson DJ, Palma D, Guckenberger M, Balermpas P, Beitler JJ, Blanchard P, et al. Practice Recommendations for Risk-Adapted Head and Neck Cancer Radiation Therapy During the COVID-19 Pandemic: An ASTRO-ESTRO Consensus Statement. Int J Radiat Oncol Biol Phys. 2020;107(4):618-27. Epub 2020/04/18. doi: 10.1016/j.ijrobp.2020.04.016. PubMed PMID: 32302681; PubMed Central PMCID: PMCPMC7194855.
8. Guckenberger M, Belka C, Bezjak A, Bradley J, Daly ME, DeRuysscher D, et al. Practice recommendations for lung cancer radiotherapy during the COVID-19 pandemic: An ESTRO-ASTRO consensus statement. Radiother Oncol. 2020;146:223-9. Epub 2020/04/29. doi: 10.1016/j.radonc.2020.04.001. PubMed PMID: 32342863; PubMed Central PMCID: PMCPMC7252074.
9. Gemici C, Yaprak G. Covid-19 outbreak in a major radiation oncology department; which lessons should be taken? Radiother Oncol. 2020;149:107-8. Epub 2020/04/29. doi: 10.1016/j.radonc.2020.03.044. PubMed PMID: 32342865; PubMed Central PMCID: PMCPMC7194801.
10. Meattini I, Franco P, Belgioia L, Boldrini L, Botticella A, De Santis MC, et al. Radiation therapy during the coronavirus disease 2019 (covid-19) pandemic in Italy: a view of the nation's young oncologists. ESMO Open. 2020;5(2). Epub 2020/04/17. doi: 10.1136/esmoopen-2020-000779. PubMed PMID: 32295769; PubMed Central PMCID: PMCPMC7199912.
11. Cesari M, Proietti M. Editorial: Geriatric medicine in Italy in the time of COVID-19. J Nutr Health Aging. 2020;24(5):459-60. Epub 2020/04/30. doi: 10.1007/s12603-020-1354-z. PubMed PMID: 32346679; PubMed Central PMCID: PMCPMC7118363.
12. Bese NS, Hendry J, Jeremic B. Effects of prolongation of overall treatment time due to unplanned interruptions during radiotherapy of different tumor sites and practical methods for compensation. Int J Radiat Oncol Biol Phys. 2007;68(3):654-61. Epub 2007/05/01. doi: 10.1016/j.ijrobp.2007.03.010. PubMed PMID: 17467926.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):930-933.
DOI: 10.28982/josam.812409

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Factors affecting mortality in trauma patients hospitalized in the intensive care unit

Travma nedeniyle yoğunbakım ünitesinde izlenen hastalarda mortaliteyi etkileyen faktörler

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Ethics Committee Approval: The study was approved by the Harran University Ethics Committee (Approval No: E.7334, Date: February 11, 2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Harran Üniversitesi etik komitesi tarafından onaylandı (Onay No: E.7334, Tarih: 11 Şubat 2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/17/2020
Yayın Tarihi: 17.11.2020

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Abstract

Aim: An accurate estimation of the prognosis of patients admitted to the intensive care unit (ICU) is of prime importance for their clinical management. The aim of this retrospective study was to investigate factors affecting mortality in trauma patients hospitalized in the ICU.

Methods: This retrospective study reviewed medical records of trauma patients who received ICU care at Harran University Medical School Anesthesiology and Reanimation Department between January 2015 and December 2019. Age, gender, comorbidities, Glasgow Coma Scale (GSC), and Acute Physiology and Chronic Health Evaluation 2 (APACHE-II) scores, Revised Trauma Score (RTS), duration of hospital and ICU stay, mortality rate, and brain death rate were reviewed for each patient. Additionally, other factors that could affect the mortality and morbidity of patients, including admission lactate level and the clinical department of referral were evaluated.

Results: A total of 155 patients comprised 76.8% men and 23.2% women. Comorbidities were present in 10.3% of the patients. Of all patients, 90.3% had been referred from the emergency service, 8.4% of them from operating theatres, and 1.3% of them from inpatient clinics. Mean duration of mechanical ventilation was 12.3 (28.6) days, mean duration of ICU stay was 8.5 (20.7) days, and the mean duration of hospital stay was 12.9 (21.7) days. Among 155 patients, 123 (79.4%) were discharged (surviving group) and mortality occurred in the remaining 32 (20.6%) patients (non-surviving group). The non-surviving group comprised 68.8% men and 31.2 women. In all patients, mean admission lactate level was 2.9(3.6) mmol/L and mean APACHE-II score was 14.1(7.1). Multivariate analysis indicated that a single unit increase in APACHE-II score increased the mortality risk by 2.45-fold. A significant relationship was found between admission lactate level, APACHE-II score, and mortality (P=0.001 for both). Mean RTS score was 10.1 (2.5) and mean GCS score was 11.7 (4.4). The analysis also indicated that a single unit increase in RTS score decreased the mortality risk by 94%, and a single unit increase in GCS score decreased the mortality risk by 69%. A significant relationship was found between decreased RTS and GCS scores and mortality (P=0.001 for both).

Conclusion: Admission GCS, APACHE-II, and RTS scores and admission lactate levels could be useful predictors of mortality and could also be guiding in the determination of prognosis in patients transferred to the ICU due to trauma.

Keywords: Mortality, Intensive care units, Trauma, Revised trauma score

Öz

Amaç: Yoğun bakım ünitelerine (YBÜ) travma nedeniyle kabul edilen hastaların prognozunun doğru tahmin edilmesi, hastaların klinik yönetimi açısından çok önemlidir. Bu çalışmada YBÜ'lerde travma nedeniyle izlenenen hastalarda mortaliteyi öngören faktörlerin belirlenmesi amaçlandı.

Yöntemler: Ocak 2015-Aralık 2019 tarihleri arasında Harran Üniversitesi Araştırma ve Uygulama Hastanesi Anesteziyoloji ve Reanimasyon YBÜ'sinde travma nedeniyle takip ve tedavi edilen hastaların; yaş, cinsiyet, komorbid hastalık, Glaskow Koma Skalaları (GKS), Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi-2 (APACHE-2) skorları, Revize Edilmiş Travma Skoru (RTS), YBÜ'si ve hastane yatış süreleri, mortalite oranları, girişteki laktat düzeyleri, YBÜ'sine geliş yerleri arşivden taranarak incelendi.

Bulgular: Bu çalışmada travma nedeniyle takip edilen 155 hasta incelendi. Hastaların %76,8'i erkek, %23,2'si kadındı. Hastaların %10.3'ünde komorbid hastalık bulunmaktaydı. YBÜ'sine alınan hastaların %90,3'ü acil servisten, %8,4'ü ameliyathaneden alındı. Hastaların ortalama mekanik ventilasyon süresi 12,3(28,6)/gün, yoğunbakım yatış süresi 8,5(20,7)/gün, hastane yatış süresi 12,9(21,7)/gün olarak bulundu. YBÜ'sine travma nedeniyle yatırılan 155 hastanın %79,4'ü taburcu edilmiş, %20,6 hayatını kaybetmiştir. Hayatını kaybeden hastaların %68,8'i erkek, %31,2'si kadındı. Travma nedeniyle YBÜ'sinde takip edilen hastaların giriş laktat düzeyi ortalaması 2,9(3,6), APACHE-2 skoru ortalaması 14,1(7,1) olarak bulundu. APACHE-2 skorundaki her 1 birimlik artışın ölüm riskini 2,45 kat arttırdığı saptandı. Giriş laktat düzeyi ve APACHE-2 skoru artışı ile mortalite arasında anlamlı ilişki saptandı (P=0.001, P=0,001). RTS ortalaması 10,1(2,5), GKS ortalaması 11,7(4,4) olarak bulundu. RTS'deki 1 birimlik artış ölüm riskini % 94, GKS'deki 1 birimlik artış ölüm riskini %69 oranında azalttığı saptandı. RTS ve GKS değerlerindeki azalma ile mortalite arasında anlamlı ilişki saptandı (P=0.001, P=0.001).

Sonuç: YBÜ'sine travma nedeniyle kabul edilen hastaların giriş GKS, APACHE-2 ve RTS gibi skorlamalarının ve giriş laktat düzeylerinin prognozun öngörülmesinde yol gösterici olabileceğini düşünmekteyiz.

Anahtar kelimeler: Mortalite, Yoğun bakım üniteleri, Travma, Revize travma skoru

How to cite/Atıf için: Atlas A, Büyükfırat E, Ethemoğlu KB, Karahan MA, Altay N. Factors affecting mortality in trauma patients hospitalized in the intensive care unit. J Surg Med. 2020;4(11):930-933.

Introduction

Intensive care unit (ICU) is a dedicated specialty in healthcare, involving multidisciplinary management of patients with acute and often life-threatening organ dysfunction or disease. ICU also provides a privileged environment with airway support, mechanical ventilation, up-to-date treatment practices, and effective administration of drugs and monitoring techniques [1]. An accurate estimation of the prognosis of patients admitted to ICU is of prime importance for their clinical management [2]. Additionally, early detection of high-risk patients leads to more appropriate use of resources, and reduces morbidity and mortality rates [3,4]. Trauma is a common cause of significant functional impairment, disability, and mortality, thus leading to health deterioration and a delay in reaching functional independence [5,6]. Trauma-induced death is the fifth leading cause of death among all age groups and the leading cause of death among individuals aged 1-44 years in the US, while it has been shown by the Turkish Statistical Institute to be the sixth leading cause of death (4.4%) along with poisoning [7,8].

Falls, falls from heights, assaults, gunshot wounds, and penetrating stab wounds as well as road traffic fatalities are considered traumas [9]. Some of these traumas are classified as severe and multiple traumas. Patients with these traumas are admitted to ICU and constitute a significant portion of critical patients [10]. In the ICU, the monitoring process is the key to reducing patients' mortality and morbidity [11,12]. In this process, an accurate estimation of the prognosis is a significant factor for successful management of trauma patients. The aim of this study was to investigate the clinical characteristics, mortality rates, and the factors affecting mortality in trauma patients hospitalized in the ICU.

Materials and methods

Study design

The retrospective cohort study reviewed medical records of 155 patients aged above 18 years who were hospitalized in our ICU due to trauma between January 2015 and December 2019. Demographic and clinical characteristics including age, gender, laboratory parameters, GCS, RTS, and APACHE-II scores, clinical department of referral, duration of hospital and ICU stay, and one-year mortality were reviewed for each patient. The study was approved by the Ethics Committee of Harran University (Approval No: E.7334, Date: February 11, 2020).

The ICU in our department is a tertiary referral unit (Level III ICU) with a total of 20 beds. Between January 2015 and December 2019, a total of 1,418 patients were admitted to our ICU (Figure 1).

Age, gender, comorbidities, Glasgow Coma Scale (GSC), Acute Physiology and Chronic Health Evaluation 2 (APACHE-II) score, Revised Trauma Score (RTS), duration of hospital and ICU stay, mortality rate, and brain death rate were reviewed for each patient, in addition to other factors that could affect the mortality and morbidity of patients, including admission lactate level and the clinical department of referral.

Statistical analysis

Data were analyzed using SPSS for Windows version 24.0 (IBM Corp. Released 2016, Armonk, NY: IBM Corp.). Descriptive data were expressed as frequency (n), percentages, mean (standard deviation (SD)), maximum, and minimum. Normal distribution of data was assessed using both analytical (Shapiro-Wilks test) and visual (histogram plots) methods. Independent groups were compared using Mann-Whitney U test. Variables found significant on univariate analysis were further analyzed using Multivariate Analysis. A p value <0.05 was considered significant.

Results

A total of 155 patients comprised 119 (76.8%) men and 36 (23.2%) women with a mean age of 37.9 (15.5) years. Of all patients, 90.3% had been referred from the emergency service, 8.4% from operating theatres, and 1.3% from inpatient clinics. Most of the patients (89.7%) had no comorbidities (Table 1).

A percutaneous tracheostomy was performed in 6.5% of the patients due to prolonged mechanical ventilation. Brain death occurred in 7.1% of the patients. Mean time from admission to enteral feeding initiation was 30.1 (12.2) hours, mean duration of mechanical ventilation was 12.3 (28.6) days, mean duration of ICU stay was 8.5 (20.7) days, and the mean duration of hospital stay was 12.9 (21.7) days. Mean admission lactate level was 2.9 (3.6) mmol/L (Table 2).

Table 1: Demographic characteristics

Variables	Total (n=155)
Age (Mean(SD))	37.9(15.5)
Gender n (%)	
Male	119 (76.8)
Female	36 (23.2)
Clinical department of referral (%)	
Emergency service	90.3
Operating theater	8.4
Inpatient clinic	1.3
Comorbidities (%)	
No	89.7
Yes	10.3

SD: Standard deviation

Table 2: Clinical characteristics

Variables	Mean(SD)	min	max
Time from admission to enteral feeding initiation (hours)	30.1(12.2)	24	72
Duration of mechanical ventilation (days)	12.3(28.6)	0	163
ICU stay (days)	8.5(20.7)	1	163
Hospital stay (days)	12.9(21.7)	1	163
Admission lactate level (mmol/L)	2.9(3.6)	0,7	26

SD: Standard deviation, ICU: Intensive care unit

Among 155 patients, 123 (79.4%) were discharged (surviving group) and mortality occurred in the remaining 32 (20.6%) patients (non-surviving group). The non-surviving group comprised 24 (68.6%) men and 11 (31.4%) women with a mean age of 35 (range, 18-65) years. In this group, no significant relationship was found between mortality, age, and gender (P=0.986). Additionally, the mean duration of ICU stay was 8 (range, 1-163) days and prolonged ICU stay was associated with increased mortality (P=0.002). In the same group, the mean admission lactate level was 4.55 (range, 2.6-26) mmol/L and a significant relationship was found between increased lactate concentration and mortality (P=0.001). On the other hand, the median APACHE-II score was 25 (range, 18-35) and a significant relationship was found between increased APACHE-II score and mortality (P=0.001). Similarly, the median RTS score was 7 (range, 1-9) and the median GCS score was 4 (range,

3-9), and a significant relationship was found between reduced RTS and GCS scores and mortality (P=0.001 for both) (Table 3).

Multivariate analysis indicated that a single unit increase in RTS score decreased the mortality risk by 94% (Odds Ratio [OR]: 0.06; 95% Confidence Interval (CI): 0.02-0.25], a single unit increase in GCS score decreased the mortality risk by 69% (OR: 0.31; 95% CI: 0.02-0.25), a single unit increase in admission lactate level increased the mortality risk by 9-fold (95% CI: 3.92-21.38), prolonged ICU stay increased the mortality risk by 1.08-fold (95% CI: 1.03-1.13), and a single unit increase in APACHE-II score increased the mortality risk by 2.45-fold (95% CI: 1.52-3.94) (Table 4).

In the surviving group, 89.4% of the patients had been referred from the emergency service and 10.6% from operating theatres. No significant relationship was found between the clinical department of referral and mortality (P=0.219). On the other hand, comorbidities were detected in 12.2% of the patients in the surviving group and in 3.1% of the patients in the non-surviving group. No significant relationship was found between the presence of comorbidities and mortality (P=0.165). Table 5 presents the distribution of the etiologies of trauma in our patients.

Mechanical ventilation was performed in 44 (35.8%) of the patients in the surviving group and no significant relationship was detected between using mechanical ventilation and mortality (P=0.996).

Table 3: Relationship between mortality and clinical characteristics and scoring systems

Variables	Total median (min-max)	Surviving group median (min-max)	Nonsurviving group median (min-max)	*P*-value
Age (years)	35 (18-75)	35 (18-75)	35 (18-65)	0.986
ICU stay (days)	3 (1-163)	3 (1-36)	8 (1-163)	0.002*
Hospital stay (days)	7 (1-163)	7 (1-78)	8 (1-163)	0.007*
Lactate level (mmol/L)	2 (0.7-26)	1.6 (0,7-4,2)	4.55 (2,6-26)	0.001*
APACHE-II score	12 (4-35)	11 (4-21)	25 (18-35)	0.001*
GCS score	15 (3-15)	15 (6-15)	4 (3-9)	0.001*
RTS score	11 (1-12)	12 (8-12)	7 (1-9)	0.001*

ICU: Intensive care unit, APACHE-II: Acute Physiology and Chronic Health Evaluation 2 (APACHE-II) score, GCS: Glasgow Coma Scale, RTS: Revised Trauma Score, *Mann-Whitney U test. *p<0.05

Table 4: Multivariate logistic regression analysis showing the relationship between prognosis and GCS, APACHE-II, RTS scores and lactate levels

Variables	OR	*P*-value	95% CI for OR	
			Lower limit	Upper limit
Age	1	0.986	0.97	1.03
GCS	0.31	0.001	0.18	0.54
APACHE-II	2.45	0.001	1.52	3.94
RTS	0.06	0.001	0.02	0.25
Lactate level (mmol/L)	9.16	0.001	3.92	21.38

OR: Odds Ratio, CI: Confidence Interval, GCS: Glasgow Coma Scale, RTS: Revised Trauma Score, APACHE-II: Acute Physiology and Chronic Health Evaluation 2 (APACHE-II) score

Table 5: Distribution of the etiologies of trauma in our patients

Etiology	n	%
Road traffic fatality	105	67.7
Fall	28	18.1
Gunshot wound	8	5.2
Assault	8	5.2
Penetrating stab wounds	3	1.9
Others	3	1.9
Total	155	100.0

Discussion

In our study, the mortality rate and the rate of trauma patients that were hospitalized in the ICU due to trauma were similar to those in studies conducted in Turkey. The results also indicated that traumatic injuries were more commonly seen among young and male individuals and increased admission lactate levels had an adverse effect on mortality. Additionally, it was revealed that APACHE-II, GCS, and RTS were significant scoring systems in the estimation of prognosis in trauma patients.

Road traffic fatalities and some other traumas constitute a major portion of cases hospitalized in ICU. It has been reported that trauma patients account for 15% of all ICU patients in USA [13]. A study conducted in Turkey revealed that trauma patients constituted 10.4% of 1,038 patients hospitalized in ICU [14], and another study reported this rate as 11.1% [15]. Similarly, the trauma patients included in our study constituted 10.9% of 1,418 patients hospitalized in ICU.

In our study, mortality occurred in 20.6% of the trauma patients included in the study. Among the studies conducted in Turkey, Adiyaman et al. [15] reported this rate as 18.9%, Unlu et al. [10] reported it as 35.8%, and Kara et al. [16] reported a similar rate of 19.4%.

Isik et al. [17] reported that road traffic fatalities accounted for 75% of their cases with head trauma. Similarly, Yucel et al. [18] reported that road traffic fatalities accounted for 37.3% of 748 cases with chest trauma. In our study, road traffic fatalities constituted 67.7% of the trauma patients hospitalized in ICU.

Previous studies conducted in Turkey reported that the incidence of trauma was relatively higher between the ages of 0-44 years and in male individuals [19,20]. Another study evaluated the ages of trauma patients hospitalized in ICU and reported that 65.9% of them were aged between 1-45 years [11]. Additionally, a recent retrospective study evaluated the medical records of 978 patients hospitalized in ICU between 2013 and 2016 and reported that 76.7% of 150 trauma patients were male [21]. Similarly, we also found that 68.3% of our trauma patients were aged between 18-45 years and 76.7% of them were male.

To date, numerous scoring systems have been developed for the determination of trauma severity and the estimation of mortality in trauma patients hospitalized in ICU [22,23]. Among these, APACHE-II, which is a physiological scoring system, is the most important and commonly used [24]. Sipahi et al. [25] found that the APACHE-II scores in the age groups of 30-39 years and 40 years or above established a significant correlation with mortality. Another study reported that increased APACHE-II scores were associated with increased mortality among trauma patients hospitalized in ICU [11]. Similarly, Kara et al. [16] and Yildirim et al. [24] reported that APACHE-II scores were significantly increased in the trauma patients that died in the ICU. In our study, the median APACHE-II score was 25 (range, 18-35) in the non-surviving group and 11 (range, 4-21) in the surviving group. Additionally, it was revealed that a single unit increase in APACHE-II score increased the mortality risk by 2.45-fold (P=0.001). These findings were consistent with those reported in the literature.

Revised Trauma Score (RTS) is a significant clinical and physiological scoring system used for the prediction of survival. When used in combination with GCS, RTS can also be useful in the prediction of mortality [26]. A previous study found that a RTS score of <6.2 was associated with increased mortality. The authors also found a significant relationship between RTS score, the duration of mechanical ventilation and mortality [11]. Eryilmaz et al. [27] reported that the mean RTS score was 6.0 (2.7) in the surviving group and 2.1 (2.1) in the non-surviving group. In our study, the median RTS score was 7 (range, 1-9) in the non-surviving group and 12 (range, 8-12) in the surviving

group. It was also revealed that a single unit increase in RTS score decreased the mortality risk by 94% and that the mortality rate increased as the RTS score decreased (P=0.001).

In our study, mean admission lactate level was 2.9 (3.6) mmol/L in all patients, which was 1.6 (range, 0.7-4.6) mmol/L in the surviving group and 4.55 (2.6-26) mmol/L in the non-surviving group. Additionally, multivariate logistic regression analysis indicated a significant relationship between increased lactate concentration and mortality (OR: 9.16; 95% CI: 3.92-21.38)**.** Manikis et al. [28] suggested that increased serum lactate concentration is associated with organ failure and increased mortality. Similarly, Ouellet et al. [29] found that increased serum lactate concentration was an indicator of impaired tissue perfusion and associated with increased mortality. A study conducted in Turkey evaluated trauma patients hospitalized in the ICU and indicated that serum lactate levels were significantly higher in the non-surviving group and associated with increased mortality [15]. Moreover, Odom et al. found a significant relationship between increased lactate levels and mortality [30]. In line with the literature, we also found a significant relationship between increased serum lactate levels and increased mortality in our patients (P=0.001).

Mean duration of ICU stay was 8.5(20.7) days in our patients, which was 8 (range, 1-163) days in the non-surviving group and 3 (1-36) days in the surviving group. Grenrot et al. [31] and Dur et al. [12] reported a mean duration of 8.6 and 5(1) days, respectively. Similarly, Unlu et al. [11] evaluated 349 patients and reported that 37.8% of the patients had a mean duration of 1-3 days, 22.6% had a mean duration of more than 14 days, and the median duration of ICU stay for all patients was 5 (range, 1-139) days. On the other hand, another study conducted in Turkey found a significant difference between the surviving and non-surviving groups regarding the duration of ICU stay [16]. As consistent with the literature, we also found a significant relationship between prolonged ICU stay and increased mortality (P=0.002).

Limitations

One of the limitations of this study is its single-center design. It is limited to one regional ICU center and its patients in a period of four years. In addition, retrospective studies can potentially reduce data quality. Failure to record some patient data in archive records may cause lack of information. Although there was very little information on parameters in our archive records, we could still access most data.

Conclusion

We suggest that admission GCS, APACHE-II, and RTS scores and lactate levels could be useful predictors of mortality and guiding in the determination of prognosis in patients transferred to the ICU due to trauma.

References

1. Morgan GE. Clinical Anesthesiology. 4th ed. McGraw-Hill Medical; 2005
2. Min H, Avramovic S, Wojtusiak J, Khosla R, Fletcher RD, Alemi F, et al. A comprehensive multimorbidity index for predicting mortality in intensive care unit patients. J Palliat Med. 2017;20:35–41.
3. Campbell AJ, Cook JA, Adey G, Cuthbertson BH. Predicting death and readmission after intensive care discharge. Br J Anaesth. 2008;100(5): 656-62.
4. Power GS, Harrison DA. Why try to predict ICU outcomes? Curr Opin Crit Care. 2014; 20(5): 544-9.
5. Joseph B, Pandit V, Aziz H, Tang A, Kulvatunyou N, Wynne J, et al. Rehabilitation after trauma; does age matter? J Surg Res 2013;184(1):541-5.
6. Gürsoy C, Gürsoy G, Gümüş Demirbilek S. Prognostic performance of optic nerve sheath diameters in CT images and serum procalcitonin levels in traumatic brain injury patients in the intensive care unit: A retrospective cohort study. J Surg Med. 2019;3(9):652-4.
7. US Department of Health and Human Services, Centers for Disease Control. (2008) Web-based Injury Statistics Query and Reporting System (WISQARS).
8. T.C. Türkiye İstatistik Kurumu Başkanlığı (TÜİK) Haber Bülteni. Ölüm Nedeni İstatistikleri, 2019. Sayı: 30626.Nisan.2019.
9. Cırak B, Guven MB, Işık S, Kıymaz N, Demir O. Acil servise başvuran travma hastaları ile ilgili epidemiyolojik bir calışma. Ulus Travma Acil Cerrahi Derg. 1999;5(3):157-9.
10. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: A Reassessment. J Trauma. 1995;38(2);185-93.
11. Ünlü AR, Ülger F, Dilek A, Barış S, Murat N, Sarıhasan B. Yoğun Bakımda İzlenen Travma Hastalarında "Revize Travma Skoru" ve "Travma ve Yaralanma Şiddeti Skoru''nun Prognoz ile İlişkisinin Değerlendirilmesi. Türk Anest Rean Der Derg. 2012;40(3):128-35.
12. Dur A, Cander B, Koçak S, Girişgin S, Gül M, Koyuncu F. Acil Yoğun Bakımda Çoklu Travma Hastaları ve Skorlama Sistemleri. Akademik Acil Tıp Derg. 2009;8(4):24-7.
13. Podoll AS, Kozar R, Holcomb JB, Finkel KW. Incidence and outcome of early acute kidney injury in critically-ill trauma patients. PLoS One. 2013 Oct 17;8(10):e77376.
14. Özbilgin Ş, Demirağ K, Sargın A, Uyar M, Moral AR. Yoğun Bakımda Kullanılan Skorlama Sistemlerinin Mortalite Tahminindeki Rolleri Açısından Karşılaştırılması. Turk J Intense Care. 2011;9(1):8-13.
15. Adıyaman E, Tokur ME, Bal ZM, Gökmen AN, Koca U. Anestezi Yoğun Bakım Ünitesinde Takip ve Tedavi Edilen Travma Hastaların Retrospektif Değerlendirilmesi. J Turk Soc Intens Care. 2019;17(3):146-53.
16. Kara İ, Altınsoy S, Gök U, Onur A, Sarıbapıççı R. Bir Numune Hastanesi Genel Yoğun Bakım Ünitesinde Travma Hastalarının Mortalite Analizi. Turk J Intense Care. 2015;13:68-74.
17. Işık HS, Bostancı U, Yıdız Ö, Özdemir C,Gökyar A. Kafa travması nedeniyle tedavi edilen 954 erişkin olgunun retrospektif değerlendirilmesi: Epidemiyolojik calışma. Ulus Travma Acil Cerrahi Derg. 2011;17(1):46-50.
18. Yücel O, Sapmaz E, Çaylak H, Gözübüyük A, Gürkök S, Dakak M, et al. Hastaneye yatırılmayı gerektiren toraks travmalı 748 olgunun analizi. Gulhane Tıp Dergisi. 2009;51:86-90.
19. Ural G, Gün İ. Dr. Nafiz Körez Sincan Devlet Has¬tanesi ve Özel Bayındır Hastanesi acil servisine kaza nedeniyle başvuranların epidemiyolojik yönden incelenmesi. Sağlık Bilimleri Dergisi. 2008;17(1):31-9.
20. Varol O, Eren ŞH, Oğuztürk H, Korkmaz İ, Bey¬dilli İ. Acil servise trafik kazası sonucu başvuran hastaların incelenmesi. C.Ü. Tıp Fakültesi Derg. 2006;28(2):55-60.
21. Yazar MA, Sarıkuş Z, Horasanlı E. Yoğun Bakım Ünitesinde Yatan Travma Hastalarında
22. 30 Günlük Mortalite Sonuçları: Üç Yıllık Retrospektif Bir Çalışma. Turk J Intensive Care. 2019;17(1):18-24.
23. McDermott FT, Cordner SM, Cooper DJ, Winship VC; Consultative Committee on Road Traffic Fatalities in Victoria. Management deficiencies and death preventability of road traffic fatalities before and after a new trauma care system in Victoria, Australia. J Trauma. 2007;63(2):331-8.
24. Hefny AF, Idris K, Eid HO, Abu-Zidan FM. Factors affecting mortality of critical care trauma patients. Afr Health Sci. 2013;13(3):731-5.
25. Yıldırım F, Kara İ, Küçük H, Karabıyık L, Katı İ. Travma Hastalarında Skorlama Sistemlerinin Yoğun Bakım Mortalitesi Açısından Değerlendirilmesi. GKDA Derg. 2016;22(1):29-33.
26. Sipahi M, Bolat E, Kantekin ÇÜ, Öztürk SA, Arslan E, Ercan U. Üçüncü Seviye Yoğun Bakım Ünitesinin İlk Yıl Değerlendirmesi. Bozok Tıp Dergisi. 2014;4(2):41-4.
27. Roorda J, Van Beeck EF, Stapert JW, Ten Wolde W. Evaluating performance of the Revised Trau¬ma score as a triage instrument in the prehospi¬tal setting. Injury. 1996;27(3):163-7.
28. Eryılmaz M, Durusu M, Cantürk G, Menteş MÖ, Özer MT, Çevik E. Adli olgularda anatomik ve fizyolojik travma skorlama sistemlerinin rolü. Ulus Travma Acil Cerrahi Derg. 2009;15(3):285-92.
29. Manikis P, Jankowski S, Zhang H, Kahn RJ, Vincent JL. Correlation of serial blood lactate levels to organ failure and mortality after trauma. Am J Emerg Med. 1995;13(6):619-22.
30. Ouellet JF, Roberts DJ, Tiruta C, Kirkpatrick AW, Mercado M, Trottier V, et al. Admission base deficit and lactate levels in Canadian patients with blunt trauma: are they useful markers of mortality? J Trauma Acute Care Surg. 2012;72(6):1532-5.
31. Odom SR, Howell MD, Silva GS, Nielsen VM, Gupta A, Shapiro NI, et al. Lactate clearance as a predictor of mortality in trauma patients. J Trauma Acute Care Surg. 2013;74(4):999-1004.
32. Grenrot C, Norberg KA, Hakansson S. Intensive care of the elderly--a retrospective study. Acta Anaesthesiol Scand. 1986;30(8):703-8.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):934-937.
DOI: 10.28982/josam.739891

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of urodynamics parameters in different age and incontinence group of women

Farklı yaş ve inkontinans gruplarındaki kadınlarda ürodinamik parametrelerin değerlendirilmesi

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Abstract

Aim: Overactive bladder syndrome (OAB) is known to have a negative impact on quality of life, and cause discomfort daily. Population-based studies on females report a prevalence of OAB which varies between 9.7% and 35.7%, with a substantial rise with increasing age. The primary aim of this analysis was to assess whether age was associated with differences in urodynamic testing parameters, using age as a continuous variable, and comparing women within wider age groups to understand physiologic variation.

Methods: In this retrospective cohort study, we evaluated the patients who were admitted to the Department of Gynecology and Obstetrics Department of Istanbul Education and Research Hospital between January 2017 and January 2020 with lower urinary tract symptoms (LUTS).

Results: We found that age, first sensation and first desire to void were strongly correlated (P=0.007, P=003 respectively), but a strong desire to void and maximum cystometric capacity were not (P=0.09, P=0.11 respectively). There was a weak negative correlation between detrusor pressure (P_{det}) and age (p=0.08). Histogram analysis of bladder compliance among stress, urge, mix incontinence and normal patients revealed that maximum compliance occurred in women of reproductive age.

Conclusion: Aging is associated with decreased self-control, thus, increased prevalence of LUTS symptoms among older women might be more accurately considered as the loss of an adaptive threshold to urinary control rather than age-associated decline in urinary functions.

Keywords: Age, Stress incontinence, Urge incontinence, Urodynamic test

Öz

Amaç: Aşırı aktif mesane sendromunun (OAB) yaşam kalitesi, normal günlük yaşam fonksiyonlarında rahatsızlık verdiği bilinmektedir. Kadınlar üzerinde yapılan nüfusa dayalı çalışmalar, artan yaşla birlikte %9,7 ve %35,7 arasında değişerek artan OAB prevalansı olduğunu bildirmektedir. Bu çalışmamızın ilk amacı, yaşın sürekli bir değişken olarak ürodinamik parametrelerde kullanılması veya ürodinami sonuçlarıyla ilişkisini değerlendirmek ve daha geniş yaş aralığındaki kadınların sonuçlarını karşılaştırarak fizyolojik değişiklikleri anlamaya çalışmaktır.

Yöntemler: Bu retrospektif kohort çalışmamızda, Ocak 2017 - Ocak 2020 tarihleri arasında İstanbul Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Anabilim Dalı'na alt üriner sistem semptomları (AÜSS) ile başvuran hastaları değerlendirdik.

Bulgular: Özellikle ilk idrar duyum hissi ve işeme için ilk arzu ve yaş arasında çok güçlü negatif korelasyon saptadık (sırasıyla P=0,007, P=0,03). Ancak işeme için güçlü istek ve maksimum sistometrik kapasite ile yaş arasında ilişki bulamadık(sırasıyla P=0,09, P=0,11). Detrüsör basıncının (Pdet) yaşla zayıf negatif korelasyonunu bulduk (P=0,08). Stres, urge, mix inkontinansı ve normal hastalarda mesane kompliansının histogram analizinde, üreme çağındaki kadınlarda maksimum komplians saptadık.

Sonuç: Menopozun inkontinans prevalansında bağımsız bir faktör olduğuna dair kanıtlar eksiktir ve gelecekte daha geniş yaş grubu kadınlarla araştırmalara ihtiyaç duyulmaktadır. Çalışmamız, büyük, heterojen ikincil bakım popülasyonunda ürodinami parametrelerini inceleyen az sayıdaki çalışmadan biridir. Yaşlanma, öz kontrolün azalmasıyla ilişkilidir, bu nedenle yaşlılarda artan AÜSS semptomları, üriner fonksiyonlarda yaşlı ilişkili düşüşten ziyade üriner kontrolde eşik kaybı olarak düşünülebilir.

Anahtar kelimeler: Yaş, Stres inkontinans, Urge inkontinans, Ürodinamik test

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Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Istanbul Education and Research Hospital (date: 2/7/2020, issue number: 2171). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Etik Kurul Onayı: Çalışmamız, İstanbul Eğitim ve Araştırma Hastanesi Etik Kurulunda 07.02.2020 tarihli 2171 karar no ile onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/19/2020
Yayın Tarihi: 19.11.2020

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How to cite/Atıf için: Atakul N, Kılıç BŞ. Evaluation of urodynamics parameters in different age and incontinence group of women. J Surg Med. 2020;4(11):934-937.

Introduction

Overactive bladder syndrome (OAB) is known to have a negative impact on quality of life, and causes discomfort daily [1–3]. Population-based studies on females report a prevalence of OAB that varies between 9.7% and 35.7%, with a substantial rise in prevalence with increasing age [4,5]. Previous studies have shown that aging induces detrusor underactivity, which is characterized by decreased bladder contraction and increased post-void residual urine (PVR) [6]. Clinical experience and the literature suggest that females may have an increase in urgency incontinence, voiding dysfunction and a decrease in bladder capacity, detrusor contractility, and urethral sphincter function with increasing age [7-9]. However, the results of these studies were based on questionnaire analyses. There have been many studies examining urodynamic changes among women at differing ages. These have, however, involved relatively small numbers of patients with no LUTS.

The difference between maximum urethral pressure (MUP) and bladder pressure (BP) is defined as closure pressure (CP). When CP is positive, the individual is continent; when it is negative or zero, it indicates incontinence.

The prevalence of aging-related diseases has been increasing, due to declining birth rate and mortality, and increasing life expectancy [10]. Urodynamically proven detrusor overactivity (DO) becomes much more common in old age, making it challenging to distinguish purely age-related changes in the bladder, from those due to DO.

Knowing age-associated changes in urodynamic parameters among females is insufficient. Thus, we analyzed age-associated changes in urodynamic parameters among women, especially in patients aged within a wide range, as studies have commonly involved the geriatric population.

The aim of this secondary analysis was to assess whether age is associated with differences in urodynamic variables of voiding, using age as a continuous variable, and comparing women with a wide age range for understanding physiologic variation.

Materials and methods

In this retrospective cohort study, we evaluated patients who were admitted to the Gynecology and Obstetrics Department of Istanbul Education and Research Hospital between January 2017 and January 2020 with lower urinary tract symptoms (LUTS). Various age groups of female patients (11-77 years old) diagnosed with stress, urge, mix incontinence and normal cystometric results who were referred to our Urodynamics Clinic were included in the study. Those with a history of SUI surgery within the past 6 months, current pregnancy, active infection demonstrated by catheterized urine dipstick analysis, a known active lesion or present injury to the perineum or urethra, or a known urethral obstruction were excluded.

Urodynamic study (UDS) was performed preoperatively by a single expert in an exclusive urodynamics room. UDS consisted of uroflowmetry followed by filling and voiding cystometry and was conducted interactively with the patient. Non-instrumented uroflowmetry was conducted when the patients felt a normal desire to void and catheterized postvoid residual urine volume (PVR) was measured. Filling and voiding cystometry were conducted with the patient in sitting position. A 6-Fr triple-lumen transurethral catheter was inserted into the urethra and connected to the pressure transducer. Prior to bladder filling, signal quality check was performed. We checked that resting values for abdominal, intravesical, and detrusor pressures were in a typical range. Cough was used to ensure that the abdominal and intravesical pressure signals responded equally. Then, the bladder was filled at a rate of 50 mL/min. The artifacts occurring during the study were immediately corrected. All measured and derived signals were displayed according to ICS standards with abdominal pressure, vesical pressure, detrusor pressure, and flow [11]. Filling volume, electromyography, and voided volume were displayed in additional curves. UDS findings and the interpretation of the results were documented immediately after the study was finished. In the uroflowmetry, maximal flow rate (Qmax), time to Qmax, voided volume, PVR, and filling cystometry data including first, strong desire to void and Valsalva leak point pressure (VLPP) were measured. Also, Qmax and detrusor pressure at Qmax (Pdet@Qmax) of voiding cystometry data were analyzed.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences 15.0 software for Windows (SPSS, Chicago, IL, USA). Distributions of UDS parameters are described using the mean and standard deviation (SD) as well as the median and inter-quartile range (IQR 1⁄4 the difference between the 75^{th} and 25^{th} percentiles) to account for the skewness of some of the distributions. We provided histograms of the frequency distributions of the urodynamic data to graphically demonstrate any skewness. Statistical comparison of medians is performed using the Wilcoxon Signed Rank test at a 0.05 significance level.

Results

Out of 120 LUTS patients, 23 had stress, 57 had urge, 10 had mix-type incontinence and 30 had normal UDS findings.

We found that age, first sensation and first desire to void were strongly correlated (P=0.007, P=003 respectively), but a strong desire to void and maximum cystometric capacity were not (P=0.09, P=0.11 respectively). We found a weak negative correlation between P_{det} and age (P=0.08). Urodynamic data of the patients are shown in table 1.

Table 1: Urodynamic data of patients

	Patients (n=120)	SD
Mean age (years)	45.2	12.7
P_{det} max (cm H2O)	33.7	32.6
P_{det} open (cm H2O)	27	27
Bladder compliance (ml/cm H2O)	48.4	71.2
Detrusor compliance (ml/cm H2O)	35.4	35.4
First sensation (ml)	109.4	77.03
First desire to void (ml)	193.6	102.9
Strong desire to void(ml)	306.2	137.2
Maximum cystometric capacity (ml)	436.1	163.3

SD: standard deviation, P_{det} max: Maximum detrusor pressure, P_{det} open: opening detrusor pressure, P_{det} Qmax: detrusor pressure at maximum flow, P_{det} max: maximum detrusor pressure during voiding

Discussion

Sensory function has been shown to decline with age, leading to a higher volume at first desire to void in older women with LUTS undergoing cystometry [12]. Consistent with our

results, a study showed that menopausal female patients taking hormone replacement therapy maintained sensory function, implying that alterations in sensory function may be a primarily age-related phenomenon. We found a strong negative correlation between age and first sensation.

Wyndaele et.al. [13] studied bladder sensation in 50 normal volunteers and their sensation values, which were slightly higher than our results. As shown in Table 1, our values were 109.4, 193.6, 306.2 and 436.1 for first sensation, first desire to void, strong desire to void and maximum cystometric capacity, respectively. However, their study group was not homogeneous, both males and females were included.

Very few studies regarding age-associated changes in urodynamic parameters have been performed in a large group of females. In a recent study, the effect of aging on urodynamic parameters has been assessed among women with stress urinary incontinence (SUI) with a mean age of 57 years [14]. They found that Qmax, voided volume and Pdet@Qmax decreased and PVR and desire to void increased significantly with age after 60 years [10]. We also found a weak negative correlation between P_{det} and age. The difference between the two studies showed that as our study had more young population, P_{det} value did not progressively decrease with age, but other hormonal or physiologic factors played a role.

Another large study in postmenopausal females reported decreased urethral sphincter function and detrusor overactivity, as expected [15]. In that, study women older than 75 years of age showed deterioration in bladder function with a high incidence of detrusor hyperactivity with or without impaired contractility, whereas urethral function changed progressively. Interestingly, a progressive decrease of MUCP even in continent middle aged women occurred with aging, whereas PVR increased. Perucchini et al. [16] reported that this decrease could be the reflection of the association of age with a loss of striated muscle in the female urethra.

Another study in two large cohorts of women with stress urinary incontinence prior to surgery with the mean age of 50 years showed that the bladder contractility index was inversely related to age, decreasing a mean of 7.68 (1.96) cm-H_2O for each 10-year age increase and no difference in PVR. Those above 65 years of age also had lower VLPP than the younger cohort, which was explained with decreased outlet resistance, which would then potentially result in lower measured voiding pressure [17].

A study presented by Basu et al. [18] used multivariate analysis to investigate the data among different age groups (22-90 years). The outcomes of the analysis showed a significant effect on voiding volume but not on any other variables studied. According to their data, age was not related to flow rate percentile, maximum flow rate, or Pdet@Qmax. The study concluded that the main driver behind alterations in voiding is the diagnosis of DO, and not age. Their findings were not consistent with previous studies, which reported that bladder capacity improved with age [19]. We showed that detrusor compliance does not decrease in a linear fashion, rather, it increases from adolesce until the reproductive age and decreases throughout advanced age. Pareto analysis, performed in the P_{det} urge incontinence and/or hypocompliance detrusor group, revealed similar findings with less linear increment (Figure 1, 2).

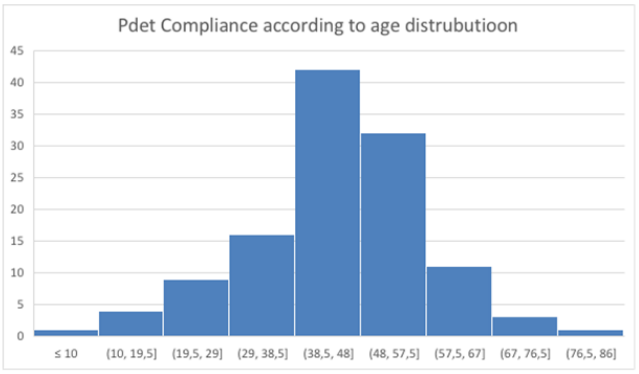

Figure 1: P_{det} compliance according to age in all groups of women. Maximum compliance occurs in women of reproductive age (patients with stress, urge, mix incontinence and normal urodynamic findings)

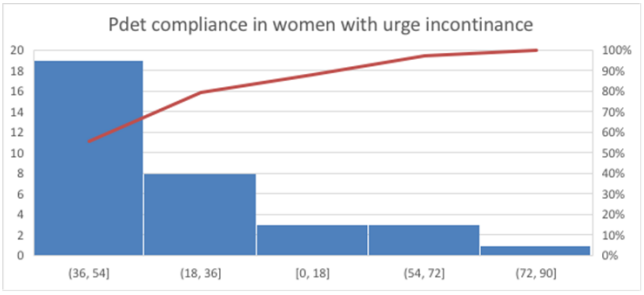

Figure 2: P_{det} compliance according to age in urge incontinence and hypocompliant bladder patients. Maximum compliance occurs in women of reproductive age, without a linear steady variance

An animal study showed that aging induces dysfunction in coordination between the urinary bladder and urethra. Thus, urethral dysfunction due to increasing age may lead to inefficient voiding with increased postvoid residual urine volume, which is often observed in the elderly population [20]. The cause of urethral dysfunction is hypothesized as decreased synthesis of NO, a molecule that relaxes urethral smooth muscle [21], and increased synthesis of the endogenous inhibitor of NO-synthase, with age [22]. Another recent animal study showed that the consistency of layer thickness and nuclear density of the bladder wall structure in mice is preserved following maturation, but this may differ in humans [10]. A correlation between urethral pressure and estrogen levels during the menstrual cycle is expected. Rud [23] showed that the decrease in urethral pressure with increasing age was continuous in a wide age group of women with no correlation with estrogen levels, however, an increase from infancy to adolescence was demonstrated. Our data lacks MUCP values, but we hypothesized that the MUCP curve in Rud's study correlates with our P_{det} curve.

Limitations

This study may include more patients with normal urodynamic findings, but their LUTS symptoms are much less than those of the incontinence population.

Evidence that menopause is an independent factor in the prevalence of incontinence remains lacking [24] and further investigation with a wide age range of women are needed for future research.

Conclusion

Our study is the one of the few studies to examine voiding parameters in a large, heterogenous, secondary care population. Further evaluation of large collections of urodynamic data could lead to the development of specific reference values

for use by urodynamics specialists. Aging is associated with a decrease in self-control, thus the increased prevalence of LUTS symptoms in the aged population might be more accurately considered as the loss of an adaptive threshold to urinary control rather than age-associated decline in urinary functions**.**

Acknowledgements

We thank our urodynamic specialist Nurse Nuray.

References

1. Coyne KS, Wein AJ, Tubaro A, et al. The burden of lower urinary tract symptoms: evaluating the effect of LUTS on health-related quality of life, anxiety and depression: EpiLUTS. BJU Int. 2009;103(Suppl 3):4–11.
2. Stewart WF, Van Rooyen JB, Cundiff GW, et al. Prevalence and burden of overactive bladder in the United States. World J Urol. 2003;20:327–36.
3. van der Vaart CH, de Leeuw JR, Roovers JP, et al. The effect of urinary incontinence and overactive bladder symptoms on quality of life in young women. BJU Int. 2002;90(6):544–9.
4. Irwin DE, Milsom I, Hunskaar S, et al. Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: results of the EPIC study. Eur Urol. 2006;50(6):1306–14.
5. Coyne KS, Sexton CC, Thompson CL, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU Int. 2009;104(3):352–60.
6. Jeong SJ, Kim HJ, Lee YJ, et al. Prevalence and clinical features of detrusor underactivity among elderly with lower urinary tract symptoms: a comparison between men and women. Korean J Urol. 2012;53:342–8
7. Stav K, Dwyer PL, Rosamilia A, Schierlitz L, Lim YN, Lee J. Midurethral sling procedures for stress urinary incontinence in women over 80 years. Neurourol Urodyn. 2010;29:1262–6.
8. Clarke B. The role of urodynamic assessment in the diagnosis of lower urinary tract disorders. Int Urogynecol J Pelvic Floor Dysfunct. 1997;8:196–9.
9. Groutz A, Gordon D, Lessing JB, Wolman I, Jaffa A, David MP. Prevalence and characteristics of voiding difficulties in women: are subjective symptoms substantiated by objective urodynamic data? Urology. 1999;54:268–72.
10. Hardy, CC, Keilich, SR, Harrison, AG, Knight, BE, Baker, DS, Smith, PP. The Aging Bladder Phenotype Is Not the Direct Consequence of Bladder Aging. Neurourology and Urodynamics. 2019; 38:2121-9.
11. Rosier, PF, Schaefer, W, Lose, G, et al. International Continence Society Good Urodynamic Practices and Terms 2016:Urodynamics, uroflowmetry, cystometry, and pressure-flow study. Neurourology and Urodynamics. 2017;36:1243–60.
12. Collas D, Malone-Lee J. Age-associated changes in detrusor sensory function in women with lower urinary tract symptoms . International Urogynecology Journal. 1996;7:24–9.
13. Wyndaele JJ. Normality in urodynamics studied in healthy adults. J Urol. 1999; 161:899–902.
14. Shin YS, On JW, Kim MK. Effect of aging on urodynamic parameters in women with stress urinary incontinence. Korean J Urol. 2015 May;56(5):393-7.
15. Valentini FA, Robain G, Marti BG. Urodynamics in women from menopause to oldest age: what motive? What diagnosis? Int Braz J Urol. 2011;37:100–7.
16. Perucchini D, DeLancey JO, Ashton-Miller JA, Galecki A, Schaer GN: Age effects on urethral striated muscle. II. Anatomic location of muscle loss. Am J Obstet Gynecol. 2002;186:356-60.
17. Zimmern P, Litman HJ, Nager CW, Lemack GE, Richter HE, Sirls L, et al. Effect of aging on storage and voiding function in women with stress predominant urinary incontinence. J Urol 2014;192
18. Basu M, Postlethwaite C, Cheema K, Duckett J. The effect of age on pressure flow parameters in women with lower urinary tract symptoms. J Obstet Gynaecol 2013;33:873–6.
19. Pfisterer M, Griffi ths D, Rosenberg L, Schaefer W, Resnick N. The impact of detrusor overactivity on bladder function in younger and older women. Journal of Urology 2006;175:1777–83.
20. Kimura, Ryu et al. Age-associated urethral dysfunction in urethane-anesthetized rats. Neurourology and urodynamics. 2018;37(4):1313-9.
21. Yoshida M, Inadome A, Murakami S. [Pharmacological analysis of neurotransmitters contributing to lower urinary tract function]. Nihon yakurigaku zasshi. FPJ. 2003;121:307–16.
22. Schulze F, Maas R, Freese R, Schwedhelm E, Silberhorn E, Böger RH. Determination of a reference value for N(G), N(G)- dimethyl-L-arginine in 500 subjects. Eur J Clin Invest. 2005;35:622–6.
23. Rud T. Urethral pressure profile in continent women from childhood to old age. Acta Obstetricia et Gynecologica Scandinavica. 1980;59:331-5.
24. Sherburn M, Guthrie JR, Dudley EC, O'Connell HE, Dennerstein L. Is incontinence associated with menopause? Obstet Gynecol. 2001;98:628-33.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):938-942.
DOI: 10.28982/josam.813042

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Complications increase in which type of duodenal diverticulum? A retrospective cohort study

Hangi duodenal divertikül tipinde komplikasyonlar artar? Retrospektif kohort çalışma

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Ethics Committee Approval: This study was approved on 3/11/2020 by the Ministry of Health Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision numbered 2013-KAEK-64. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Sağlık Bakanlığı İstanbul Medeniyet Üniversitesi Göztepe Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu tarafından 11.03.2020 tarihinde 2013-KAEK-64 sayılı kararla onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/23/2020
Yayın Tarihi: 23.11.2020

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Abstract

Aim: In endoscopic retrograde cholangiopancreatography (ERCP), a diverticulum increases complications such as perforation and pancreatitis. We must know which type of diverticulum increases the complications to develop a strategy. The aim of this study is to examine the safety of the ERCP procedure in terms of diverticulum types.

Methods: A total of 864 patients aged 65 years and over who underwent ERCP from January 2010 to November 2019 were identified and analyzed in this retrospective cohort study. Demographic findings, indications, successful cannulation rates and complications were compared between groups with and without duodenal diverticula.

Results: Of the patients who underwent ERCP, 56.4% were female. The mean age of all patients was 77.39 (65-90) years. The most common indications were common bile duct stones (92.1%). Other indications included cholangitis (1.4%), sphincter Oddi dysfunction (1.6%), pancreatitis (2.1%), Mirizzi syndrome (2.7%), postoperative gallbladder fistula (0.7%), periampullary tumor formation (0.57%) and biliary stenosis (0.23%). Among all patients, 848 (98.1%) had no complications, 2 (0.34%) developed pancreatitis, 1 (0.17%) developed cholangitis and bleeding occurred in 1 (0.17%) patient in the group without a duodenal diverticulum. Among patients with a type I diverticulum, 4 (12.9%) had pancreatitis and 3 (9.6%) had bleeding. One patient (1.16%) had pancreatitis, 1 (1.16%) had cholangitis and 2 (2.33%) had bleeding among the type II group, while in the type III group, 1 (0.64%) had pancreatitis and 1(0.64%) had a perforation. Mortality was seen in 2 (0.23%) patients. A total of 5 (0.57%) periampullary tumors were detected in the study.

Conclusion: Our study revealed that patients with a duodenal diverticulum experience more complications than the normal population. Among them, the rate is insignificantly increased in those with a type I duodenal diverticulum. Further studies are needed on this subject.

Keywords: Endoscopic retrograde cholangiopancreatography, Duodenum, Diverticulum, Pancreatitis

Öz

Amaç: ERCP prosedüründe divertikül oluşumu perforasyon ve pankreatit gibi komplikasyonları artırır. Hangi tip divertikülün komplikasyonları artırdığını bilmeli ve bunun için bir strateji geliştirebilmeliyiz. Bu çalışmanın amacı, ERCP işleminin güvenliğini divertikül türleri açısından incelemektir.

Yöntemler: Ocak 2010'dan Kasım 2019'a kadar ERCP prosedürü uygulanan 65 yaş ve üstü 864 hasta retrospektif bir kohort çalışmasında belirlendi ve analiz edildi. Duodenal divertikülü olan ve olmayan gruplar arasında demografik bulgular, endikasyonlar, başarılı kanülasyon oranları ve komplikasyonlar karşılaştırıldı.

Bulgular: ERCP uygulanan hastaların %56,4'ü kadındı. Tüm hastaların ortalama yaşı 77,39 (65-90) yıldı. En yaygın endikasyonlar %92,1 ile safra kanalı taşlarıdır. Diğer endikasyonlar arasında %1,4 kolanjit, %1,6 sfinkter Oddi disfonksiyonu, %2,1 pankreatit, %2,7 Mirizzi sendromu, %0,7 postoperatif safra kesesi fistülü, %0,57 periampullar tümör oluşumu ve %0,23 ile safra darlığıdır. 864 hastanın 848'inde (%98,1) komplikasyon görülmedi. Duodenal divertikülü olmayan grupta 2 (%0,34) pankreatit, 1 (%0,17) kolanjit ve 1 (%0,17) kanama meydana geldi. Tip I grupta 4 (%12,9) hastada pankreatit ve 3 (%9,6) hastada kanama görüldü. Tip II grupta 1 (%1,16) hastada pankreatit, 1 (%1,16) hastada kolanjit ve 2 (%2,33) hastada kanama meydana geldi. Tip III grupta 1 (%0,64) hastada pankreatit ve 1 (%0,64) hastada perforasyon gelişti. Mortalite 2 (%0,23) hastada görüldü. Çalışmada toplam 5 (%0,57) hastada periampuller tümör tespit edildi.

Sonuç: Sonuç olarak, bu çalışmada duodenal divertikülü olan hastaların normal popülasyona göre daha fazla komplikasyon yaşadıkları gösterilmiştir. Ancak duodenal divertikül tipleri arasında özellikle tip 1 duodenal divertikülü olanların daha fazla komplikasyon yaşadığı görüldü, ancak istatistiksel olarak anlamlı değildi. Bu durum bize bu konuda yeni çalışmalara ihtiyaç olduğunu gösteriyor.

Anahtar kelimeler: Endoskopik retrograd kolanjiyopankreatografi, Duodenal, Divertikül, Pankreatit

How to cite/Atıf için: Akaydın M, Akay T, Leblebici M. Complications increase in which type of duodenal diverticulum? A Retrospective cohort study. J Surg Med. 2020;4(11):938-942.

Introduction

A periampullary duodenal diverticulum (PAD) is a clinico-anatomic formation with the papillae residing at the edge of or within a 2.5 cm radius around the diverticulum in the duodenum. Although this formation is found incidentally in radiological imaging studies, it may present many difficulties in ERCP due to its pathological status. Various publications have shown that PAD causes many diseases including common bile duct (CBD) stones due to its anatomic character. In studies dealing with PAD, it is found in 9-32.8% of the patients. The wide range indicates the heterogeneity of the study group [1]. Boix et al. [2] divided the PAD into types based on its anatomic position: The ones where the papillae are inside the diverticulum are Type I (Figure 1), the ones where the papillae reside on the edge of the diverticulum are Type II (Figure 2) and the ones with papillae located around the diverticulum are Type III (Figure 3).

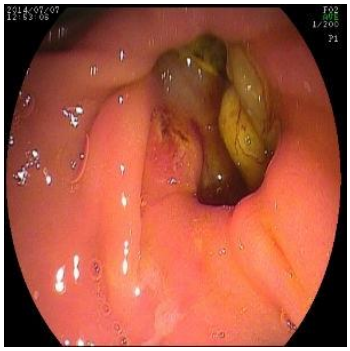

Figure 1: Image of papillae within the diverticulum (Type I)

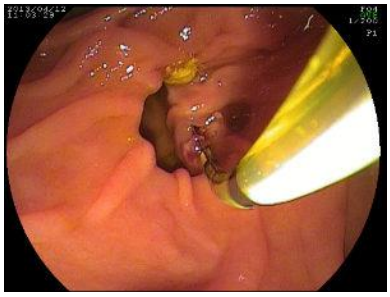

Figure 2: Papillae at the edge of the diverticulum (Type II)

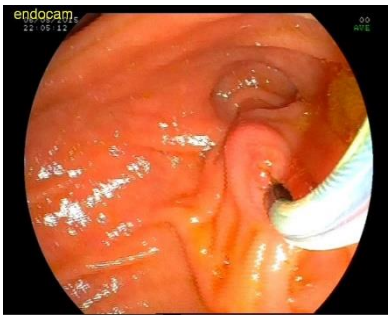

Figure 3: Papillae located around the diverticulum (Type III)

Panteris et al. [3] have classified PAD according to whether the papillae are within the diverticulum. According to their study, the Type II and Type III groups, stated by Boix et al. [4], constitute Type A, and Type I constitutes Type B. ERCP is an invasive procedure for the treatment of biliary and pancreatic disorders rather than diagnosis. This procedure is known to carry many complication risks, such as pancreatitis, bleeding, and perforation, all of which may lead to serious mortality, especially in elderly patients [5]. However, given the benefits of ERCP, which removes the need for surgery and reduces the burden of various interventions on the patient, it is an indispensable procedure, especially in cases requiring CBD intervention [6].

The aim of this study is to investigate demographic findings, indications, successful cannulation rates and post-ERCP complications according to diverticulum types.

Materials and methods

A total of 864 patients who were referred to the ERCP endoscopy unit between January 2010 and November 2019 were retrospectively analyzed. Among them, 273 patients (31.5%) had a periampullary diverticulum in the duodenum, 31 of which were Type I, 86 were Type II, and 156 were Type III. Demographic findings, indications, successful cannulation rates and complications were investigated among these groups. All patients included in the study signed a consent form prior to the ERCP procedure.

Prophylactic antibiotics were routinely administered to all patients prior to ERCP procedures. ERCP was performed under sedation with topical 10% Xylocain® (lidocaine, AstraZeneca, Cambridge, Britain) followed by intravenous Aldolan® (pethidine HCl, G.L. Pharma GmbH, Lannach, Austria) and Dormicum® (midazolam, Roche, Basel, Switzerland). Buscopan® (Hyposin-N-butyl bromide, Boehringer Ingelheim, Ingelheim, Germany) was used to reduce intestinal peristalsis. After papillary cannulation, contrast material was injected. Endoscopic sphincterotomy was performed in both groups.

Bleeding was defined as at least a two-point decrease in hemoglobin, with no other source of bleeding in endoscopy. Acute pancreatitis was defined as a three-fold increase in lipase value in the patient's biochemical tests after ERCP. Cholangitis was defined as the occurrence of Charcot triad (pain, fever, jaundice).

This study was approved on 3/11/2020 by the Ministry of Health Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision numbered 2013-KAEK-64.

Statistical analysis

Chi-square test or Fisher's exact test were used for statistical analysis of categorical data. Ratios were calculated in 95% confidence. All data analyses were performed using SPSS statistical software program, version 19.0 Windows (SPSS Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results

Among the included 864 patients over 65 years of age who underwent ERCP, 487 (56.4%) were female and 377 (43.6%) were male. The mean age of all patients was 77.39 (65-90) years, 77.35 years among patients without a diverticulum, 76.71 years in the type I group, 77.63 years in the type II group and 77.56 years in the type III group.

CBD stones (92.1%) were the most common indication in all patient groups included in the study. These patients presented with a low rate (1.4%) of cholangitis. Other indications included sphincter Oddi dysfunction (1.6%), pancreatitis (2.1%), biliary compression due to acute cholecystitis (Mirizzi syndrome) (2.7%), postoperative gallbladder fistula (0.7%),

periampullary tumoral formations (0.57%) and biliary tract stenosis (0.23%).

Cannulation was performed with sphincterotome in 563 (95.2%) of 591 patients without a diverticulum, 28 (90.3%) of 31 type I patients, 76 (88.3%) of 86 type II patients and 144 (92.3%) of 156 type III patients. In a total of 53 (6.1%) patients, cannulation was tried with pre-cut. In the first pre-cut trial, 31 of these patients were successfully cannulated. After 3 days of rest (the regression of the edema in the papillae was expected), 16 of the non-cannulated patients were cannulated so that a total of 49 (5.6%) patients were cannulated. In 26 patients without a diverticulum, 2 patients in type I group, 10 patients in type II group, and 11 patients in type III group were cannulated with pre-cut (Table 1).

Table 1: Selective and pre-cut cannulation success between the non-duodenal diverticulum and the type I, type II and type III groups with duodenal diverticulum

Cannulation success	Non diverticulum n (%)	Type I n (%)	Type II n (%)	Type III n (%)	Total n (%)
Selective cannulation	563 (95.2%)	28 (90.3%)	76 (88.3%)	144 (92.3%)	811 (93.8%)
Unsuccessful	2 (0.33%)	1 (3.22%)	0	1 (0.64%)	4 (0.46%)
Pre-cut success	26 (4.39%)	2 (6.45%)	10 (11.7%)	11 (7.05%)	49 (5.6%)
Total	591	31	86	156	864

In two patients in the non-duodenal diverticulum group, pre-cut cannulation could not be performed. One of these patients had cholangitis. The patient underwent choledochal exploration under antibiotherapy as an open surgical procedure. The patient was mortal in the postoperative period due sepsis. The other patient had facet stones up to 2 cm in size. Since the stones of this patient could not be broken with a stone crushing device, the patient underwent open surgery. Choledochal exploration and T tube placement was performed and the patient was discharged with surgical recovery.

Pre-cut cannulation was unsuccessful in one patient in type I group. This patient developed bleeding during the procedure and underwent emergency exploration because the bleeding could not be controlled by saline with adrenaline, balloon compression and coagulation with electrocautery. Duodenotomy was performed to control the bleeding and the pathology of the common bile duct was intervened. Postoperative period was uneventful, and the patient was discharged.

Pre-cut cannulation failed in one patient in the type III group. This patient had a periampullary tumor, developed perforation during ampullectomy and was immediately operated. Hepaticopancreaticojejunostomy was performed. In the postoperative period, the patient died due to pulmonary embolism despite anticoagulant therapy.

No complications were encountered in 587 (99.3%) of 591 patients (patients without a duodenal diverticulum). Two (0.34%) had pancreatitis, 1 (0.17%) had cholangitis and 1 (0.17%) had bleeding. One of the patients who developed pancreatitis had edematous pancreatitis, which regressed with medical treatment. Necrotizing pancreatitis progressed in the follow-up of the other patient with pancreatitis. The patient remained under long-term follow-up, and percutaneous catheter drainage was applied when abscess developed. Since the patient who developed cholangitis could not be cannulated, she was operated immediately but died in the postoperative period due to sepsis. Balloon compression was applied to the bleeding patient during the procedure and bleeding was controlled.

Of the 31 patients in the type I group, 24 (77.4%) had no complications. In this group, 4 (12.9%) patients had pancreatitis and 3 (9.6%) had bleeding. A patient who developed bleeding was urgently operated. Bleeding of the other two patients was controlled by saline irrigation with adrenaline and balloon compression. Contrast injection was not applied to the pancreatic duct of the other three patients except one. Pancreatic cannulation was performed with a standard sphincterotome in these patients. Edematous pancreatitis developed in these patients and regressed with medical treatment.

In the type II group, 83 (96.5%) of 86 patients had no complications. 1 (1.16%) had pancreatitis, 1 (1.16%) had cholangitis and 2 (2.33%) had bleeding. Among these patients, edematous pancreatitis developed in the patient with pancreatitis and his clinical condition regressed with medical treatment. Adrenaline saline irrigation and balloon compression were applied to the patients with bleeding complications. In one of these patients, blood pressure increased due to usage of excessive adrenaline solution during the procedure, the procedure was postponed, and cannulation was achieved 3 days later. Another patient developed cholangitis after pre-cut and underwent ERCP. However, Sump Syndrome occurred, and food residues were cleaned from the CBD and a stent was placed. The patient was discharged uneventfully 1 month after stent withdrawal.

Among 156 patients in type III group, only two patients developed complications. Pancreatitis and perforation developed in 1 (0.64%) patient each. Pancreatitis regressed with medical treatment. Perforation occurred during the ampullectomy procedure in a patient with ampullary tumoral mass and the patient was taken to operation immediately.

Of the 864 patients, 848 (98.1%) had no complications, 8 (0.93%) had pancreatitis, 6 (0.69%) had bleeding, 2 (0.23%) had cholangitis and 1 (0.12%) had perforation. The frequency of complications in the group with duodenal diverticula (Type 1, type 2, and type 3) was significantly higher compared to the group without ($p<0.001$). Mortality was seen in 2 (0.23%) patients for reasons explained above (Table 2).

Table 2: Prevalence of complications between the group without duodenal diverticulum and type I, type II and type III groups with duodenal diverticulum

Complication	Non diverticulum n (%)	Type I n (%)	Type II n (%)	Type III n (%)	Total n (%)
Pancreatitis	2 (0.34%)	4 (12.90%)	1 (1.16%)	1 (0.64%)	8 (0.93%)
Bleeding	1 (0.17%)	3 (9.68%)	2 (2.33%)	0 (0.00%)	6 (0.69%)
Cholangitis	1 (0.17%)	0 (0.00%)	1 (1.16%)	0 (0.00%)	2 (0.23%)
Perforation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.64%)	1 (0.12%)
No complications	587 (99.32%)	24 (77.42%)	83 (96.51%)	154 (98.72%)	848 (98.15%)
Total	591(100.00%)	31(100.00%)	86(100.00%)	156(100.00%)	864(100.00%)

Pearson Chi Square, $P<0.001$

We observed that the incidence of complications increased significantly in patients with a duodenal diverticulum. When we asked the question of whether the likelihood of complications would be different according to the types, we found that pancreatitis and bleeding complications were higher in the Type I group than the other groups and the population without diverticula. However, the number of patients was insufficient for statistical evaluation.

A total of 5 (0.57%) periampullary tumors were detected in the study, 3 patients (0.5%) of which belonged to the non-duodenal diverticulum group and 2 (1.2%), to the type III group.

Discussion

In the previously published studies, the results were affected by the significant heterogeneity. Therefore, in this study, homogeneity was aimed for, comparing patients over 65 years of age with diverticula [7].

In their study, Tham and Kelly [8] reported that the rates of mortality, morbidity and successful cannulation following ERCP between patients with and without PAD were highly similar, which contradicted with our results. They also confirmed that localization of the Vater ampulla near only one diverticulum significantly increased the incidence of stone in the bile duct. Choledocholithiasis was found in 64% of patients with diverticula and 33% of patients without. Zoepf et al. [9] reached similar results. In their studies, 46% CBD stones were found in the diverticulum group and 33% in the diverticulum-free group. In our study, CBD stones were the most common indication with a rate of 92.1%. Other indication rates were similar to those of other studies [10].

The selective cannulation of the bile duct is main step for a successful ERCP and the prerequisite to get maximum benefit. Despite advances and new developments in endoscopic accessories such as endoscopic instruments, selective biliary cannulation fails in %5-15 of cases, even in expert, high-volume centers [11]. Repeating ERCP within a few days of the first failed pre-incision reduces the risk of complications by reducing the edema of the papilla and increases the chance of cannulation [12-15]. In our study, cannulation was performed with a sphincterotome in 563 (95.2%) of 591 patients without diverticula, 28 (90.3%) of 31 type I patients, 76 (88.3%) of 86 type II patients and 144 (92.3%) of 156 type III patients. In a total of 53 (6.1%) patients, cannulation was tried with pre-cut. In the first pre-cut trial, 31 of these patients were successfully cannulated. After 3 days of rest (regression of the edema in the papillae was expected), 16 of the non-cannulated patients were cannulated so that a total of 49 (5.6%) patients were cannulated.

In the study of Ketwaroo et al. [16] on 1325 patients, it was concluded that the formation of a diverticulum does not make a difference in cannulation success during ERCP. However, in many studies, it was concluded that the presence of a diverticulum is one of the difficult cannulation criteria which reduces cannulation success rates. In these studies, the success rates for ERCP in the presence of diverticulum were between 61-97.2% [17]. The European Gastrointestinal Endoscopy Society has suggested that selective cannulation may not be sufficient in patients with a duodenal diverticulum and advanced procedures such as pre-cut can be limited [18].

Duodenal diverticula are incidental unless they become symptomatic. If they affect the biliary tract, they can cause many complications such as biliary obstruction, cholangitis, pancreatitis, bleeding, and perforation. It was thought that the mechanical stress of the Oddi sphincter diverticulum and bacterial growth were effective in the formation of these complications [19]. In our study, complication rates were significantly increased in patients with duodenal diverticula.

Among the general population, the most common complication associated with ERCP is pancreatitis with an incidence of 1.3-30%. Although multiple risk factors for pancreatitis have been reported after ERCP, predisposing factors include the vast usage of contrast agent, multiple cannulation attempts and manipulations in the pancreatic duct [20].

There are different views on the association of PAD with pancreatitis. Some investigators have suggested that pancreatitis is not associated with PAD. Others have reported a higher rate of acute pancreatitis in patients with PAD [21]. In our study, we found significantly higher complication rates in PAD patients compared to non-PAD patients. In addition, patients with type I PAD have higher complication rates than patients with type 2 or type 3 PAD. In their study, Sun et al. suggested that the papillae residing within the diverticulum may compress the pancreatic duct to cause pancreatitis [22]. In our study, 848 (98.1%) of 864 patients had no complications, 8 (0.93%) had pancreatitis, 6 (0.69%) had bleeding, 2 (0.23%) had cholangitis and 1 (0.12%) had perforation.

Gastrointestinal bleeding most commonly occurs after endoscopic sphincterotomy and its incidence is estimated to be between 5% and 30% [23]. In some studies, the incidence of bleeding in elderly patients undergoing ERCP was not high [24]. In our study, especially in patients with type I PAD, the bleeding complication was high. Two of these were intervened endoscopically, and the other patient was taken into surgery emergently.

Digestive system perforation is a rare but serious complication of ERCP. Its occurrence depends on the anatomy of the distal segment of the common bile duct and the length of the major duodenal papillotomy. Procedures susceptible to this complication include Billroth II gastrectomy, endoscopic sphincterotomy, intraluminal injection of contrast material, and dilation of the bile duct stenosis [25]. Conservative treatment is sufficient in most studies [26]. In our study, perforation occurred during an ampullectomy procedure in a patient with a periampullary tumor and a stent was placed because of the tumor component and it was thought that conservative follow-up would not be appropriate.

In their study, Sun et al. [27] presented a negative correlation between the presence of a PAD and periampullary carcinoma prevalence, a finding which had not been reported previously in the literature. In another study from Korea, it was found that the risk of cancer increased in the region affected by the diverticulum. However, in our study, a similar number of periampullary tumors were detected in patients with and without diverticula. Therefore, it is not possible to mention a statistically verifiable relationship between a diverticulum and cancer. However, we believe that the presence of a periampullary tumor in the group farthest from the diverticulum will support the opinion of Sun et al.

Death from ERCP is rare (less than 0.5%) and is mostly associated with cardiopulmonary complications. Although advanced age is thought to be one of the common factors increasing risk, multivariate analyses do not support this idea [28]. Two (0.23%) patients also died in our study; the mortality of both were due to ERCP-independent factors.

Strengths and limitations

The strengths of the study are that the use of pre-cut sphincterotomy according to routine ERCP procedures is routinely performed in patients who cannot undergo standard sphincterotomy, and the expectation for reduction of the

papillary edema increases the chances of a sphincterotomy and reflects on the results.

Considering the limitations of the study, percutaneous transhepatic cholangiography (PTC) can be performed in the presence of interventional radiology in patients whose bile ducts cannot be intervened, to regress and treat the patient's disease. However, it is not applied in our hospital. Also, we think that further, larger studies are needed to investigate complication rates between duodenal diverticulum types.

Conclusions

Our study revealed that patients with a duodenal diverticulum experience more complications than the normal population. The rate is insignificantly increased in those with a type I duodenal diverticulum. Further studies are needed on this subject.

References

1. Major P, Dembiński M, Winiarski M, Pędziwiatr M, Rubinkiewicz M, Stanek M, et al. A Periampullary Duodenal Diverticula in Patient with Choledocholithiasis-Single Endoscopic Center Experience. Pol Przegl Chir. 2016;88(6):328-33.
2. Boix J, Lorenzo-Zuniga V, Ananos F, Domenech E, Morillas RM, Gassuli MA. Impact of periampullary duodenal diverticula at endoscopic retrograde cholangiopancreatography: a proposed classification of periampullary duodenal diverticula. Surg Laparosc Endosc Percutaneous Tech. 2006;16:208-11.
3. Corral JE, Mousa OY, Kröner PT, Gomez V, Lukens FJ. Impact of Periampullary Diverticulum on ERCP Performance: A Matched Case-Control Study. Clin Endosc. 2019;52(1):65-71.
4. Panteris V, Vezakis A, Filippou G, Karamanolis D, Rizos S, et al. Influence of juxtapapillary diverticula on the success or difficulty of cannulation and complication rate. Gastrointest Endosc. 2008;68:903-10.
5. Akcakaya A, Ozkan OV, Bas G, Karakelleoglu A, Kocaman O, Okan I, et al. Mechanical lithotripsy and/or stenting in management of difficult common bile duct stones. Hepatobiliary Pancreat Dis Int. 2009;8(5):524-8.
6. Niu F, Liu YD, Chen RX, Niu YJ. Safety and efficacy of enhanced recovery after surgery in elderly patients after therapeutic endoscopic retrograde cholangiopancreatography. Wideochir Inne Tech Maloinwazyjne. 2019;14(3):394–400.
7. Kouklakis G, Gatopoulou A, Lirantzopoulos N, Efraimidou E, Manolas K. Evaluation of guide wire cannulation technique in elderly patients with choledocholithiasis. J Gastrointestin Liver Dis. 2009;18(2):185-8.
8. Tham T, Kelly M: Association of periampullary duodenal diverticula with bile duct stones and with technical success of endoscopic retrograde cholangiopancreatography. Endoscopy. 2004;36:1050-53.
9. Zoepf TD, Zoepf S, Arnold JC, Benz C, Riemann JF. The relationship between juxtapapillary duodenal diverticula and disorders of the biliopancreatic system: analysis of 350 patients. Gastrointestinal Endoscopy. 2001;54(1):56–61.
10. Jayaraj M, Mohan BP, Dhindsa BS, Mashiana HS, Radhakrishnan G, Dhir V, et al. Periampullary Diverticula and ERCP Outcomes: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2019;64:1364-76. doi: 10.1007/s10620-018-5314-y.
11. Chen Q, Jin P, Ji X, Du H, Lu J. Management of difficult or failed biliary access in initial ERCP: A review of current literature. Clin Res Hepatol Gastroenterol. 2019;43(4):365-72.
12. Manes G, Paspatis G, Aabakken L, Anderloni A, Arvanitakis M, Ah-Soune P, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy. 2019;51(5):472-91.
13. Colan-Hernandez J, Aldana A, Concepcion M, Chavez K, Gomez C, Mendez-Bocanegra A, et al. Optimal timing for a second ERCP after failure of initial biliary cannulation following precut sphincterotomy: an analysis of experience at two tertiary centers. Surg Endosc. 2017;31:3711.
14. Tanisaka Y, Ryozawa S, Mizuide M, Harada M, Fujita A, Ogawa T, et al. Analysis of the factors involved in procedural failure: Endoscopic retrograde cholangiopancreatography using a short-type single-balloon enteroscope for patients with surgically altered gastrointestinal anatomy. Dig Endosc. 2019;31(6):682-9.
15. Chen YI, Callichurn K, Chatterjee A, Desilets E, Fergal D, Forbes N, et al. ELEMENT TRIAL: study protocol for a randomized controlled trial on endoscopic ultrasound-guided biliary drainage of first intent with a lumen-apposing metal stent vs. endoscopic retrograde cholangio-pancreatography in the management of malignant distal biliary obstruction. Trials. 2019;20(1):696.
16. Ketwaroo G, Qureshi W. ERCP Success Rate and Periampullary Diverticula: The Pocket Makes No Difference. Dig Dis Sci. 2019;64(5):1072-3.
17. Mohammad Alizadeh AH, Afzali ES, Shahnazi A, Mousavi M, Mirsattari D, et al. ERCP features and outcome in patients with periampullary duodenal diverticulum. ISRN Gastroenterol. 2013;2013:217261 doi: 10.1155/2013/217261.
18. Testoni PA, Mariani A, Aabakken L, Arvanitakis M, Bories E, Costamagna G, et al. Papillary cannulation and sphincterotomy techniques at ERCP: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2016;48:657-83.
19. Khan BA, Khan SH, Sharma A. Lemmel's Syndrome: A Rare Cause of Obstructive Jaundice Secondary to Periampullary Diverticulum. Eur J Case Rep Intern Med. 2017;4(6):000632.eCollection 2017.
20. Masci E, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, et al. Complications of diagnostic and therapeutic ERCP: A prospective multicenter study. Am J Gastroenterol. 2001;96(2):417-23.
21. Uomo G, Manes G, Ragozzino A, Cavallera A, Rabitti PG. Periampullary extraluminal Duodenal diverticula and acute pancreatitis: an under estimated etiological association. The American Journal of Gastroenterology. 1996;91(6):1186-8.
22. Sun Z, Bo W, Jiang P, Sun Q. Different Types of Periampullary Duodenal Diverticula Are Associated with Occurrence and Recurrence of Bile Duct Stones: A Case-Control Study from a Chinese Center. Gastroenterol Res Pract. 2016;6:1-8.
23. Fatima J, Baron TH, Topazian MD, Houghton SG, Iqbal CW, Ott BJ, et al. Pancreaticobiliary and duodenal perforations after periampullary endoscopic procedures: diagnosis and management. Arch Surg. 2007;142(5):448-54; discussion 454-5.
24. Fritz E, Kirchgatterer A, Hubner D, Aschl G, Hinterreiter M, Stadler B, et al. ERCP is safe and effective in patients 80 years of age and older compared with younger patients. Gastrointest Endosc. 2006;64(6):899-905.
25. Osnes M, Rosseland AR, Aabakken L. Endoscopic retrograde cholangiography and endoscopic papillotomy in patients with a previous Billroth-II resection. Gut. 1986;27(10):1193-8.
26. Chong VH, Yim HB, Lim CC. Endoscopic retrograde cholangiopancreatography in the elderly: outcomes, safety and complications. Singapore Med J. 2005;46(11):621-6.
27. Choi CS, Choi SC, Seo GS, Cho EY, Cho HJ, Kim YS, et al. Association between diverticulosis and colonic neoplasm in Koreans. The Korean Journal of Gastroenterology. 2007;49(6):364-8.
28. Agarwal N, Sharma BC, Sarin SK. Endoscopic management of acute cholangitis in elderly patients. World J Gastroenterol. 2006;12(40):6551-5.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):943-946.
DOI: 10.28982/josam.810439

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Childhood obesity: Is it related to feeding type of the infant?

Çocukluk çağı obezitesi: Bebeklik döneminde beslenme şekli ile ilişkili mi?

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Ethics Committee Approval: The approval of was obtained from the Ethics Committee of Clinical Research at Haydarpasa Numune Training and Research Hospital (issue no: HNEAH-kaek 2019/KK/163, date: 12/16/2019). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma için Haydarpaşa Numune Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu'ndan onay alındı (sayı no: HNEAH-kaek 2019/KK/163, tarih: 16.12.2019). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/23/2020
Yayın Tarihi: 23.11.2020

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Abstract

Aim: The prevalence of childhood obesity has risen currently, and the relationship between feeding types in the infancy period and childhood obesity remains controversial. It is aimed to investigate the impact of feeding practices in the first six months of life on early childhood obesity in exclusively breast-fed, exclusively formula-fed, and mixed (breast milk and formula) fed Turkish infants.

Methods: This study was conducted in the Department of Pediatrics at Haydarpasa Numune Training and Research Hospital with 545 children aged between 2-5 years. We asked the parents various questions to determine the feeding patterns during infancy. Three groups were formed: Exclusively breastfeed, exclusively formula-fed and the mixed (breast milk and formula) fed group. Obesity rates were determined according to body mass index (BMI) and compared.

Results: Among a total of 545 children, with a mean age of 3.4 years, there were 285 (52,3%) females. Evaluation based on BMI revealed that the obesity (≥95th percentile) rate was 8.8% and the percentage of overweight children was significantly higher in the only formula-fed group (28.2%) compared to those who were only breast-fed (16.8%) (P=0.009).

Conclusions: Our findings showed that feeding the child exclusively with formula during the first six months of life may increase body weight during early childhood more than feeding solely breast milk. Therefore, it is necessary to promote breastfeeding to prevent childhood obesity.

Keywords: Obesity, Breast milk, Formula, Infant

Öz

Amaç: Çocukluk çağında obezite prevalansı günümüzde artmıştır, bebeklik dönemindeki beslenme şekli ile çocukluk çağı obezitesi arasındaki ilişki hala tartışmalıdır. Çalışmamızda ilk 6 ayda sadece anne sütüyle beslenen, sadece mama ile beslenen ve karma (anne sütü + mama) beslenen Türk bebeklerde beslenme uygulamalarının erken çocukluk çağı obezitesi üzerindeki etkisinin araştırılması amaçlanmıştır.

Yöntemler: Bu çalışma Haydarpaşa Numune Eğitim ve Araştırma Hastanesi pediatri bölümünde 2-5 yaş arası 545 çocuk ile yapıldı. Anne babalara ilk 6 aydaki bebeklik döneminde beslenme tiplerini belirlemek için anket yapıldı. Sadece anne sütüyle beslenen, sadece mama ile beslenen ve karma (anne sütü + mama) beslenen bebekler olarak beslenme şekillerine göre 3 grup oluşturuldu; 2-5 yaş çocukların vücut kitle indeksi hesaplandı ve bu gruplara göre obezite görülme oranı belirlendi ve birbirleri ile karşılaştırma yapıldı.

Bulgular: 285'i (%52, 3) kız olmak üzere toplam 545 çocuğun yaş ortalaması 3,4 idi. Vücut kitle indeksine göre yapılan değerlendirmede obezite (≥95 persantil) oranı genel olarak %8,8 olarak tespit edildi. Fazla kilolu çocukların yüzdesi ise sadece formül mama ile beslenen grupta (%28,2) hiç formül mama ile beslenmeyenlere (%16,8) göre anlamlı olarak yüksek bulundu (P=0,009).

Sonuçlar: Bulgularımız, mamayla beslenmenin vücut ağırlığını anne sütünden daha fazla artırabileceğini gösterdi; bu nedenle özellikle erken çocukluk çağındaki obeziteyi önlemek için ilk 6 ayda sadece anne sütü ile beslenmeyi teşvik etmek gereklidir.

Anahtar kelimeler: Obezite, Anne sütü, Formül mama, İnfant

How to cite/Atıf için: Ünsür EK, Akıcı N, İşançlı DK. Childhood obesity: Is it related to feeding type of the infant? J Surg Med. 2020;4(11):943-946.

Introduction

Obesity is defined as the storage of fat in the body due to energy intake exceeding expenditure. Overweight or obese children include those who are over normal weight for their age and height [1]. The prevalence and severity of childhood obesity has increased significantly throughout the world [2] and in Turkey [3]. Childhood obesity also increases the likelihood of adult obesity and leads to obesity-related complications such as hypertension, type 2 diabetes, and cardiovascular morbidities [4].

The etiology of obesity is multifactorial and complex, involving the interaction between genetic, biological, and environmental factors and ecological influences. Many factors present in the first 1000 days of life (from conception up to the age of 2 years) are strongly associated with weight in later life. It has been suggested that the early life period is particularly sensitive to environmental "programming" [5]. In particular, rapid weight gain in early life due to feeding practices has been shown to be a risk factor for later obesity [6]. However, the data are controversial. According to the accelerated postpartum weight gain hypothesis, formula feeding alone increases the fat mass of infants and may cause obesity in later life [7].

While formula feeding was associated with obesity risk in some studies [8,9], others did not report a significant difference in body mass index (BMI) between formula-fed and breast-fed infants [10,11]. In the various meta-analyses published in Western countries, breastfeeding was reported to reduce the risk of childhood obesity, but this relationship is controversial in studies which are performed across many other countries. These differences may be due to ethnicity, sample size, varying definitions of overweight and obesity, socioeconomic status, parental obesity, and birth weight [8].

In the present study, we aimed to investigate the impact of feeding practices (etc. exclusively breast-fed, only formula-fed and breast milk combined with formula) in the first six months of life on early childhood obesity among the Turkish population, because of the differing reports in the literature.

Materials and methods

This cross- sectional study was conducted in the Department of Pediatrics at Haydarpasa Numune Training and Research Hospital between January-February 2020. We determined the feeding patterns during the infancy of 545 children (aged 2-5 years) by asking the parents when they visited our pediatric clinic for routine controls. The study group included children with normal birth weights (2500-4000g) without any malformations, chronic diseases or physical disabilities that could affect growth and nutritional status. A questionnaire was prepared to determine the socio-demographic data, physical examination findings and growth parameters of the children. The same healthcare providers asked the questions to all parents (mostly mothers) after obtaining their consent. The age of the children when they visited the clinic, gender, gestational age, birth weight, birth dates of the children and pregnancy history were inquired. The age of the mothers at the birth, education level and socioeconomic status were also noted.

The mothers were asked about the beginning of feeding, for how long the child received breast milk or formula, introduction of complementary food and total duration of breast milk or formula consumption with complementary food. According to the feeding patterns of the infants during the first six months of life, three study groups were formed. The first group was exclusively breastfed, the second group was exclusively formula-fed, and the third group was mixed fed, including a combination of formula and breastfeeding.

The growth parameters of children, such as the weight, relative weight, height, and body mass index (BMI), were evaluated during routine controls. All children were weighed naked with the same, delicate scales and their heights were measured with the Herpenden Statiometry. The relative weight was calculated by the ratio of the child's weight to the weight of the normal child of the same age. Obesity was determined by calculating body mass index (BMI), as weight in kilograms divided by height in meters squared. We defined overweight as BMI between the 85th to <95th percentiles and obesity as BMI at or above the 95th percentile based on Turkish Child Growing Charts.

Statistical analysis

Statistical analyses were performed with the SPSS 25.0 software. Data were expressed as mean (standard deviation), numbers and/or percentages, where appropriate. Categorical and continuous variables between the groups were compared with the chi-square test and t-test, respectively. An overall type I error of 5% was used to infer statistical significance.

Results

Among 545 children with a mean age of 3.4 years (range: 2-5 years), 285 (52.3%) were female. The mean birthweight and gestational age of the children were 3200 gr (range: 2500-4000 g) and 38+3 (range: 38+1-39+6 weeks) weeks, respectively.

No children had a history of a chronic disease and all had normal physical examination findings in routine controls. The parents of the children had middle socio-economic status and education levels (most had graduated from the high school). No mothers had gestational diabetes mellitus or any other chronic diseases and feeding patterns of the mothers during the pregnancy were almost similar.

According to body mass index (BMI), 15.6% (n=85) of children were underweight (<5 percentile), 18.6% (n=101) were overweight (≥85th percentile), and obesity (≥95th percentile) rate was 8.8%. Based on body weight evaluation, the percentage of low weight (≤ -2 SD) females (3.9%) were significantly higher than males (0.8%) (P=0.045) (Table 1).

Table 1: Growth parameters of the children

	Total	Boys (n=260)	Girls (n=285)
Patients (%)	100.0	47.7	52.3
Mean age (years)	3.4	2.7	3.3
Mean gestational age (week)	38+3	38+2	38+3
Mean birthweight (gr)	3200	3275	3185
Mean height (cm)	89	90.5	98
Mean weight (kg)	12.6	13	15.4
Mean BMI (kg/cm^2)	16.12	16.03	15.6

BMI: body mass index

The percentages of children who were exclusively breast-fed, exclusively formula-fed and mixed-fed during the first six months of life were 91.9% (n=501), 15.8% (n=86), and 31.6% (n=172), respectively. The mean feeding time with breast milk and formula were 15.6 (8.9) months (0.1-48 months) and

10.8 (7.6) months (0.5-42 months), respectively. The mean time until introduction of complementary food was 6.4 (1.9) months (range: 1.5-24 months).

Based on BMI, the percentage of overweight children was significantly higher in the exclusively formula-fed group (28.2%) compared to the exclusively breast-fed group (16.8%) (P=0.009). No statistically significant difference was found regarding the growth parameters of the children who were mixed fed.

There was no statistically significant difference between the three groups in terms of feeding types (only breast milk, only formula or mixed fed group) with regards to gender (Table 2). The percentage of overweight children was lower (18.3% vs 36.8 %) and underweight children was higher (17.1% vs 0%) (P=0.043) among exclusively breast-fed males. The percentage of overweight children was significantly higher among formula fed males compared to those who did receive formula at all (11.1 vs. 3.6%, P=0.042). Among females, the percentage of overweight was significantly higher in the mixed fed group (breast milk + formula) compared to the exclusively breast-fed group (8.2% vs. 4.8%, P=0.03) (Table 3).

Table 2: Comparison of feeding type by gender

	Total	Boys (n=260)	Girls (n=285)	*P*-value
Breastmilk alone				
Yes	501 (91.9)	241 (48.1)	260 (51.9)	0.637
No	44 (8.1)	19 (43.2)	25 (56.8)	
Formula alone				
Yes	86 (15.7)	36 (41.9)	50 (58.1)	0.242
No	359 (84.3)	224 (48.8)	235 (51.2)	
Breastmilk + Formula				
Yes	172 (31.5)	75 (43.6)	97 (56.4)	0.198
No	273 (68.5)	185 (49.6)	188 (50.4)	

Table 3: Growth status in boys and girls by feeding type

		SD-based BW category			Percentile-based BMI category		
		Underweight (≤-2 SD)	Normal weight (>-2 to +2 SD)	Overweight (>2 SD)	Underweight (<5th percentile)	Normal weight (5th to 85th percentile)	Overweight (≤85th percentile)
Boys	Breastmilk alone						
	Yes	0.0%	94.7%	5.3%	0.0%	63.2%	36.8%
	No	0.8%	94.6%	4.6%	17.1%	64.6%	18.3%
	P-value	0.916			0.043		
	Formula alone						
	Yes	0.4%	96.%	3.6%	15.6%	67.0%	17.4%
	No	2.8%	86.1%	11.1%	17.1%	48.6%	34.3%
	P-value	0.042			0.05		
	Breastmilk + Formula						
	Yes	0.5%	95.7%	3.8%	16.3%	67.4%	16.3%
	No	1.3%	92.%	6.7%	14.7%	57.3%	28.0%
	P-value	0.479			0.099		
Girls	Breastmilk alone						
	Yes	0.%	84.%	16.0%	16.0%	60.0%	24.0%
	No	4.2%	90.8%	5.0%	15.4%	67.7%	16.9%
	P-value	0.055			0.651		
	Formula alone						
	Yes	4.3%	89.8%	6.0%	14.0%	69.8%	16.2%
	No	2.%	92.%	6.0%	22.0%	54.0%	24.0%
	P-value	0.754			0.097		
	Breastmilk + Formula						
	Yes	5.9%	89.4%	4.8%	12.8%	70.2%	17.0%
	No	0.%	91.8%	8.2%	20.6%	60.8%	18.6%
	P-value	0.03			0.175		

BMI: body mass index, BW: body weight, SD: standard deviation

Discussion

The Centers for Disease Control and Prevention (CDC) [12] report that childhood obesity is more prevalent in developing countries. The overall prevalence of obesity in children is 18.5%, affecting 13.7 million children and adolescents, and obesity prevalence among children aged 2-5 years is 13.9% [12]. In our study, we found that 18.6% of children under 5 years of age were overweight and 8.8% were obese based on BMI. According to Childhood Obesity Survey of Turkey (COSI-TUR) 2016 data [13], the rate of overweight children was 14.6% and the obesity rate was 9.9% in Turkey. The Turkish Demographic and Health Survey (TDHS, 2018) [14] reported the rate of overweight children rates under 5 years of age as 8 %. Our findings are similar to these national surveys.

Today, although the importance of breastfeeding is accepted by the countries all over the world, breastfeeding rates are still low. According to the UNICEF 2018 report, analysis of data from 123 countries shows that 4%, or 1 in 25 babies, are never breastfed in low- and middle-income countries. In high-income countries, 21% of babies or more than 1 in 5 babies are never breastfed [15]. In our country, based on the data from TDHS, exclusively breast-feeding rate is 41% in the first five months of life, and continuation of breastfeeding is 66% for the first year and 34% for the second year. The average breastfeeding period is 16.7 months, and time until introduction of complementary food is 6-8 months in 85% of children [14]. According to TDHS, low-middle-income and educated mothers continue to breastfeed longer than others. In our study, the breastfeeding rate in the first six months was 91.9%, the rate of only formula-fed and mixed (breast milk + formula) fed infants were 15.8%, and 31.6%, respectively. These promising findings may be due to the mothers' education and income levels (high school-middle income).

Breastfeeding has many well-known benefits on maternal and child health [16-18]. The relationship between breastfeeding and childhood obesity is controversial and less conclusive in the literature [10,19-24]. It may be due to adjusted confounding factors such as ethnicity, sample size, maternal obesity, obesity / overweight definitions, socioeconomic status of children, and birth weights [8]. It is still unclear which breastfeeding mechanism could protect against overweight and obesity. One of the physiological mechanisms proposed as long-term breastfeeding is that longer exposure to maternal hormones in breast milk could theoretically alter the baby's lipid metabolism and increase the risk of obesity in later life [25]. Similarly, in a recent Chinese cohort study, they reported that exclusively breastfeeding for a shorter period of time (3-6 months) improved children's growth status [26]. Conversely, short breastfeeding time may exacerbate early growth, which is linked to higher obesity later in life [27,28].

It is currently known that rapid weight gain in infancy is associated with later obesity. Breast milk provides adequate energy and nutrients and is considered the ideal food for infants younger than 6 months. Several potential mechanisms may explain how breastfeeding can protect against rapid infant weight gain, including better appetite control and lower protein intake than formula-fed infants. Infant formula has a higher protein / nitrogen content than breast milk and may cause metabolic responses such as increased insulin and insulin-like growth factor-1 (IGF-1) secretion, leading to excessive and rapid weight gain [7-9]. In addition, breast milk contains hormones such as leptin, adiponectin, and ghrelin, which can affect long-term appetite, and the presence of these hormones, growth factors, and

bioactive factors in breast milk can inhibit adipocyte differentiation [29]. We found that the rate of obesity (28.2%) in the exclusively formula-fed group was more prevalent than that in the breastfed group (16.8%) in children aged ≤ 5 years, regardless of gender. This finding was compatible with most of the studies in the literature [30-32], and it is encouraging that the rate of exclusively formula feeding is not exceedingly high in our study. Also, rapid weight gain of the infant can be associated not only with the type of milk consumed, but also with the way of feeding. Regardless of the type of milk, feeding with a bottle is different from breastfeeding, and its effect on infant weight gain has been reported in numerous studies [9,32-34].

In a study from Turkey, Kondolot et al. [33] investigated the risk factors for overweight and obesity in preschool children and reported that there were no associations between the gender and breastfeeding, or formula-feeding. In the other studies, akin to ours, associations were reported between obesity and gender [32]. Especially in the exclusively formula-fed group, the percentage of overweight males were significantly higher (3.6%). Among females, the percentage of overweight was significantly higher in the mixed fed group (breast milk + formula) compared to the exclusively breastfed group (8.2% vs. 4.8%).

Early beginning time of complementary food, especially in formula-fed infants, leads to higher food intake and higher rates of rapid infant weight gain compared to breast-fed infants [28]. In our study, the mean time until introduction of complementary food was (6.4) (1.9) months (range: 1.5-24 months), which was in accordance with recommendations, thus, it should not have influenced the results.

Limitations

First, we did not determine the bottle-feeding rates regardless of milk type, for it may also influence the weight gain of the infants. Second, breastfeeding data were based on self-report of mothers. Although it is thought that maternal recall was valid and reliable, self-reporting may lead to inaccurate disclosure of information. The other limitation was that the feeding style of the mothers when they were pregnant and weight gain were not recorded, but we excluded the children who were small and large for gestational age according to birthweight to standardize the birth weight of the children.

Conclusion

The overweight/obesity prevalence among pre-school children increase in many developing and developed countries, just as in Turkey. It is accepted that effective interventions of obesity should begin as early as infancy. Despite our limitations, our findings show that formula feeding may increase body weight more than breast milk; therefore, it is necessary to encourage the mothers to breastfeed and promote healthcare programs about breastfeeding practices in infancy period to prevent childhood obesity in developing countries.

References

1. Akıncı A. Obesity in children. Children's Endocrinology and Diabetes Association Hand Book 2018;1:5-6.
2. Lobstein T, Jackson-Leach R, Moodie ML, Hall DK, Gortmaker SL, Swinburn BA, et al. Child and adolescent obesity: part of a bigger picture. The Lancet. 2015;385(9986):2510–20. doi: 10.1016/S0140-6736(14)61746-3.
3. Santas F, Santas G. Prevalence of pre-school children for overweight/obesity in Turkey. World Journal Pediatrics. 2018;14:77–83. doi: 10.1007/s12519-017-0103-9.
4. Raimi TH, Odusan O. Association of hypertension with generalized obesity in rural southwestern Nigeria. J Surg Med. 2020;4(3):177-81. doi: 10.28982/josam.593387
5. WooBaidal JA, Locks LM, Cheng ER, et al. Risk factors for childhood obesity in the first 1000 days: a systematic review. Am J Prev Med. 2016;50:761-79. doi: 10.1016/j.amepre.2015.11.012.
6. Bell KA, Wagner CL, Feldman HA, Shypailo RJ, Belfort MB. Associations of infant feeding with trajectories of body composition and growth. Am J Clin Nutr. 2017;106(2):491-8. doi: 10.3945/ajcn.116.151126.
7. Rzehak P, Oddy WH, Mearin ML, Grote V, Mori TA, Szajewska H, et al. Infant feeding and growth trajectory patterns in childhood and body composition in young adulthood. Am J Clin Nutr. 2017;106:568 80. doi: 10.3945/ajcn.116.140962.
8. Park SJ, Lee HJ. Exclusive breastfeeding and partial breastfeeding reduce the risk of overweight in childhood: A nationwide longitudinal study in Korea. Obesity Research & Clinical Practice. 2018;12(2):222-8. doi: 10.1016/j.orcp.2018.01.001.
9. Appleton J, Russell CG, Laws R, Fowler C, Campbell K, Denney-Wilson E. Infant formula feeding practices associated with rapid weight gain: A systematic review. Matern Child Nutr. 2018;14(3). doi: 10.1111/mcn.12602
10. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, et al. Effects of promoting increased duration and exclusivity of breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: a randomized trial. JAMA. 2013 March 13;309(10):1005–13. doi: 10.1001/jama.2013.167.
11. Hopkins D, Steer CD, Northstone K, Emmett PM. Effects on childhood body habitus of feeding large volumes of cow or formula milk compared with breastfeeding in the latter part of infancy. Am J Clin Nutr. 2015;102:1096–103. doi: 10.3945/ajcn.114.100529.
12. Centers for Disease Control and Prevention (CDC). NCHS Data Brief. October 2017; No. 288:4
13. Yılmazbaş P, Gökçay G. Childhood Obesity and Prevention. J Child. 2018;18(3):103-12. doi:10.5222/j. child.2018.59389.
14. Turkey National Demographic and Health Survey (TDHS) Report. 2018;143-6.
15. United Nations Children's Fund (UNICEF), Breastfeeding: A Mother's Gift, for Every Child, 2018;1-13.
16. Hanson LÅ. Session 1: Feeding and infant development breast-feeding and immune function. Proc Nutr Soc. 2007;66(3):384–96. doi: 10.1017/S0029665107005654.
17. Leung AKC, Sauve RS. Breast is best for babies. J Natl Med Assoc. 2005;97(7):1010–19. PMID: 16080672
18. Tharner A, Luijk MP, Raat H, Ijzendoorn MH, Bakermans-Kranenburg MJ, Henriette AM, et al. Breastfeeding and its relation to maternal sensitivity and infant attachment. J Dev Behav Pediatr. 2012;33(5):396–404. doi: 10.1097/DBP.0b013e318257fac3.
19. Casazza K, Pate R, Allison DB. Myths, presumptions, and facts about obesity. N Engl J Med. 2013;368(23):2236–7. doi: 10.1056/NEJMc1303009.
20. Martin RM, Kramer MS, Oken E, Rifas-Shiman SH, Thompson, Yang S, et al. Effects of promoting longer-term and exclusive breastfeeding on adolescent adiposity, blood pressure, and longitudinal growth trajectories: evidence from the PROBIT cluster-randomized trial. JAMA Pediatr. 2017;171(7). doi: 10.1001/jamapediatrics.2017.0698.
21. Zheng J-S, Liu H, Li J, Chen Y, Wei C, Shen G, et al. Exclusive breastfeeding is inversely associated with risk of childhood overweight in a large chinese cohort. The Journal of nutrition. 2014;144(9):1454–9. doi: 10.3945/jn.114.193664
22. Estévez-González M, del Pino AS, Henríquez-Sánchez P, Peña-Quintana L, Saavedra-Santana P.Breastfeeding during the first 6 months of life, adiposity rebound and overweight/obesity at 8 years of age. International Journal of Obesity. 2016;40(1):10–13. doi: 10.1038/ijo.2015.228
23. Van der Willik EM, Vrijkotte TG, Altenburg TM, Gademan MG, Kist-van Holthe J. Exclusively breastfed overweight infants are at the same risk of childhood overweight as formula fed overweight infants. Archives of Disease in Childhood. 2015;100(10):932–7. doi: 10.1136/archdischild-2015-308386
24. Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, et al. Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5 y: evidence from a large randomized trial. American Journal of Clinical Nutrition. 2007;86(6):1717–21. doi: 10.1093/ajcn/86.5.1717
25. O'Tierney PF, Barker DJ, Osmond C, Kajantie E, Eriksson JG. Duration of breast-feeding and adiposity in adult life. The Journal of Nutrition. 2009;139(2):422S–5S. doi: 10.3945/jn.108.097089
26. Tian Q, Gao X, Sha T, Chen,C, Li,L, He Q, et al. Effect of Feeding Patterns on Growth and Nutritional Status of Children Aged 0-24 Months: A Chinese Cohort Study. PLoS One. 2019;14(11). doi: 10.1371/journal.pone.0224968
27. Carling SJ, Demment MM, Kjolhede CL, Olson CM. Breastfeeding Duration and Weight Gain Trajectory in Infancy. Pediatrics, January 2015;Vol 135, no1, p 111-119. doi: 10.1542/peds.2014-1392
28. Pluymen LM, Wijga AH, Gehring U, Koppelman GH, Smit HA, Rossem L, et al. Early introduction of complementary foods and childhood overweight in breastfed and formula-fed infants in the Netherlands: the PIAMA birth cohort study. European Journal of Nutrition. 2018;57:1985–93. PMID: 29470690
29. Savino F, Fissore MF, Liguori SA, Oggero R. Can hormones contained in mothers' milk account for the beneficial effect of breastfeeding on obesity in children? Clin Endocrinol (Oxf). 2009;71:757–65. doi: 10.1111/j.1365-2265.2009.03585.x
30. Wallby T, Lagerberg D, Magnusson M. Relationship Between Breastfeeding and Early Childhood Obesity: Results of a Prospective Longitudinal Study from Birth to 4 Years. Breastfeed Med. Jan/Feb 2017;12:48-53. doi: 10.1089/bfm.2016.0124
31. Ma J, Qiao Y, Zhao P, Li W. Breastfeeding and childhood obesity: A 12-country study. Matern Child Nutr 2020 Jul;16(3):1-9. doi: 10.1111/mcn.12984.
32. Malekzadeh JM, Synaii S, Koor BE, Falsafian G, Nakhaie MR. Growth Indices of Exclusively Breastfed Until 6 Months Age and Formula-Fed Infants in Southwest of Iran. Int J Prev Med. 2019;10:207. doi: 10.4103/ijpvm.IJPVM_36_18
33. Kondolot M, Poyrazoğlu S, Horoz D, Borlu A, Altunay C, Balcı E, et al. Risk factors for overweight and obesity in children aged 2-6 years. J Pediatr Endocrinol Metab. 2017;30(5):499505. doi: 10.1515/jpem-2016-0358.
34. Li Ruoweli, Magadia, J, Fein SB. Risk of Bottle-feeding for Rapid Weight Gain During the First Year of Life. Archives of Pediatrics & Adolescent Medicine. 2012;166(5):431. doi: 10.1001/archpediatrics.2011.1665.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):947-951.
DOI: 10.28982/josam.808114

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Comparison of blood culture results and clinical biochemistry laboratory parameters in geriatric patients with regards to infective agents

Geriatrik hastalarda kan kültürü sonuçları ile klinik biyokimya laboratuvar parametrelerinin enfeksiyon ajanlarına göre karşılaştırılması

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Ethics Committee Approval: The Clinical ethics committee of Istanbul Maltepe University Faculty of Medicine approved the study protocol (2019/900/37). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolünü İstanbul Maltepe Üniversitesi Tıp Fakültesi Klinik Etik Kurulu onayladı (2019/900/37). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/23/2020
Yayın Tarihi: 23.11.2020

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Abstract

Aim: Bacterial infections can cause life-threatening sepsis and should be identified and managed accurately, especially in the elderly. We aim to examine the relationships between positive blood cultures, Gram staining pattern and biochemistry parameters, in particular, procalcitonin (ProCT) levels.

Methods: This was a single center retrospective study, in which patients with positive blood cultures detected in Maltepe University Faculty of Medicine Research and Education Hospital were included. Two groups were formed according to age and evaluated with regards to bacterial Gram staining and biochemistry laboratory findings. Group 1 consisted of patients under 65 years of age (n=69) and Group 2 included those over 65 years of age (n=198).

Results: Two hundred and sixty-seven episodes of bacteremia (Gram-negative: 49.43%, Gram-positive bacteremia: 50.56%) were evaluated in two groups. CRP values, lymphocyte and thrombocyte counts, creatinine, AST, ALT, albumin, CRP/albumin ratio values were similar between two groups (P>0.05 for all), while leukocyte counts, neutrophil counts and BUN values were lower in group 1 (P=0.020, P=0.020 and P<0.001 respectively) and ProCT levels were lower in group 2 (P=0.049). ProCT values (independent of age) had significantly increased in patients with Gram-negative bacteremia (P<0.001 in both group 1 and 2).

Conclusion: ProCT measurement can be helpful as a distinguishing biomarker in different bloodstream infections, regardless of age.

Keywords: Bacteremia, Elderly, Procalcitonin

Öz

Amaç: Bakteriyel enfeksiyonlar yaşamı tehdit ederek sepsise neden olabilir ve özellikle yaşlılarda doğru bir şekilde tanı konmalı ve yönetilmelidir. Çalışmamızda kan kültürlerinde üreme olan hastaların, Gram boyama paterni ve biyokimya parametrelerinin, özellikle prokalsitonin (ProCT) seviyeleri temelinde incelenmesi amaçlanmıştır.

Yöntemler: Tek merkezli retrospektif bu çalışmada, Maltepe Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi'nde kan kültürü pozitif olan hastalar çalışmaya dahil edildi. Altmış beş yaş altı genç grup (n=69) ve 65 yaş üstü yaşlı grup (n=198), bakteriyel Gram boyama ve biyokimya laboratuvar bulgularına göre tanımlandı ve değerlendirildi.

Bulgular: 267 bakteriyemi epizodu (Gram negatif: %49,43 ve Gram pozitif: %50,56) iki ayrı yaş grubunda değerlendirildi. CRP değerleri, lenfosit ve trombosit sayıları, kreatinin, AST, ALT, albümin, CRP/albümin oranı değerleri iki grup arasında istatistiksel olarak anlamlı bulunmazken (P>0,05), lökosit sayıları (P=0,020), nötrofil sayıları (P=0,020) ve BUN değerleri (P<0,001) yaşlı grupta yüksek, ProCT seviyeleri ise düşük (P=0,049) olarak saptandı. ProCT değerleri (yaştan bağımsız olarak) Gram-negatif bakteriyemili hastalarda anlamlı olarak yüksek olarak ölçüldü (her iki grup için de P<0,001).

Sonuç: Prokalsitonin ölçümü, yaşa bakılmaksızın farklı kan dolaşımı enfeksiyonlarında ayırt edici bir biyobelirteç olarak yardımcı olabilir.

Anahtar kelimeler: Bakteriyemi, Yaşlı, Prokalsitonin

How to cite/Atıf için: Karadeniz A, Sıtar ME, İpek BÖ. Comparison of blood culture results and clinical biochemistry laboratory parameters in geriatric patients with regards to infective agents. J Surg Med. 2020;4(11):947-951.

Introduction

Imaging modalities and medical laboratory techniques are used to assist clinicians in diagnosis, after anamnesis and physical examination. Clinical laboratories are one of the key components in evidence-based medicine. They make a great contribution to medical decisions such as patient follow-up, visit frequency, definite diagnosis, length of hospital stay, discharge, surgery timing, emergency triage, risk assessment, prognostication, therapy, pharmaceutical dose arrangement and prediction of disease course in the general health system [1] . In our increasingly aging world population, due to low fertility and high longevity rates, the duty of laboratories in the health system will undoubtedly increase.

After entering the medical literature in the 1970s, Procalcitonin (ProCT) began to attract attention at an increasing speed [2]. Assicot et al. expressed the basis of clinical utility of ProCT and its substantial effect on bacterial septicemia in the early '90s, which was a pioneering research [3]. In today's modern world, ProCT is frequently used in the differentiation of infectious agents, noninfectious inflammatory states and monitoring antibacterial therapy [4,5]. As it is known, clinical courses of elderly patients are more uncertain than younger ones. Extraordinary symptoms related to infection may be described in cases of admission to the emergency room or the outpatient clinic, or the patients may not show any symptoms at all. Early diagnosis of the diseases, including sepsis, is of immense importance for the course of the disease. Interpretation of infection biomarkers (including ProCT), which are evaluated in the clinical diagnostic laboratories, may differ in elderly and young patients, just like clinical follow-up. Increased glucose intolerance, obesity, disability, sedentary lifestyle, polypharmacy, musculoskeletal comorbidities, absence or exclusion in reference interval studies, and/or unbalanced diet can be counted as the main reasons for this burden in elderly [6]. These changes in geriatric populations undoubtedly affect the laboratory test results directly, and the interpretation of the results indirectly. ProCT evaluation may provide valuable information at the onset of septicemia in differentiating Gram staining and fungal infections in non-geriatric patients [7]. As examples of studies on this subject, Charles et al., Yan et al. and Friend et al. concluded that ProCT levels were higher in Gram-negative bacteremia [7-9]. It can be stated that ProCT demonstrated encouraging results for pre-diagnosis of Gram-negative bacteremia [10]. Numerous studies have been found in current medical literature, including identification of the infectious agents and determination of clinical decision thresholds for ProCT. However, the scarcity of studies involving geriatric population and giving clear results is remarkable. When the problem regards the elderly, the scope changes significantly. It has low sensitivity for infection presence analysis (24%) and low discrimination rate in local infections in geriatrics [11,12]. In a study investigating the role of serum inflammatory markers in the diagnosis of sepsis, the positive predictive value of ProCT was 58 percent for elderly patients [13]. Based on previous information, this present study was planned to examine the relationships between length of hospital stay, invasive procedures, presence of a catheter, positive blood cultures, Gram staining pattern, C reactive protein (CRP), complete blood counts (CBC), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, albumin, and CRP/albumin ratio results. It was designed to compare the aforementioned parameters with ProCT results and its feasibility at the onset of infection.

Materials and methods

This retrospective observational data mining study was conducted by evaluation of laboratory information system and hospital information system of Istanbul Maltepe University Faculty of Medicine Research and Education Hospital, from June 2016 to December 2019. Patients with positive blood cultures, over 18 years of age, who were evaluated by infectious diseases specialists, were recruited for this current study. The study included two groups: The young group (Group 1, n=69, 34 males, 35 females) under 65 years of age and the geriatric group (Group 2, n=198, 105 females, 93 males) over 65 years of age (Figure 1). The Clinical Ethics Committee of Istanbul Maltepe University, Faculty of Medicine approved the study protocol (2019/900/37).

Phlebotomy procedure and blood analysis

After venipuncture, phlebotomies were performed, serum tubes were held in an upright position for at least 30 minutes and then centrifuged for at least 15 minutes at 2500 RPM. Serum ProCT, CRP, BUN, creatinine, AST, ALT, ferritin, and albumin levels were rapidly measured using Siemens Dimension RxL Max®(Germany), Roche Hitachi Modular e170® (Switzerland), Roche Cobas E411® (Switzerland) and Abbot Architect i1000SR® (United States of America) devices according to manufacturer's instructions. Whole blood tubes were gently inverted seven - eight times in room temperature and then complete blood count analysis was performed using Sysmex XT-1800® (Japan) and Sysmex XT-2000® (Japan) devices. At least two different levels of internal quality control materials were studied for each device and analytical parameter prior to measurements, and the results were followed according to Westgard rules [14]. In addition to internal quality control tests, periodic external quality tests were also studied for each analytical test and their suitability was documented. For culture analysis, blood samples were collected from patients during febrile episodes and/or in case of severe suspicion of bacteremia. At least two sets of blood samples were obtained from different peripheral veins and at least one of them was from a central venous catheter if the patient had one. BioMérieux BacT / ALERT 3D® (France) automatic blood culture system was used for blood cultures. Bacteremia was defined as the isolation of the bacteria from at least two or more bottles of blood cultures with associated signs and symptoms of systemic infection. Positive blood cultures were evaluated by Gram stain, and 5% sheep blood agar or MacConkey agar were used for incubation at 35 °C for 24 hours. Bacteria were identified using standard techniques of bacteriology. Recurrent results of patients with the same bacterial growth in repeating blood cultures were not included in this study. Blood culture examinations and measurements of infection biomarkers were performed independently of each other in different areas. Blood collection and all other analytical procedures were performed according to the requirements of

Istanbul Maltepe University Faculty of Medicine Education and Research Hospital Quality Management.

Statistical analysis

All statistical data analyses were done with Microsoft Excel 2010® (Microsoft Corporation, USA) and SPSS version 21.0® (SPSS Inc. Chicago, IL, USA). After determining the mean, median and standard deviations of the results, unpaired t-tests were used for comparing two groups (based on age and gram staining) because both groups consisted of separate patients [15]. Demographic data of the patients were presented numerically, and risk analyses were calculated as percentages. Chi square independence test was used to analyze categorical variables. $P<0.05$ was considered statistically significant.

Results

Among Group 1, the number of patients with Gram-negative and Gram-positive bacteremia were 38 and 31, respectively. In Group 2, these values were 94 and 104, respectively (Figure 1). To examine the relationship between age and Gram staining pattern, chi-square test was performed, which yielded insignificant results ($P=0.27$). In both age groups, *Enterobacteriaceae* species were found more frequently in terms of Gram-negative organisms grown in blood culture (Figure 1). *Staphylococcus* species were more frequent in laboratory data and culture analysis of patients with Gram-positive bacteremia. Among the staphylococcus spp., it is noteworthy that coagulase negative bacteria are detected in blood cultures more than others. CRP-values, lymphocyte and thrombocyte counts, creatinine, AST, ALT, albumin, CRP/albumin ratio values were similar between Groups 1 and 2 ($P>0.05$ for all, Table 1), while leukocyte counts, neutrophil counts and BUN values were lower in Group 1 ($P=0.020$, $P=0.020$ and $P<0.001$ respectively) and ProCT levels were lower in Group 2 ($P=0.049$) (Table 1). When patients younger than 65 years of age were compared according to Gram staining pattern, there was no difference in CRP values ($P=0.639$) and leukocyte count ($P=0.370$), while a statistically significant difference was detected in ProCT results ($P<0.001$, Table 2).

Table 1: Measured biochemical parameters of all patients and their comparison

Test parameter	Group 1 (<65 years of age)	Group 2 (≥65 years of age)	*P*-value
ProCT mean (SD) (ng/mL)	20.1 (32.8)	12.9 (23.4)	0.049*
CRP mean (SD) (mg/L)	15.1 (8.6)	12.6 (13.1)	0.187
Leukocyte count mean (SD) (per µL)	9,376 (6,592)	11,615 (6,915)	0.020*
Neutrophil count mean (SD) (per µL)	7,380 (5,593)	9,414 (6,492)	0.020*
Lymphocytes count mean (SD) (per µL)	1,379 (2,333)	1,297 (955)	0.685
Thrombocyte count mean (SD) (per µL)	183,742 (141,465)	201,959 (118,813)	0.299
BUN mean (SD) (mg/dL)	30.1 (24.8)	45.6 (34,3)	<0.001**
Creatinine mean (SD) (mg/dL)	2.1 (4.9)	1.7 (1.8)	0.331
AST mean (SD) (IU/L)	75 (97)	129 (434)	0.307
ALT mean (SD) (IU/L)	71 (106)	82 (181)	0.634
Albumin mean (SD) (g/dL)	2.54 (0.52)	2.53 (0.54)	0.893
CRP/Albumin ratio mean (SD)	6.4 (4.3)	5.3 (4.8)	0.094

Table 2: ProCT (Procalcitonin), CRP (C Reactive Protein) and leukocyte count results according to age groups and gram staining pattern of cases with bacteremia

Test parameter	Group 1 (<65 years of age)			Group 2 (≥65 years of age)		
	Patients with Gram negative bacteremia	Patients with Gram positive bacteremia	*P*-value	Patients with Gram negative bacteremia	Patients with Gram positive bacteremia	*P*-value
ProCT mean (SD) (ng/mL)	31.3 (37.8)	6.01 (16.87)	<0.001**	22.4 (29.8)	4.5 (9.8)	<0.001**
CRP mean (SD) (mg/L)	14.6 (7.9)	15.7 (9.4)	0.639	11.05 (8.08)	13.9 (16.3)	0.168
Leukocyte count mean (SD) (per µL)	8,742 (6,598)	10,173 (6,605)	0.370	12,117 (8075)	11,166 (5,686)	0.336

For gram staining patterns in the geriatric population, similar to that in the group below 65 years of age, there was a statistically significant difference between ProCT values ($P<0.001$), while CRP values ($P=0.168$) and leukocyte counts ($P=0.336$) were similar (Table 2). When ProCT values were evaluated independent of age, a significant increase was found in patients with Gram-negative bacteremia ($P<0.001$) (Table 3). However, in this age-independent evaluation, no significant difference was found between CRP ($P=0.431$), leukocyte count ($P=0.829$) and CRP / albumin ratio ($P=0.119$) according to gram staining pattern (Table 3). When ProCT results of patients with Gram-negative bacteremia were evaluated by age, there was no statistically significant difference between Groups 1 and 2 ($P=0.148$, Figure 2).

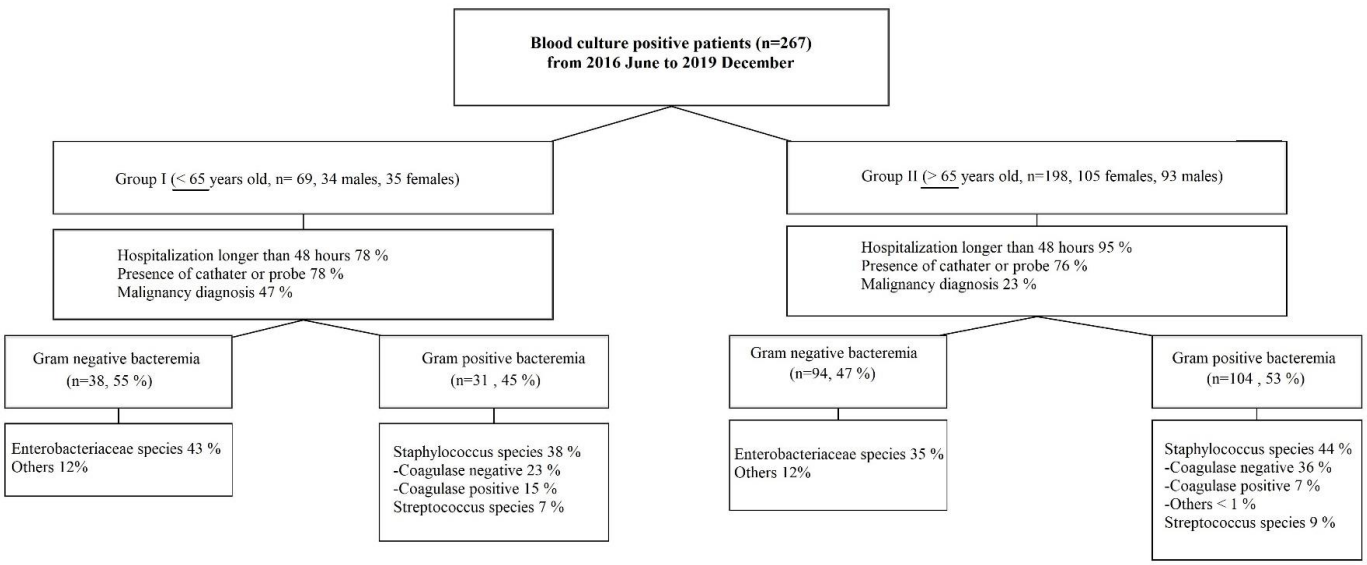

Figure 1: Blood culture results of both groups and their Gram staining distinctions

Table 3: ProCT (Procalcitonin), CRP (C reactive protein), leukocyte count, and CRP / albumin ratio results of all patients based on Gram staining pattern

Test parameter	Gram negative bacteremia (49.43 %)	Gram positive bacteremia (50.56 %)	*P*-value
ProCT mean (SD) (ng/mL)	25.1 (32.4)	4.9 (11.8)	<0.001**
CRP mean (SD) (mg/L)	13.9 (8.5)	12.6 (14.9)	0.431
Leukocyte count mean (SD) (per μL)	11,120 (7,768)	10,938 (5,899)	0.829
CRP / Albumin ratio mean (SD)	6.1 (4.3)	5.1 (5.1)	0.119

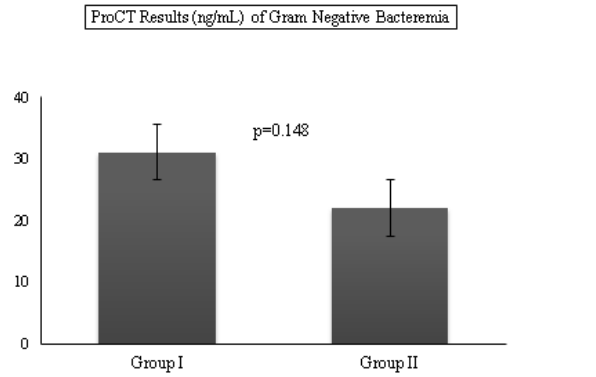

Figure 2: ProCT (Procalcitonin) results of two groups with Gram-negative bacteremia

Discussion

It is especially important to get an idea about the clinical course of elderly patients. Evaluation of blood culture results obtained during febrile periods in patients with a suspected serious infection is vital. Etiological agent variety can be challenging for the clinicians [16]. The time to start antibiotic treatment, the effectiveness of the dose administered, the type of the infective agent and the patient's response to treatment are the determining factors in the clinical course. In total, 267 episodes of bacteremia were evaluated in our study. Gram-negative bacteremia was identified in 49.43% (n=132), and Gram-positive bacteremia was identified in 50.56% (n=135) of these cases. There are different percentage rates for different patient groups in previous literature. One of the studies from our country revealed that 55.4% of 807 bacteremia episodes was caused by Gram-positive and 44.6% were caused by Gram-negative bacteria [17]. Daskalaki et al. [18] investigated bacteremia among renal transplant recipients, Prabhash et al. [19] studied infection in cancer patients and these studies confirmed that even if vastly different patient groups were included in the studies, bacterial growth outcomes were quite similar to our results.

In this current study, the fact that ProCT values were significantly higher in patients with Gram-negative bacteremia in both age groups was important. Li et al. evaluated ProCT levels in patients with sepsis and suspected sepsis, and found that ProCT levels were significantly increased in Gram-negative sepsis compared to Gram-positive or fungal sepsis [20]. Lin et al. [21] investigated ProCT levels in positive blood culture results in febrile patients with burn, and concluded that ProCT levels were significantly higher in Gram-negative infections. This finding is consistent with other relevant literature, as well [7,22]. However, the same findings could not be reached regarding CRP values and leukocyte counts. Liu et al. evaluated serum ProCT and CRP levels in patients with sepsis and found that serum ProCT levels were significantly elevated in Gram-negative sepsis compared to Gram-positive sepsis, but they did not detect a difference in CRP levels [23]. Bilgili et al. [24] evaluated septic patients with bacteremia in the intensive care unit to report significant differences in terms of CRP and ProCT in the Gram-negative group, but similar leukocyte levels. The fact that this result does not change by age should also be considered an important finding for the current literature. In Gram-negative bacteremia, which is more severe than Gram-positive bacteremia, higher ProCT values will enable clinicians to take early precautions. This parameter, which will contribute to the early detection of Gram-negative sepsis in intensive care units, will provide a chance for more effective and aggressive treatment to the patients. It will also provide valuable contributions during follow-up of patients' response to treatment, apart from CRP-values and leukocyte counts.

Limitations

This study had some notable restrictions. First, the number of young patients was lower and studies with larger cohorts are needed. This can be rationally explained, as the immune status of young individuals is stronger, and they rarely encounter comorbid diseases. Current study involved blood culture positivity encountered for about three and a half years. The number of patients that will be recruited for future studies can be increased, including the patient groups from different hospitals & regions. In addition, more comprehensive data can be obtained by increasing the biomarker diversity to be studied in clinical laboratories.

Conclusions

High serum ProCT values are highly valuable for Gram-negative bloodstream infections. It should always be kept in mind that physicians are advised to order less but effective laboratory tests for the elderly to avoid conflicting results. Even if there are some uncertainties, ProCT is an ideal marker, regardless of patient age.

References

1. Hallworth MJ. That '70%' claim again…. Annals of clinical biochemistry. 2018;55(4):517-8.
2. Sitar ME, Ipek BO, Karadeniz A. Procalcitonin in the diagnosis of sepsis and correlations with upcoming novel diagnostic markers. Int J Med Biochem. 2019;2(3):132-40.
3. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet (London, England). 1993;341(8844):515-8.
4. Meisner M. Update on procalcitonin measurements. Annals of laboratory medicine. 2014;34(4):263-73. Epub 2014/07/02. doi: 10.3343/alm.2014.34.4.263.
5. Eddy F, Joyce A, Dryden M, Saeed K. Procalcitonin in Older Patients; Promoting Antibiotic Stewardship in Complex Patients. J Infect Non Infect Dis. 2015;1(002).
6. Vásárhelyi B, Debreczeni LA. Lab Test Findings in the Elderly. EJIFCC. 2017;28(4):328-32.
7. Charles PE, Ladoire S, Aho S, Quenot J-P, Doise J-M, Prin S, et al. Serum procalcitonin elevation in critically ill patients at the onset of bacteremia caused by either Gram negative or Gram positive bacteria. BMC infectious diseases. 2008;8(1):38.
8. Yan ST, Sun LC, Jia HB, Gao W, Yang JP, Zhang GQ. Procalcitonin levels in bloodstream infections caused by different sources and species of bacteria. The American journal of emergency medicine. 2017;35(4):579-83.
9. Friend KE, Burgess JN, Britt RC, Collins JN, Weireter LN, Novosel TJ, et al. Procalcitonin elevation suggests a septic source. The American Surgeon. 2014;80(9):906-9.
10. Lai L, Lai Y, Wang H, Peng L, Zhou N, Tian Y, et al. Diagnostic Accuracy of Procalcitonin Compared to C-Reactive Protein and Interleukin 6 in Recognizing Gram-Negative Bloodstream Infection: A Meta-Analytic Study. Disease markers. 2020;2020.
11. Stucker F, Herrmann F, Graf JD, Michel JP, Krause KH, Gavazzi G. Procalcitonin and infection in elderly patients. Journal of the American Geriatrics Society. 2005;53(8):1392-5.
12. Lai CC, Chen SY, Wang CY, Wang JY, Su CP, Liao CH, et al. Diagnostic value of procalcitonin for bacterial infection in elderly patients in the emergency department. Journal of the American Geriatrics Society. 2010;58(3):518-22.
13. Talebi-Taher M, Babazadeh S, Barati M, Latifnia M. Serum inflammatory markers in the elderly: are they useful in differentiating sepsis from SIRS? Acta Medica Iranica. 2014:438-42.
14. Klee GG, Westgard JO. Quality management. Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics-E-Book.90.
15. Kul S. Uygun Istatistiksel Test Seçim Kılavuzu/Guideline For Suitable Statistical Test Selection. Plevra Bülteni. 2014;8(2):26.
16. Arabacı Ç, Kutlu O. Evaluation of microorganisms isolated from blood cultures and their susceptibility profiles to antibiotics in five years period. Journal of Surgery and Medicine. 2019;3(10):729-33.
17. Demirbakan H, Dağlar D, Yıldırım Ç, Öztürk F, Öngüt G, Yaman M, et al. Kan kültürlerinden izole edilen bakteriler ve antibiyotiklere duyarlılıkları. Türk Mikrobiyol Cem Derg. 2005;35(3):183-8.
18. Daskalaki E, Koukoulaki M, Bakalis A, Papastamopoulos V, Belesiotou E, Perivolioti E, et al. Blood stream infections in renal transplant recipients: a single-center study. Transplantation proceedings. 2014;46(9):3191-3. Epub 2014/11/26. doi: 10.1016/j.transproceed.2014.10.033.

19. Prabhash K, Medhekar A, Ghadyalpatil N, Noronha V, Biswas S, Kurkure P, et al. Blood stream infections in cancer patients: a single center experience of isolates and sensitivity pattern. Indian journal of cancer. 2010;47(2):184-8. Epub 2010/05/08. doi: 10.4103/0019-509x.63019.
20. Li S, Rong H, Guo Q, Chen Y, Zhang G, Yang J. Serum procalcitonin levels distinguish Gram-negative bacterial sepsis from Gram-positive bacterial and fungal sepsis. J Res Med Sci. 2016;21:39-. doi: 10.4103/1735-1995.183996.
21. Lin J-C, Chen Z-H, Chen X-D. Elevated serum procalcitonin predicts Gram-negative bloodstream infections in patients with burns. Burns. 2020;46(1):182-9.
22. Wang D, Tao X, Guo W, Liu H, Cheng S, Wang J. The diagnostic ability of procalcitonin to differentiate Gram-negative bacteria from Gram-positive bacteria and fungal bloodstream infections in critically ill patients. European Journal of Inflammation. 2019;17:2058739219841469.
23. Liu H, Zhang M, Guo J, Li J, Su L. Procalcitonin and C-reactive protein in early diagnosis of sepsis caused by either Gram-negative or Gram-positive bacteria. Irish Journal of Medical Science (1971-). 2017;186(1):207-12.
24. Bilgili B, Haliloglu M, Aslan MS, Sayan I, Kasapoglu US, Cinel I. Prokalsitoninin Bakteriyemik Gram Negatif Sepisisin Gram Pozitif Sepsisten Ayrımında Tanısal Doğruluğu/Diagnostic Accuracy of Procalcitonin for Differentiating Bacteraemic Gram-Negative Sepsis from Gram-Positive Sepsis. Turkish Journal of Anaesthesiology and Reanimation. 2018;46(1):38-44.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):952-955.
DOI: 10.28982/josam.736881

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Can hematologic inflammation markers be the indicator of early pregnancy loss?

Hematolojik enflamasyon belirteçleri erken gebelik kaybının göstergesi olabilir mi?

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Ethics Committee Approval: Noninvasive Clinic Ethical Committee of Bozok University (Decision no: 2017-KAEK-189_2019.11.13_01, date: 11/13/2019) has approved the study protocol. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolünü Bozok Üniversitesi Noninvazif Klinik etik Kurulu (Karar no: 2017-KAEK-189_2019.11.13_01, tarih: 13.11.2019) onayladı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Pregnancy loss occurs in 50% of human pregnancies and is the most common complication of early pregnancy. The aim of this study is to evaluate the relationship between early pregnancy loss and inflammation with hematological markers.

Methods: This case-control study was carried out between January 2016-March 2019 in our clinic to evaluate the cases of early pregnancy loss. The early pregnancy loss group consisted of 94 patients, while the control group consisted of 104 women giving normal birth. Demographic data and complete blood count results of the groups were obtained from the patient files and hospital information management systems.

Results: There were no statistically significant differences in terms of age and body mass index between the two groups. Pregnancy losses in the abortion group occurred at an average of 9.03 (3.62) weeks. In the abortus group, platelet count (P=0.003), NLR (P=0.036), PLR (P=0.032) and plateletcrit (P=0.007) were higher, while LMR (P=0.034) was lower, compared to the control group.

Conclusions: Hematological inflammation parameters are easy to perform and cost-effective examinations. In our study, the success of these parameters to predict early pregnancy loss was evaluated, and it was found that although there are significant differences in hematological inflammation markers between the groups, the sensitivity and specificity of these markers are low.

Keywords: Early pregnancy loss, Inflammation, Hematologic markers

Öz

Amaç: İnsan gebeliklerinin yaklaşık %50'sinde gebelik kaybı meydana gelmektedir ve erken gebeliğin en sık görülen komplikasyonudur. Bu çalışmanın amacı, erken gebelik kaybı ile inflamasyon arasındaki ilişkiyi hematolojik belirteçler ile değerlendirmektir.

Yöntemler: Çalışma Ocak 2016 / Mart 2019 tarihleri arasında kliniğimizde gerçekleşmiş olan erken gebelik kaybı olgularını değerlendiren, olgu-kontrol çalışmasıdır. Erken gebelik kaybı grubu 94 hasta, kontrol grubu ise 104 miadında doğum yapmış kadından oluşturuldu. Grupların demografik verilerine ve tam kan sayımı sonuçlarına hasta dosyaları ve hastane bilgi yönetim sistemi taranarak ulaşıldı.

Bulgular: İki grup arasında yaş ve vücut kitle indeksi açısından istatistiksel olarak anlamlı bir fark yoktu. Abortus grubunda gebelik kayıpları ortalama 9,03 (3,62) haftada gerçekleşmiştir. Abortus grubunda kontrol grubuna kıyasla platelet sayısı (P=0,003), NLR (P=0,036), PLR (P=0,032) ve plateletkrit (P=0,007) yüksek olarak saptanmıştır. Diğer taraftan, LMR (P=0,034) abortus grubunda düşük olarak saptanmıştır.

Sonuçlar: Hematolojik enflamasyon parametreleri kolay ulaşılabilen ve maliyet olarak ucuz tetkiklerdir. Çalışmamızda bu parametrelerin erken gebelik kaybını öngörme başarısı değerlendirilmiş ve sonuç olarak, gruplar arasında hematolojik inflamasyon belirteçlerinde anlamlı farklılıklar olmasına rağmen, bu belirteçlerin duyarlılık ve özgüllüğünün düşük olduğu bulunmuştur.

Anahtar kelimeler: Erken gebelik kaybı, Enflamasyon, Hematolojik belirteçler

How to cite/Atıf için: Onat T, Kırmızı DA, Çaltekin MD, Başer E, Yalvaç ES. Can hematologic inflammation markers be the indicator of early pregnancy loss? J Surg Med. 2020;4(11):952-955.

Introduction

Early pregnancy loss (abortus) is defined as loss of pregnancy before the 20th gestational week [1]. The World Health Organization defined abortus as pregnancy losses in which the fetus weighed less than 500 gr. It is the most common complication in the early pregnancy period [1]. Its incidence in clinically diagnosed pregnancies is around 8-20% [2]. Abortus occurs mostly in the first 12 weeks [3]. Early pregnancy loss reduces in women who gave birth. Considering all pregnancy losses, only about 50% of fertilized oocytes result in a live birth [4]. The most important risk factor is maternal age. Increasing maternal age increases also the risk of abortus and it reaches about 80% at the age of 45 [5]. Having a miscarriage history, smoking, and a body mass index of <18.5 and >25 kg/m2 can be deemed as other risk factors [6-8]. In about half of the abortus cases, chromosome anomalies were found as a cause [9].

Inflammation was most identified in the pathological evaluation of abortus materials [3]. On the other hand, inflammation in the early stages of pregnancy, in particular, is deemed as one of the physiological features of pregnancy [10]. The severity of inflammation plays an active role in the process to progress to a successful implantation or abortus [10]. In the etiology of abortus, it is not known exactly at what stage and how inflammation is effective.

Inflammation plays a key role in many diseases today. Therefore, many studies are carried out on the evaluation of inflammation. Direct measurement of inflammatory mediators, neutrophil and lymphocyte count, and parameters such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) are among the methods used. Studies show that these markers have prognostic value in coronary artery disease, ulcerative colitis, and preeclampsia [11-13]. In addition, these markers are used for predicting mortality and morbidity in various types of cancer [14,15]. These markers were additionally studied to predict obstetric complications such as preeclampsia, intrauterine growth retardation, and preterm delivery [16-19].

This study aims to evaluate the relationship between early pregnancy loss and inflammation with hematological markers.

Materials and methods

This retrospective case-control study was carried out by evaluating the files of the abortus cases that occurred in our clinic between January 2016-March 2019 and hospital information management systems after obtaining ethics approval from the Noninvasive Clinic Ethical Committee of Bozok University (Decision no. 2017-KAEK-189_2019.11.13_01, dated 13/11/2019).

Patients with chronic diseases (thyroid, kidney, liver, type I-II diabetes mellitus), acute-chronic inflammatory diseases, uterine anomalies which cause abortus, along with those who became pregnant with assisted reproductive techniques were excluded from the study. Patients who became pregnant spontaneously and gave normal birth were included in the control group.

Age, body mass index (BMI), gravida, parity and first trimester hematological parameters (leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, platelet, plateletcrit and average platelet volume) of both groups were noted. Neutrophil-leukocyte ratio (neutrophil count/leukocyte count), platelet-lymphocyte ratio (platelet count/lymphocyte count), and lymphocyte-monocyte ratio (lymphocyte count/monocyte count) were calculated.

Statistical analysis

Analysis of the study data was performed using the SPSS 20.0 program. $P<0.05$ was considered statistically significant. Histogram and Kolmogorov-Smirnov test were used to evaluate the distribution of data. Numerical data were shown as mean (standard deviation). Correlation analyses of the data were made by Pearson or Spearman test, as needed. The diagnostic cut-off values of the tests were determined by Receiver Operations Curve (ROC) analysis.

Results

A total 203 pregnant women were included in our study, 94 of which constituted the abortus group, and 109 age- and BMI-compatible pregnant women constituted the control group. The mean age of the pregnant women included in our study was 30.7 (6.37) years, and their mean BMI values were 25.79 (1.61) kg/m^2 (Table 1). Pregnancy losses in the abortus group occurred in an average of 9.03 (3.62) weeks. There was no difference between the abortus and control groups in terms of age, BMI, gravida, parity, leukocyte count, neutrophil count, lymphocyte count, monocyte count, mean platelet volume (MPV), and hemoglobin values (Table 2) ($P>0.05$). In the abortion group, platelet count ($P=0.003$), NLR ($P=0.036$), PLR ($P=0.032$) and plateletcrit ($P=0.007$) were higher compared to the control group, while LMR ($P=0.034$) was lower. The optimal ROC cut-off value of plateletcrit for abortus was calculated as 0.26 with a sensitivity of 60.6% and a specificity of 52.3% (AUC: 0.609) (Figure 1, Table 3). The optimal ROC cut-off value of platelet for abortus was calculated as 227.0 (x10^3/μL) with a sensitivity of 71.3% and a specificity of 47.7% (AUC: 0.621) (Figure 1, Table 3).

Table 1: Demographic features

Parameters	All participants (n:203)
Age	30.7 (6.37)
Average abortus period (week)	9.03 (3.62)
BMI (kg/m^2)	25.79 (1.61)
Gravida	2.86 (1.48)
Parity	2.00 (1.20)
Leukocyte (x10^3/μL)	9.47 (2.49)
Hemoglobin (gr/dl)	12.4 (1.36)
Platelet (x10^3/μL)	249.0 (72.0)

Table 2: Comparison of variables between groups

	Abortus group (n:94)	Control group (n:109)	*P*-value[∝]
Age (year)	31.51 (6.72)	30.00 (5.99)	0.097
VKİ (kg/m^2)	25.89 (1.62)	25.71 (1.61)	0.341
Gravidity	3.05 (1.58)	2.69 (1.67)	0.120
Parity	1.41 (1.13)	1.58 (1.24)	0.415
Leukocyte (x10^3/ μL)	9.37 (2.68)	9.56 (2.30)	0.266
Neutrophil (x10^3/ μL)	6.52 (2.56)	6.79 (1.86)	0.102
Lymphocyte (x10^3/ μL)	2.10 (0.60)	2.08 (0.61)	0.818
Monocyte (x10^3/ μL)	0.57 (0.16)	0.61 (0.16)	0.193
Hemoglobin (gr/dl)	12.56 (1.45)	12.30 (1.27)	0.090
Platelet (x10^3/ μL)	263.55 (68.70)	237.04 (72.87)	0.003
Plateletcrit (%)	0.27 (0.06)	0.25 (0.07)	0.007
MPV (fl)	10.45 (0.99)	11.51 (8.99)	0.175
NLR	3.46 (2.48)	3.45 (1.14)	0.036
LMR	3.49 (1.37)	3.79 (1.22)	0.034
PLR	134.13 (48.11)	121.31 (45.77)	0.032

[∝] Mann-Whitney U test, MPV: Mean platelet volume, NLR: Neutrophil-leukocyte rate, LMR: Lymphocyte-monocyte rate, PLR: Platelet- lymphocyte rate

Table 3: Sensitivity and specificity of hematological markers

Parameters	Area Under Curve	*P*-value	Sensitivity (%)	Specificity (%)
Platelet	0.621	0.003	71.3	47.7
Plateletcrit	0.609	0.007	60.6	52.3
LMR	0.414	0.034	52.3	31.9
NLR	0.414	0.036	56.4	33.1
PLR	0.587	0.032	59.6	51.4

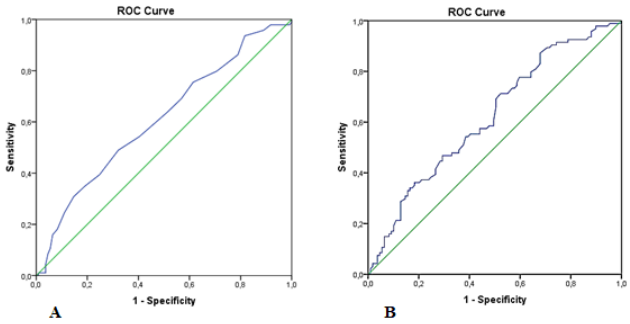

Figure 1: Diagnostic performance of plateletcrit (A) and platelet (B) in prediction of early pregnancy loss

Discussion

Abortus is the most common pregnancy complication seen in the early pregnancy period. With the advancing health services and technology, the frequencies of severe hemorrhage and infection have decreased [20]. In the evaluation of abortus materials, inflammation was shown in the decidua in the implantation area [21]. Investigating the changes of systemic inflammation markers in abortus cases, our study was planned to seek an answer to whether these markers can be used in the diagnosis of failed pregnancy in the early pregnancy period. We found that platelet count, plateletcrit, NLR, PLR, and LMR values were significantly different.

Since platelets also function as acute-phase reactants in the human body, an increased number of platelets and changes in platelet markers can be an indication of inflammation [22]. However, platelet functions can also change physiologically. Platelets play a role in the development of spiral arteries to adapt to pregnancy [23]. We found that platelet count and plateletcrit were significantly higher in the abortus group. However, in terms of MPV, there was no significant difference between the two groups. There is contradictory information on this subject in the literature. Kara et al. [24] compared spontaneous abortus and healthy pregnancy patients and found that MPV were similar, while the platelet count of the abortus was significantly higher. In addition to platelet counts, Kaplanoglu et al. [25] found a difference in MPV, as well. Eroglu et al. [25], on the other hand, suggested that MPV cannot be used as a diagnostic test. In the light of these results, we think that the platelet count increases in response to inflammation as an acute phase reactant. MPV directly shows platelet functions. Large platelets are more active in proinflammatory and prothrombotic aspects. In abortus cases, large platelets are thought to migrate to the damaged area through the circulation in parallel to inflammation and MPV is thought to decrease consequently [26].

Increased plateletcrit and PLR have been shown to affect the prothrombotic and proinflammatory processes [27]. Plateletcrit and PLR, therefore, have been studied in many obstetric complications. Yücel et al. [16] found that the rate of plateletcrit decreased significantly in severe preeclampsia patients. In our opinion, the fact that the severe preeclampsia cases are high in this study leads to a decrease in the platelet counts, which causes MPV to increase and plateletcrit to decrease significantly. However, in our study, we observed that with the increase of platelet count parallel to inflammation, MPV decreased and plateletcrit increased significantly. Ata et al. [28] obtained similar results in their study. Again, a statistically significant moderate positive correlation between plateletcrit and PLR and a highly positive correlation between plateletcrit and platelet count found in our study help explain this situation. We think that PLR, on the other hand, increases as an indicator of inflammation.

NLR and LMR, other hematologic inflammatory markers, were significantly different between the two groups in our study. LMR has been studied in the recent years to predict the success of prognosis and treatment, especially in several types of cancer [14, 29]. Based on our research in the literature, we found that the relationship between LMR and abortus was not priorly investigated. Therefore, ours is the first study evaluating LMR along with other parameters. The fact that inflammation indicators, NLR and LMR, were significantly higher in abortus cases supports the inflammatory markers.

It is not yet clear whether the inflammatory process is the cause or the consequence. The fact that anti-inflammatory therapy does not increase live birth rates suggests that inflammation is a consequence [30].

Limitations

The retrospective and single-center nature of our study, being based on a single complete blood count result, and the fact that we did not investigate other inflammatory markers appear to be factors which reduce its strength.

Conclusion

We found that plateletcrit and platelet counts were superior to others, and that there was a significant relationship between plateletcrit, platelet count, NLR, PLR, and LMR and abortus. However, this relationship is not enough to predict abortus. Given the contradictory data in the literature, more comprehensive and prospective studies are needed to confirm our results.

References

1. Regan L, Rai R. Epidemiology and the medical causes of miscarriage. Baillieres Best Pract Res Clin Obstet Gynaecol. 2000;14:839-54.
2. Wang X, Chen C, Wang L, Chen D, Guang W, French J. Conception, early pregnancy loss, and time to clinical pregnancy: a population-based prospective study. Fertil Steril. 2003;79:577-84.
3. Karlı P. Abortus Sonuçlarının Retrospektif Değerlendirilmesi, İki Yıllık Deneyim. AU Sağlık Bil Derg. 2017;3:565-70.
4. Rai R, Regan L. Recurrent miscarriage. Lancet. 2006;368:601-11.
5. Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. BMJ. 2000;320:1708-12.
6. Regan L, Braude PR, Trembath PL. Influence of past reproductive performance on risk of spontaneous abortion. BMJ. 1989;299:541-5.
7. Ness RB, Grisso JA, Hirschinger N, Markovic N, Shaw LM, Day NL, et al. Cocaine and tobacco use and the risk of spontaneous abortion. N Engl J Med. 1999;340:333-9.
8. Landres IV, Milki AA, Lathi RB. Karyotype of miscarriages in relation to maternal weight. Hum Reprod. 2010;25:1123-6.
9. Amegah AK, Klevor MK, Wagner CL. Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: A systematic review and meta-analysis of longitudinal studies. PloS One. 2017;12:e0173605.
10. Sacks G, Redman C, Sargent I. Monocytes are primed to produce the Th1 type cytokine IL-12 in normal human pregnancy: an intracellular flow cytometric analysis of peripheral blood mononuclear cells. Clin Exp Immunol. 2003;131:490-7.
11. Oylumlu M, Ozler A, Yildiz A, Oylumlu M, Acet H, Polat N, et al. New inflammatory markers in pre-eclampsia: echocardiographic epicardial fat thickness and neutrophil to lymphocyte ratio. Clin Exp Hypertens. 2014;36:503-7.
12. Tamhane UU, Aneja S, Montgomery D, Rogers E-K, Eagle KA, Gurm HS. Association between admission neutrophil to lymphocyte ratio and outcomes in patients with acute coronary syndrome. Am J Cardiol. 2008;102:653-7.
13. Celikbilek M, Dogan S, Ozbakır O, Zararsız G, Kücük H, Gürsoy S, et al. Neutrophil–lymphocyte ratio as a predictor of disease severity in ulcerative colitis. J Clin Lab Anal. 2013;27:72-6.
14. Li T, Xu H, Yang L, Tan P, Wei Q. Predictive value of preoperative lymphocyte-to-monocyte ratio for patients with upper tract urothelial carcinoma. Clin Chim Acta. 2019;492:50-6.

15.Choi YH, Lee JW, Lee SH, Choi JH, Kang J, Lee BS, et al. A high monocyte-to-lymphocyte ratio predicts poor prognosis in patients with advanced gallbladder cancer receiving chemotherapy. Cancer Epidemiol Biomarkers Prev. 2019;28:1045-51.
16.Yücel B, Ustun B. Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, mean platelet volume, red cell distribution width and plateletcrit in preeclampsia. Pregnancy Hypertens. 2017;7:29-32.
17.Daglar H, Kirbas A, Kaya B, Kilincoglu F. The value of complete blood count parameters in predicting preterm delivery. Eur Rev Med Pharmacol Sci. 2016;20:801-5.
18.Koroglu N, Tayyar A, Tola EN, Cetin BA, Ozkan BO, Bahat PY, et al. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, mean platelet volume and plateletcrit in isolated intrauterine growth restriction and prediction of being born small for gestational age. Arch Med Sci Civil Dis. 2017;2:139-44.
19.Akgun N, Namli Kalem M, Yuce E, Kalem Z, Aktas H. Correlations of maternal neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) with birth weight. J Matern Fetal Neonatal Med. 2017;30:2086-91.
20.Zhang J, Gilles JM, Barnhart K, Creinin MD, Westhoff C, Frederick MM. A comparison of medical management with misoprostol and surgical management for early pregnancy failure. N Engl J Med. 2005;353:761-9.
21.Kwak JY, Beer AE, Kim SH, Mantouvalos HP. Immunopathology of the implantation site utilizing monoclonal antibodies to natural killer cells in women with recurrent pregnancy losses. Am J Reprod Immunol. 1999;41:91-8.
22.Ünsal E, Aksaray S, Köksal D, Şipit T. Potential role of interleukin 6 in reactive thrombocytosis and acute phase response in pulmonary tuberculosis. Postgrad Med J. 2005;81:604-7.
23.Sato Y, Fujiwara H, Konishi I. Role of platelets in placentation. Med Mol Morphol. 2010;43:129-33.
24.Kara PH, Ünlüer S. Are There any Predictive Values of Mean Platelet Volume (MPV) and MPV/Platelet Count Ratio in Patients with Spontaneous Abortion? Eurasian J Emerg Med. 2017;16:57.
25.Kaplanoglu M, Yuce T, Bulbul M. Decreased mean platelet volume is associated with the developing stage of fetoplacental unit in spontaneous abortion. Int J Clin Exp Med. 2015;8:11301.
26.Eroglu M, Keskin U, Yildirim A, Saygi IA, Gun I, Topuz S. Can mean platelet volume predict abortion? Med Glas. 2013;10:283-7.
27.Cakmak EA EA, Erturk M, Kalkan AK, Satılmısoglu MH, Gul M. Association between New Platelet Indices and Calcific Aortic Stenosis: Plateletcrit and Platelet to Lymphocyte Ratio. Van Tıp Derg. 2016;23:330-7.
28.Ata, N., Kulhan, M., Kulhan, N. G., & Turkler, C. Can neutrophil-lymphocyte and platelet-lymphocyte ratios predict threatened abortion and early pregnancy loss?. Ginekologia Polska. 2020;91:210-5.
29.Choi YH, Lee JW, Lee SH, Choi JH, Kang J, Lee BS, et al. A high monocyte-to-lymphocyte ratio predicts poor prognosis in patients with advanced gallbladder cancer receiving chemotherapy. Cancer Epidemiol Biomarkers Prev. 2019;28:1045-51.
30.Laskin CA, Bombardier C, Hannah ME, Mandel FP, Ritchie K, Farewell V, et al. Prednisone and aspirin in women with autoantibodies and unexplained recurrent fetal loss. N Engl J Med. 1997;337:148-54.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):956-959.
DOI: 10.28982/josam.799750

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

The relationship between AB0 blood groups and COVID-19

AB0 kan grupları ile COVID-19 arasındaki ilişki

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Ethics Committee Approval: The study was approved by Kafkas University Ethics Committee (No: 80576354-050-99/147, date: 6/25/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Kafkas Üniversitesi Etik Kurulu tarafından onaylandı (No: 80576354-050-99/147, tarih: 25.06.2020). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Although COVID-19 infection spreads very quickly, not every individual is infected at the same rate. It should be investigated whether blood groups affect this difference in susceptibility to COVID-19. This study was conducted to investigate whether there was a relationship between AB0 and Rh blood groups and COVID-19 patients.

Methods: A total of 535 patients suspected of COVID-19 who were admitted to the emergency departments and pandemic polyclinics of 3 different hospitals were included in this prospective cohort study. The patients were divided into two groups as those with positive and negative results according to the swab test. According to the ABO and Rh subgroups of the patients whose blood groups were known, each patient was evaluated for the presence of COVID-19. The data on patients' age, gender, complaints during the admission, blood groups, and swab test results were recorded in the study forms, and statistical analyses were performed.

Results: The mean age of the patients was 45.5 (22.2) years. There were 291 (54.40%) males and 244 (45.60%) females. It was observed that most patients had A Rh + blood group (n=225, 42.1%). When age groups were compared in terms of gender, swab test results, and blood groups, no significant differences were found (P=0.307, P=0.316 and P=0.694, respectively).

Conclusion: We found that no specific blood group increased the risk of getting infected with COVID-19. However, according to our results, those with A Rh – and A Rh +, 0 Rh - and AB Rh - blood groups had a higher risk of catching COVID-19, while those with 0 Rh + blood group had a lower risk.

Keywords: Blood group, COVID-19, Pandemic, Infection

Öz

Amaç: COVID-19 enfeksiyonu toplumda çok hızlı yayılmasına rağmen her birey aynı hızla enfeksiyona yakalanmamaktadır. Bireylerin COVID-19'a yakalanmasındaki bu farklılıkların temelinde genetik olarak kan grupların bir etkisinin olup olmadığı araştırılmalıdır. Bu çalışma ABO ve Rh kan grupları ile COVID-19 hastaları arasında bir ilişki olup olmadığını araştırmak amaçlı yapılmıştır.

Yöntemler: 3 farklı hastanenin acil servis ve pandemi polikliniklerine başvuran toplam 535 Covid-19 şüpheli hasta bu prospektif kohort çalışmasına dahil edildi. Hastalar, alınan sürüntü testine göre pozitif ve negatif sonuç olmak üzere iki gruba ayrıldı. Kan grupları belli olan hastalardan ABO ve Rh alt gruplarına göre her hasta Covid-19 varlığı açısından değerlendirildi. Hastaların yaş, cinsiyet, başvuru anındaki şikayetleri, kan grupları ve sürüntü test sonuçları verileri çalışma formlarına kayıt edilip istatistiksel analizleri yapıldı.

Bulgular: Hastaların yaş ortalaması (standart sapması) 45,5 (22,2) yıl idi. Toplam 291 (%54,40) erkek ve 244 (%45,60) kadın hasta vardı. Kan gruplarına bakıldığında en fazla 225 (%42,1) ile A Rh + kan grubuna sahip hastalar olduğu görüldü. Yaş gruplarıyla; cinsiyet ile ve sürüntü test sonuçları ile kan grupları arasında karşılaştırıldığında anlamlı bir farklılık bulunmadı (sırasıyla P=0,307, P=0,316, P=0,694).

Sonuç: Spesifik bir kan grubunda COVID-19'a yakalanma riskinde artış olmadığı görüldü. Ancak A Rh – ve A Rh +, 0 Rh - ve AB Rh - kan gruplarının COVID-19'a yakalanma riskinin yüksek olduğunu, 0 Rh + kan grubunda ise hastalığa yakalanma riskinin daha düşük olduğunu tespit ettik.

Anahtar kelimeler: Kan grubu, Covid-19, Pandemi, Enfeksiyon

How to cite/Atıf için: Gür A, Ekmekyapar M, Şahin L. The relationship between AB0 blood groups and COVID-19. J Surg Med. 2020;4(11):956-959.

Introduction

Coronaviruses (CoV) are a large family of viruses that can present with a wide range of disease severity, from a mild infection to more serious ones, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most common symptoms of the infection are fever, cough, and dyspnea. In more serious cases, pneumonia, severe acute respiratory infection, renal failure and death in advanced clinical conditions may occur [1]. The pandemic caused by the novel SARS CoV-2 (SARS-CoV-2) has rapidly spread all around the world since the end of 2019 as Coronavirus Disease 2019 (COVID-19) and has been declared a pandemic by the World Health Organization [2].

In many studies, it has been reported that susceptibility to viral infections is associated with AB0 blood groups. It has been observed that the 0-blood group has a protective effect against blood-borne infections and that people with A blood type are more likely to be infected with hepatitis B and HIV viruses. Norwalk virus and hepatitis B virus are also known to be associated with blood groups [3-5]. Various genetic factors affecting susceptibility towards SARS and its prognosis have been identified [6]. Furthermore, in few studies on SARS-CoV-1, it has been demonstrated that there is a relationship between the risk of infection and the blood groups and that the 0 blood group is partially protective against SARS-CoV-1 [7, 8].

Although COVID-19 infection spreads very quickly, not every individual is infected at the same rate. It should be investigated whether blood groups affect this difference in susceptibility to COVID-19, for which no predictive biological marker has been identified yet. In this study, we aimed to investigate whether AB0 blood groups are biological markers and whether there is any relationship between susceptibility to COVID-19 and AB0 blood groups.

Materials and methods

The study began after receiving the ethical approval numbered 80576354-050-99/147 and dated 6/25/2020 from Kafkas University Ethics Committee.

In this prospective cohort study, the patients suspected of COVID-19 who were admitted to the emergency departments and COVID-19 pandemic polyclinics of tertiary hospitals in Kars, Erzurum, and Malatya with any symptoms were examined. Within the scope of the study, the patients or their parents, if any, were informed about the aim of the study.

Patients' age, gender, complaints for admission, blood groups, reverse-transcriptase polymerase chain reaction (RT-PCR), and chest computed tomography (CT) findings were recorded. All patients with radiological imaging chest CT findings compatible with COVID-19 were included in the study. In radiological imaging, ground-glass appearance specific to COVID-19, the presence of consolidation areas and paving stone appearance were considered in favor of COVID-19.

A nasopharyngeal swab was taken from the patients whose tomography findings were compatible with COVID-19. The swab results were recorded as positive and negative. It was checked whether the ABO and Rh blood groups of the admitted patients were registered in the hospital automation system or whether they had an official document indicating their blood groups. The blood groups of the patients, whose blood type was known, were recorded. No interventional procedure was performed on the patients for blood group determination. All age groups were included in our study. The patients whose blood group could not be learned in any way, whose RT-PCR result was unknown and who were pregnant were excluded from the study.

Statistical analysis

SPSS 22.0 (SPSS Inc., Chicago, IL, United States) program was used to analyze the data obtained. We expressed continuous variables as mean (standard deviations) or median (interquartile range (IQR)). Categorical data were presented as numbers (percentage). A normality analysis was performed. Non-parametric tests were performed for non-normally distributed independent variables. The Pearson chi-square test and Z test were used for statistical analysis. $P<0.05$ was considered statistically significant.

Results

A total of 535 patients from three different centers were included in the study. The mean age of all patients was 45.5 (22.2) years. There were 44 (8.25%) patients aged between 0-18 years, 357 (66.75%) aged between 19-65 years, and 134 (25.0%) aged 66 years and over. Among all, 291 (54.40%) were male and 244 (45.60%) were female.

When the patients' complaints for admission to the emergency department were evaluated, it was determined that the most common complaint was fever (n=246, 46.0%), followed by sore throat (n=125, 23.4%), shortness of breath, and cough (n=91, 17.0%) and muscle and joint pain (n=73, 13.6%).

The most frequent blood groups of the patients were A Rh + (n=225, 42.1%), followed by 0 Rh + (n=122, 22.8%), B Rh+ (n=68, 12.7%), AB Rh+ (n=38, 7.1%), A Rh- (n=35, 6.5%), 0 Rh- (n=29, 5.4%), B Rh- (n=10, 1.9%), and AB Rh- (n=8, 1.5%).

Test results of 155 (29.0%) patients were positive, and 380 (71.0%) patients were negative.

There were no significant differences in terms of blood groups according to age ($P=0.307$), genders according to blood groups ($P=0.316$), and RT-PCR results according to blood groups ($P=0.694$) (Table 1).

Table 1: Distribution of blood groups according to age, gender, and RT-PCR test results

		Blood Groups (n (%))								
		0 Rh -	0 Rh +	A Rh -	A Rh+	B Rh-	B Rh+	AB Rh-	AB Rh+	*P*-value
Age	0-18	1 (2.3%)	5 (11.4%)	2 (4.5%)	23 (52.3%)	1 (2.3%)	6 (13.6%)	1 (2.3%)	5 (11.4%)	
	19-65	23 (6.4%)	82 (23.0%)	20 (5.6%)	154 (43.1%)	7 (2.0%)	47 (13.2%)	5 (1.4%)	19 (5.3%)	0.307
	≥66	5 (3.7%)	35 (30.6%)	13 (9.7%)	48 (35.8%)	2 (1.5%)	15 (11.2%)	2 (1.5%)	14 (10.4%)	
Gender	Male	18 (6.2%)	73 (25.1%)	17 (5.8%)	115 (39.5%)	8 (2.7%)	34 (11.7%)	6 (2.1%)	20 (6.9%)	
	Female	11 (4.5%)	49 (20.1%)	18 (7.4%)	110 (45.1%)	2 (0.8%)	34 (11.7%)	2 (0.8%)	18 (7.4%)	0.316
RT-PCR	Positive	8 (5.2%)	33 (21.3%)	9 (5.8%)	66 (42.6%)	3 (1.9%)	19 (12.3%)	1 (0.6%)	16 (10.3%)	
	Negative	21 (5.5%)	89 (23.4%)	26 (6.8%)	159 (41.8%)	7 (1.8%)	49 (12.9%)	7 (1.8%)	22 (5.8%)	0.694
Total		29 (5.4%)	122 (22.8%)	35 (6.5%)	225 (42.1%)	10 (1.9%)	68 (12.7%)	8 (1.5%)	38 (7.1%)	

When we compared our patients with the blood group data of Turkey's population, we observed some differences. In Turkey, it was observed that individuals of a certain blood group

did not have a high rate of catching the disease. However, 0 Rh - (P<0.001), A Rh + (P=0.040), A Rh - (P<0.001), and AB Rh - (P<0.001) blood groups had a high rate of getting infected. It is observed that only patients in the 0 Rh + (P<0.001) blood group contracted the disease less often (Table 2). No difference was found between the rates of catching the disease between individuals with B Rh + (P=0.320), B Rh – (P=0.547), and AB Rh + (P=0.606) blood groups (Table 2).

Table 2: Comparison between the study group and blood groups in Turkey's population

Blood Groups	Study Group (%)	Turkey's Population (%)	%95CI	*P*-value	Z
0 Rh (+)	22.8	29.8	0.1924 - 0.2636	0.004	3.5
0 Rh (-)	5.4	3.9	0.4978 - 0.5822	0.001	7.1
A Rh (+)	42.1	37.8	0.3792 - 0.4628	0.040	2.1
A Rh (-)	6.5	5.0	0.6161 - 0.6839	0.001	6.9
B Rh(+)	12.7	14.2	0.0988 - 0.1552	0.320	1
B Rh(-)	1.9	1.8	0.1568 - 0.2232	0.547	0.6
AB Rh (+)	7.1	7.2	0.6715 - 0.7485	0.606	0.5
AB Rh(-)	1.5	1.0	0.1197 - 0.1803	0.001	3.9

Discussion

A large number of studies have begun to be conducted on COVID-19, which is expressed as severe acute respiratory syndrome caused by SARS-CoV-2 that emerged in Wuhan city of China in December 2019 [9, 10]. In these studies, parameters such as risk factors for the mortality of patients, epidemiological characteristics of the disease, and susceptibility to COVID-19 were investigated [2, 11, 12]. The investigation of whether SARS-CoV-2 infects cells according to AB0 blood groups constituted the subject of the study. It has been demonstrated that SARS-CoV infects individuals according to AB0 blood groups and can synthesize ABH antigens in pneumocytes, the enterocytes of the small intestine, and kidney distal tubular epithelial cells [13]. Nevertheless, there is no study on the use of biological markers to predict susceptibility to COVID-19. There have not been enough studies indicating the relationship between AB0 blood groups and COVID-19. In our study, we examined the relationship between COVID-19 and the blood groups of 535 patients treated for COVID-19 and found that there was no direct relationship between COVID-19 and a specific blood group.

In a study conducted in Wuhan, AB0 blood groups of 265 patients infected with COVID-19 were retrospectively analyzed, and blood groups of the patients diagnosed with COVID-19 were A in 39.3%, B in 25.3%, AB in 9.8%, and 0 in 25.7% [14]. Compared to the control group, the rate of those with blood group A was significantly higher (39.3% vs. 32.3%, P=0.017) while those with blood group 0 was significantly lower (25.7% vs. 33.8%, P<0.001) among COVID-19 positive patients [14]. In another study conducted during the SARS outbreak in Hong Kong, it was reported that individuals with 0 blood group had a much lower risk of getting infected by SARS-CoV compared to other blood groups [7]. In our study, in accordance with the literature, the ratio of blood group A was higher (48.6% vs. 42.8%) in COVID-19 patients compared to Turkey's average. Analysis of blood group A according to Rh + and Rh – revealed that the rates of patients with A Rh+ and A Rh- blood groups were significantly higher compared to Turkey's average (42.1% vs. 37.8%, and 6.5% vs. 5%, respectively). In addition, ratio of COVID-19 patients with blood group 0 was lower than Turkey's average (28.2% vs. 33.7%), in accordance with the literature. Analysis of blood group 0 according to Rh + and Rh – revealed that the rates of patients with 0 Rh+ blood group was lower compared to Turkey's average (22.9% vs. 29.8%), and that of patients with 0 Rh- blood group was higher (5.4% vs. 3.9%). We can say that individuals with 0 Rh – blood group may have a lower ratio of catching COVID-19. However, individuals with A Rh +, A Rh – and 0 Rh + blood groups may be at higher risk.

There are studies showing that the risk of infection increases in individuals with A blood group. However, the risk of infection decreases in individuals with 0 blood group when the distributions of AB0 blood groups of COVID-19 patients are compared with the local population [14,15]. While our results resembled the afore-mentioned studies, it was observed that the risk of infection increased not only in the A blood group but also in the AB Rh – blood group.

In a study including 186 COVID-19 patients with a mean age of 42 years, the percentage of female patients was 46.2% [16]. Our study was consistent with the literature; the mean age of the patients was 45.52 years, and 45.60% (244 patients) were females. In a study which compared the blood groups of COVID-19 patients according to age groups and genders, no significant differences were found (P=0.314 and P=0.314, respectively) [17]. The same was true for our results.

In another study evaluating the blood groups of COVID-19 patients, it was determined that blood group A was the most common (57%), followed by blood group 0 (24.8%). When the healthy control group and the COVID-19 patient group were compared, the ratio of COVID-19 infection was statistically significantly higher in those with blood group A (57% - 38%, P<0.001) [16]. It is reported that blood group A Rh+ is the most common, with 37.8% of all blood groups throughout Turkey [18]. Likewise, in our study, we most frequently found blood group A with 48.6% and blood group 0 with 28.2% in patients with COVID-19. The least common blood group was AB with 8.6%. When the blood groups of COVID-19 patients were compared with Turkey's average, the incidence of infection was statistically higher in those with A Rh + and A Rh -. Although AB Rh – was the least common blood group in the population, the incidence of infection was statistically higher in COVID-19 patients. There was no statistically significant difference between COVID-19 patients with B Rh +, B Rh - and AB Rh + blood groups and the normal population.

In order to obtain more accurate and reliable results in studies on blood groups in COVID-19 patients, we believe that it will be more accurate to compare the blood groups of individuals with COVID-19 disease with the blood groups of the general population in the regions where the disease is present. We can say that the relationship between COVID-19 disease and blood groups should not be evaluated alone, and the rate of catching to COVID-19 depends on many factors.

Limitations

Considering the differences in the distribution of blood groups according to the regions, our first limitation is that our study was conducted in a specific region. Another limitation is that not all risk factors of COVID-19 patients included in the study can be ruled out.

Conclusion

Although there is no increase in the risk of catching COVID-19 in a specific blood group, we can say that A blood group (A Rh – and A Rh +), 0 Rh - and AB Rh - blood groups

have a higher risk of catching COVID-19. On the contrary, 0 Rh + blood group has a lower risk of catching the disease, and B blood group (B Rh+ and B Rh -) and AB Rh + blood group are at the same risk as the population.

References

1. Zhu J, Zhong Z, Ji P, Li H, Li B, Pang J, et al. Clinicopathological characteristics of 8697 patients with COVID-19 in China: a meta-analysis. Fam Med Com Health. 2020;8:e000406. doi: 10.1136/fmch-2020-000406.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020 Feb 15;395(10223):507-13. doi: 10.1016/S0140-6736(20)30211-7.
3. Batool Z, Durrani SH, Tariq S. Association Of Abo And Rh Blood Group Types To Hepatitis B, Hepatitis C, Hiv And Syphilis Infection, A Five Year' Experience In Healthy Blood Donors In A Tertiary Care Hospital. J Ayub Med Coll Abbottabad. 2017 Jan-Mar;29(1):90-2.
4. Lindesmith L, Moe C, Marionneau S, Ruvoen N, Jiang X, Lindblad L, et al. Human susceptibility and resistance to Norwalk virus infection. J Nat Med. 2003 May;9(5):548-53..
5. Jing W, Zhao S, Liu J, Liu M. ABO blood groups and hepatitis B virus infection: a systematic review and meta-analysis. BMJ Open. 2020;10(1):e034114. doi: 10.1136/bmjopen-2019-034114.
6. Gu J, Korteweg C. Pathology and pathogenesis of severe acute respiratory syndrome. Am J Pathol. 2007;170:1136–47.
7. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PK, Margaret HL, et al. ABO blood group and susceptibility to severe acute respiratory syndrome. JAMA. 2005;293(12):1450-1. doi: 10.1001/jama.293.12.1450-c
8. Cooling L. Blood groups in infection and host susceptibility. Clinical Microbiology Reviews. 2015;28(3):801-70. doi: 10.1128/CMR.00109-14
9. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al A novel coronavirus from patients with pneumonia in China, 2019. New Engl J Med. 2020;382:727–33.
10. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395:1054–62.
11. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061.
12. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respirat Med. 2020;8:e21.
13. Chen J, Subbarao K. The immunobiology of SARS. Ann Rev Immunol. 2007;25:443–72.
14. Juyi L, Xiufang W, Jian C, Yi C, Aiping D, Ming Y. Association between ABO blood groups and risk of SARS-CoV2 pneumonia. Br J Haematol. 2020 Jul;190(1):24-7. doi: 10.1111/bjh.16797
15. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, et al. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. medRxiv preprint. 11 March, 2020. doi: 10.1101/2020.03.11.20031096.
16. Göker H, Karakulak EA, Demiroğlu H, Ayaz MC, Büyükaşık Y, İnkaya AC, et al. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. Turkish Journal of Medical Sciences. 2020;50:679-83. doi: 10.3906/sag-2005-395.
17. Wua Y, Fengb Z, Lia P, Yua Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. Clinica Chimica Acta. 2020;509:220–3.
18. https://www.kanver.org/EKutuphane/GruplamaLaboratuari, erişim; 16 Mart 2020.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):960-964.
DOI: 10.28982/josam.797459

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of risk factors for surgical site infection after cesarean section

Sezaryen sonrası yara yeri enfeksiyonu için risk faktörlerinin değerlendirilmesi

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Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital with a decision number of 2011-KAEK-25 2020/10-13. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, Sağlık Bilimleri Üniversitesi Bursa Yüksek İhtisas Araştırma ve Eğitim Hastanesi Etik Kurulu tarafından 2011-KAEK-25 2020/10-13 karar numarası ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Surgical site infection after cesarean section is an important and common health issue. Although there are several studies researching risk factors in the literature, limited data is present evaluating these factors in the Turkish population. In this study, we aimed to determine the risk factors and provide management protocols for the Turkish population.

Methods: In this retrospective case-control study, 76 patients between 16-45 years of age who underwent cesarean section and were hospitalized for surgical site infection within 6 weeks and 149 patients who had no postpartum infection between June 2016 and December 2017 were included. Sociodemographic features, laboratory parameters, comorbid diseases and surgical characteristics were recorded. SPSS 21.0 was used for statistical analysis and *P*-value <0.05 was considered statistically significant.

Results: The rate of surgical site infection requiring hospitalization was 1% (76/7590). In the infection positive group, body mass index and fasting blood glucose levels were higher (*P*<0.001 and *P*=0.021). Moreover, preoperative hemoglobin was lower and surgery time was longer in this group (*P*<0.001 and *P*=0.005). In logistic regression analysis, the risk of surgical site infection was found to increase by 1.4-fold with increased body mass index (OR 1.463, 95%CI 1.273-1.681, *P*<0.001) and 1.2-fold with higher fasting glucose level (OR 1.21, 95%CI 1.16-1.37, *P*=0.007). Patients with shorter surgery time (OR 0.749, 95%CI 0.709-0.789, *P*=0.010) and high preoperative hemoglobin levels (OR 0.532, 95%CI 0.408-0.695, *P*<0.001) had decreased infection risk.

Conclusion: The risk factors of surgical site infection after cesarean section are generally modifiable. Thus, healthcare providers should inform patients for postpartum infection and risk factors during pregnancy and eliminate these factors if possible.

Keywords: Cesarean, Risk factors, Surgical site infection

Öz

Amaç: Sezaryen sonrası gelişen yara yeri enfeksiyonu önemli ve sık bir sağlık sorunudur. Literatürde ilişkili risk faktörlerini gösteren çalışmalar mevcut olmakla birlikte Türk popülasyonunda sezaryen sonrası yara yeri enfeksiyonu için risk faktörlerini değerlendiren çok kısıtlı veri bulunmaktadır. Çalışmamızın amacı toplumumuzdaki bu risk faktörlerini belirlemek ve önleyici protokoller geliştirmek için veri sağlamaktır.

Yöntem: Bu retrospektif olgu-kontrol çalışmamıza Haziran 2016-Aralık 2017 tarihleri arasında hastanemize başvuran, 16-45 yaşında ve kliniğimizde sezaryen olup postpartum 6 hafta içinde yara yeri enfeksiyonu nedeniyle yatış yapılan 76 hasta ile takiplerinde herhangi bir enfeksiyon bulgusu saptanmayan 149 hasta dahil edildi. Hastaların sosyodemografik özellikleri, laboratuvar parametreleri, ek hastalık varlığı ve cerrahi özellikleri kaydedildi. İstatistiksel analizler için SPSS 21,0 programı kullanıldı ve *P*<0,05 değeri anlamlı kabul edildi.

Bulgular: Hastane yatışı gerektiren yara yeri enfeksiyonu oranımız %1 (76/7590) olarak bulundu. Risk faktörleri açısından değerlendirildiğinde vücut kitle indeksi ve açlık kan şekeri yara yeri enfeksiyonu olan grupta anlamlı olarak yüksek bulundu (*P*<0,001 ve *P*=0,021). Yine bu grupta preoperatif hemoglobin değerleri daha düşük bulunurken, cerrahi süresi ise daha uzun idi (*P*<0,001 ve *P*=0,005). Lojistik regresyon analizinde vücut kitle indeksi artışının enfeksiyonu 1,4 kat (OR 1,463, %95 CI 1,273-1,681, *P*<0,001), açlık kan şekeri yüksekliğinin ise 1,2 kat (OR 1,21, %95 CI 1,16-1,37, *P*=0,007) arttırdığı gösterildi. Ayrıca cerrahi süresinin kısalmasının (OR 0,749, %95 CI 0,709-0,789, *P*=0,010) ve preoperatif hemoglobin değerindeki artışın (OR 0,532, %95 CI 0,408-0,695, *P*<0,001) riski azalttığı saptandı.

Sonuç: Sezaryen sonrası gelişen yara yeri enfeksiyonu risk faktörlerinin büyük bir kısmı modifiye edilebilir özelliktedir. Bu nedenle hastalar postpartum gelişebilecek enfeksiyon ve risk faktörleri konusunda gebelik takipleri süresince bilgilendirilmeli, bu risk faktörleri mümkün olduğunca ortadan kaldırılmalıdır.

Anahtar kelimeler: Sezaryen, Risk faktörleri, Yara yeri enfeksiyonu

How to cite/Atıf için: Çakmak BD, Dündar B, Türker ÜA, Temur M, Özdemir H, Üstünyurt E, Özgen G. Evaluation of risk factors for surgical site infection after cesarean section. J Surg Med. 2020;4(11):960-964.

Introduction

Cesarean section (CS), the incidence of which reaches nearly one-third of all births worldwide, is one of the most common surgical procedures [1]. Although it is obvious that CS provides improvements in maternal and fetal outcomes, it could be associated with surgical site infection (SSI). The SSI after CS complicates approximately 3-15% of the deliveries, depending on the definition of infection, antibiotic prophylaxis protocol and sociodemographic characteristics of the study population [2]. Another challenging issue for detecting the incidence is the under-reported data according to the short hospital stay and inadequate surveillance system after discharge [3]. SSI can result in prolonged hospital stay, readmission, reoperation, increased health care costs and impairments in physiosocial status [4]. The three SSI classifications according to the US Centers for Disease Control and Prevention include superficial, deep and organ or space infection [5]. Each category has specific criteria, while the diagnosis of all is based on clinical data. It presents with erythema, induration and purulent or serous discharge, and usually develops in the first week after CS [6,7].

The SSI after CS can be affected by patient and health care providers characteristics and perioperative conditions [8]. Many risk factors have been claimed for SSI after CS, which include obesity, diabetes mellitus, hypertension, multiple pregnancies, tobacco use, previous CS, labor induction, presence of chorioamnionitis, large incision, long operation time, steroid use, thick subcutaneous tissue, emergent cesarean delivery and inadequate or inappropriate antibiotic prophylaxis [1,7]. Prophylactic antibiotic use, tight control of blood glucose and blood pressures, preoperative skin preparation, hair removal with clippers, vaginal cleaning, tractional placental removal instead of manual removal and subcutaneous suturing in patients with subcutaneous tissue >3 centimeter are suggested strategies for preventing SSI after CS [3,7].

To the best of our knowledge, there is only a few data in the literature about the risk factors of SSI after CS in Turkish population. In this study, we aimed to determine those risk factors and provide data to be used to develop preventive protocols in our population.

Materials and methods

This retrospective case-control study was conducted in a high-volume university-affiliated research and training hospital between June 2016 and December 2017. Approval was obtained from the Ethics Committee of University of Health Sciences, Bursa Yuksek Ihtisas Research and Training Hospital with the decision number 2011-KAEK-25 2020/10-13.

We included 76 patients between 16-45 years of age who underwent CS in our hospital and were re-admitted within 6 weeks of CS for SSI and 149 age-matched women who underwent CS in our hospital without any signs of infection during their follow-up.

Power analysis was performed to determine the required number of patients in the study group, which was a minimum of 73 individuals for each group for 85% power.

Patients whose data were unavailable during postoperative 6 weeks, those aged <16 and >45 years, who underwent concomitant surgical procedures with CS and patients who were followed-up without hospitalization were excluded.

Maternal age, gravidity, parity, height, weight, laboratory parameters such as fasting glucose, hemoglobin and hematocrit levels, hospital stay, presence of gestational diabetes (GDM), pre-pregnancy diabetes, hypertensive disorders of pregnancy, tobacco use status, operation time, indication for CS, labor induction, steroid use, postpartum hemorrhage, blood loss, history of chorioamnionitis and the number of prior CS were recorded from medical files. Body mass index (BMI) was calculated by dividing the weight by the square of height.

In our clinic, uteruses were routinely repaired with single layer and continuous technique, subcutaneous suturing was performed in patients with a subcutaneous tissue thickness>3 cm, preventive antibiotic prophylaxis were routinely administered intravenously as 3 g of cephazolin: 2 g before cesarean section, and 1 g at the 12^{th} postoperative hour.

SSI was defined as infections which occurred within one month of surgery with no implants, and within the first year in the presence of an implant. Superficial SSI was defined as the infections limited to the skin and subcutaneous tissue accompanied by at least one of the following: 1) Purulent drainage from the superficial incision, 2) Diagnosis of superficial infection by the physician, 3) Presence of signs or symptoms such as pain, tenderness, swelling or heat, if the culture was negative, and 4) Positive culture obtained from superficial incision. Deep SSI was defined as the infections involving deep soft tissue such as the fascia and muscles with at least one of the following: 1) Purulent drainage originating from the deep incision but not from the organ/space area, 2) Deep incision which spontaneously dehisced or was opened by a surgeon in patients with fever and pain, 3) Infection in the deep incisional area detected by direct examination, during reoperation or radiologic imagining, 4) Diagnosis of deep incisional SSI made by the physician [9].

For patients who were hospitalized for SSI, cultures were routinely obtained and gentamicin along with ceftriaxone were administered in the absence of any contraindications. Culture positive and clinically unrecovered patients were consulted with infection diseases. In wound hematomas, we evacuated the clot under sterile conditions, ligated or cauterized the bleeding vessels and reclosed the wound. For seromas, evacuation by needle aspiration and compressive dressing were performed. Superficial infections such as cellulitis were treated with antibiotics instead of incision and drainage. In case of purulent drainage and dehiscence, incision and drainage were performed. In the presence of necrotic tissue, we debrided the necrotic tissue to provide healthy tissue for wound healing. Once necrotic tissue was completely removed, wet dressing was placed. In fascial dehiscence, we chose urgent surgical intervention.

A diagnosis of GDM was confirmed if one or more of these were present in 75 g oral glucose tolerance test (OGTT): Fasting glucose ≥92 mg/dl, ≥180 mg/dl at 1 hour, ≥153 mg/dl at 2 hours. In two step testing, patients underwent 100-gram OGTT if 50-gram OGTT glucose levels were ≥140 mg/dl. In 100-gram OGTT, GDM was established if two or more of the following were present: Fasting blood levels ≥95 mg/dl, ≥180 mg/dl at 1

hour, ≥155 mg/dl at 2 hours and ≥140 mg/dl at 3 hours. Hypertension was defined as the systolic pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg before pregnancy or at any time of gestation. Chorioamnionitis was considered as maternal fever accompanied by at least one of the following: Maternal heart rate >100 beats per minutes, fetal heart rate >160 beats per minute and abdominal tenderness. Cesarean section operations which were performed for acute fetal distress, arrest of labor and severe hypertensive disorders, were categorized as emergent cesarean section. Postpartum hemorrhage was defined as blood loss greater than 1000 milliliters after CS or hemorrhage that impaired the hemodynamic stability of patients.

Statistical analysis

All statistical analyses were carried out with SPSS 21.0 (Stastical Package for Social Sciences). Kolmogorov Smirnov test was performed to evaluate whether the variables were distributed normally. Data were expressed as mean (standard deviation), median (minimum-maximum) and percentage. Student t test was used to compare normally distributed continuous variables between two groups while Mann Whitney U test was used for non-normally distributed continuous ones. Chi-square test was performed for categorical variables. The estimated risks of variables for SSI were determined by logistic regression analysis. An α value ≤0.05 was considered statistically significant.

Results

A total of 17380 deliveries were performed during the study period. The rate of patients who underwent CS was 43% (7590 patients) in the study group while the remaining gave birth with spontaneous or intervened vaginal delivery. The incidence of SSI, which required hospitalization for treatment was 1% (76/7590) in our study.

Superficial SSI was detected in 69 (90.8%) patients. C-reactive protein levels of SSI group were 24.8- 476 mg/dl (min-max). Intravenous antibiotherapy was administered in all patients whereas secondary suturing was used in 23 patients (30.3%) and debridement was performed in 52 patients (68.4%). Culture was positive in 12 patients (15.8%).

Baseline demographic, laboratory, and obstetric features of SSI (n=76) and control (n=149) groups are presented in Table 1. Maternal age, gravida, parity, GDM, pregestational diabetes, hypertensive disorders, cigarette use, drain placement, anesthesia method (general or spinal), urgent CS, steroid usage, meconium-stained amniotic fluid, and presence of chorioamnionitis were similar between two groups (P>0.05). BMI was higher in the SSI group compared to controls (P<0.001) while preoperative hemoglobin and hematocrit levels were lower in the SSI group (P<0.001). The SSI group had longer surgery time and higher fasting glucose levels than the control group (P=0.005 and P=0.021 respectively).

Estimated risks of SSI associated with risk factors were calculated by logistic regression analysis and are demonstrated in Table 2. Compared with the control group, patients with high BMI had 1.4-fold increased risk of SSI (OR 1.463; 95% CI 1.273-1.681, P<0.001). Likewise, patients with high fasting blood glucose levels had 1.2 increased risk of SSI (OR 1.21; 95% CI 1.06-1.37, P=0.007). Patients with high hemoglobin levels and short surgery time had a decreased risk of SSI (OR 0.532; 95% CI 0.408-0.695, P<0.001 and OR 0.947; 95%CI 0.909-0.987, P=0.010).

Table 1: Features of patient and control group

	Surgical Site Infection Group (n=76)	Control Group (n=149)	*P*-value
Age (years)	28.21(6.77)	27.76(5.79)	0.607
Gravida (n)	3(1-6)	3(1-5)	0.225
Parity (n)	2 (1-5)	2 (1-4)	0.522
Body mass index (kg/m²)	35.84(2.66)	33.62(2.76)	<0.001
Tobacco use (n,%)	4 (5.3%)	6 (4%)	0.670
Gestational diabetes (n,%)	6 (7.9%)	12 (8.1%)	0.967
Diabetes mellitus (n,%)	9 (11.8%)	8 (5.4%)	0.082
Hypertension (n, %)	7 (9.2%)	13 (8.7%)	0.904
Hemoglobin (mg/dl)	10.43(1.45)	11.42(1.23)	<0.001
Hematocrit (%)	31.52(4.08)	34.19(3.55)	<0.001
Fasting blood glucose (mg/dl)	95.40(29.74)	86.67(18.67)	0.021
Steroid use (n,%)	8 (10.5%)	15 (10.1%)	0.914
Emergent caesarean section (n,%)	20 (26.3%)	30 (20.1%)	0.291
General Anesthesia (n,%)	16 (21.1%)	30 (20.1%)	0.872
Operation time (minute)	46.14(8.96)	42.56(8.69	0.005
Drain placement (n,%)	4 (5.3%)	7 (4.7%)	0.852
Meconium stained amniotic fluid (n,%)	6 (7.9%)	12 (8.1%)	0.967
Presence of chorioamnionitis (n,%)	8 (10.5%)	16 (10.7%)	0.961

Table 2: Logistic regression analysis to predict risk factors for surgical site infection

	P-value	Odds ratio	95% CI for EXP(B)	
			Lower	Upper
Body mass index	<0.001	1.463	1.273	1.681
Preoperative hemoglobin	<0.001	0.532	0.408	0.695
Operation time	0.010	0.749	0.709	0.789
Fasting blood glucose	0.007	1.21	1.16	1.37
Age	0.396	1.025	0.968	1.087

Discussion

In this study, BMI and blood glucose levels were higher in the SSI group, while preoperative hemoglobin levels were lower and the operation times, longer. Increased levels of hemoglobin and shorter operation times were preventive for SSI.

The CS rates have been increasing continuously in our country and all over the world. Consequently, the incidence of SSI following CS is gradually increasing. CS constitutes 32% of all births in United States of America and the 2-7% of all cesarean sections were complicated with SSI [7]. Similarly, Haidar et al. [2] reported the incidence of SSI following CS as 6.5%. In the study of Johnston et al. [8], SSI following CS was 16.5%. The data from our country about CS-related SSI is quite limited. In the present study, the frequency of SSI requiring hospitalization was 1%, which is less than the literature. This may be owing to the inclusion of patients hospitalized with diagnosis of SSI only. The frequency of SSI was reported as high as 16.5% by Johnston et al., which may be due to including patients with diabetes mellitus or GDM or patients without good glycemic control in their study.

Many risk factors have been defined for SSI, one of which is increased BMI. Obesity was shown to increase the risk of surgical site complications such as seroma, hematoma, and dehiscence by at least 2-3 times [10-12]. Dotters-Katz et al. [13] reported BMI as a risk factor for SSI in patients with chorioamnionitis who underwent CS. Kawakita et al. [7] stated that SSI following CS was increased 2-2.8 times when BMI exceeded 30 kg/m² and 3.7 times when BMI exceeded 35 kg/m². Likewise, we found that increased BMI was a risk factor for development of SSI; it increased the risk of SSI 1.4 times. This direct relationship between BMI and SSI can be explained through increased thickness of subcutaneous fatty tissue or longer operation times.

According to our findings, high fasting blood glucose level is another risk factor for SSI. Hyperglycemia, known to be

associated with disturbed angiogenesis, leads to impairment in wound healing. The interaction of glucose with several growth factors may be responsible for increased risk of SSI [8]. Diabetes has been a widely accepted risk factor for SSI in past decades. Takoudes et al. [14] reported diabetes as a risk factor for SSI. Chaim et al. claimed that GDM, probably causing impairment in surgical site recovery, increased the risk of SSI [15]. In patients who underwent cardiothoracic surgery, both diabetes and postoperative hyperglycemia were associated with 2-2.5 times increased risk of SSI [16]. In the study evaluating the relationship between postpartum glycemic control and SSI, mean blood glucose levels were higher in the SSI group. On the other hand, in the same study, they could not definitely show its association with SSI and finally reported that instantaneous increases in blood glucose levels were not predictive for SSI [8]. When patients with and without postoperative SSI following CS were compared, neither the frequency of diabetes mellitus nor GDM were significantly different from each other in another study [13]. In their study including 3696 patients with SSI, Haidar et al. [2] did not determine an increased frequency of diabetes mellitus or GDM. Similarly, in the present study, the frequency of diabetes mellitus and GDM were not different between two groups. This may be due to the close monitorization of patients with diabetes mellitus and GDM, which results in better glycemic control. We found that fasting blood glucose level was a risk factor, which is an unmodifiable instant finding.

Excessive blood loss or chronic preoperative anemia can be sorted as other factors affecting postoperative surgical site recovery. In the literature, it is claimed that in case of low hemoglobin levels, the oxygenation of surgical site is decreased, and the macrophage activity is disturbed [17]. In a study of Guzman et al., every 100 ml blood loss was found to increase the risk of SSI by 1.3 times [18]. In another study, in patients who had blood loss requiring postpartum transfusion, the incidence of SSI was significantly higher [2]. Wodajo et al. [19] showed that when hemoglobin levels were lower than 11 mg/dl, the risk of SSI increased 2.6 times. On the other hand, Chaim et al. investigated the incidence of postpartum anemia among patients who developed postpartum endometritis and SSI and observed that postpartum anemia was more common in the endometritis group, and not significantly higher in the SSI group [15]. In our study, we found that hemoglobin levels were lower in the SSI group and higher hemoglobin levels were protective against SSI.

One of the risk factors we determined in this study was operation time. In patients who developed SSI, we observed that operation time was significantly longer compared to control group. In previous studies, when the operation time for CS exceeded 38 minutes, the risk of SSI increased [20]. In the study by Wodajo et al. [19], in operations lasting longer than 1 hour, SSI was observed 12 times more commonly. In another study from Nigeria, the rates of SSI in the longer and shorter operative time groups were 55% and 31.7%, respectively [21]. The results of researches conducted in Tanzania and China supported the presence of a correlation between operation times and SSI [22-24]. The underlying mechanism of this correlation may be explained as the increased contamination of surgical site by microorganisms with longer operation time.

Limitations

Our study has several limitations. First, this is a retrospective study with small sample size. Second, patients who were diagnosed with SSI and treated in clinics other than our hospital were not included in this study. Third, we only included patients who were hospitalized for SSI. Lastly, many factors such as the surgeon, single- or two-layer closure of Kerr incision, thickness of subcutaneous tissue, application of subcutaneous suture, type of incision, whether the surgical site is washed or not and the type of skin suturing, all of which are risk factors for SSI in the literature, were not evaluated due to the retrospective design of the current study.

One strength of this study is that this is a single center study providing the opportunity of minimizing the differences in surgical and postoperative care procedures.

There are a plenty of risk factors for SSI, most of which are modifiable. For that reason, patients should be informed about the possibility of postpartum SSI and associated modifiable risk factors.

Conclusion

Optimum weight gain should be offered according to BMI and if required, patients should be referred to dietitians for professional support. Particularly if high fasting blood glucose levels are determined in the first antenatal visit, close monitorization of blood glucose level should be performed and endocrinologic consultation should be considered if it persists. Prepartum anemia should be diagnosed and treated promptly with appropriate iron supplementation either by oral or parenteral route. Lastly, surgical procedure should be performed under maximum sterile conditions and operation time should be optimum.

References

1. Hamilton BE, Martin JA, Osterman MJK, Curtin SC, Matthews TJ. Births: Final Data for 2014. National Vital Statistics Reports, vol. 64, no. 12. National Center for Health Statistics: Hyattsville, MD, USA, 2015.
2. Haidar ZA, Nasab SH, Moussa HN, Sibai BM, Blackwell SC. Caesarean Delivery Surgical Site Infection: What are Expected Rates and Potentially Modifiable Risk Factors? J Obstet Gynaecol Can. 2018;40(6):684-9. doi: 10.1016/j.jogc.2017.09.020.
3. Castillo E, McIsaac C, MacDougall B, Wilson D, Kohr R. Post-Caesarean Section Surgical Site Infection Surveillance Using an Online Database and Mobile Phone Technology. J Obstet Gynaecol Can. 2017;39(8):645-51.
4. Blumenfeld YJ, El-Sayed YY, Lyell DJ, Nelson LM, Butwick AJ. Risk factors for prolonged post partum length of stay following cesarean delivery. Am J Perinatol. 2015;32(9):825–32.
5. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of healthcare–associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control. 2008;36:309–32.
6. Olsen MA, Butler AM, Willers DM, Devkota P, Gross GA, Fraser VJ. Risk factors for surgical site infection after low transverse cesarean section. Infect Control Hosp Epidemiol. 2008;29(6):477–84.
7. Kawakita T, Landy HJ. Surgical site infections after cesarean delivery: epidemiology, prevention and treatment. Maternal Health Neonatology and Perinatology. 2017;3:12.
8. Johnston RC, Gabby L, Tith T, Eaton K, Westermann M, Wing DA. Immediate postpartum glycemic control and risk of surgical site infection. The Journal of Maternal-Fetal & Neonatal Medicine. 2016;30(3):267-71.
9. Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG. CDC definitions of nosocomial surgical site infections, 1992; A modification of CDC definitions of surgical wound infections. Infection Control Hosp Epidemiol. 1992;13:606-8.
10. Stamilio DM, Scifres CM. Extreme obesity and post cesarean maternal complications. Obstet Gynecol. 2014;124:227–32.
11. Vermillion ST, Lamoutte C, Soper DE, Verdeja A. Wound infection after cesarean: effect of subcutaneous tissue thickness. Obstet Gynecol. 2000;95:923–6.
12. Subramaniam A, Jauk VC, Figueroa D, Biggio JR, Owen J, Tita ATN. Risk factors for wound disruption following cesarean delivery. J Matern Fetal Neonatal Med. 2014;27:1237–40.
13. Dotters-Katz SK, Feldman C, Puechl A, Grotegut CA, Heine RP. Risk factors for post-operative wound infection in the setting of chorioamnionitis and cesarean delivery. J Matern Fetal Neonatal Med. 2016;29(10):1541-5.
14. Takoudes TC, Weitzen S, Slocum J, Malee M. Risk of cesarean wound complications in diabetic gestations. Am J Obstet Gynecol. 2004;191:958–63.
15. Chaim W, Bashiri A, Bar-David J, Shoham-Vardi I, Mazor M. Prevalence and Clinical Significance of Postpartum Endometritis and Wound Infection. Infectious Diseases in Obstetrics and Gynecology. 2000;8:77-82.
16. Latham R, Lancaster AD, Covington JF, Pirolo JS, Thomas CS. The association of diabetes and glucose control with surgical-site infections among cardiothoracic surgery patients. Infect Cont Hosp Epidemiol. 2001;22:607–12.
17. Gordillo GM, Sen CK. Revisiting the essential role of oxygen in wound healing. Am J Surg. 2003;186:259–63.

18. Guzman MA, Prien SD, Blann DW. Post-cesarean related infection and vaginal preparation with povidone-iodine revisited. Primary Care Update OB/GYNS 2002;9(6):206–9.
19. Wodajo S, Belayneh M, Gebremedhin S. Magnitude and Factors Associated With Post-Cesarean Surgical Site Infection at Hawassa University Teaching and Referral Hospital, Southern Ethiopia: A Cross-sectional Study. Ethiop J Health Sci. 2017;27:283-90.
20. Opoien HK, Valbo A, Grinde-Andersen A, Walberg M. Post-cesarean surgical site infections according to CDC standards: rates and risk factors. A prospective cohort study. Acta Obstet Gynecol Scand. 2007;86:1097–102.
21. Jido TA, Garba ID. Surgical-site Infection following cesarean section in Kano, Nigeria. Ann Med Health Sci Res. 2012;2:33–6.
22. Mpogoro FJ, Mshana SE, Mirambo MM, Kidenya BR, Gumodoka B, Imirzalioglu C. Incidence and predictors of surgical site infections following caesarean sections at Bugando Medical Centre, Mwanza, Tanzania. Antimicrob Resist Infect Control. 2014;3:25.
23. Gong S, Guo H, Zhou H, Chen L, Yu Y. Morbidity and risk factors for surgical site infection following cesarean section in Guangdong Province, China. Obstet Gynecol Res. 2012;38:509-15.
24. National Collaborating Centre for Women's and Children's Health (UK), author Prevention and treatment of surgical site infection: NICE Clinical Guidelines. London: RCOG Press; 2008. pp. 45–55.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):965-969.
DOI: 10.28982/josam.804514

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effect of bone metastases on survival in lung cancer

Akciğer kanserinde kemik metastazlarının sağkalıma etkisi

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Ethics Committee Approval: Ethics committee approval was obtained from Afyonkarahisar Health Sciences University on 7/3/2020 with the number 2020/303. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Afyonkarahisar Sağlık Bilimleri Üniversitesi 03.07.2020 tarih ve 2020/303 tarihli kararı ile etik kurul onayı alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: The most common sites of distant metastasis in lung cancers are bones. In our study, we aimed to investigate the incidence of bone metastasis in lung cancers, and the effects of single and multiple bone metastases on survival. We conducted such a study to contribute to the literature due to the small number of studies on this subject.

Methods: Lung cancer patients diagnosed with bone metastases in our hospital between January 2012-December 2018 were identified. A total of 103 (60.59%) patients with single bone metastasis, and 67 (39.41%) patients with multiple bone metastases were included in the study. Patients' demographic characteristics, symptoms, radiological findings, diagnostic methods, histological subtypes, survival, biochemistry values, tumor markers were analyzed retrospectively according to single and multiple bone metastases. A cohort study was conducted, and the results were presented as mean and standard deviation for continuous variables, and percentage for categorical variables.

Results: Among the 170 patients included in the study, 147 (86.5%) were male, and 23 (13.5%) were female. The overall mean age of the patients was 64.32 (9.965) years. The most common symptom was dyspnea, reported by 58 (34.1%) patients. Bronchoscopic biopsy was most used for diagnosis, in 116 (68.2%) patients. Among patients with adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma, the number of those with single and multiple bone metastases were 44 (55%) and 36 (45%), 37 (75.5%) and 12 (24.5%), and 22 (53.7%) and 19 (46.3%), respectively. Vertebrae were the most common site of metastasis in single bone metastases. The mean survival times of adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma patients with single and multiple bone metastases were 14.93 (11.8) and 13.03 (9.32), 15.55 (9.41) and 9.42 (5.744), and 10.55 (8.32) and 8.79 (4.171) months, respectively.

Conclusion: No significant differences were detected in terms of survival between adenocarcinoma and small cell lung cancer patients with single and multiple bone metastases. However, multiple bone metastases were observed to significantly decrease survival in squamous cell carcinoma.

Keywords: Lung cancer, Histological subtypes, Metastasis, Survival

Öz

Amaç: Akciğer kanserlerinde en sık uzak metastaz yerleri kemiklerdir. Çalışmamızda akciğer kanserlerinin kemik metastazı insidansını, tek ve multıpl kemik metastazlarının sağkalıma etkisini araştırmayı amaçladık. Bu konudaki çalışmaların az olması nedeniyle literatüre katkı sağlamak amacıyla böyle bir çalışma yaptık.

Yöntem: Ocak 2012-Aralık 2018 yılları arasında kemik metastazı yapmış akciğer kanseri hastaları tespit edildi. Tek kemik metastazı tespit edilen 103(%60.59), multipl kemik metastazı tespit edilen 67(%39,41) hasta çalışmaya alındı. Hastaların demografik özellikleri, semptomları, radyolojik bulguları, tanı yöntemleri, histolojik alt tipleri, tek ve multıpl kemik metastazlarına göre sağkalım, biyokimya değerleri, tümör markırları retrospektif incelendi. Kohort çalışması yapıldı, sürekli değişkenler için ortalama, standart sapmaya, kategorik değişkenler için yüzdeye göre analizi yapıldı.

Bulgular: Çalışmaya 147 (%86,5)'si erkek, 23 (%13,5)'ü kadın 170 hasta dahil edildi. Yaş ortalaması 64,32(9,965) idi. En sık semptom 58 (%34,1) hastada izlenen dispneydi. Tanıda 116 (%68,2) hasta ile en sık bronkoskopik biyopsi kullanılmıştı. 80 hastada adenokarsinoma (44 (%55) hastada tek kemikte, 36 (%45) hastada multıpl kemikte metastaz), 49 hastada skuamöz hücreli karsinoma (37 (%75,51) hastada tek kemikte, 12 (%24,49) hastada multıpl kemikte metastaz), 41 hastada küçük hücreli akciğer karsinomu (22 (%53,65) hastada tek kemikte, 19 (%46,35) hastada multıpl kemikte metastaz) izlendi. Tek kemik metastazlarında en sık metastaz yeri vertebralardı. Adenokarsinomada tek kemik metastazlarında sağkalım (ay) 14,93 (11,795), multıpl kemik metastazlarında sağkalım (ay) 13,03 (9,321), squamöz hücreli karsinomada tek kemik metastazlarında sağkalım (ay) 15,55 (9,414), multıpl kemik metastazlarında sağkalım (ay) 9,42 (5,744), küçük hücreli akciğer karsinomunda tek kemik metastazlarında sağkalım (ay) 10,55 (8,319), multıpl kemik metastazlarında sağkalım (ay) 8,79 (4,171) idi.

Sonuç: Adenokarsinom ve küçük hücreli akciğer kanserlerinde tek kemik metastazı ile multıpl kemik metastazı arasında sağkalım açısından fark izlenmezken, skuamöz hücreli karsinomada multıpl kemik metastazlarının sağkalımı anlamlı derecede azalttığı izlendi.

Anahtar kelimeler: Akciğer kanseri, Histolojik alt tip, Metastaz, Sağkalım

How to cite/Atıf için: Aydın S, Balcı A. The effect of bone metastases on survival in lung cancer. J Surg Med. 2020;4(11):965-969.

Introduction

Lung cancer is the most diagnosed cancer among males. It is the leading cause of cancer-related deaths in developed and less developed countries. Non-small cell lung cancer (NSCLC) is the most common type, accounting for 80% [1].

Bones are the third most common place of metastasis in all cancer types [2]. Bone metastasis is one of the late-stage common complications of malignant tumors. It can be seen in all types of cancer, especially breast, prostate, and lung cancers [3].

In lung cancers, bones are the most common and earliest metastatic sites. Bone metastasis develops in 30-40% of lung cancer patients [4]. Lung cancer is responsible for 30-70% of bone metastases. Bone metastasis is present in 20-30% of patients with lung cancer at the time of diagnosis [5].

There are many factors affecting bone metastasis in lung cancer, including age, gender, number of primary lesions, histological subtypes, serum markers, and treatment regimens [5].

Bone metastases are often painful and cause serious morbidity [6]. Pain is caused by the release of cytokines and chemical mediators that stimulate the periosteum and bone, and the mechanical stress of the tumor tissue in osteolytic lesions [5]. It may cause pathological fractures in bones, skeletal system problems, spinal cord compression, and hypocalcemia [7].

Currently, studies on the relationship between primary lung cancers and bone metastases and the effect of bone metastases on survival are rare. Median survival has been reported to vary between 12 and 33 months in patients with prostate, breast, and kidney cancers with bone metastasis [8], while the 1-year survival rate in lung cancers is between 9.5% and 12% [9]. As the time between the time of diagnosis and the time of metastasis development increases, the survival time increases [10].

Materials and methods

Patients diagnosed with lung cancer in our hospital between 1 January 2012-31 December 2018 were retrospectively analyzed. Patients with multiorgan and non-bone tissue metastases, along with those without metastases were excluded, and patients with single or multiple bone metastases were included in the study.

Clinical and demographic data were extracted from physical and electronic medical records. The patients' ages, genders, symptoms, diagnostic methods used, pathology results (histological types), radiological findings and reports, metastasis locations, smoking statuses, other accompanying lung diseases and whether there was a family history of cancer were noted. Active smokers were classified as "smokers" (currently smoking), those who smoked but quit were "ex-smokers" and those who never smoked were "nonsmokers."

Among laboratory values, erythrocyte sedimentation rate, C-reactive protein (CRP), albumin, total protein, Alkaline Phosphatase (ALP), Calcium (ca), and Lactate Dehydrogenase (LDH) levels were recorded.

Cancer markers of the patients were examined. The levels of carcinoembryonic antigen (CEA), CA 19-9 and CA 125 were noted.

Information on imaging methods such as chest radiography, thoracic computed tomography (CT), brain CT, abdominal CT, abdominal ultrasonography (USG), positron emission tomography (PET-CT) and bone scintigraphy were evaluated. Staging was performed with TNM classification according to The World Health Organization (WHO) staging criteria. Histological subtypes were classified according to the International Classification of Diseases for Oncology, 3rd Edition.

The treatment group was classified into chemotherapy, radiotherapy, and combined therapy (chemotherapy + radiotherapy).

The performances of the patients were determined according to the criteria of the Eastern Cooperative Oncology Group (ECOG), as follows: 0: Carries on with normal activities, 1: Has symptoms of the disease, but can walk and perform daily activities, 2: Is out of bed more than 50% of their time, sometimes needs help. 3: In bed more than 50% of the time, needs someone's care, 4: Fully bedridden; hospitalization may be required.

The most frequent site of metastasis, the histological subtypes, and mean survival times were compared between patients with single and multiple bone metastases.

Statistical analysis

Kaplan-Meier method was used to evaluate the monthly survival outcomes in lung cancers with bone metastases. SPSS v20 program was used for statistical analysis to evaluate the data obtained in this study. Data were presented as mean, standard deviation, number of persons and percentages. Compliance of quantitative data to normal distribution were evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson's chi-square and Fisher's exact tests were used to compare qualitative data. $P<0.05$ was considered statistically significant.

Results

A total of 170 patients who were diagnosed with lung cancer in our clinic between January 2012 and December 2018 and found to have bone metastases were included in the study. The mean age of the patients was 64.32 (9.965) years. There were 147 (86.5%) males and 23 (13.5%) females. Among them, 65 (38.2%) were active smokers, 78 (45.9%) were ex-smokers, 26 (15.3%) were non-smokers. The average pack-year rate was 43.21 (16.248). Lung cancer was accompanied by other lung diseases such as asthma and chronic obstructive pulmonary disease in 105 (61.8%) of the patients. There was a family history of cancer in 64 (38.8%) patients. In terms of performance scores, thirty-six patients (21.2%) were ECOG 0, 58 (34.1%) patients were ECOG 1, 52 (30.6%) patients, ECOG 2, 16 (9.4%) patients, ECOG 3, and 8 (4.6%) patients were identified as ECOG 4 (Table 1).

The most common symptom was dyspnea, seen in 58 (34.1%) patients. Other symptoms included cough in 45 (26.6%) patients, chest pain in 36 (21.1%) patients, musculoskeletal pain in 18 (10.6%) patients, and hoarseness in 7 (4.1%) patients. Hemoptysis was observed in 6 (3.5%) (Figure 1).

In radiological examinations and reports, the most common finding was a primary cancer mass and nodule appearance in 106 (62.4) patients. This was followed by hilar

fullness in 21 (12.4%) patients, effusion in 20 (11.8%), consolidation in 14 (8.2%), atelectasis in 5 (2.9%), and cavity in 4 (2.4%).

The tumors were in the right upper lobe in 41 (24.1%) patients, the left upper lobe in 41 (24.1%) patients, the right lower lobe in 36 (21.8%) patients, the right middle lobe in 16 (9.4%) patients, and the left lower lobe in 18 (10.6%). Primary site could not be determined in 18 (10.6%) patients (Figure 2).

Table 1: Demographic characteristics of the patients

	n	%
Total Patients	170	100
Gender		
Male	147	86.5
Female	23	13.5
Smoking		
Active Smoker	65	38.2
Exmoker	78	45.9
Nonsmoker	26	15.3
Other Lung Diseases		
Yes	105	61.8
No	65	38.2
Cancer History in The Family		
Yes	64	38.8
No	106	61.2
ECOG		
0	36	21.2
1	58	34.1
2	52	30.6
3	16	9.4
4	8	4.6

ECOG Score: Eastern Cooperative Oncology Group Performance Score

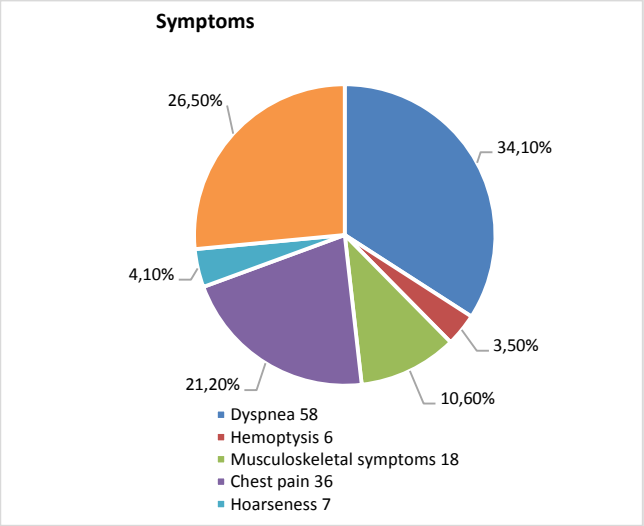

Figure 1: Patients' symptoms

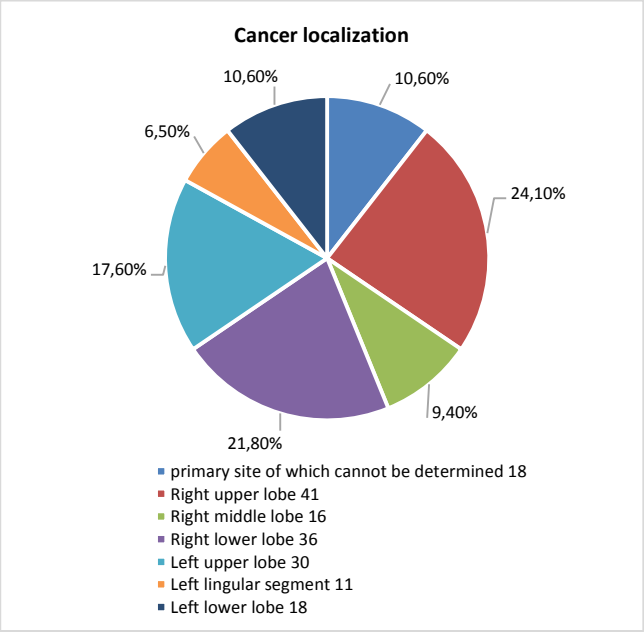

Figure 2: Cancer localizations

In 116 (68.2%) of the patients, biopsy was obtained with bronchoscopy, in 31 (18.2%), with transthoracic fine needle aspiration biopsy (TTIAB), and in 17 (10%), with other methods (cytology, mediastinoscopy-guided biopsy, Video Assisted Thoracic Surgery (VATS), biopsies taken from peripheral lymph nodes and metastatic lesions). Six (3.5%) were diagnosed with closed pleural biopsy.

When the laboratory data of the patients were examined, it was found that calcium levels of patients with squamous cell carcinoma were higher than those with adenocarcinoma and small cell lung carcinoma (P<0.001), and CEA levels were higher in those with adenocarcinoma (P=0.013). There were no significant differences between the groups in terms of LDH, ALP, total protein, sedimentation rate, CRP, albumin, Ca 19-9, Ca 125 levels (Table 2).

Table 2: Laboratory findings

	Squamous cell carcinoma	Adenocarcinoma	Small cell lung carcinoma	Total	*P*-value
LDH(U/L)	343(62-6161)	440(46-5104)	460(38-2603)	416(38-6161)	0.054
ALP(U/L)	102(51-733)	113(0-1319)	94(0-931)	100(0-1319)	0.585
*Ca(mg/dL)	9.35 (1.85)	8.29 (19.4)	8.15 (18.8)	8.57 (1.43)	<0.001
Total protein(g/dL)	6.29(0.57-61.60)	5.83(2.98-75.40)	6.06(3.57-76.10)	6.1(0.57-76.1)	0.800
*Sedimentation rate (mm/h)	65.97 (31.18)	58.77 (37.57)	54.26 (35.6)	59.79 (35.41)	0.341
CRP (mg/L)	9.89(0.23-46.20)	8.19(0.13-46.50)	7.13(0.03-35.90)	8.1(0.13-46.50)	0.113
CEA (ng/dL)	4.26(0.5-1000)	9.37(1.38-2393)	3.71(0,62-645)	4.81(0.5-2393)	0.013
Ca 19-9(U/mL)	17.13(0.6-832)	12.76(0-8425)	18.23(1.58-1969)	15.41(0-8425)	0.467
Ca 125(U/mL)	21.17(7.57-1154)	50.54(5.37-765.7)	21.44(15.91-28.72)	28.72(5.37-1154)	0.442
*Albumin (g/dL)	2.92 (0.67)	2.86 (0.68)	3.02 (0.82)	2.81 (1.17)	0.528

LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase, ca: calcium, CRP: C-Reactive Protein, CEA: Carcinoembryonic Antigen, * mean (standard deviation)

Among those with bone metastases, the most common histological subtype was adenocarcinoma with 80 patients (47.06%), followed by squamous cell carcinoma (n=49, 28.82%), and small cell lung carcinoma (n=41, 24.12%). The most common type causing multiple bone metastases was adenocarcinoma with 36 (53.73%) patients, followed by small cell lung carcinoma with 19 (28.36%) patients and squamous cell carcinoma with 12 (17.91%) patients.

In all lung cancer types which cause bone metastasis, the most common site of metastasis was the vertebrae with 52 (30.58%) patients. The most common cancer type causing single bone metastasis was adenocarcinoma with 24 (30%) patients. This was followed by squamous cell carcinoma with 17 (34.69%) patients and small cell lung carcinoma with 11 (26.82%) patients. Multiple bone metastases were observed in 36 (45%) patients with adenocarcinoma, 19 (46.34%) patients with small cell lung carcinoma with and 12 (24.48%) patients with squamous cell carcinoma (Table 3).

In terms of treatment, 70 patients received chemotherapy, 3 received radiotherapy, 97 received combined therapy (chemotherapy and radiotherapy) and 24 received bisphosphonates.

The mean survival times of adenocarcinoma, squamous cell carcinoma, and small cell lung carcinoma patients with single and multiple bone metastases were 14.93 (11.8) and 13.03 (9.32), 15.55 (9.41) and 9.42 (5.744), and 10.55 (8.32) and 8.79 (4.171) months, respectively (Figures 3, 4). Single and multiple bone metastases were observed to significantly affect survival in squamous cell carcinoma (P=0.013). The overall survival of patients with adenocarcinoma, squamous cell carcinoma, and

small cell lung carcinoma were 14.07 (10.71), 13.91 (8.96), and 9.73 (6.70) months, respectively (Table 4).

Table 3: Bone metastasis locations in lung cancers according to histological subtypes

	Single bone metastasis					Multiple bone metastasis	Total
Histological subtype	Spine	Skull	Bones of limbs	Thoracic wall	Pelvis		
Squamous cell carcinoma n (%)	17(34.6)	2(4.08)	6(12.24)	10(20.40)	2(4.08)	12(24.49)	49(100)
Adenocarcinoma n (%)	24(30)	2(2.5)	4(5)	9(11.25)	5(6.2)	36(45)	80(100)
Small cell lung carcinoma n (%)	11(26.8)	1(2.43)	3(7.31)	5(12.19)	2(4.87)	19(46,34)	41(100)
Total n (%)	52(30.5)	5(2.9)	13(7.6)	24(14.11)	9(5.29)	67(39.4)	170(100)

Table 4: Survival by histological subtype and bone metastasis status

Histological subtype	Survival (month)	Single bone metastasis survival (month)	Multiple bone metastasis survival (months)	*P*-value*
Squamous cell carcinoma n (%)	13.91(8.957)	15.55(9.414)	9.42(5.744)	0.013
Adenocarcinoma n (%)	14.07(10.717)	14.93(11.795)	13.03(9.321)	0.365
Small cell lung carcinoma n (%)	9.73(6.705)	10.55(8.319)	8.79(4.171)	0.564

*Kaplan-Meier

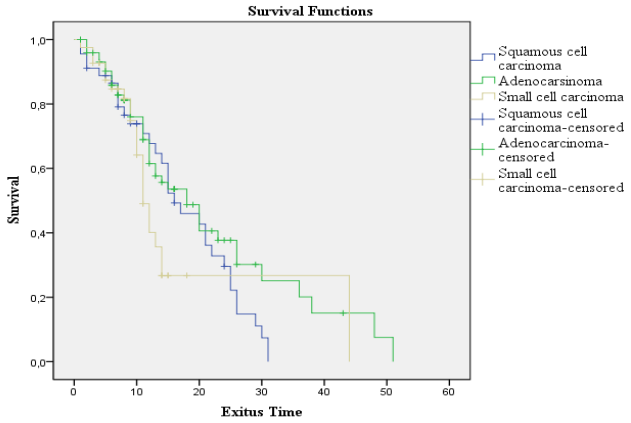

Figure 3: Single bone metastasis survival (month) curve

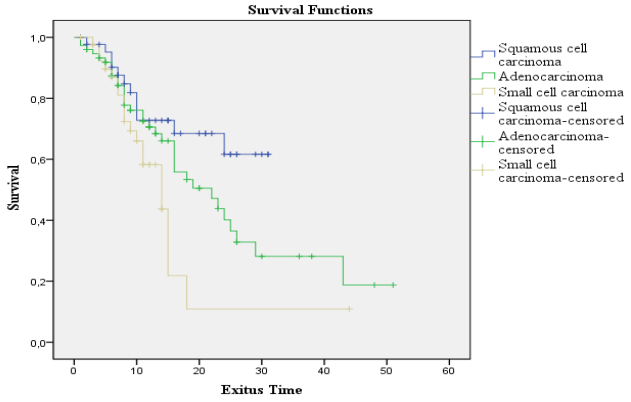

Figure 4: Multiple bone metastasis survival (month) curve

Discussion

Lung cancer is most common in the 40-70 years-age range. Its incidence increases in the 6th and 7th decades. In studies on lung cancers, it was observed that 90% of the cases were male [11].

In our study, the age range was 33-85 years, with an overall mean age of 64.32(9.965) years. A total of 147 (86.5%) patients were male and 23 (13.5%) were female, which were coherent with data reported in the literature.

ECOG performance scores are a measure of general well-being and activities of daily living for cancer patients. Although the ECOG score is used to evaluate the overall survival in cancer patients, it has been found that patients with high ECOG scores show less tolerance to chemotherapy and radiotherapy [12]. ECOG score has been accepted as a prognostic factor for bone metastases in lung cancer [5]. In our study, in terms of performance scores, 36 patients (21.2%) were ECOG 0, 58 (34.1%) patients were ECOG 1, 52 (30.6%) patients, ECOG 2, 16 (9.4%) patients, ECOG 3, and 8 (4.6%) patients were identified as ECOG 4. In the literature, the most common symptoms in lung cancers were dyspnea (3-60%) and cough (8-75%) [13]. In our study, the most common complaints of our patients were dyspnea in 58 (34.1%) patients and cough in 45 (26.5%) patients. These symptoms were followed by chest pain in 36 (21.1%), musculoskeletal pain in 18 (10.6%), hoarseness in 7 (4.1%) and hemoptysis in 6 (3.5%).

According to Bircan et al. [14], the most common locations of primary lung cancers were the right upper lobe (25.3%), left upper lobe (24.1%), right middle lobe (9.2%), right lower lobe (18.4%), left lower lobe (20.7%) and non-localized in 2.3%. In our study, the tumors of 41 (24.1%) patients were in the right upper lobe, 41 (24.1%) patients, in the left upper lobe, 36 (21.8%) patients, in the right lower lobe, 16 (9.4%) patients, in the right middle lobe, and 18 (10.6%) patients, in the left lower lobe. Primary site could not be determined in 18 (10.6%) patients.

Cavitation can be observed in chest radiographs, especially in squamous cell carcinoma, adenocarcinoma, and large cell cancers. It is reported that 16% of lung cancers show cavitation [15]. When the radiological studies and reports of our patients were examined, the most common finding was the appearance of primary cancer mass and nodule in 106 (62.4) patients, followed by hilar fullness in 21 (12.4%) patients, effusion in 20 (11.8%) patients, consolidation in 14 (8.2%) patients, atelectasis in 5 (2.9%) patients, and cavity in 4 (2.4%) patients.

In their study on 168 lung cancer patients, Li Zhang et al. [5] found the overall median survival as 13 months, the rates of 1 and 2-year survivals as 54.3% and 12.9%, respectively, and stated that bone metastases negatively affect survival and prognosis in lung cancer patients.

In our study, the mean survival times in squamous cell carcinoma, adenocarcinoma and small cell lung carcinoma with bone metastases were 13.91 (8.96), 14.07 (10.72) and 9.73 (6.71) months, respectively. We found a statistically significant difference in survival times between squamous cell carcinoma patients with single and multiple bone metastases.

There are publications claiming that the prognosis of adenocarcinoma with multiple bone metastases is worse than those of small cell and squamous cell carcinomas, and that bone metastases are independent prognostic factors in adenocarcinoma [16].

Wang et al. [17] found that adenocarcinomas have a higher incidence of bone metastasis and that the vertebrae are the most common sites of involvement.

In our study, the most common metastasis site in all lung cancer types was the vertebrae and the most common histologic subtype which metastasized to the vertebrae was squamous cell carcinoma, with a rate of 34.69%. This was followed by adenocarcinoma (30%) and small cell lung carcinoma (26.82%). The subtype with the most common multiple bone metastasis was small cell lung carcinoma with a rate of 46.34%, which was followed by adenocarcinoma (45%) and squamous cell carcinoma (24.48%).

In their study, Lee et al. [18] showed that increased serum CEA levels may be an indicator of increased bone metastasis potential in stage IV lung cancers.

Our univariate analysis revealed that the mean calcium level of squamous cell carcinoma patients with bone metastases was 9.35 (1.85) mg/dL and the CEA value of adenocarcinoma patients with bone metastases was 9.37 (1.38-2393) ng/dL, both of which were significantly different compared to the other groups. LDH, ALP, total protein, sedimentation rate, CRP, CA 19-9, CA 125, and albumin values were similar between all groups.

Univariate and multivariate analyses revealed that histological type, clinical stage, ECOG scores, serum ALP levels, and the number of bone metastases were important prognostic factors. Histological subtype in lung cancers is a crucial factor in bone metastases [5].

Limitations

The date of diagnosis was considered as the date the patients were diagnosed with various tests performed in our hospital. Previous symptoms and their durations were unknown. While searching the database, some deficiencies were detected in the proportion of patients with bone metastasis. Most of the lung cancer cases with distant organ metastases had multi-organ metastases and only the cases with bone metastases were included in our study. This caused a decrease in the number of included patients.

Conclusions

Histological subtype and stage of lung cancer are principal factors in bone metastases. Among all histological subtypes, the most common site of metastasis was the vertebrae. In our study, squamous cell carcinoma was the most common subtype with single bone metastases, while adenocarcinoma was most detected in those with multiple bone metastases. The survival times of squamous cell carcinoma patients with single and multiple bone metastases were significantly different. Further studies are required to elucidate the effects of bone metastases on survival in lung cancer patients, as well as its relationship with histological subtypes.

References

1. Niu Y, Lin Y, Pang H, Shen W, Liu L, Zhang H. Risk factors for bone metastasis in patients with primary lung cancer A systematic review. Medicine. 2019;98:3. doi: 10.1097/MD.0000000000014084
2. Ibrahim T, Mercatali L, Amadori D. Bone and cancer: the osteoncology. Clin Cases Miner Bone Metab. 2013;10:121–3.
3. Brodowicz T, O'Byrne K, Manegold C. Bone matters in lung cancer. Ann Oncol. 2012;23:2215-22.
4. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27:165–76.
5. Zhang L, Gong Z. Clinical Characteristics and Prognostic Factors in Bone Metastases from Lung Cancer. Med Sci Monit, 2017;23:4087-94. doi: 10.12659/MSM.902971
6. Svensson E, Christiansen CF, Ulrichsen SP, Rørth MR, Sørensen HT. Survival after bone metastasis by primary cancer type: a Danish population-based cohort study. BMJ Open. 2017;7:e016022. doi:10.1136/bmjopen-2017-016022
7. Husaini H, Wheatley-Price P, Clemons M, Shephered FA. Prevention and management of bone metastases in lung cancer: a review. J Thorac Oncol. 2009;4:251–9.
8. Santoni M, Conti A, Procopio G, Porta C, Ibrahim T, Barni S, et al. Bone metastases in patients with metastatic renal cell carcinoma: are they always associated with poor prognosis? J Exp Clin Cancer Res. 2015;34:10.
9. Santini D, Barni S, Intagliata S, Falcona A, Ferrau F, Galetta D, et al. Natural history of non-small-cell lung cancer with bone metastases. Sci Rep. 2015;5:18670.
10. Cetin K, Christiansen CF, Sværke C, Jacobsen JB, Sørensen HT. Survival in patients with breast cancer with bone metastasis: a Danish population-based cohort study on the prognostic impact of initial stage of disease at breast cancer diagnosis and length of the bone metastasis-free interval. BMJ Open. 2015;5:e007702.
11. Goksel T, Akkoclu A. Patern of lung cancer in Turkey, 1994-1998. Respiration. 2002;69:207-10.
12. De Kock I, Mirhosseini M, Lau F, Thai V, Downing M, Quan H, et al. Conversion of Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group Performance Status (ECOG) to Palliative Performance Scale (PPS) and the interchangeability of PPS and KPS in prognostic tools. J Palliat Care. 2013;29:163–9.
13. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial Evaluation of the patient with lung cancer. Symptoms, signs, laboratory tests, and paraneoplastic syndromes. Chest. 2003;123:97-104.
14. Bircan AH, Öztürk Ö, Şahin Ü, Özaydın N, Akkaya A. Akciğer kanseri tanısı alan olgularımızın Retrospektif değerlendirilmesi. SDÜ Tıp Fak Derg. 2005;2(3):1-6.
15. Balcı P, Altay C. Akciğer Kanserinde Radyolojik Bulgular. turkradyolojiseminerleri.org doi: 10.5152/trs.2014.025
16. Kadota K, Sima CS, Arcila ME, Hedvat C. KRAS Mutation Is a Significant Prognostic Factor in Early-stage Lung Adenocarcinoma. Am J Surg Pathol. 2016;40:1579–90.
17. Wang Z, Ning L, Li H, Yang YM. Clinical observation of percutaneous osteoplasty in the treatment of 92 lung cancer patients with extraspinal bone metastases. Tumor. 2014;34(5):443–9.
18. Lee DS, Kim SJ, Kang JH, Hong SH, Jeon EK, Kim YK, et al. Serum carcinoembryonic antigen levels and the risk of whole-body metastatic potential in advanced non-small cell lung cancer. J Cancer. 2014;5:663–9.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):970-973.
DOI: 10.28982/josam.795283

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Comparison of non-severe COVID-19 pneumonia patients treated with lopinavir/ritonavir and favipiravir

Lopinavir/ritonavir ve favipiravir ile tedavi edilen ağır olmayan COVID-19 pnömoni hastalarının karşılaştırılması

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Ethics Committee Approval: Ethics committee approval was obtained from the ethics committee of Ümraniye Training and Research Hospital (Date: 5/28/2020, No: 209). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Etik kurul onayı Ümraniye Eğitim ve Araştırma Hastanesi Etik Kurulu'ndan alındı (Tarih: 28.05.2020, No: 209). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: There is no proven medical treatment for COVID-19 to date. We aimed to evaluate the effectiveness of LPV/r and FVR treatments in non-severe COVID-19 pneumonia patients and compare the clinical outcomes.

Methods: In this retrospective cohort study, the data of non-severe COVID-19 pneumonia patients treated with lopinavir/ritonavir and FVR were analyzed.

Results: A total of 91 non-severe COVID-19 patients, 33 (36.2%) treated with LPV/r and 58 (63.8%) treated with FVR, were included in the study. The mean ages of the LPV/r group and FVR group were 53.1 (13) years and 57.2 (17.44) years, respectively (P=0.24). There was no statistically significant difference between the two groups in terms of comorbidities (P=0.06). FVR patients had higher radiological weight scores than LPV/r patients, but this was not statistically significant (8.67 (3.7) vs 7.66 (3.22) P=0.2, respectively). While SpO_2 levels of FVR patients at the time of admission were lower than those of LPV/r patients, CRP levels were higher (92.22 (2.8) vs 97.87 (2.05), P<0.001, respectively and 75.42 (62) vs 45.42 (49.92), P=0.02, respectively). FVR patients had a shorter fever regression time than LPV/r patients (2.7 (0.9) vs 4 (1), P<0.001, respectively). Post-treatment neutrophil, lymphocyte, N/L ratio and D-Dimer levels decreased more in FVR group compared to the LPV/r group (P=0.01, <0.001, 0.001, <0.001, respectively).

Conclusion: Although non-severe COVID-19 patients using FVR had lower oxygen saturations, more widespread radiological involvement, and higher CRP levels at admission, we found that FVR was more effective in improving laboratory parameters and controlling fever than LPV/r treatment. The efficacy of lopinavir/ritonavir and FVR warrants further verification by future, larger studies.

Keywords: COVID-19, Non-severe pneumonia, Favipiravir, Lopinavir/ritonavir

Öz

Amaç: Günümüzde COVID-19 için kanıtlanmış bir medikal tedavi yoktur. Çalışmamızda ağır seviyeli olmayan COVID-19 pnömoni hastalarında LPV/r ve FVR tedavilerinin etkinliğini değerlendirerek, LPV/r ile FVR ile tedavi edilen hastalar arasındaki klinik sonuçları karşılaştırmayı amaçladık.

Yöntemler: Bu çalışma retrospektif bir kohort çalışmasıdır. Lopinavir/ritonavir ve FVR ile tedavi edilen ağır seviyeli olmayan COVID-19 pnömoni hastalarının verileri incelendi.

Bulgular: 33'ü (%36,2) LPV/r ve 58'i (%63,8) FVR ile tedavi edilen, toplam 91 ağır seviyeli olmayan COVID-19 pnömoni hastası çalışmaya dahil edildi. LPV/r grubunun yaş ortalaması 53,1 (13), FVR grubunun yaş ortalaması 57,2 (17,4) idi (P=0,24). Her iki grup arasında komorbidite varlığı açısından istatiksel olarak anlamlı fark yoktu (P=0,06). FVR hastalarının LPV/r hastalarına göre radyolojik ağırlık skoru daha yüksekti ancak bu istatistiksel olarak anlamlı değildi (sırasıyla 8,67 (3,7) ve 7,66 (3,22), P=0,2). FVR hastalarının başvuru esnasındaki SpO_2 seviyeleri LPV/r hastalarına göre daha düşük, CRP seviyeleri daha yüksekti (sırasıyla 92,22 (2,8) ve 97,87 (2,05), P<0,001, 75,42 (62) ve 45,42 (49,92), P=0,02). FVR hastalarında LPV /r hastalarına göre ateşin düşme süresi daha kısa idi (sırasıyla 2,7 (0,9) ve 4 (1), P<0,001). FVR kullanan hastalarda tedavi sonrasında LPV/r kullanan hastalara göre Nötrofil, Lenfosit, N/L oranı ve D-Dimer seviyelerinin daha fazla düştüğü saptandı (sırasıyla P=0,01, <0,001, 0,001, <0,001).

Sonuç: FVR kullanan hastaların, başvuru esnasında daha düşük oksijen saturasyonlarına, daha yaygın radyolojik tutulumlarına ve daha yüksek CRP seviyelerine sahip olmasına rağmen LPV/r kullanan hastalara göre laboratuvar parametrelerinin düzelmesinde ve ateşin kontrol altına alınmasında daha etkili olduğunu saptadık. COVID-19 hastalarında LPV/r ve FVR tedavilerinin etkinliği üzerine daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: COVID-19, Ağır olmayan pnomoni, Favipiravir, Lopinavir/ritonavir

How to cite/Atıf için: Ayten Ö, Şaylan B. Comparison of non-severe COVID-19 pneumonia patients treated with lopinavir/ritonavir and favipiravir. J Surg Med. 2020;4(11):970-973.

Introduction

Starting from Wuhan/China in December 2019, COVID-19 turned into a pandemic that affected the entire world. As of the end of June 2020, the number of people infected with SARS-CoV-2 has exceeded 10 million and the number of COVID-19 related deaths has exceeded 500 thousand worldwide. In the same period, more than 190 thousand of infected people were reported in Turkey, while the death toll exceeded 5000 [1].

There is currently no proven treatment for COVID-19. Treatment is planned experimentally, considering the clinical experience in SARS and MERS outbreaks and the antiviral activity of some drugs. However, there is not enough data about the effectiveness of the antiviral drugs and at which stage we should use them. Therefore, treatment guidelines and used antiviral agents differ among countries [2]. Although antiviral therapy is generally used in patients with severe and critical COVID-19, there are no studies in the literature regarding the use of antiviral therapy in non-severe (mild and moderate) COVID-19 patients.

Lopinavir/ritonavir (LPV/r) is a proteinase inhibitor in coronaviruses that acts by inhibiting the 3CLpro proteinase, which is responsible for processing the polypeptide product into protein components in the RNA genome [3]. Early LPV/r usage in SARS has been shown to reduce intubation rates, ARDS development and mortality [4-5]. However, this positive effect has not yet been demonstrated in COVID-19 patients [6].

Favipravir (FVR) is a purine analogue that is an RNA-dependent RNA polymerase inhibitor (RDRI) [7]. It has been used in the treatment of COVID-19, considering that it can also be effective in the SARS-CoV-2 virus, an RNA virus known to contain RDRI. Limited number of studies have demonstrated that the use of FVR in COVID-19 patients controls symptoms such as cough and fever in a shorter time and reduces the time for radiological recovery and virus removal [8-9].

In this study, we aimed to evaluate the effectiveness of LPV/r and FVR treatments in non-severe COVID-19 pneumonia patients and compare the clinical outcomes.

Materials and methods

Study population

Ninety-one moderate-level COVID-19 patients, who were followed between 10 March 2020 and 1 May 2020 in Istanbul Sultan Abdülhamid Education and Research Hospital, were included in the study. The patients were divided into two groups as those using FVR (Group 1, n=58) or LPV/r (Group 2, n=33). Ethics committee approval was obtained from the ethics committee of Ümraniye Training and Research Hospital. Inclusion criteria were as follows: 1. Being over 18 years old 2. Having a positive PCR test for COVID-19 3. Despite being COVID PCR negative, being clinically, laboratory and radiologically diagnosed with COVID-19 4. Having newly emerged infiltration compatible with COVID-19 pneumonia in computed tomography 5. SpO_2 level at room air $\geq$ 90% and respiratory rate <30/min 6. Being followed up in an inpatient clinic and using Lpv/r for at least 7 days and FVR for at least 5 days. Exclusion criteria were as follows: 1. Being under the age of 18 2. Being pregnant or breastfeeding 3. Having no findings compatible with COVID-19 pneumonia in computed tomography 4. SpO_2 level in the room air <90% and respiratory rate >30 /min 5. Using LPV/R less than 7 days or FVR less than 5 days. SARS-CoV-2 was detected by next-generation sequencing or real-time RT-PCR method.

Lopinavir/ritonavir and Favipiravir treatment protocol

In the LPV/r group, 2 x 2 200/50 mg LPV/r was used for at least 7 days. In the FVR group, 2x 600 mg FVR was used for the next 4 days after a loading dose of 2x1600 mg for the first day (5 days in total).

Collection of data and evaluation of treatment effectiveness

The demographic and clinical features, laboratory findings and treatment parameters of the patients were obtained from the hospital information system. Demographic features, patient symptoms and comorbidities, progression rates to intensive care unit, laboratory parameters during and after treatment (WBC, neutrophil, lymphocyte, neutrophil/lymphocyte ratio, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP)) were all recorded. Computed tomography was performed to all patients. The severity of radiological findings was evaluated by scoring between 0-20 according criteria described by Chang et al [10]. Based on this classification system, severity of lung involvement was scored as none (0%) (0 points), minimal (1-25%) (1 point), mild (26-50%) (2 points), moderate (51-75%) (3 points) and severe (76-100%) (4 points) by evaluating the percentage of involvement for each lobe. Total radiological weight score was obtained by summing the scores of 5 lobes (0-20).

Statistical analysis

Because of the suitability of the Central Limit Theorem, parametric tests were used without normality testing [11]. In the analysis of the data, mean and standard deviation, minimum and maximum values were used for scales, and frequency and percentage values were used for defining categorical variables. Non-parametric tests were used for LDH and D-Dimer measurements, because of the high deviations from the mean. Student's t and Mann-Whitney U tests were used to compare the means of the two independent groups, and Paired t test was used to compare the means of two dependent groups. Chi-square test statistics were used to evaluate the relationship between categorical variables. Exposure ratio (odds ratio) of the variables that were related to the treatment status are given. $P<0.05$ was considered statistically significant. In the evaluation of the data, www.e-picos.com New York software and MedCalc statistics package program were used.

Results

Ninety-one patients who were hospitalized with the diagnosis of non-severe COVID-19 pneumonia were included in the study. Their mean age was 55.7 ± 16 years. The patients were divided into two groups as those using LPV/r (n=33) and FVR (n=58). While the mean age of patients using LPV/r was 53.1 (13) years, that of patients using FVR was 57.2 (17.44) years ($P=0.24$) (Table 1). At least one comorbid disease was present in 45 patients (49.5%). There was no statistically significant difference between the two groups in terms of presence of

comorbidities (P=0.06) (Table 1). The frequency of coronary artery disease was higher in the FVR (P=0.04) group. A total of 3 patients (3.3%) (2 patients (6.1%) in the LPV/r group and 1 (1.7%) in the FVR group) were transferred from the in-patient clinic to the intensive care unit. There were no deaths in either group. FVR patients had insignificantly higher radiological weight scores than LPV/r patients (8.67 (3.7) vs 7.66 (3.22), P=0.2, respectively). SpO_2 levels of FVR patients at admission were lower than those of LPV/r patients (92.22 (2.8) vs 97.87 (2.05), P<0.001, respectively). FVR patients had a shorter fever regression time compared to LPV/r patients (2.7 (0.9) vs 4 (1), P<0.001, respectively) (Table 1).

Table 1: Demographics, baseline and clinical characteristics of patients treated with LPV/r and FVR

Variables		Total (n=91) n (%)	LPV/r (n=33) N (%)	FVR (n=58) n (%)	*P*-value*
Gender	Male	59 (64.8)	20 (60.6)	39 (67.2)	0.52
	Female	32 (35.2)	13 (39.4)	19 (32.8)	
Age	Mean (SD) (years)	55.7(16)	53.1(13.1)	57.2(17.4)	0.24
Comorbidities	Yes	45 (49.5)	12 (36.4)	33 (56.9)	0.06
	No	46 (50.5)	21 (63.6)	25 (43.1)	
Hypertension	Yes	32 (35.2)	11 (33.3)	21 (36.2)	0.78
	No	59 (64.8)	22 (66.7)	37 (63.8)	
Diabetes	Yes	13 (14.3)	3 (9.1)	10 (17.2)	0.28
	No	78 (85.7)	30 (90.9)	48 (82.8)	
Arrhythmia	Yes	6 (6.6)	-	6 (10.3)	0.06
	No	85 (93.4)	33 (100)	48 (89.7)	
CAD	Yes	7 (7.7)	-	7 (12.1)	0.04
	No	84 (92.3)	33 (100)	51 (87.9)	
CRAD (COPD/ Asthma)	Yes	6 (6.6)	1 (3)	5 (8.6)	0.41
	No	85 (93.4)	32 (97)	53 (91.4)	
Signs and symptoms					
Fever	Yes	77 (84.6)	26 (78.8)	51 (87.9)	0.24
	No	14 (15.4)	7 (21.2)	7 (12.1)	
Cough	Yes	59 (64.8)	19 (57.6)	40 (69)	0.27
	No	32 (35.2)	14 (42.4)	18 (31)	
Dyspnea	Yes	22 (24.2)	8 (24.2)	14 (24.1)	0.99
	No	69 (75.8)	25 (75.8)	44 (75.9)	
Diarrhea and nausea	Yes	21 (23.1)	4 (12.1)	17 (29.3)	0.06
	No	70 (76.9)	29 (87.9)	41 (70.7)	
Headache	Yes	8 (8.8)	1 (3)	7 (12.1)	0.14
	No	83 (91.2)	32 (97)	51 (87.9)	
Transfer to ICU	Yes	3 (3.3)	2 (6.1)	1 (1.7)	0.26
	No	88 (96.7)	31 (93.9)	57 (98.3)	
Radiological weight score	Mean (SD)	9.3 (3.55)	7.66 (3.22)	8.67 (3.7)	0.2
SpO_2 level (room air)	Mean (SD)	93.18 (2.85)	97.87 (2.05)	92.22 (2.8)	<0.001
Clinical length of stay (day)	Mean (SD)	11.1 (3.7)	11.5 (3)	10.9 (4)	0.51
Fever response time (day)	Mean (SD)	3.2 (1.18)	4 (1)	2.7 (0.9)	<0.001

N: number, SD: standard deviation, Min: minimum, Max: maximum, CAD: coronary artery disease, CRAD: chronic respiratory airway disease, COPD: chronic obstructive pulmonary disease, GIS: gastrointestinal system, ICU: intensive care unit. *P is significant at the level of <0.05. (Chi-square test, Student's t test)

Prognostic laboratory parameters at the time of hospital admission were compared between the two groups (Table 2). CRP values were higher in FVR patients compared to the LPV/r group (75.42 (62) vs 45.42 (49.92), P=0.02, respectively). There was no statistical difference between WBC, Neutrophil, Lymphocyte, N/L ratio, LDH and D-Dimer levels (Table 2).

Clinical and prognostic laboratory parameters before and after Lpv/r and FVR treatments were also compared (Table 3). After the treatment, N/L ratio and LDH significantly decreased and WBC significantly increased in the LPV/r group (P=0.01, P=0.01, P=0.05, respectively), and neutrophil, lymphocyte, N/L ratio, CRP and LDH levels significantly decreased and SpO_2 levels significantly increased (P<0.02, <0.001, <0.001, <0.001, <0.001, respectively) in the FVR group (Table 3). Post-treatment neutrophil, lymphocyte, N/L ratio and D-Dimer levels were significantly decreased in patients using FVR when compared to patients using LPV/r (0.01, <0.001, 0.001, <0.001, respectively) (Table 3).

Table 2: Comparison of laboratory parameters at presentation of patients treated with LPV/r and FVR

Variables	Total (n=91)	LPV/r (n=33) x̄ (SD)	FVR (n=58) x̄ (SD)	*P*-value*
WBC (K/mm3)	5.95 (1.95)	5.67 (1.91)	6.11(1.97)	0.3
Neutrophil (K/mm3)	3.4 (2.3)	4.06 (1.82)	4.53 (1.99)	0.27
Lymphocyte (K/mm3)	2.2 (1.82)	1.33 (0.94)	1.14 (0.46)	0.22
N/L ratio	2.97 (2.7)	3.78 (2.57)	4.44 (2.43)	0.23
CRP (mg/L)	64.54 (59.68)	45.42 (49.92)	75.42 (62.39)	0.02
LDH (U/L)	613.86 (745.35)	527.03 (284.98)	663.27 (908.15)	0.4
D-Dimer (µg/L)	809.41(1329.75)	666.23(715.01)	873.6(1528.74)	0.6

N: number, SD: standard deviation, WBC: white blood cell, N/L ratio: neutrophil/lymphocyte ratio, CRP: C-reactive protein, LDH: lactate dehydrogenase. *P is significant at the level of <0.05. (Student's t test/Mann-Whitney U)

Table 3: Comparison of prognostic laboratory and clinical parameters before and after LPV/r and FVR treatment

	LPV/r (n=33)			FVR (n=58)			*P*-value *
Variables	Before treatment x̄ (SD)	After treatment x̄ (SD)	*P*-value	Before treatment x̄ (SD)	After treatment x̄ (SD)	*P*-value	
WBC (K/mm3)	5.67 (1.91)	6.4 (2.7)	0.05	6.11 (1.97)	6.2 (1.9)	0.77	0.17
Neutrophil (K/mm3)	4.06 (1.82)	3.81 (1.67)	0.35	4.53 (1.99)	3.86 (1.65)	<0.02	0.01
Lymphocyte (K/mm3)	1.33 (0.94)	1.52 (0.48)	0.29	1.14 (0.45)	1.75 (0.64)	<0.001	<0.001
N/L ratio	3.78 (2.57)	2.69 (.35)	0.01	4.44 (2.43)	2.4 (1.11)	<0.001	0.0001
CRP (mg/L)	45.42 (49.92)	49.11 (65.39)	0.79	75.42 (62.39)	19.41 (30.63)	<0.001	0.39
LDH (U/L)	527.03 (284.98)	400.15 (91.52)	0.01	663.27(908.15)	399.2 (104.9)	<0.001	0.49
D-Dimer (µg/L)	686.33 (737.86)	936.41 (959.97)	0.54	873.6 (1528.74)	557.7 (580.39)	0.39	<0.001
SpO_2	94.87 (2.05)	94.72 (1.82)	0.72	92.22 (2.8)	95.37 (2.6)	<0.001	0.13

N: number, SD: standard deviation, WBC: white blood cell, N/L ratio: neutrophil/lymphocyte ratio CRP: C-reactive protein, LDH: lactate dehydrogenase. *P is significant at the level of <0.05. (Paired t test/Wilcoxon test/Student's t test)

Discussion

There are limited data regarding the effectiveness of LPV/r and FVR treatments in patients with non-severe COVID-19 pneumonia. This retrospective study is the first to evaluate the effects of LPV/r and FVR treatments on clinical and laboratory parameters in that patient group.

In our study, we found that FVR was more effective in improving laboratory parameters and controlling fever when compared to LPV/r in non-severe COVID-19 patients, despite lower oxygen saturation, more widespread radiological involvement, and higher CRP levels. In their study, Cai et al. [8] showed that in COVID-19 patients with SpO_2 >93% and respiratory rate <30 /minute who received FVR, viral clearance was faster compared to those who received LPV/r (4 vs. 11 days). They also showed that radiological recovery (91.43% vs. 62.22%) was better. No comparison of clinical and laboratory parameters was made in this study.

Approximately 20% of COVID-19 patients progress to multi-organ dysfunction, including respiratory failure, septic shock, acute cardiac injury, or acute renal failure [12-13]. In our study, only 3 patients were transferred to the intensive care unit due to respiratory failure. None of them died. Although the number of patients using FVR was higher than patients using LPV/r (n=58 vs n=33), the proportion of patients transferred to the intensive care unit was insignificantly lower (1.7% vs 6.1%).

High AST, ALT, total bilirubin, LDH, D-Dimer, CRP, WBC levels and low lymphocyte values were shown to be associated with progression in COVID-19 patients [14]. A recent meta-analysis also states that patients with severe COVID-19 have higher levels of neutrophils, LDH, D-Dimer, CRP, WBC levels and lower lymphocyte counts than patients with non-

severe COVID-19 [15]. In our study, Neutrophil, Lymphocyte, N/L ratio and D-Dimer levels were significantly decreased after FVR treatment when compared to LPV/r.

In their study, Cao et al. [7] compared standard treatment with Lpv/r in 199 severe COVID-19 patients. They found no significant differences in clinical improvement (hazard ratio for clinical improvement: 1.31, 95% confidence interval [CI], 0.95 to 1.80) and mortality (9.2% vs. 25.0%, respectively, difference: -5.8 percentage points; 95% CI, -17.3 to 5.7). In our study, a decrease in N/L ratio and LDH levels, and a significant increase in WBC values were observed after LPV/r treatment. Two patients were transferred to the intensive care unit despite receiving treatment, but there were no deaths. It can be easily concluded that the major reason for the absence of mortality was the study being conducted among non-severe patients.

Although the use of FVR in COVID-19 has been approved in China, the use of favipiravir has not been mentioned in the treatment guidelines [16]. There are limited publications on the use of FVR in the treatment of COVID-19. In a study comparing FVR with arbidol in COVID-19 patients, it was shown that cough and fever reduction time was shorter in the favipiravir group, although there was no difference between the two groups in terms of clinical recovery on the 7th day of treatment (1.75 days vs 1.70 days, respectively, P<0.001) [9]. In our study, the fever decline time was shorter in FVR patients compared to LPV/r patients (2.7 (0.9) vs 4 (1)).

Limitations

The most important limitation of our study is its retrospective cohort design, which is why the side effects associated with the use of Lpv/r and FVR could not be evaluated in this study. However, none of the patients had to stop taking the drug due to side effects.

Conclusion

Although non-severe COVID-19 patients using FVR had lower oxygen saturations, more widespread radiological involvement, and higher CRP levels at admission, we found that FVR treatment was more effective in improving laboratory parameters and controlling fever than LPV/r. The efficacy of lopinavir/ritonavir and FVR warrants further verification in future study.

References

1. World Health Organization (WHO): Coronavirus Disease (COVID-2019) Situation Reports, 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports. Accessed 30 June 2020.
2. Ayten O, Ozdemir C, Akturk UA, Sen N, Potential Treatment of COVID-19. Coronavirus Disease 2019 (COVİD 19) and Lung. Euroasian Journal of Pulmonology. 2020;22(4):35-44.
3. Morse JS, Lalonde T, Xu S, Liu WR. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. Chembiochem. 2020;21(5):730-8.
4. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, et al. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. Hong Kong Med J. 2003;9(6):399–406.
5. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. Thorax. 2004;59(3):252-6.
6. De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem. Asian J. 2019;14:3962–8.
7. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med. 2020;382:1787-99.
8. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental treatment with favipiravir for COVID-19: An open-label control study. Engineering 2020 March 18. [E-pub ahead of print] doi: 10.1016/j.eng.2020.03.007
9. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir versus arbidol for COVID-19: A trial. BioRxiv 2020 April 15. [E-pub ahead of print] doi: 10.1101/2020.03.17. 20037432
10. Chang Y, Yu C, Chang S, Galvin JR, Liu H, Hsiao C, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology. 2005;236(3):1067–75.
11. Norman, G. Likert scales, levels of measurement and the laws of statistics. Advances in Health Sciences Education. 2010;15(5):625-32.
12. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497–506.
13. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-9.
14. Giovanni PG, Maccaferrib M, Ruinia C, Tomasia A, Ozbend T. Biomarkers associated with COVID-19 disease progression. Critical Reviews in Clinical Laboratory Sciences. 2020;57(6):389-99.
15. Bao J, Li C, Zhang K, Kang H, Chen W, Gu B, Comparative analysis of laboratory indexes of severe and non-severe patients infected with COVID-19. Clinica Chimica Acta. 2020;509:180-94.
16. National Health Commission & State Administration of Traditional Chinese Medicine: Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia, The 7th edition, 2020 March 3. http://www.nhc.gov.cn/yzygj/s7653p/202002/ 8334a832 6d. Accessed 30 June 2020.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):974-977.
DOI: 10.28982/josam.736846

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

C-reactive protein/albumin ratio in patients with multiple sclerosis and its relationship with disease subtype and disability

Multiple skleroz hastalarında C-reaktif protein/albümin oranı ve hastalık alt tipi ve disabilite ile ilişkisi

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Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, Konya Training and Research Hospital Ethical Committee (5/8/2020, 38-15). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma, Sağlık Bilimleri Üniversitesi, Konya Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (08.05.2020, 38-15). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: This study was presented as an oral presentation at the 15st Uludag Neurology Days Congress in Bursa, Turkey in March 2020.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Oxidative stress and inflammation are the cause of demyelination and axonal damage in patients with Multiple Sclerosis (MS). Serum C-reactive protein (CRP) and albumin levels are used as a marker of systemic inflammation and oxidative stress for many diseases. In this study, we aimed to determine the level of CRP/albumin ratio in patients with MS and its relationship with disease subtype and disability.

Methods: This cross-sectional study was conducted in patients treated for MS disease. One hundred twenty MS patients and 62 healthy controls were included. Sociodemographic characteristics were questioned. MS subtype was determined. Disability was calculated with Expanded Disability Status Scale (EDSS). Patients were divided into 3 groups: EDSS 0-3 (minor), 3.5-4.5 (moderate) and 5.0 or higher (major). Attack frequency, albumin and CRP serum levels were noted, and hemogram was analyzed with fluorescence flow cytometry.

Results: There were 71 (59.2%) female and 49 (40.8%) male patients in the study, and their mean age was 39.49 (11.47) years. Leukocyte value was higher and albumin was lower in patients with MS (P=0.046, P=0.006). In progressive MS patients, CRP and CRP/albumin ratio was higher and albumin level was lower compared to the relapse remitting subtype (P<0.01). Patients with high EDSS had higher CRP and CRP/albumin ratio and lower albumin levels (P<0.01). A low correlation was detected between the number of attacks and CRP/albumin ratio (P=0.032; r=0.196).

Conclusion: We detected that albumin level and CRP/albumin ratio are related with subtype and activity of MS disease.

Keywords: Multiple sclerosis, Hypoalbuminemia, CRP/albumin ratio

Öz

Amaç: Oksidatif stres ve inflamasyon Multiple Skleroz (MS) hastalarında demiyelinizasyon ve aksonal hasarın sebebidir. Serum C-reaktif protein (CRP) ve albümin düzeyleri birçok hastalıkta sistemik inflamasyon ve oksidatif stresin belirteci olarak kullanılmaktadır. Bu çalışmada, MS hastalığında CRP/albümin düzeyinin saptanması, hastalık alt tipi ve dizabilite ile ilişkisini değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu kesitsel çalışma MS hastalığı nedeniyle tedavi edilen hastalarda yapıldı. Çalışmaya 120 MS hastası ve 62 sağlıklı kontrol alındı. Sosyodemografik özellikler sorgulandı. MS subtipi belirlendi. Dizabilite genişletilmiş özürlülük durum ölçeği (EDSS) ile hesaplandı. Hastalar EDSS 0-3 (hafif), 3,5-4,5 (orta) ve 5,0 veya üzeri (ağır) olmak üzere 3 gruba ayrıldı. Atak sıklığı belirlendi. Albümin ve CRP serum seviyesi belirlendi. Hemogram floresans akış sitometrisi ile ölçüldü.

Bulgular: Çalışmada 71 (%59,2) kadın ve 49 (%40,8) erkek hasta vardı. Yaş ortalamaları 39,49 (11,47) idi. MS hastalarında lökosit değeri daha yüksek, albümin ise düşüktü (P=0,046; 0,006). Progresif MS hastalarında relapsing remitting alt tipine göre CRP ve CRP/albümin oranı daha yüksek, albümin seviyesi daha düşüktü (P<0,01). EDSS yüksek olan hastalarda CRP ve CRP/albümin oranı daha yüksek, albümin seviyesi daha düşüktü (P<0,01). Atak sayısı ile CRP/albümin oranı arasında zayıf korelasyon saptandı (P=0,032; r=0,196).

Sonuç: Bu çalışmada albümin seviyesi ve CRP/albümin oranının MS hastalığında hastalık alt tipi ve aktivitesi ile ilişkili olduğu ortaya konulmuştur.

Anahtar kelimeler: Multiple skleroz, Hipoalbüminemi, CRP/albümin oranı

How to cite/Atıf için: Eren F, Demir A. C-reactive protein/albumin ratio in patients with multiple sclerosis and its relationship with disease subtype and disability. J Surg Med. 2020;4(11):974-977.

Introduction

Axonal damage and neurodegeneration are present in the etiopathogenesis of many acute and chronic neurological diseases. Neurogenerative diseases (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, etc.), inflammatory diseases (Multiple Sclerosis (MS) etc.) and traumatic brain diseases are examples of these [1, 2]. MS is a chronic disease of the central nervous system characterized by demyelination and different degrees of axonal degeneration [3]. There are many different immunological mechanisms in demyelination and axonal damage formation in this disease. Oxidative stress contributes directly and indirectly to this process [4].

Oxidative stress occurs when the balance between the production and destruction of reactive oxygen species (ROS) is disturbed. As ROS is released in cells, antioxidant molecules increase. Thus, neuronal damage is reduced. However, increased ROS release causes many diseases [5, 6]. Proinflammatory conditions (including oxidative stress) are important for MS disease and its progression [7, 8]. Myelin damage occurs because of immune hyperactivation in the early stage of disease. In the chronic period, structural and functional damage occur due to oxidative stress [9].

Serum C-reactive protein (CRP) and albumin are frequently used in routine clinical practice, for diagnosis of acute diseases and evaluation of treatment response. There are many studies which show that it can be used to evaluate prognosis in patients with coronary artery disease, ischemic stroke, sepsis, and cancer [10-13]. Serum albumin is a negative acute phase reactant. It is thought that albumin level may be associated with prognosis of many acute and chronic diseases [10, 14]. CRP/albumin ratio is used as a marker of systemic inflammation and oxidative stress for many diseases [15-17]. In our study, it was aimed to determine the level of CRP/albumin ratio in patients with MS and its relationship with disease subtype and disability.

Materials and methods

Participants and ethical procedure

The sample size was calculated with the G-power program before study. When patient /control ratio was kept at 2, a minimum 144 of samples (96 patients, 48 controls) were required for medium effect size in two-way variance analysis. One hundred twenty MS patients (between 18-65 years of age, treated for at least 1 year) and 62 healthy controls were included in the study between 1 January 2017 and 31 December 2019. The data were collected retrospectively. The study was approved by University of Health Sciences Turkey, Konya Training and Research Hospital, Ethics Committee (5/8/2020; 38-15). The principles of the Declaration of Helsinki and Guidelines for Good Clinical Practices were adhered to during the study. The diagnosis of disease was re-analyzed according to McDonald's criteria [18]. Patients with acute MS attack, active systemic infection (bacterial, viral, or fungal), endocrinological, metabolic, hematological diseases, smoking and alcohol abuse, recent abnormal weight gain or loss, and those who were pregnant, or breastfeeding were excluded from the study.

The duration (years) of MS disease, attacks, and frequency of attacks during the disease period were questioned. Patients were divided into two groups according to the number of attacks (<5: Rare attacks, ≥5: Frequent attacks), and into 3 main groups according to disease types: Relapsing remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS).

Data collection materials

Expanded disability status scale (EDSS)

The extended disability status scale (EDSS) is the most used test in the assessment of disability for MS patients. Total score varies between 0 and 10 (0: Normal neurological examination, 10: Death associated with MS). Disability increases with increasing values from 0 to 10 [19]. Disability due to disease was divided into 3 groups according to EDSS results: 0-3 (minor), 3.5-4.5 (moderate), 5.0 or higher (major).

Laboratory measurements

Blood samples were collected from the antebrachial veins of the patients admitted to outpatient clinic between 09:00-12:00. Separator gel tubes were used for serum tests and potassium-EDTA tubes were used for blood count. Blood was centrifuged at 5000 rpm for 10 minutes and separated to serum. Hemogram was tested with fluorescence flow cytometry. Albumin was measured with spectrophotometric measurement (Cobas 8000 series c702 modular analyzer). CRP level was determined using the immunoturbidimetric method (Wako Chemicals, Osaka, Japan) on a Hitachi 7600 chemistry analyzer (Hitachi, Tokyo, Japan).

Statistical analysis

Data were analyzed with SPSS® version 16.0 statistical package software (SPSS Inc., Chicago, IL, United States). Mean (standard deviation) and median (min-max) values were used to summarize the numerical data. Number (n) and percentage (%) were used to summarize the categorical data. Distribution of data was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Student T test (normally distributed) and Mann Whitney U test (non-normally distributed) were used for comparison of two groups, while one-way ANOVA and Kruskal Wallis tests were used for comparing three groups. The relationship between numerical data was evaluated by Spearman Correlation test. Correlation coefficients were as follows: 0-0.25 weak, 0.25-0.50 weak-medium, 0.50-0.75 strong, 0.75-1.00 very strong. *P*-value <0.05 was considered statistically significant.

Results

One hundred twenty MS patients, consisting of 59.2% (n=71) females, and 40.8% (n=49) males and 62 controls were included in the study. Disease characteristics and blood values of patients are summarized in Tables 1 and 2.

Albumin values were compared between patient and control groups. Leukocyte value was higher and albumin value was lower in MS patients (P=0.046, P=0.006, respectively). Blood values of patient and control groups are presented in Table 3. There was no difference in blood parameters between genders (P>0.05).

The number of attacks was divided into 2 groups, as <5, and ≥5, between which blood values of MS patients were compared (P> 0.05). MS patients in the study were divided into

3 groups according to EDSS results, as follows: EDSS 0-3.0: Minor disability, 3.5-4.5: Moderate disability, and 5.0 or higher: Major disability. Blood values of these 3 groups are summarized in Table 4. CRP values were higher and albumin levels were lower in the group with major disability compared to the other two groups (P<0.05 for both). Albumin level and CRP/albumin ratio significantly differed across all groups. Patients with high EDSS had low albumin levels and high CRP/albumin ratios (P<0.05).

Table 1: Disease subtype, attack, and disability in patients with multiple sclerosis

		Number (n)	Percentage (%)
	Female	71	59.2
	Male	49	40.8
MS type	PRMS	91	75.8
	SPMS	24	20.0
	PPMS	5	4.2
Attack number	<5	76	63.3
	≥5	44	36.7
Disability	EDSS 0-3	67	55.8
(0-10)	EDSS 3.5-4.5	33	27.5
	EDSS 5.0 or higher	20	16.7

RRMS: Relapsing remitting multiple sclerosis, SRMS: Secondary progressive multiple sclerosis, PPMS: Primary progressive multiple sclerosis, EDSS: Expanded Disability Status Scale

Table 2: Disease characteristics and blood parameters in patients with multiple sclerosis

	Mean (SD)	Median(min-max)
Age (years)	39.49 (11.47)	39.00 (19.00-64.00)
Disease duration (years)	8.60 (5.50)	8.00 (1.00-26.00)
Attack number	4.35 (2.99)	3.00 (1.00-20.00)
EDSS (0-10)	2.69 (1.84)	2.00 (0.00-7.00)
Leukocyte (10^3/mm^3)	7.00 (2.16)	6.82 (2.81-15.09)
CRP (mg/l)	4.02 (2.19)	3.11 (2.33-17.00)
Albumin (g/L)	40.77 (3.57)	41.00 (29.80-48.00)
CRP/albumin ratio	0.10 (0.05)	0.07 (0.05-0.43)

SD: Standard deviation, EDSS: Expanded Disability Status Scale, CRP: C-reactive protein, min: minimum, max: maximum

Table 3: Blood parameters in patients with multiple sclerosis and control group

	Control group (n=62) Mean (SD)	Patient group (n=120) Mean (SD)	P-value
Leukocyte (10^3/mm^3)*	7.86 (1.95)	7.46 (2.16)	0.056
Albumin (g/L)*	42.77 (3.47)	40.77 (3.57)	0.006
C-reactive protein (CRP) (mg/l)**	3.88 (1.72)	4.02 (2.19)	0.312
CRP/albumin ratio **	0.09 (0.03)	0.10 (0.05)	0.205

*: Independent sample T test, **: Mann Whitney U test

Table 4: Blood parameters in patients with multiple sclerosis according to disability group

	EDSS 0-3[a] (n=67) Mean (SD)	EDSS 3.5-4.5[b] (n=33) Mean (SD)	EDSS 5.0 or higher[c] (n=20) Mean (SD)	P-value
Leukocyte (10^3/mm^3)*	6.96 (2.29)	6.81 (2.20)	7.43 (1.58)	0.235
Albumin (g/L)**	42.46 (2.99)	39.59 (3.12)	37.05 (2.28)	<0.001$^{(a-b)}$ <0.001$^{(a-c)}$ 0.016$^{(b-c)}$
C-reactive protein (CRP) (mg/l)**	3.63 (1.77)	3.87 (1.80)	5.59 (3.18)	<0.001$^{(a-c)}$ 0.004$^{(b-c)}$
CRP/albumin ratio **	0.08 (0.04)	0.09 (0.05)	0.14 (0.07)	0.004$^{(a-b)}$ <0.001$^{(a-c)}$ <0.001$^{(b-c)}$

EDSS: Expanded Disability Status Scale, *: One-way Anova, **: Kruskal Wallis test

MS patients were compared according to disease subtypes (Table 5). Albumin values were higher, and CRP and CRP/albumin values were lower in patients with RRMS compared to those with SPMS (P<0.001, P<0.05, respectively).

CRP and CRP/albumin levels increased with increasing disease duration (P=0.038, P<0.001, r=0.190, r=0.321, respectively). A negative correlation was detected between disease duration and albumin level (P<0.001, r=-0.342), number of attacks and albumin level (P=0.032, P=0.011, r=0.196, r=-232, respectively), and EDSS and albumin level (P<0.001, r=-0.574), while a positive correlation was detected between the number of attacks and CRP/albumin level (P<0.001, P<0.001, r=0.375, r=0.586, respectively), and EDSS, CRP and CRP/albumin level (P<0.001, P<0.001, r=0.375, r=0.586, respectively).

Table 5: Blood parameters in patients with multiple sclerosis according to disease subgroup

	RRMS[a] (n=91) Mean (SD)	SPMS[b] (n=24) Mean (SD)	PPMS[c] (n=5) Mean (SD)	P-value
Leukocyte (10^3/mm^3)*	6.93 (2.35)	7.44 (1.32)	5.78 (1.31)	0.313
Albumin (g/L)*	41.43 (3.42)	38.30 (3.26)	40.59 (2.83)	<0.001$^{(a-b)}$
C-reactive protein (CRP) (mg/l)**	3.47 (1.41)	5.85 (3.37)	5.27 (1.36)	<0.001$^{(a-b)}$ 0.004$^{(a-c)}$
CRP/albumin ratio **	0.08 (0.03)	0.15 (0.08)	0.13 (0.04)	<0.001$^{(a-b)}$ 0.009$^{(a-c)}$

RRMS: Relapsing remitting multiple sclerosis, SRMS: Secondary progressive multiple sclerosis, PPMS: Primary progressive multiple sclerosis, *: One-way Anova, **: Kruskal Wallis test

Discussion

MS is a chronic disease characterized by demyelination of central nervous system, accompanied by axonal and neuronal degeneration. Demyelination is a complex process that includes inflammation and oxidative stress [3]. Oxidative stress and neuronal damage occur with exceeding the antioxidant capacity of metabolism [20]. ROS, which occurs with oxidative stress, causes neuronal degeneration with proinflammation. In many neurological diseases, the antioxidant capacity of the brain decreases, and it becomes more prone to inflammation [21,22]. Although many different parameters have been used to evaluate the inflammation and oxidative process, an objective measurement method has not been determined. CRP/albumin ratio is one of the parameters for evaluating oxidative stress and inflammation, which is used especially for acute diseases, along with evaluation of neurodegenerative diseases [15,17]. As a result of literature review, no study which evaluates the CRP/albumin ratio in patients with MS was found.

Hematological and biochemical tests (including CRP and albumin) provide qualitative and quantitative information. They are cheaper and easier to access than many inflammatory biomarkers such as interleukin 6 and tumor necrosis alpha (TNF-α). The ratio of these two parameters (CRP/albumin ratio) is a marker used to evaluate inflammation, oxidative stress, and prognosis [10,11,15,17].

CRP is an acute phase protein synthesized in hepatocytes secondary to cytokines during inflammation. Its serum level increases in acute inflammation. However, it is known to be associated with chronic inflammation [23]. Its level increases during the inflammatory process, in which it participates directly [24]. Molecular based studies have shown that the level of CRP increases in local neuronal tissues in some neurodegenerative diseases (Alzheimer's disease, etc.) [25,26].

Serum CRP level is higher in patients with neuromyelitis optica (NMO) than MS and healthy controls, and in MS patients compared to healthy controls. It is also increased in female NMO patients than female healthy controls. However, there is no difference between the genders in terms of CRP levels in patients with MS. There is a positive correlation between attack frequency, disease duration and EDSS with CRP level [27]. Some studies show that CRP level is not different between RRMS patients and the control group [28]. Neutrophil/lymphocyte ratio and CRP are higher in MS patients (especially with high EDSS scores). These markers are associated with a poor prognosis [29]. However, cerebral antioxidant capacity is lower in progressive MS disease [22]. In our study, serum CRP level and CRP/albumin ratio were similar between the patient and control groups, but they were higher in PPMS and SPMS patients compared to those with RRMS. There

was no difference between genders. A positive correlation was detected between attack number, CRP level and CRP/albumin ratio, all of which were similar in patients with different attack frequencies (over 5, 5 and below). Especially in groups with high EDSS, serum CRP and CRP/albumin ratio were higher. Inflammation is higher in patients with progressive MS and high EDSS values. CRP and CRP/albumin ratio are associated with disease activity and disability in patient with MS.

Serum albumin eliminates free oxygen radicals and has antioxidant activity. Hypoalbuminemia is associated with oxidative stress and inflammation. Some studies show that there is a negative correlation between CRP and albumin levels [30]. Albumin level is lower in MS patients than healthy controls (especially in PPMS and SPMS subgroups) [14]. In our study, albumin level was lower in patients with MS, especially in those with SPMS and high EDSS scores, akin to the literature.

Limitations

The fact that the number of PPMS and SPMS subgroup patients were low, and the study's cross-sectional nature are limitations which both restrict our causal conclusion. Prospective studies with larger patient groups are needed.

Conclusion

CRP/albumin ratio is related to the number of attacks, EDSS and disease duration in patients with MS. It is especially higher in progressive MS subgroups. CRP/albumin ratio may be important in evaluating disability, attack frequency and MS subtype in patients with MS.

Acknowledgments

The author would like to thank Dr. Güllü Eren from Necmettin Erbakan University, Meram Faculty of Medicine, Department of Public Health and Dr. Recep Aygül from Selcuk University, Faculty of Medicine, Department of Neurology.

References

1. Coleman M. Axon degeneration mechanisms: commonality amid diversity. Nat Rev Neurosci. 2005;6(11):889-98. doi: 10.1038/nrn1788.
2. Coleman MP, Perry VH. Axon pathology in neurological disease: a neglected therapeutic target. Trends Neurosci. 2002;25(10):532-7. doi: 10.1016/s0166-2236(02)02255-5.
3. Lassmann H. Pathogenic mechanisms associated with different clinical courses of multiple sclerosis. Fronti Immunol. 2019;9:3116. doi: 10.3389/fimmu.2018.03116.
4. Su KG, Banker G, Bourdette D, Forte M. Axonal degeneration in multiple sclerosis: the mitochondrial hypothesis. Curr Neurol Neurosci Rep. 2009;9(5):411-7. doi: 10.1007/s11910-009-0060-3.
5. Rojo AI, McBean G, Cindric M, Egea J, López MG, Rada P, et al. Redox control of microglial function: Molecular mechanisms and functional significance. Antioxid Redox Signal. 2014;21(12):1766-801. doi: 10.1089/ars.2013.5745.
6. Moretti M, Fraga DB, Rodrigues A. Preventive and therapeutic potential of ascorbic acid in neurodegenerative diseases. CNS Neurosci Ther. 2017;23(12):921-9. doi: 10.1111/cns.12767.
7. Carvalho C, Moreira PI. Oxidative Stress: A Major player in cerebrovascular alterations associated to neurodegenerative events. Front Physiol. 2018;9:806. doi: 10.3389/fphys.2018.00806.
8. Lutton EM, Farney SK, Andrews AM, Shuvaev VV, Chuang GY, Muzykantov VR, et al. Endothelial targeted strategies to combat oxidative stress: Improving outcomes in traumatic brain injury. Front Neurol. 2019;10:582. doi: 10.3389/fneur.2019.00582.
9. Miller E, Wachowicz B, Majsterek I. Advances in antioxidative therapy of multiple sclerosis. Curr Med Chem. 2013;20(37):4720-30. doi: 10.2174/09298673113209990156.
10. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A, et al. C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. N Engl J Med. 2004;350(14):1387-97. doi: 10.1056/NEJMoa032804.
11. Kaptoge S, Di Angelan¬tonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of cor¬onary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet 2010;375(9709):132-40. doi: 10.1016/S0140-6736(09)61717-7.
12. Matsuo R, Ago T, Hata J, Wakisaka Y, Kuroda J, Kuwashiro T, et al. Plasma C-reactive protein and clinical outcomes after acute ischemic stroke: a prospective observational study. PLoS One. 2016;11(6):e0156790. doi: 10.1371/journal.pone.0156790.
13. Windgassen EB, Funtowicz L, Lunsford TN, Harris LA, Mulvagh SL. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. Postgrad Med. 2011;123(1):114-9. doi: 10.3810/pgm.2011.01.2252.
14. Oliveira SR, Kallaur AP, Reiche EMV, Kaimen-Maciel DR, Panis C, Lozovoy MAB, et al. Albumin and protein oxidation are predictors that differentiate relapsing-remitting from progressive clinical forms of multiple sclerosis. Mol Neurobiol. 2017;54(4):2961-8. doi: 10.1007/s12035-016-9860-z.
15. Yazar HO, Yazar T, Aygün A, Kaygisiz Ş, Kirbaş D. Evaluation of simple inflammatory blood parameters in patients with migraine. Ir J Med Sci. 2020;189(2):677-83. doi: 10.1007/s11845-019-02136-y.
16. Ju SY, Ma SJ. High C-reactive protein to albumin ratio and the short-term survival prognosis within 30 days in terminal cancer patients receiving palliative care in a hospital setting: A retrospective analysis. Medicine 2020;99(9). e19350. doi: 10.1097/MD.0000000000019350.
17. Yazar T, Yazar HO. Evaluation of C-reactive protein/albumin ratio according to stage in patients with idiopathic parkinson disease. Turkish J Neurol. 2019;25(3):123-8. doi: 10.4274/tnd.galenos.2019.13334.
18. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018;17(2):162-73. doi: 10.1016/S1474-4422(17)30470-2.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology 1983;33(11):1444-52. doi: 10.1212/wnl.33.11.1444.
20. Frati A, Cerretani D, Fiaschi AI, Frati P, Gatto V, La Russa R, et al. Diffuse axonal injury and oxidative stress: A comprehensive review. Int J Mol Sci. 2017;18(12). pii: E2600. doi: 10.3390/ijms18122600.
21. Siotto M, Filippi MM, Simonelli I, Landi D, Ghazaryan A, Vollaro S, et al. Oxidative stress related to iron metabolism in relapsing remitting multiple sclerosis patients with low disability. Front Neurosci. 2019;13:86. doi: 10.3389/fnins.2019.00086.
22. Choi IY, Lee P, Adany P, Hughes AJ, Belliston S, Denney DR, et al. In vivo evidence of oxidative stress in brains of patients with progressive multiple sclerosis. Mult Scler. 2018;24(8):1029-38. doi: 10.1177/1352458517711568.
23. Luan YY, Yao YM. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Front Immunol. 2018;9:1302. doi: 10.3389/fimmu.2018.01302.
24. Vachatova S, Andrys C, Krejsek J, Salavec M, Ettler K, Rehacek V, et al. Metabolic syndrome and selective inflammatory markers in psoriatic patients. J Immunol Res. 2016;2016:5380792. doi: 10.1155/2016/5380792.
25. Yasojima K, Schwab C, McGeer EG, McGeer PL. Human neurons generate C-reactive protein and amyloid P: upregulation in Alzheimer's disease. Brain Res. 2000;887(1):80-9. doi: 10.1016/s0006-8993(00)02970-x.
26. Mancinella A, Mancinella M, Carpinteri G, Bellomo A, Fossati C, Gianturco V, et al. Is there a relationship between high C-reactive protein (CRP) levels and dementia? Arch Gerontol Geriatr. 2009;49(1):185-94. doi: 10.1016/j.archger.2009.09.028.
27. Shu Y, Li R, Qiu W, Chang Y, Sun X, Fang L, Kermode AG. Association of serum gamma-glutamyltransferase and C-reactive proteins with neuromyelitis optica and multiple sclerosis. Mult Scler Relat Disord. 2017;18:65-70. doi: 10.1016/j.msard.2017.09.021.
28. Hon G, Hassan M, van Rensburg SJ, Abel S, Marais DW, van Jaarsveld P, et al. Immune cell membrane fatty acids and inflammatory marker, C-reactive protein, in patients with multiple sclerosis. Br J Nutr. 2009;102(9):1334-40. doi: 10.1017/S0007114509382185.
29. Guzel I, Mungan S, Oztekin ZN, Ak F. Is there an association between the Expanded Disability Status Scale and inflammatory markers in multiple sclerosis?. J Chin Med Assoc. 2016;79(2):54-7. doi: 10.1016/j.jcma.2015.08.010.
30. Yeun JY, Levine RA, Mantadilok V, Kaysen GA. C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. Am J Kidney Dis. 2000;35(3):469-76. doi: 10.1016/s0272-6386(00)70200-9.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):978-981.
DOI: 10.28982/josam.717046

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of portal vein variations in multidetector CT

Vena porta varyasyonlarının multidetector CT'de değerlendirilmesi

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Ethics Committee Approval: This study was approved by Mevlana University Faculty of Medicine Clinical Trials Ethical Committee (Date and number: 12.03.2014 3/12/2014 and 26857650/015). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Mevlana Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır (Tarih ve sayı: 12.03.2014 ve 26857650/015). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: It is important for surgeons to have a comprehensive knowledge of vascular anatomy when performing liver interventions. For example, liver transplantation requires a vast understanding of vascular anatomy and variations. This study aimed to evaluate the intrahepatic branching pattern of the portal vein to find out unknown variations.

Methods: Multidetector computed tomography images of the abdomen region were used from the PACS archives of Selcuk University Medical Faculty Hospital. Images of 838 patients (464 females and 374 males) who had no hepatic pathologies were examined. Images were evaluated in terms of the presence of variations, and the cases were divided into groups, all of which were compared in terms of gender.

Results: A previously unknown variation of the portal vein was detected in 4.9% of the patients: The left portal vein curved reversely after its origination from the main portal vein, supplying liver segments II and IV, after which it branched to supply segment III. In addition, four types of previously known variations of the portal vein were detected. Normal anatomic branching of portal vein was detected in 82.6% of the patients.

Conclusion: A previously unknown variation was detected. Awareness of this variation and other known variations is significant in hepatic transplantation, surgery, and interventions.

Keywords: Portal vein, Multidetector CT, Variation of the Portal Vein, Couinaud segmentation, Liver

Öz

Amaç: Cerrahların, karaciğer müdahalelerini gerçekleştirirken kapsamlı bir vasküler anatomi ye sahip olmaları gereklidir. Karaciğer transplantasyonu operasyonu vasküler anatomi ve varyasyonlar hakkında iyi bir bilgi gerektirir. Bu çalışma amacı, bilinmeyen varyasyonları bulmak için portal venin intrahepatik dallanma paterninin değerlendirilmesidir.

Yöntemler: Bu kesitsel çalışma, çok yönlü BT (MDCT) kullanan bir araştırma makalesidir. Karaciğer patolojisi olmayan 838 hastanın (464 kadın ve 374 erkek) çok dedektörlü BT görüntüleri incelendi. Görüntüler varyasyon varlığı açısından değerlendirildi. Sonuç olarak, vakalar gruplara ayrıldı. Tüm gruplar cinsiyete göre analiz edildi.

Bulgular: Hastaların %4,9'unda daha önce bilinmeyen bir portal ven varyasyonu tespit edildi: sol portal ven, ana portal venden çıktıktan sonra ters yönde eğrilir. Karaciğerin II ve IV segmentlerini besler ve segment III'ü besler. Ayrıca, portal damarın önceden bilinen dört çeşidi de tespit edildi. Hastaların %82,6'sında portal vende normal anatomik dallanma bulundu.

Sonuç: Önceden bilinmeyen bir varyasyon tespit edildi. Bu varyasyonun ve diğer bilinen varyasyonların farkında olunması, karaciğer transplantasyonu, cerrahi ve girişimlerde çok önemlidir.

Anahtar kelimeler: Portal ven, Multidetector BT, Portal ven varyasyonu, Couinaud segmentasyonu, Karaciğer

How to cite/Atıf için: Ulusoy M, Bolatlı G, Koplay M, Acar M, Zararsız İ. Evaluation of portal vein variations in multidetector CT. J Surg Med. 2020;4(11):978-981.

Introduction

The portal vein is an important blood vessel that conducts blood from the gastrointestinal tract and spleen to the liver. It is formed by the combination of the superior mesenteric vein and the splenic vein and divides into the right and left branches to enter the liver. Branches of the portal vein are distributed according to Couinaud segmentation and involved in the liver's blood supply. Couinaud segmentation divides the liver into eight functionally independent segments, each with its own vascular inflow, outflow, and biliary drainage [1-5].

Around 20,000 liver transplants are performed annually all over the world [1]. Complex hepatobiliary surgical and vascular intervention procedures have also increased immensely. Lack of awareness of anatomical variations can result in serious complications when dealing with such procedures [2-5]. There are some portal vein variations detected so far. This study was performed to evaluate the variations of portal vein and describe undefined variations if found.

Materials and methods

Tomographic images of 838 patients without any liver pathologies (374 males and 464 females) who underwent abdominal MDCT imaging for any reason at the Hospital of Selcuk University, Medical Faculty were examined. The examination was conducted with 256-section double-tube CT (Siemens, Somatom, Definition Flash, Germany) device at a routine section thickness of 3 mm, and 1 mm section intervals and 1 mm section thickness after reconstruction. The incidence and type of portal vein variations were defined with multiplanar reconstruction (MPR), maximum intensity projection (MIP), and 3D volume rendering images [4,6-9]. This study was approved by the Clinical Trials Ethical Committee of Mevlana University, Faculty of Medicine (Date and number 3/12/2014 and 26857650/015).

Statistical analysis

Statistical analyses were performed by the Statistical Package for Social Sciences, version 15.0 (SPSS. Inc, Chicago, Illinois, USA). Descriptive statistical methods (mean, standard deviation, frequency, correlation) were used. The incidences of portal vein variations were compared between males and females. $P<0.05$ was considered statistically significant.

Results

Normal branching pattern of the portal vein was detected in 345 male and 347 female patients (82.6%; Figures 1 and 2). Portal veins which branched out of the ordinary were considered variations, which occurred in 246 (29.4%, 129 males, 117 females) patients (Figure 1).

A previously unknown variation was detected in 4.9% of the patients (22 males and 19 females). The left portal vein curved reversely after its origination from the main portal vein, supplying the liver segments II and IV, then branching to supply segment III (Figure 3).

Four other types of variations previously reported by other studies were detected. They are as follows:

Trifurcation of the main portal vein into the left portal vein, right anterior portal vein, and right posterior portal vein was detected in 8.6% of patients (35 males and 37 females, Figure 4).

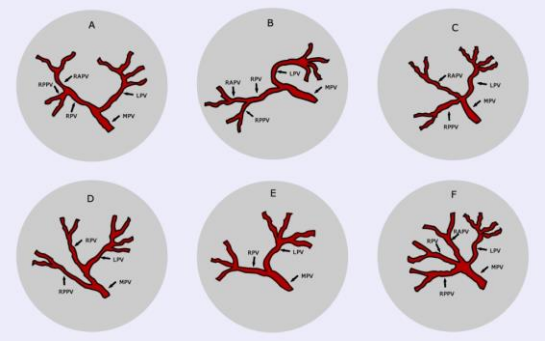

Figure 1: Drawing of (PV) portal vein variations. A: Normal (classic) main PV branching pattern, B: Main PV output and segmentation branching variation of left PV. C: Trifurcation. D: Right posterior PV as the first branch of the main PV. E: Segmental branching variance of right PV divided into three branches. F: Quartifurcation. (MPV: Main portal vein; LPV: Left portal vein; RPV: Right portal vein; RPPV: Right posterior portal vein; RAPV: Right anterior portal vein).

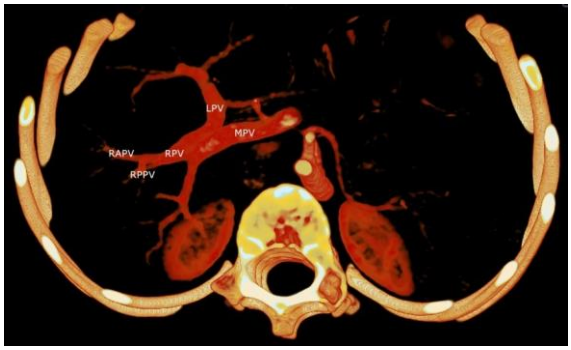

Figure 2: MDCT axial image showing, normal anatomy of intrahepatic segmentation branching PV. (MPV: Main portal vein; LPV: Left portal vein; RPV: Right portal vein; RPPV: Right posterior portal vein; RAPV: Right anterior portal vein). (Figure 1-A)

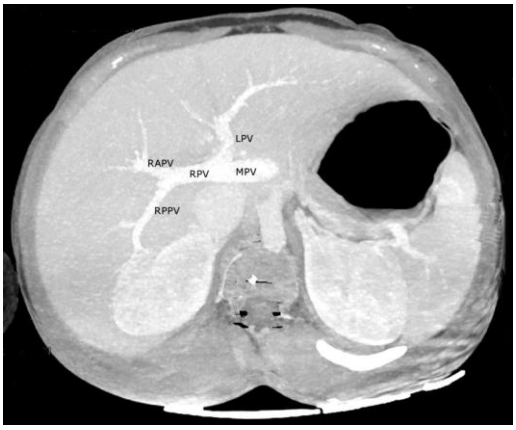

Figure 3: MDCT axial image showing segmental branching variation of left PV. (MPV: Main portal vein; LPV: Left portal vein; RPV: Right portal vein; RPPV: Right posterior portal vein; RAPV: Right anterior portal vein). (Figure 1-B)

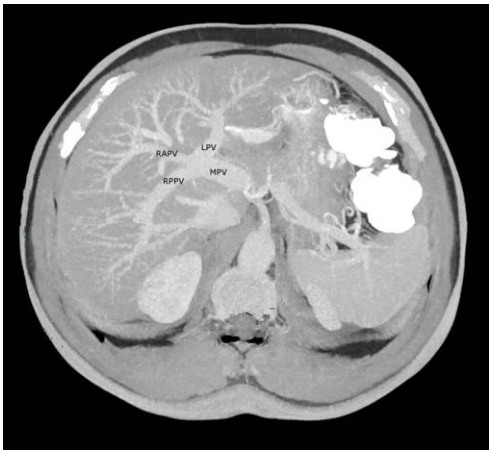

Figure 4: MDCT axial image showing, trifurcation variation of PV. (MPV: Main portal vein; LPV: Left portal vein; RPPV: Right posterior portal vein; RAPV: Right anterior portal vein). (Figure 1-C)

The right posterior portal vein as a first branch of main portal vein: The first branch of main portal vein is right posterior portal vein, it continues to the right for a short distance, and divides into right anterior portal vein and left posterior vein. This variation was detected in 8.9% of the patients (42 males and 33 females, Figure 5).

Segmentary branching of the right portal vein into 3 parts was detected in 5.7% of the patients (25 males and 23 females, Figure 6).

Quartifurcation of the main portal vein into right portal vein, left portal vein, right anterior portal vein, and right posterior portal vein (all these branches originate from the same root of the portal vein) was detected in 1.2% of the patients (5 males and 5 females, Figure 7).

There was no significant difference between males and females for incidences of all variation types (P=0.08).

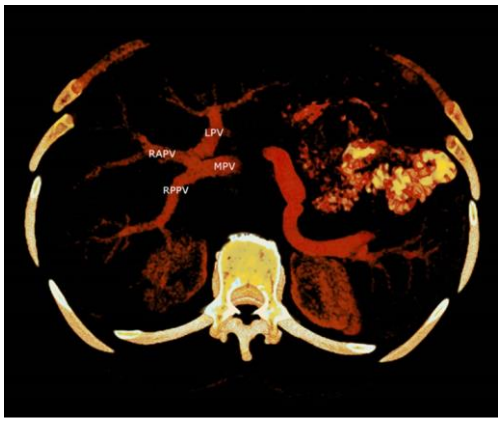

Figure 5: MDCT axial image showing, right posterior portal vein arising from MPV. (MPV: Main portal vein; LPV: Left portal vein; RPPV: Right posterior portal vein; RAPV: Right anterior portal vein). (Figure 1-D)

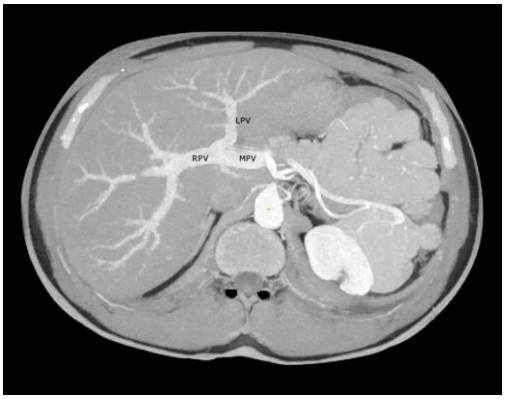

Figure 6: MDCT axial image showing, segmental branching variation of right PV. (MPV: Main portal vein; LPV: Left portal vein; RPV: Right portal vein). (Figure 1-E)

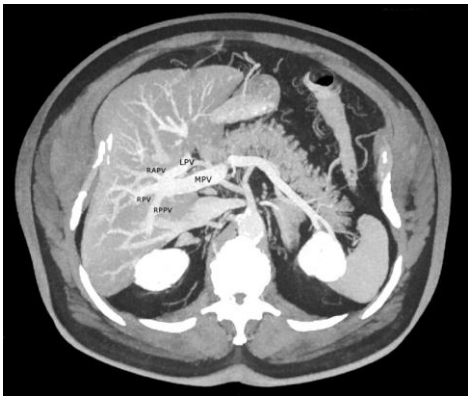

Figure 7: MDCT axial image showing Quartifurcation variation of PV. (MPV: Main portal vein; LPV: Left portal vein; RPV: Right portal vein; RPPV: Right posterior portal vein; RAPV: Right anterior portal vein). (Figure 1-F)

Discussion

Complications during liver transplantation may result from portal vein variations, most of which include branching variations according to segmentation in the liver. In the literature, there are a lot of studies conducted on this subject. According to these studies and this present study, approximately 20 % of people have portal vein variations [10-14], some of which are accompanied by an anomaly. We found portal vein branching variation in cases with normal abdominal MDCT findings and determined that the results of the studies reporting variations were similar to ours. Understanding these variations facilitates determination of the portal vein segment that will be ligated.

A previously unknown portal vein variation was detected in the present study. In this variation, the left portal vein curved reversely after its origination from the main portal vein, supplying liver segments II and IV, then branching to supply segment III. Awareness of this variation is important, especially in left hepatic lobe interventions. The fact that we have not found another study reporting this variation may be because of ethnicity. For example, Munguti et al. [4] reported low (51%) incidence of normal portal vein branching anatomy in a black Kenyan population.

In 2002, Gallego reported that the variants in the normal branching pattern of the intrahepatic portal vein have been reported since 1957, and they were seen in about 20% of the population. The most common variations include origination of the right posterior portal vein from the main portal vein (4.7 - 5.8%), right anterior portal vein originating from the left portal vein (2.9 - 4.3%) and main portal vein trifurcation (7.8%-10.8%). The incidence of trifurcation variation in our study was 8.6%. Akgul et al. [10], Baba et al. [11], Covey et al. [15], Koc et al. [12], Takaishi et al. [14], and Sureka et al. [13] reported the incidences of this variation as 12.3%, 5.2%, 9%, 11.1%, 6.1% and 6.8%, respectively.

In 2002, Akgul et al. [10] found the prevalence of intrahepatic portal venous branching variations on helical CT images. They did not specify a typing in their study and reported the incidence of right posterior portal vein variation as a first branch of main portal vein as 0.3%, while it was 8.9% in our study. Baba et al. [11], Covey et al. [15], Koc et al. [12], Takaishi et al. [14], and Sureka et al. [13] reported incidence of this variation as 2.6%, 13%, 9.7%, 4.7% and 5% respectively. However, that reported by Akgul et al. [10] was exceptionally low.

In a study by Covey et al. [15] examining portal vein variations in 200 CT portographies, the authors reported that knowing the presence of portal vein variations is important also in transhepatic portal vein embolization and percutaneous interventions such as transhepatic intraparenchymal portosystemic shunting. The incidence of segmentary branching of the right portal vein in our study is 5.7%. Covey et al. [15], Koc et al. [12], and Sureka et al. [13] reported the incidence of this variation as 7%, 3% and 4%, respectively.

Iqball et al. [7] studied liver segmentation and portal vein variations in their review. They grouped the variables under 5 types in accordance with the definition by Cheng Y et al: Type 1, which occurred in 65% to 80% of general population, was

defined as the one in which the right portal vein branched into the right anterior portal vein (RAPV) and right posterior PV (RPPV) from the main portal vein. Type 2 indicated portal trifurcation and had an incidence of 10.9 - 15% among the general population. They defined portal trifurcation as branching of the right anterior, right posterior, and left portal vein from the main portal vein. Type 3 or "Z" anomaly was branching of the right posterior PV directly from the main portal vein. This was the second most common type with an incidence between 0.3 - 7%. The authors stated that right portal vein trifurcation was seen in 0.6 - 2.69%. Type 5 was defined as the right vein trifurcation in which the branch of segment VI is the first branch of right portal vein, with an incidence of 1.34 - 2.4%. The incidence of quartifurcation variation in our study is low, as in the other studies [7,12,16-18].

Incidences of previously known variations detected in the present study are similar with the incidences reported in other studies.

Limitations

Our study was studied on a single race in a single hospital, therefore, the differences of variations based on race could not be determined. Individuals whose variation is screened retrospectively were healthy, thus, the connection between the detected variations and diseases was not determined.

Conclusion

A previously unknown variation was detected with an important incidence in the present study. Awareness of this variation and other known variations is imperative in hepatic transplantation, surgery, and interventions. Well understanding of intrahepatic portal vein variations with the increasing use of abdominal MDCT will reduce the possible risk in practice.

References

1. Matesanz R, Rosa G. Liver transplantation: The Spanish experience. Digestive and Liver Disease Supplements. 2009;3:75-81.
2. Hu GH, Shen LG, Yang J, Mei JH, Zhu YF. Insight into congenital absence of the portal vein: is it rare? WJG. 2008;14(39):5969-79.
3. Kim TS, Noh YN, Lee S, Song SH, Shin M, Kim JM, et al. Anatomic similarity of the hepatic artery and portal vein according to the donor-recipient relationship. Transplant Proc. 2012;44(2):463-65. doi: 10.1016/j.transproceed.2012.01.062
4. Munguti J, Awori K, Odula P, Ogeng'o J. Conventional and variant termination of the portal vein in a black Kenyan population. Folia Morphol (Warsz). 2013;72(1):57-62.
5. Vauthey JN, Yamashita S. Perfecting a challenging procedure: The Nagoya portal vein guide to left trisectionectomy. Surgery. 2017;161(2):355-6. doi: 10.1016/j.surg.2016.07.030
6. Fishman EK. From the RSNA refresher courses: CT angiography: clinical applications in the abdomen. Radiographics. 2001;21:3-16. doi: 10.1148/radiographics.21.suppl_1.g01oc23s3
7. Iqbal S, Iqbal R, Iqbal F. Surgical Implications of Portal Vein Variations and Liver Segmentations: A Recent Update. J Clin Diagn Res. 2017;11(2):AE01-AE05. doi: 10.7860/JCDR/2017/25028.9453
8. Madoff DC, Hicks ME, Vauthey JN, Charnsangavej C, Morello FA, Ahrar K, et all. Transhepatic portal vein embolization: anatomy, indications, and technical considerations. Radiographics. 2002;22(5):1063-76. doi: 10.1148/radiographics.22.5.g02se161063
9. Pang G, Shao G, Zhao F, Liu C, Zhong H, Guo W. CT virtual endoscopy for analyzing variations in the hepatic portal vein. Surg Radiol Anat. 2015;37(5):457-62. doi: 10.1007/s00276-015-1463-2
10. Akgul E, Inal M, Soyupak S, Binokay F, Aksungur E, Oguz M. Portal Venoz Variation. Prevalance with contrast-enhanced helical CT. Acta Radiolagica. 2002;43:315-9.
11. Baba Y, Hokotate H, Nishi H, Inoue H, Nakajo M. Intrahepatic portal venous variations: demonstration by helical CT during arterial portography. J Comput Assist Tomogr. 2000;24(5):802-8.
12. Koc Z, Oguzkurt L, Ulusan S. Portal vein variations: clinical implications and frequencies in routine abdominal multidetector CT. Diagn Interv Radiol. 2007;13(2):75-80.
13. Sureka B, Patidar Y, Bansal K, Rajesh S, Agrawal N, Arora A. Portal vein variations in 1000 patients: surgical and radiological importance. Br J Radiol. 2015;8820150326. doi: 10.1259/bjr.20150326
14. Takeishi K, Shirabe K, Yoshida Y, Tsutsui Y, Kurihara T, Kimura K, et all. Correlation Between Portal Vein Anatomy and Bile Duct Variation in 407 Living Liver Donors. Am J Transplant. 2015;15(1):155-60.
15. Covey AM, Brody LA, Getrajdman GI, Sofocleous CT, Brown KT. Incidence, patterns, and clinical relevance of variant portal vein anatomy. AJR Am J Roentgenol. 2004;183(4):1055-64. doi: 10.2214/ajr.183.4.1831055
16. Schmidt S, Demartines N, Soler L, Schnyder P, Denys A. Portal vein normal anatomy and variants: implication for liver surgery and portal vein embolization. Semin Intervent Radiol. 2008;25(2):86-91. doi: 10.1055/s-2008-1076688
17. Gallego C, Velasco M, Marcuello P, Tejedor D, Campo LD, Friera A. Congenital and Acquired Anomalies of the Portal Venous System. Radiographics. 2002;22:141-59.
18. Cheng YF, Huang TL, Chen CL, Sheen-Chen SM, Lui CC, Chen TY, et al. Anatomic Dissociation between the Intrahepatic Bile Duct and Portal Vein: Risk Factors for Left Hepatectomy. World J Surg. 1997;21:297-300.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):982-985.
DOI: 10.28982/josam.823768

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Laparoscopic sleeve gastrectomy: Correlation of gastric emptying and weight loss

Laparoskopik sleeve gastrektomi: Mide boşalması ve kilo kaybı arasındaki ilişki

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Ethics Committee Approval: The study was approved by the Ethics Committee of CHGUV (27/04/2016). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma CHGUV Etik Komitesi tarafından onaylandı (27/04/2016). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Laparoscopic Sleeve Gastrectomy (LSG) has become a popular technique as a definitive procedure in obesity treatment. It has been linked to an alteration in gastric motility and gastric emptying. The purpose of the study is to analyze the changes in gastric emptying (GE) after LSG produces and its correlation with weight loss after surgery.

Methods: The preoperative and postoperative GE was estimated by gastric emptying scintigraphy at 1 month and 18 months in 52 successive patients who underwent LSG surgery. The gastric emptying scintigraphy was conducted after the ingestion of TC^{99m} sulfur colloid labeled solid food. Images were obtained using a gamma camera at 0, 30, 60, 120, 180 and 240 minutes. Calculations were made to find out the half time gastric emptying ($T_{½}$) and the retention percentage at 2 and 4 hours.

Results: The $T_{½}$ preoperatively, at 1 month and at 18 months were 101.1 (44) minutes, 88.6 (51.5) minutes and 80.7 (53) minutes, respectively (P<0.05). Before the operation, and at the 1st and 18th months postoperatively, the percentage of retention at 2 hours were 33.4% (17.4), 26.1% (18.5), and 28.6% (15.2), respectively (P<0.05), and that at 4 hours were 5.8% (18.3), 4.5% (16.2), and 2.8% (12.6), respectively (P>0.05). The volume of the gastric reservoir increased from 239.5 (88.7) ml to 280.8 (100.8) ml (P<0.05) at 1 and 18 months after the operation. There was an inverse correlation between GE and the weight loss data at the first postoperative month, which did not remain at the 18th postoperative month.

Conclusion: According to our series, LSG with an initial transection at 4 cm from the pylorus affects gastric emptying but is not significantly correlated with weight loss.

Keywords: Gastric emptying scintigraphy, Gastric volume, Weight loss, Sleeve gastrectomy, Morbid obesity

Öz

Amaç: Laparoskopik Sleeve Gastrektomi (LSG), obezite tedavisinde kesin çözüm olarak popüler bir teknik haline gelmiştir. LSG, mide motilitesi ve mide boşalmasında değişiklikle ilişkilendirilmiştir. Bu çalışmanın amacı, LSG sonrası mide boşalmasındaki (MB) değişiklikleri ve ameliyat sonrası kilo kaybı ile ilişkisini analiz etmektir.

Yöntemler: LSG ameliyatı geçiren 52 ardışık hastada mide boşalması, ameliyat öncesi ve ameliyattan sonraki 1 ve 18. aylarda, TC99m sülfür kolloid etiketli katı gıda alımından sonra, mide boşalma sintigrafisi ile değerlendirildi. Görüntüler 0, 30, 60, 120, 180 ve 240. dakikalarda bir gama kamera kullanılarak elde edildi. İkinci ve 4. saatlerde mide boşalmasının (T½) yarısı ve retansiyon yüzdesini bulmak için hesaplamalar yapıldı.

Bulgular: Ameliyat öncesi, ve postoperative 1 ve 18. Aylarda $T_{1/2}$ sırasıyla 101.1 (44) dakika, 88.6 (51.5) dakika ve 80.7 (53) dakika idi (P <0.05). Ameliyat öncesi ve ameliyat sonrası 1. ve 18. aylarda 2. saatteki retansiyon yüzdesi sırasıyla % 33.4 (17.4), % 26.1 (18.5) ve % 28.6 (15.2) (P <0.05), aynı değerler 4. saatte sırasıyla % 5.8 (18.3), % 4.5 (16.2) ve % 2.8 (12.6) idi (P> 0.05). Mide rezervuar hacmi operasyondan sonraki 1. ve 18. aylarda 239.5 (88.7) ml'den 280.8 (100.8) ml'ye (P <0.05) yükseldi. GE ile postoperatif ilk ayda kilo verme verileri arasında ters bir korelasyon saptandı, ancak bu korelasyon postoperatif 18. ayda izlenmedi.

Sonuç: Serimize göre pilorun 4 cm distalinden transeksiyonla yapılan LSG mide boşalmasını etkilemekte ancak kilo kaybı ile anlamlı bir korelasyon göstermemektedir.

Anahtar kelimeler: Mide boşalma sintigrafisi, Mide hacmi, Kilo kaybı, Tüp mide ameliyatı, Morbid obezite

How to cite/Atıf için: Sancho C, Bruna M, Sánchez R, Cózar MP, Forner J. Laparoscopic sleeve gastrectomy: Correlation of gastric emptying and weight loss. J Surg Med. 2020;4(11):982-985.

Introduction

Gastric emptying (GE) of liquid food is directed by the gastric tone of the fundus (regulated by vagal and hormonal stimulation), while the propulsive contractions of the antrum are the primary mechanism for gastric emptying of solid food. Normal GE requires intact antropyloric coordination. Such coordination can be modified depending on whether a greater or lesser antral resection was performed, as in the case of sleeve gastrectomy (SG) [1].

Intragastric pressure is yet another mechanism that may justify alterations in GE, which in this surgery is significantly higher, reaching values of 40 mmHg, while an intact stomach produces approximately 19 mmHg (11-26 mmHg) of pressure [2]. Thus, increased intragastric pressure leads to reduced gastric distensibility, which in turn promotes accelerated GE in a resected antrum and may even lead to dumping syndrome [2].

Therefore, the mechanisms that may be involved in altering GE after a SG are [3] include functional anatomical modification, reduction of the gastric reservoir, alteration of the gastric pacemaker and interdigestive motility, alteration of antropyloric coordination and alteration of the neurohormonal mechanism. Published studies on GE of solid food after restrictive surgeries yield contradictory results. Some show accelerated emptying [4,5] and others, no notable change [6]. The objective of this prospective study is to analyze the changes in gastric emptying following LSG produces and the correlation between gastric emptying and weight loss after surgery.

Materials and methods

Inclusion and exclusion criteria

This was a quasi-experimental study utilizing a within-subject design, evaluating the pre- and post-intervention (at 1 month and 18 months) parameters in a 52-patient sample with morbid obesity (MO) who met the National Institute of Health's (NIH) criteria [7] to undergo LSG surgery at the University General Hospital of Valencia-Spain between January 2016 and June 2019.

Anthropometric data were gathered at all stages of the study. Comorbidities and their progression, weight loss by means of the percentage of excess weight lost (%EWL) and the percentage of excess BMI lost (%EBMIL) [8], barium swallow, volume calculation and gastric emptying scintigraphy results were noted.

The Ethical Committee of the hospital approved the study, and informed consent was obtained from all patients.

Surgical technique

LSG surgery is performed with a standardized technique by four surgeons from the same facility. A 36 Fr bougie was employed to configure the gastric tract, initiating the transection 4 cm from the pylorus until the angle of His with an endo linear stapler and no reinforcement.

The 30-day surgical complications were noted according to the Clavien-Dindo surgical classification [9].

Gastric emptying scintigraphy

Radioisotope Tc^{99m} sulfur colloid was utilized and mixed with solid food. All medications that may affect gastric motility was withheld 2 days prior to the procedure. Diabetic patients arrived with their blood glucose correctly controlled. The meal consisted of a 120 g plain omelet, 20 g of wholewheat toast and 25 g single-dose strawberry jam. This meal contained 255 Kcal (72% carbohydrates, 24% protein, 2% fat and 2% fiber). Images were obtained by means of a gamma camera with a high resolution and low energy collimator (Philips Nuclear Medicine).

The study is conducted in the morning following 8 hours of fasting, with food intake lasting 10 minutes. Static images are obtained immediately after ingestion in a standing position with an anterior and posterior projection and image acquisition at 0, 30, 60, 120, 180 and 240 minutes. All patients completed the study within 6 hours (Figures 1 and 2).

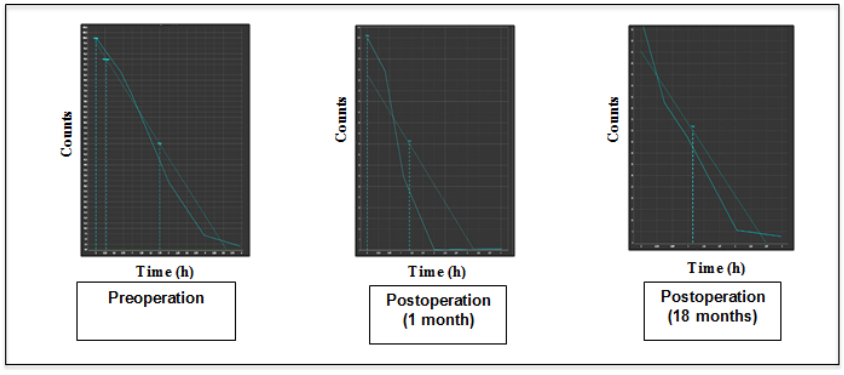

Figure 1: Indicative pre- and postoperative (1 month and 18 months) gastric emptying curves in a single patient

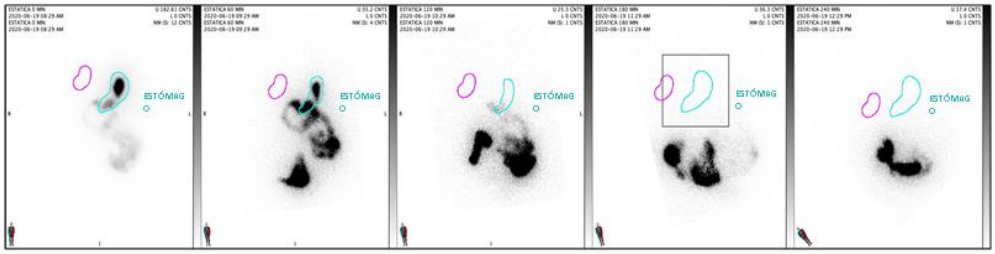

Figure 2: Anterior static images of a single patient at 0, 60, 120, 180 and 240 minutes after consumption of radiolabeled meal, demonstrating accelerated gastric emptying

Variables included:

Half time gastric emptying ($T_{½}$): Time (minutes) needed for the stomach to empty 50% of its contents into the duodenum.

Percentage of retention at 2 hours.

Percentage of retention at 4 hours.

Gastric emptying speed was classified as normal, delayed, or accelerated according to the percentage of retention ≤60% in 2 hours; >60% in 2 hours or <30% in one hour, respectively.

Barium swallow

The gastric volume was evaluated by means of barium swallow examinations. Volume estimations were performed in anterior-posterior and 90º lateral projections by the same radiologist according to a previously described technique [10] using geometric formulas for the gastric body (cylinder) and for the antrum (truncated cone).

Statistical analysis

The program used for statistical study was SPSS Statistics v.22 for Windows. It calculated the mean and its standard deviation and the median with the interquartile range if it did not adhere to a normal distribution. The statistical analysis was carried out applying McNemar's test for qualitative variables and Student's *t*-test for the comparison of means in paired quantitative variables. Pearson´s correlation test was used to test for correlations between variables. Results were statistically significant when $P<0.05$.

Results

Fifty-two patients (64.4% women and 34.6% men) with a median age of 46 years (25-63 years) were included in the study. One month after the intervention, 43/52 patients (82.7%) completed the study and at 18 months, 42/52 patients (80.8%) completed the study. A total of 42 patients completed the study. Ten patients were lost to follow-up: 6 patients dropped out of the study and 4 patients left due to post-operative complications.

There were 6 cases of postoperative complications, all of which were major (GIIIB) (wound dehiscence and hemoperitoneum, and 1 case of late complication (stenosis of the gastroplasty that required conversion to by-pass at 12 months postoperatively). No deaths were reported.

Tables 1 and 2 show the progression of anthropometric data and comorbidities in the different stages of the study.

Gastric emptying scintigraphy

Most of the patients in our series (71.1%) exhibit normal emptying in the preoperative study. Postoperatively, a significant increase in accelerated gastric emptying occurs at 1 and 18 months (40% and 35.7%, respectively) (Table 3 and 4).

There was a tendency for an inverse correlation between GE (percentage of retention at 2 hours) and the weight loss data (%EWL, %EBMIL) at 1 month (r =-2.37, p = 0.116; r = - 2.38, P=0.116, respectively), which did not remain at 18 months (r = 0.02, P=0.898; r = 0.043, P=0.788) (Figure 3).

Barium swallow

The following table shows the results of gastric volume calculated preoperatively, at 1 month and at 18 months (Table 5). There was no correlation between GE (percentage of retention at 2 hours) and the gastric volume at 1 month (r =-0.72 p = 0.639) and at 18 months (r = 0.95 P=0.551).

Table 1: Anthropometric characteristics of the subjects

Characteristic	PRE	1M	18M	*P*-value
BMI (kg/m^2)	45 (5.6)	37.9 (5.8)	29.4 (5.2)	<0.05
Waist circumference (cm)	125 (12)	114.2 (11.5)	98.3 (13.4)	<0.05
%EBMIL (%)	-	36.9 (17.2)	77.6 (25)	<0.05
%EWL (%)	-	32.2 (14.7)	67.6 (21.2)	<0.05

Values are expressed as mean and its standard deviation, BMI: body mass index; %EWL: percentage of excess weight lost; %EBMIL: percentage of excess BMI lost

Table 2: Obesity-related comorbidities

Comorbidities	PRE n (%)	1M Outcome	n	%	18M Outcome	n	%
HTA	16 (38.1%)	Remission	0	0	Remission	6	37.5
		Improvement	10	62.5	Improvement	6	37.5
		Unchanged	6	37.5	Unchanged	4	25
		Total	16	100	Total	16	100
DM	10 (23.8%)	Remission	0	0	Remission	6	60
		Improvement	8	80	Improvement	4	40
		Unchanged	2	20	Unchanged	0	0
		Recurrence	0	0	Recurrence	0	0
		Total	10	100	Total	10	100
DL	14 (33.3%)	Remission	0	0	Remission	7	50
		Improvement	6	42.8	Improvement	4	28.5
		Unchanged	8	57.2	Unchanged	3	23.1
		Total	14	100	Total	14	21.4
OSA	19 (45.2%)	Remission	3	14.3	Remission	12	63.2
		Improvement	3	19	Improvement	5	26.3
		Unchanged	13	66.7	Unchanged	2	10.5
		Total	19	100	Total	19	100

HTA: Hypertension, DM: Diabetes mellitus, DL: dyslipidemia, OSA: Obstructive sleep apnea

Table 3: Gastric emptying speed pre- and postoperatively (1 and 18 months)

Characteristic	PRE		1M		18M		*P*-value
	n	%	n	%	n	%	
Gastric Emptying							<0.05
Accelerated	8	15.4	18	40	15	35.7	
Delayed	7	13.5	3	6.6	3	7.1	
Normal	37	71.1	24	53.4	24	57.2	
Total	52	100	45	100	42	100	

Table 4: Gastric emptying pre- and postoperatively (1 and 18 months)

Characteristic	PRE	1M	18M	*P*-value
TG ½ (min)	101.1 (44)	88.6 (51.5)	80.7 (53)	< 0.05 *
Percentage of retention 2 h (%)	33.4 (17.4)	26.1 (18.5)	28.6 (15.2)	< 0.05 +
Percentage of retention 4 h (%)	5.8 (18.3)	4.5 (16.2)	2.8 (12.6)	NS

Values are expressed as mean and its standard deviation, TG ½: 50% gastric emptying, * PRE-1M y PRE-18M; + PRE-1M

Table 5: Gastric volume pre- and postoperatively (1 and 18 months)

Characteristic	PRE	1M	18M	*P*-value
Gastric volume (ml)	1812 (517.24)	239.5 (88.7)	280.8 (100.6)	<0.05
Percentage of reduced volume 1M (%)	-	85.6 (6.95)	-	
Percentage of increased volume 18M (%)	-	-	18.98 (23.15)	
n	52	49	42	

Values are expressed as mean and its standard deviation

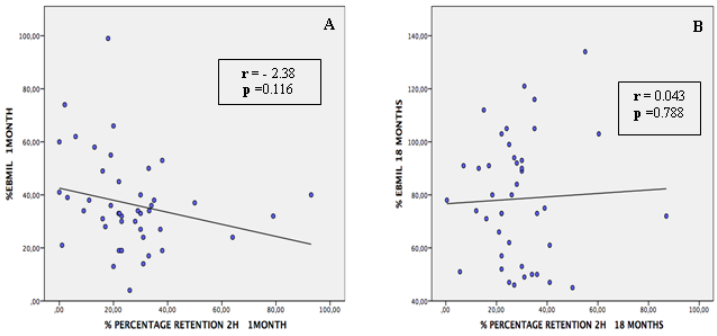

Figure 3: Correlation between gastric emptying and weight loss at 1 month and 18 months (A: %EBMIL and Percentage of retention 2h at 1 month, B: %EBMIL and Percentage of retention at 2h at 18 months)

Discussion

After SG, the gastric reservoir function becomes substantially reduced due to the removal of gastric relaxation or food accommodation capacity after resection. Consequently, alterations in gastric emptying can be observed [1].

Most of the patients in our series presented a normal preoperative isotope gastric emptying test and, although more

than half of the patients showed normal gastric emptying after the SG, a significant increase in accelerated gastric emptying was evident (40% at one month and 35.7% at 18 months) with respect to the preoperative (15.4%) status.

The effect of SG on obesity is based on three pillars of action: The restrictive effect, the hormonal effect, and alteration in gastric motility. The first two mechanisms have been widely researched with solid scientific evidence since the works published by Gagner [11,12], while the final mechanism is more complex and could be related to gastric emptying [13].

In fact, several mechanisms may be implicated in the alteration of gastric emptying after SG [2,3,6,13]. One of them is the reduced gastric volume that leads to an increase in intragastric pressure and consequently, reduced gastric wall distensibility [2]. The present study did not find any significant correlation between the 2-hour or the 4-hour retention rates and gastric volume. Another factor is an antropyloric coordination altered by antral resection. This may justify the dissimilar results published in the scientific literature whereby some authors present no alteration in gastric emptying after SG [6] with a transection at 6 cm from the pylorus and using a 48Fr bougie, while other authors show accelerated gastric emptying after SG with a transection at 5 cm from the pylorus and using a 34Fr bougie [4,5]. For this study, the technique was systematized, maintaining a distance of 4 cm from the pylorus using a 36Fr bougie, and was always conducted by the same surgical team. These data are more in line with studies that observe accelerated post-operative gastric emptying.

The implication of gastric emptying in morbid obesity also remains unclear. Accelerated gastric emptying may lead to poor satiety and increased intake, which would lead to an increase in BMI [14]. On the other hand, some studies do not find significant differences between gastric emptying in standard weight and obese patients [15]. Consequently, no conclusive data exist to include accelerated gastric emptying as a factor involved in weight loss after LSG. No significant correlation between BMI and the percentage of retention in gastric emptying was found, in line with Berstine's study [6].

Limitations

Our study has limitations, including the small sample size and short follow-up, for which a good validation of results is necessary over time.

Conclusions

The current study proves that LSG causes a significant increase in accelerated gastric emptying in the postoperative period. However, these results have no effect on weight loss.

Large scale studies are needed to evaluate the effect of LSG on gastric emptying to either confirm or refute its involvement as a mechanism of action in post-LSG weight loss.

References

1. Braghetto I, Davanzo C, Korn O, Csendes A, Valladares H, Herrera E, et al. Scintigraphic Evaluation of Gastric Emptying in Obese Patients Submitted to Sleeve Gastrectomy Compared to Normal Subjects. Obes Surg. 2009;19(11):1515-21. doi: 10.1007/s11695-009-9954-z
2. Yehoshua RT, Eidelman LA, Stein M, Fichman S, Mazor A, Chen J, et al. Laparoscopic Sleeve Gastrectomy—Volume and Pressure Assessment. Obes Surg. 2008;18(9):1083-8. doi 10.1007/s11695-008-9576-x
3. Popescu A-L, Ioniță-Radu F, Jinga M, Gavrilă A-I, Săvulescu F-A, Fierbințeanu-Braticevici C. Laparoscopic sleeve gastrectomy and gastroesophageal reflux. Rom J Intern Med. 2018;56(4):227-32. doi 10.1007/s11695-007-9006-5
4. Melissas J, Koukouraki S, Askoxylakis J, Stathaki M, Daskalakis M, Perisinakis K, et al. Sleeve Gastrectomy — A Restrictive Procedure? Obes Surg. 2007;17(1):57-62.
5. Melissas J, Leventi A, Klinaki I, Perisinakis K, Koukouraki S, de Bree E, et al. Alterations of Global Gastrointestinal Motility After Sleeve Gastrectomy: A Prospective Study. Ann Surg. 2013;258(6):976-82. doi 10.1007/s11695-008-9791-5
6. Bernstine H, Tzioni-Yehoshua R, Groshar D, Beglaibter N, Shikora S, Rosenthal RJ, et al. Gastric Emptying is not Affected by Sleeve Gastrectomy—Scintigraphic Evaluation of Gastric Emptying after Sleeve Gastrectomy without Removal of the Gastric Antrum. Obes Surg. 2009;19(3):293-8.
7. Hubbard VS, Hall WH. Gastrointestinal Surgery for Severe Obesity. Obes Surg. 1991 Sep;1(3):257-265. doi: 10.1381/096089291765560962.
8. Sabench Pereferrer F, Domínguez-Adame Lanuza E, Ibarzabal A, Socas Macias M, Valentí Azcárate V, García Ruiz de Gordejuela A, et al. Criterios de calidad en cirugía bariátrica: revisión de conjunto y recomendaciones de la Asociación Española de Cirujanos y de la Sociedad Española de Cirugía de la Obesidad. Cir Esp. 2017;95(1):4-16. doi10.1016/j.ciresp.2016.09.007
9. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. Ann Surg. 2004;240(2):205-13. doi: 10.1097/01.sla.0000133083.54934.ae.
10. Grifo I, Bruna M, Puche J, Jareño S, Navarro C, Gómez R, et al. Gastrectomia vertical: importancia del volumen gástrico resecado. BMI-journal .2017;7(1):1304-8
11. Gumbs AA, Gagner M, Dakin G, Pomp A. Sleeve Gastrectomy for Morbid Obesity. Obes Surg. 2007;17(7):962-9. doi:10.1007/s11695-007-9151-x
12. Gagner M. Faster Gastric Emptying after Laparoscopic Sleeve Gastrectomy. Obes Surg. 2010;20(7):964-5. doi:10.1007/s11695-010-0086-2
13. Pilone V, Tramontano S, Micco RD, Monda A, Hasani A, Izzo G, et al. Gastric emptying after sleeve gastrectomy: statistical evidence of a controlled prospective study with gastric scintigraphy. Minerva Chir. 2013;68(4):9. PMID: 24019046.
14. Cardoso-Júnior A, Gonzaga Vaz Coelho L, Savassi-Rocha PR, Vignolo MC, Abrantes MM, Miranda de Almeida A, et al. Gastric Emptying of Solids and Semi-solids in Morbidly Obese and Non-obese Subjects: An Assessment Using the 13C-Octanoic Acid and 13C-Acetic Acid Breath Tests. Obes Surg. 2007;17(2):236-41. doi:10.1007/s11695-007-9031-4
15. Verdich C, Lysgård Madsen J, Toubro S, Buemann B, Holst J, Astrup A. Effect of obesity and major weight reduction on gastric emptying. Int J Obes. 2000;24(7):899-905. doi: 10.1038/sj.ijo.0801250.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):986-989.
DOI: 10.28982/josam.748864

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Association of Borna disease virus with autism spectrum disorder in Turkish children

Türk çocuklarda Borna hastalığı virüsü ve otizm spektrum bozukluğu ilişkisi

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Etik Kurul Onayı: Çalışmaya Ordu Üniversitesi Tıp Fakültesi Etik Kurulu tarafından izin verildi (2017/126). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study received financial support from Ordu University Scientific Research Project Fund (No; AP-1725).
Finansal Destek: Yazarlar, bu çalışmanın Ordu Üniversitesi Bilimsel Araştırma Proje Fonu'ndan mali destek aldığını beyan etmişlerdir (No; AP-1725).

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Autism spectrum disorders are lifelong neurodevelopmental disorders whose pathogeneses are not fully understood. Borna disease virus is a neurotropic virus that affects the central nervous system. Considering the neuropsychiatric and behavioral effects of the virus, it can be suggested that it may play a role in autism spectrum disorder. However, there are insufficient evidence to support this. In this study, we aimed to investigate the presence of Borna disease virus in patients with autism spectrum disorders and healthy controls.

Methods: This case-control study, performed in children with autism spectrum disorders and a control group, included patients with autism who visited the Child and Adolescent Psychiatry outpatient clinic between December 2017 - December 2018. Borna virus positivity was assayed with the ELISA method in serum samples. Data was analyzed using SPSS version 22.

Results: The study included 63 children diagnosed with autism spectrum disorder and 31 healthy controls. The age range of autism patients was 3-14 years, their mean age was 7.83 (1.96) years, and The Childhood Autism Rating Scale score was 51.09 (5.71). The seropositivity rate for Borna disease virus in the autism and healthy control groups were 25.39% and 25.80%, respectively (P=0.966). For all patients, seropositivity rate was 25.53%.

Conclusion: No relationship was found between autism spectrum disorders and Borna disease virus. The clinical significance of Borna disease virus positivity in society is unknown. We conclude that Borna disease virus is not involved in the pathogenesis of autism spectrum disorders.

Keywords: Borna disease virus, Autism spectrum disorder, Seroprevalence, Etiology

Öz

Amaç: Otizm spektrum bozuklukları yaşam boyu nörogelişimsel bozukluklardır ve patogenezi günümüzde tam olarak anlaşılamamıştır. Borna hastalığı virüsü, merkezi sinir sistemini etkileyen nörotropik bir virüstür. Virüsün nöropsikiyatrik ve davranışsal etkileri göz önüne alındığında, otizm spektrum bozukluğunda rol oynayabileceği ileri sürülebilir. Ancak, bunu destekleyecek yeterli kanıt yoktur. Bu çalışmada otizm spektrum bozukluğuna sahip hastalarda ve sağlıklı kontrol grubunda Borna hastalığı virüsü varlığının araştırılması amaçlanmıştır.

Yöntemler: Bu çalışma otizm spektrum bozukluğu tanısı almış ve kontrol grubundaki çocuklarda yapılan bir vaka kontrol çalışmasıdır. Çalışmaya Aralık 2017 - Aralık 2018 tarihleri arasında Çocuk ve Ergen Psikiyatri polikliniğine başvuran otizmli çocuklar dahil edilmiştir. Serum örneklerinde ELISA yöntemi ile Borna virüsü pozitifliği değerlendirilmiştir. Veriler SPSS sürüm 22 kullanılarak analiz edilmiştir.

Bulgular: Çalışmaya otizm spektrum bozukluğu tanısı almış 63 çocuk ve 31 sağlıklı kontrol grubu dahil edildi. Otizm hastalarının yaş aralığı 3-14 yıl, ortalama yaş 7,83 (1,96) ve Çocukluk Otizmini Derecelendirme Ölçeği skoru ortalama 51,09 (5,71) olarak saptandı. Otizm grubunda ve sağlıklı kontrol grubunda Borna hastalığı virüsü seropozitiflik oranı sırasıyla %25,39 ve %25,80 idi (P=0,966). Tüm hastalar için seropozitiflik oranı %25,53 saptandı.

Sonuç: Otizm spektrum bozukluğu ile Borna hastalığı virüsü arasında ilişki saptanmadı. Borna hastalığı virüsünün toplumdaki pozitifliğinin klinik önemi bilinmemektedir. Sonuç olarak Borna hastalığı virüsünün, otizm spektrum bozukluğunun patogenezinde rol oynadığını düşünmüyoruz.

Anahtar kelimeler: Borna hastalığı virüsü, Otizm spektrum bozukluğu, Seroprevalans, Etyoloji

How to cite/Atıf için: Yıldırım AA, Çetinkol Y, Esnafoğlu E, Çalgın MK. Association of Borna disease virus with autism spectrum disorder in Turkish children. J Surg Med. 2020;4(11):986-989.

Introduction

Autism spectrum disorders (ASD) are life-long neurodevelopmental disorders, characterized by insufficient social communication and limited repetitive behaviors or areas of interest [1,2]. The prevalence of ASD is increasing at alarming dimensions globally. Latest epidemiological studies have reported the prevalence of ASD as 1.5% [3]. Despite several studies explaining the etiopathogenesis of ASD, it is still not fully understood. Though there is a high genetic effect, it is a multifactorial disease resulting from mutual interactions with environmental factors [4]. Among these environmental factors, it is proposed that viral infections experienced in the early stages of development may be causative. The mechanisms causing neurodevelopmental disorders linked to viral infections are proposed to include direct central nervous system (CNS) infections, affecting other tissues in the body, triggering pathologies in the CNS or in the immune system or a combination of these factors. Borna virus is also among the suspected viruses [5].

Borna disease virus (BDV) is an enveloped, unsegmented, single-stranded RNA virus with negative polarity belonging to the *Mononegavirales* order. It is a neurotropic virus affecting the central nervous system, especially the limbic structures [6,7]. Borna disease (BD) was first described in the 18th century as an epidemic disease in horses. Initially considered to be a chronic progressive meningoencephalitis causing neurological symptoms in horses and sheep, it was later identified to affect all warm-blooded mammals. BDV may cause behavioral abnormalities like anxiety, aggressiveness, cognitive deficiencies, and hyperactivity without encephalitic changes in animals [8-10]. Behavioral disease studies in animals have led to the thought that this disease may be associated with some neuropsychiatric diseases in humans. It is thought that BDV may infect humans and animals by direct contact with infected secretions, contaminated food, and vertical routes [8,11]. Serologic evidence in humans was first reported in 1985 [12]. Though the links with a variety of diseases have been topics of study through the years, the outcomes caused in humans are not clear [13]. In humans, BDV was associated with four cases of encephalitis in Germany and resulted in the death of 3 [14]. The properties of the virus and the virus genome being shown in psychiatric diseases like schizophrenia and bipolar disease, which affect a high proportion of the general population but have unknown etiology, have strengthened the possibility of this relationship [15-18]. Whether BDV contributes to neurodevelopmental disorders in children or its effects are unknown. Young animals have been shown to be more susceptible to persistent Bornavirus infection [19]. There is a need for advanced studies about the effect of this neurotropic virus in children, especially in early childhood.

Considering the neuropsychiatric and behavioral effects of BDV, it is proposed to possibly play a role in ASD pathogenesis. However, there are insufficient evidence to support this. This study aimed to investigate the presence of BDV among ASD patients and healthy controls.

Materials and methods

Ethics

The details of the study were explained to the families of the patients and their consents were obtained. The study was approved by Ordu University Clinical Research Ethics Committee (2017/126) and conducted according to the principles of Helsinki Declaration.

Selection and description of participants

This case control study involved ASD patients admitted to the Child and Adolescent Psychiatry outpatient clinics between December 2017 and December 2018. The age range of ASD patients was 3-14 years and their mean age was 7.83 (1.96) years. The healthy control group was selected from those attending the same department and pediatric department due to minor complaints in the similar age range. The study included 63 ASD patients (19 females and 44 males) and 31 healthy children (14 females and 17 males) in the control group. Patients were diagnosed by a pediatric psychiatrist according to Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria [1]. Childhood Autism Rating Scale (CARS) was applied to assess the severity of autism in patients. Children with comorbid diseases in the ASD group or those with unclear diagnoses were excluded from the study.

Childhood Autism Rating Scale

Childhood Autism Rating Scale comprises 15 items and is used to measure the severity of autism. CARS is assessed after detailed interviews with the family and observation of the child. The items assess relationships with people, imitation, listening response, emotional response, object use, body use, adaptation to change, visual response, smell, taste and touch responses, fear or nervousness, verbal communication, non-verbal communication, activity level, level and consistency of intellectual response and general impression. They are scored from 1 to 4 and the total score is calculated. Scores below 30 are normal, those between 30-36.5 indicate mild-moderate autism, while a score of 37 or higher denote severe autism [20].

Detection of Borna Disease Virus

Ten milliliter blood samples from patients were separated while drawing blood for routine tests. Blood samples were centrifuged at 3000 rpm for 15 minutes. Separated serum samples were stored under appropriate conditions (-80°C) in the microbiology laboratory and tested for Bornavirus protein with the human Borna disease virus (BDV) ELISA kit (Abbexa Ltd., Cambridge Science Park, Cambridge, CB4 0EY, UK). This kit is pre-coated with a polyclonal IgG antibody specific for BDV and detects BDV protein in sera. There is no known cross-reactivity with other proteins/viruses. The results are assessed as positive or negative according to the manufacturer's recommendations.

Statistical analysis

The statistical package program Statistical Package for Social Sciences (IBM SPSS for Windows, Ver.22) was used in the calculations. Means and standard deviations were obtained for continuous variables while categorical variables were summarized using frequency and percentage. The student's t-test was applied to assess differences between numerical variables. Chi-square test was used to compare categorical variables. Kruskal-Wallis test was performed to compare the means of more than two groups. *P*-value <0.05 was considered statistically

significant. Considering Cohen's chi square analysis criteria, the average power was calculated as 0.30, alpha=0.05 and n (sample width) =94, and the power was 0.837 [21]. G-Power 3.1.9.2 statistics program was used to power and sample size.

Results

The study included 63 ASD patients and 31 healthy controls. The age range of the children participating in the study was 3-12 years. The mean CARS score of ASD patients was 51.09 (5.71). Detailed information about the children is summarized in Table 1. The seropositivity rate for BDV in the ASD and control groups were 25.39% (n=16) and 25.80% (n=8), respectively, which were similar (*P*=0.096). Borna disease virus seroprevalences are presented in Table 2. Its incidence was insignificantly different among females and males in the ASD group (42.85% vs. 20.83%, respectively) (*P*=0.098). There was no difference when compared to categorized age groups. The seropositivity rate in all individuals included in the study was 25.53% (n=24). The mean titrations of the healthy individuals, mild-heavy and severe autism patients were similar (χ2=2.042, *P*=0.360). Distribution of titer median values by severity of disease is shown in Figure 1.

Table 1: Characteristics of the groups

Characteristics	Total ASD patients (n=63)			
	Mild-moderate ASD n=26 (%)	Severe ASD n=37 (%)	Healthy control n=31 (%)	*P*-value
Gender, Female/Male	4/22 (15.4/84.6)	10/27 (27/73)	14/17 (45/55)	0.173
Age mean (SD)	5.67 (1.99)	6.44 (2.60)	8.75 (2.71)	0.097
CARS mean (SD)	32.82 (3.68)	54.85 (2.7)	-	-

ASD: Autism spectrum disorders, CARS: Childhood Autism Rating Scale

Table 2: Borna disease virus seroprevalence of groups

	Total ASD (n=63)			
	Mild-moderate ASD	Severe ASD	Control group	χ2/*P*-value
BDV positive (n/%)	5 / 19.2	11 / 29.7	8 / 25.8	0.87/0.64
BDV negative (n/%)	21 / 80.8	26 / 70.3	23 / 74.2	0.87/0.35
Titers mean (SD)	0.160 (0.17)	0.237 (0.25)	0.270 (0.41)	2.04/0.36

BDV: Borna disease virus, ASD: Autism spectrum disorders

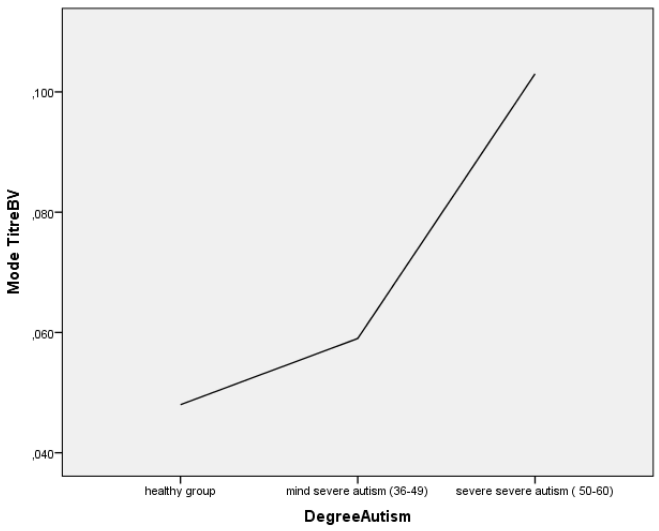

Figure 1: Distribution of titer median values according to the severity of the disease

Discussion

Neuropathology associated with BDV has been demonstrated in animal models. Studies show that infected neonatal rats developed autism-like behavior changes [22-24]. In a study of rats, Hans et al. [25] showed that the virus caused significant changes in synaptic functions, especially damaging neuronal functions, and noted that this may cause neurobehavioral disease in humans. BDV's neurotropic characteristics and ability to create persistent noncytolytic infections and proven outcomes in animal studies strengthen the possibility that viral contact may cause a pathology in humans. It is unknown whether BDV contributes to neurodevelopmental disorders in children. There is a need for advanced studies about the effect of this neurotropic virus in children, especially in the early childhood period. Though BDV has been researched in the etiology of many neuropsychiatric diseases, the number of studies regarding autistic children are limited. No study was observed in the literature, except for the work of Honda et al. [26]. A study of autistic children by Honda et al. reported the antibody prevalence against Bornavirus in children with ASD as 7.4%. In this study, positivity was higher in the 2-5 age group, and there was no significant difference according to gender. In our study, BDV positivity was 25.39% in the ASD group and there was no significant difference compared to the control group. There was no difference between age groups in our study. Similarly, no significant difference was found between genders. Both the number of BDV positivity and titer values were insignificantly higher in the severe autism group compared to those with mild-moderate autism. In another study in children, BDV seroprevalence was investigated. Patti et al. [27] reported 59% BDV seroprevalence in healthy children aged 0-18 years. This rate is quite high and showed the need for risk assessment in children. Unlike our study, male gender, and positivity at the age of 1-3 were higher. None of these studies had a control group.

Previously, Güngör et al. [28] researched the presence of BDV among patients with subacute sclerosing panencephalitis in Turkey and did not identify a significant correlation but reported similar seropositivity rates of 22% in the general population. Determination of positive values in both the patient and control groups are an indicator of presence of BDV contact in our country. However, our results do not support the theory that BDV may contribute to the pathogenesis of ASD.

Limitations

The small number of patients is a limiting aspect of our study. Furthermore, the effects of BDV should be investigated especially at early ages, which is a critical period in the neurodevelopmental process.

Conclusion

In our study, BDV positivity was 25.39% in the ASD group and there was no significant difference compared to the control group. The clinical significance of Borna disease virus positivity in society is unknown. We conclude that Borna disease virus is not involved in the pathogenesis of autism spectrum disorders.

References

1. Swedo SE, Baird C. Neurodevelopmental Disorders; Autism Spectrum Disorder. In: Kupfer DJ, editor. American Psychiatric Association: Diagnostic and statistical manual of mental disorders. Arlington: American Psychiatric Publishing; 2013. pp. 50-59.
2. Ekici B, Konuk FK, Dursun ŞS, Unay ÖS, Tatlı B. Neuroplay method combined with home-based Ayres sensory integration for autism: A case report. J Surg Med. 2020;4(3):246-7. doi: 10.28982/josam.613563
3. Lyall K, Croen L, Daniels J, Fallin MD, Ladd-Acosta C, Lee BK, et al. The Changing Epidemiology of Autism Spectrum Disorders. Annu Rev Public Health. 2017;38:81-102. doi: 10.1146/annurev-publhealth-031816-044318
4. Matsuzaki H, Iwata K, Manabe T, Mori N. Triggers for autism: genetic and environmental factors. J Cent Nerv Syst Dis. 2012;22(4):27-36. doi: 10.4137/JCNSD.S9058
5. Libbey JE, Sweeten TL, McMahon WM, Fujinami RS. Autistic disorder and viral infections. J Neurovirol. 2005;11(1):1-10. doi: 10.1080/13550280590900553

6. Lipkin WI, Briese T, Hornig M. Borna disease virus fact and fantasy. Virus Res. 2011;162(1-2):162-72. doi: 10.1016/j.virusres.2011.09.036
7. Kinnunen PM, Palva A, Vaheri A, Vapalahti O. Epidemiology and host spectrum of Borna disease virus infections. J Gen Virol. 2013;94:247-62. doi: 10.1099/vir.0.046961-0
8. Richt JA, Pfeuffer I, Christ M, Frese K, Bechter K, Herzog S. Borna disease virus infection in animals and humans. Emerg Infect Dis. 1997;3(3):343-52. doi: 10.3201/eid0303.970311
9. Dittrich, W, Bode L, Ludwig H, Kao M, Schneider K. Learning deficiencies in Borna disease virus infected but clinically healthy rats. Biol Psychiatry. 1989;26:818-28. doi: 10.1016/0006-3223(89)90122-4
10. Hornig, M, Weissenbock H, Horscroft N, Lipkin WI. An infection based model of neurodevelopmental damage. Proc Natl Acad Sci. 1999;96:12102-7. doi: 10.1073/pnas.96.21.12102
11. Ando T, Takino T, Makita K, Tajima M, Koiwa M, Hagiwara K. Seroepidemiological analysis of vertical transmission relative risk of Borna disease virus infection in dairy herds. J Vet Med Sci. 2016;78(11):1669-72. doi: 10.1292/jvms.16-0156
12. Amsterdam JD, Winokur A, Dyson W, Herzog S, Gonzalez F, Rott R, et al. Borna disease virus. A possible etiologic factor in human affective disorders? Arch Gen Psychiatry. 1985;42(11):1093-6. doi: 10.1001/archpsyc.1985.01790340077011
13. Carbone KM. Borna Disease Virus and Human Disease. Clin Microbiol Rev. 2001;14(3):513-27. doi: 10.1128/CMR.14.3.513-527.2001
14. European Centre for Disease Prevention and Control. Acute encephalitis associated with infection with Borna disease virus 1–Germany. Stockholm: ECDC; 2018.
15. Bode L, Zimmermann W, Ferszt R, Steinbach F, Ludwig H. Borna disease virus genome transcribed and expressed in psychiatric patients. Nature Med. 1995;1:232-6. doi: 10.1038/nm0395-232
16. de la Torre JC, Bode L, Durrwald R, Cubitt B, Ludwig H. Sequence characterization of human Borna disease virus. Virus Res. 1996;44:33-44. doi: 10.1016/0168-1702(96)01338-x
17. Sauder C, Muller A, Cubitt B, Mayer J, Steinmetz J, Trabert W, et al. Detection of Borna disease virus (BDV) antibodies and BDV RNA in psychiatric patients: evidence for high sequence conservation of human blood derived BDV RNA. J Virol. 1996;70:7713-24. doi: 10.1128/JVI.70.11.7713-7724.1996
18. Kishi M, Nakaya T, Nakamura Y, Zhong Q, Ikeda K, Senjo M, et al. Demonstration of human Borna disease virus RNA in human peripheral blood mononuclear cells. FEBS Letters. 1995;3645:293-7. doi: 10.1016/0014-5793(95)00406-y
19. Hirano N, Kao M, Ludwig H. Persistent, tolerant or subacute infection in Borna disease virus infected rats. J Gen Virol. 1983;64:1521-30. doi: 10.1099/0022-1317-64-7-1521
20. Schopler E, Reichler RJ, De Vellis RF, Daly K. Toward objective classification of childhood autism: Childhood autism rating scale (CARS). Journal of Autism and Developmental Disorders. 1980;10(1):91-103. doi: 10.1007/BF02408436
21. Cohen J. Statistical Power Analysis for the Behavioral Sciences. New York: Department of Psychology New York University; 1988.
22. Pletnikov MV, Rubin SA, Vasudevan K, Moran TH, Carbone KM. Developmental brain injury associated with abnormal play behavior in neonatally Borna disease virus infected Lewis rats: a model of autism. Behavioural Brain Res. 1999;100:43-50. doi: 10.1016/s0166-4328(98)00111-9
23. Lancaster K, Dietz DM, Moran TH, Pletnikov MV. Abnormal social behaviors in young and adult rats neonatally infected with Borna disease virus. Behavioural Brain Research. 2007;176:141-8. doi: 10.1016/j.bbr.2006.06.013
24. Li C, Xu X, Zhang X, Cheng K, Guo Y, Jie J, et al. Activation of ERK / CREB / BDNF pathway involved in abnormal behavior of neonatally Borna virus-infected rats. Neuropsychiatr Dis Treat. 2018;15(14):3121-32. doi: 10.2147/NDT.S176399
25. Hans A, Bajramovic JJ, Syan S, Perret E, Dunia I, Brahic M, et al. Persistent, noncytolytic infection of neurons by Borna disease virus interferes with ERK 1/2 signaling and abrogates BDNF-induced synaptogenesis. FASEB J. 2004;18(7):863-5. doi: 10.1096/fj.03-0764fje
26. Honda T, Sofuku K, Matsunaga H, Tachibana M, Mohri I, Taniike M, et al. Prevalence of antibodies against Borna disease virus proteins in Japanese children with autism spectrum disorder. Microbiol Immunol. 2018;62:473-6. doi: 10.1111/1348-0421.12603
27. Patti AM, Vulcano A, Candelori E, Donfrancesco R, Ludwig H, Bode L. Borna disease virus infection in Italian children. A potential risk for the developing brain? APMIS Suppl. 2008;124:70-3. doi: 10.1111/j.1600-0463.2008.00m12.x
28. Güngör S, Anlar B, Turan N, Yılmaz H, Helps CR, Harbour DA. Antibodies to Borna disease virus in subacute sclerosing panencephalitis. Pediatr Infect Dis J. 2005;24(9):833-4. doi: 10.1097/01.inf.0000178307.70429.75.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):990-993.
DOI: 10.28982/josam.812873

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Detection of unexpected coronavirus disease (COVID-19) involvement in lung bases on abdominal CT of patients presenting with abdominal symptoms

Abdominal şikayetler ile başvuran hastalarda karın BT'de akciğer bazallerinde beklenmedik koronavirüs hastalığı (COVID-19) tutulumunun saptanması

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Ethics Committee Approval: This study was approved by the Ethical Committee of Afyonkarahisar Health Sciences University, Faculty of Medicine (2020/369). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Afyonkarahisar Sağlık Bilimleri Üniversitesi Tıp Fakültesi Etik Kurulu (2020/369) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Coronavirus disease 2019 (COVID-19) can present with nonspecific abdominal symptoms. The aim of this study is to emphasize the importance of detecting lung basis involvement on abdominal computed tomography (CT) in patients hospitalized with abdominal complaints without known COVID-19 disease.

Methods: CT images of 250 patients who underwent abdominopelvic CT scan due to various abdominal complaints were retrospectively evaluated. Inclusion criteria included patients presenting with primary abdominal complaints without respiratory symptoms, who had suspicious COVID-19 CT findings on lung basis. COVID-19 was not among the differential diagnoses of these patients at the time of admission. CT images of 240 patients were included.

Results: Among 240 patients, twelve (8 females, 4 males, aged 30-69 years) had suspicious findings of COVID-19 on lung bases. Presenting complaints were abdominal pain (n=7), lack of appetite (n=5), diarrhea (n=7), vomiting (n=3), nausea (n=4) and gastric pain (n=1). Lung base CT findings included ground-glass opacities (100%), which were peribronchovascular (66.6%), bilateral (91.6%), peripheral (91.6%), or multifocal (58.3%). Cases were confirmed with laboratory testing.

Conclusion: Considering that some patients present with nonspecific abdominal complaints, identifying the characteristic signs of COVID-19 incidentally in the visualized part of the lung basis on abdominal CT is important for early diagnosis, the protection of health professionals, and in reducing the spread of disease.

Keywords: Coronavirus, Lung base, Abdominal CT, COVID-19, SARS-CoV-2

Öz

Amaç: Koronavirüs hastalığı 2019 (COVID-19), spesifik olmayan karın şikayetleri ile karşımıza çıkabilir. Bu çalışmanın amacı, abdominal yakınmalarla başvuran hastalarda akciğer bazallerindeki bulgulara bakarak COVID-19 tanısı koymada abdomen BT'nin önemini vurgulamaktır.

Yöntemler: Çeşitli abdominal şikayetler nedeniyle abdominopelvik BT taraması yapılan 250 hastanın görüntüleri geriye dönük olarak değerlendirildi. Dahil etme kriterleri, başlangıçta solunum şikayetleri olmaksızın abdominal yakınma ile başvuran, akciğer bazallerinde COVID-19 şüpheli BT bulguları olan, ancak başvuru anında COVID-19 ön tanısı olmayan hastaları içerir. 240 hastanın BT görüntüleri çalışmaya dahil edildi.

Bulgular: 240 hastadan 12'sinde (8K, 4M; 30-69 yaş) akciğer bazallerinde şüpheli COVID-19 bulguları vardı. Başvuru şikayetleri iştahsızlık (n=5), karın ağrısı (n=7), ishal (n=7), bulantı (n=4), kusma (n=3) ve mide ağrısı (n=1) idi. Akciğer bazalleri tutulumunun dağılımı peribronkovasküler (%66,6), bilateral (%91,6), periferik (%91,6) veya multifokal (%58,3) olan buzlu cam opasiteleri (%100) idi. Vakalar laboratuvar testleri ile doğrulandı.

Sonuç: Bazı hastaların nonspesifik karın şikayetleri ile başvurduğu düşünülürse; abdominal BT'de akciğer bazallerinin tetkike dahil kısımlarında COVID-19' un tipik belirtilerini tespit etmek, zamanında tanı koymak, sağlık çalışanlarını korumak ve hastalığın yayılmasını azaltmak açısından çok önemlidir.

Anahtar kelimeler: Koronavirüs, Akciğer bazalleri, Abdomen BT, COVID-19, SARS-CoV-2

How to cite/Atıf için: Özgül E, Kaya F, Korkmaz D. Detection of unexpected coronavirus disease (COVID-19) involvement of lung bases on abdominal CT of patients presenting with abdominal symptoms. J Surg Med. 2020;4(11):990-993.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new type of coronavirus, was initially identified in December 2019 in Wuhan City, China. World Health Organization (WHO) announced this disease as a global pandemic on March 11, 2020 with more than 118,000 confirmed cases in 114 countries, and 4,291 deaths [1]. Clinical diseases caused by SARS-CoV-2 infection are called coronavirus disease 2019 (COVID-19) [2].

COVID-19 may present with typical symptoms such as shortness of breath, cough, fever, while it may also present with nonspecific abdominal complaints such as nausea, vomiting and diarrhea. Of 204 patients, 50.5% of patients reported gastrointestinal (GI) symptoms on presentation in a study in China [3].

As of June 2, 2020, there were 6 million verified cases and 371,000 deaths worldwide. Global economic losses exceeded $2.7 trillion [2]. It is especially important for patients who present with extrapulmonary symptoms to be diagnosed early to provide treatment on time and prevent spread. In the recent weeks, some patients visited our hospital with various abdominal complaints, underwent abdominal multidetector computed tomography (MDCT) and had characteristic COVID-19 involvement of the lung bases without respiratory symptoms. They were subsequently confirmed positive for COVID-19. First indicators of disease were the lung base involvements detected on abdomen computed tomography (CT).

Abdominal radiologists should know that the disease may also occur with abdominal symptoms and pay attention to the lung bases included in the examination. The goal of this study is to emphasize the importance of detecting lung basis involvement on abdominal CT in patients admitted to hospital with abdominal complaints without known COVID-19 disease.

Materials and methods

Patients

We retrospectively analyzed the abdominal CT images of 250 patients who underwent abdominal MDCT screening in our radiology department due to varied abdominal complaints between July 1, 2020 and July 15, 2020. When patients with lung trauma were excluded, a total of 240 CTs remained. Inclusion criteria included patients presenting with primary abdominal complaints without respiratory symptoms, who had suspicious COVID-19 CT findings on lung basis. COVID-19 was not among the differential diagnoses of these patients at the time of admission. CT lung base findings, clinical characteristics including symptoms, laboratory findings, gender, and age were noted. Presence of ground-glass opacities (GGOs), consolidation, septal thickening, morphological round lesions, 'crazy paving' pattern, multifocal involvement, peripheral distribution, bilateral involvement, and pleural effusion were assessed on the bases of the lungs. We found 12 patients with unexpected lung base findings on abdominal CT who were suspicious for Covid-19. SARS-CoV-2 polymerase chain reaction (PCR) laboratory test was performed to confirm the diagnosis.

CT protocol

Patients were scanned with a CT scanner (Toshiba Aquilion (80x2), Otawara, Japan). MDCT was performed after 1-2 ml/kg iodinated nonionic contrast agent, with an iodine concentration of 300 mg/cc, was intravenously administered. CT images were obtained with the following parameters while the patient was holding breath: Slice thickness: 2 mm, tube voltage 120 kVp, reconstruction index: 1 mm, pitch: 0.75. Slices were extended from lung basis to the end of pelvis. From axial CT images, sagittal and coronal multiplanar reconstructed (MPR) images were obtained. All images were transferred to a picture archiving communication system (PACS) workstation and examined by an abdominal radiologist with 15 years of experience and a thoracic radiologist with 12 years of experience. Two radiologists made joint decisions for lung base CT findings.

Results

Patients

Twelve of 240 patients (8 females, 4 males) had suspicious findings of COVID-19 on lung bases. Their ages ranged between 30-69 (mean 54.5) years. The presenting complaints of the patients were abdominal pain (n=7), lack of appetite (n=5), diarrhea (n=7), vomiting (n=3), nausea (n=4) and gastric pain (n=1). None of the patients had fever or cough. The average time from symptom onset to abdominal CT was 6.6 days (range, 3-15 days). Three patients (25%) had underlying health conditions (1 lung cancer, 1 diabetes mellitus and 1 chronic renal disease).

Blood laboratory results

All patients had elevated serum C-reactive protein (CRP), lactic acid dehydrogenase (LDH) and ferritin levels. In addition, the Aspartate Aminotransferase (AST) levels of three patients (25%), Alanine transaminase (ALT) levels of two patients (16.6%), and the D-dimer levels of 9 patients (75%) were elevated. Hemoglobin was lower in 8 (66.6%) of the patients. Eleven (91.6%) patients had lymphopenia. Table 1 shows the interquartile and median ranges of selected blood laboratory values.

Table 1: Blood laboratory values

Parameter [normal range]	Value
C-reactive protein (CRP) [0–5.0 mg/L]	37.9 (16.9-99.8)
Lactic acid dehydrogenase (LDH) [135-225 U/L]	336 (241-631)
Aspartate aminotransferase (AST) [1–35 U/L]	32.25 (15-74)
Alanine transaminase (ALT) [1–45 U/L]	23.0 (5-77)
Procalcitonin [0–0.49 ng/mL]	0.15 (0.1-0.4)
D-dimer [0–0.5 µg/mL]	0.74 (0.38-1.64)
Ferritin (males) [30–400 ng/mL]	758.3 (411-2000)
Ferritin (females) [15–150 ng/mL]	826.3 (211-1145)
White blood cell count (WBC) [4.5–11.0 K/µL]	6.6 (3.2-10.7)
Lymphocyte % [20-52]	15.9 (9.5-19.5)
Hemoglobin (Hb) (males) [13.9–16.3 g/D]	11.8 (8.7-15.4)
Hemoglobin (Hb) (females) [11.7–15.0 g/DL]	9.65 (5.7-12.4)

Values are given as median with interquartile range in parentheses unless otherwise stated. Reference ranges are given below each laboratory value name in brackets.

Imaging results

GGOs (n=12, 100%) were the most common lung base involvement patterns on abdominal CT. They were mostly peribronchovascular (n=8, 66.6%) (Figure 1), bilateral (n=11, 91.6%), peripheral (n=11, 91.6%) (Figure 2, 3), or multifocal (n=7, 58.3%) (Figure 4) in distribution. Septal thickening was observed in 2 patients. None of the patients had pleural effusion, cavitation, solid nodules, or halo sign.

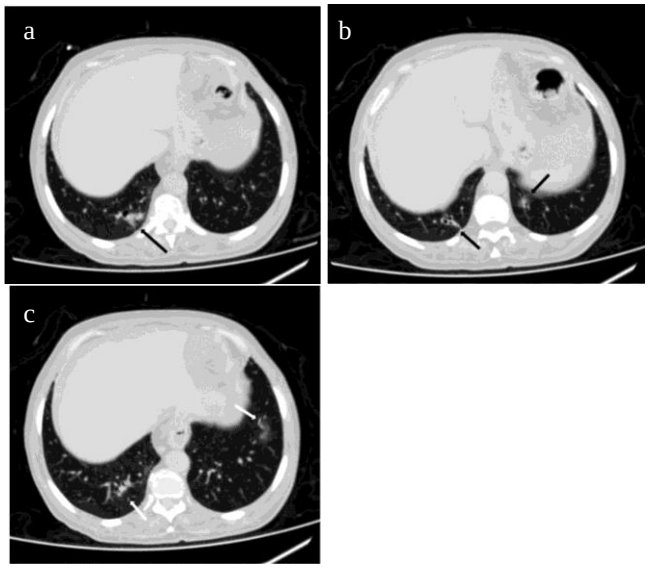

Figure 1: 69-year-old female patient who presented with lack of appetite, diarrhea, and abdominal pain. Axial abdominopelvic CT images with lung windows (a, b, c) demonstrate bilateral, peribronchovascular ground-glass nodules and opacities in lower lobes (arrows). After abdominal CT findings raised concern for COVID-19, the patient was found positive for coronavirus disease.

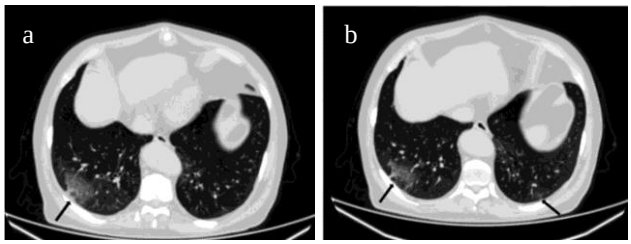

Figure 2: 47-year-old male patient who presented with lack of appetite and vomiting. Axial abdominopelvic CT images with lung windows (a, b) show bilateral, peripheral, ground-glass opacities in lung bases (arrows). The patient was found positive for coronavirus disease after abdominopelvic CT findings raised concern for COVID-19.

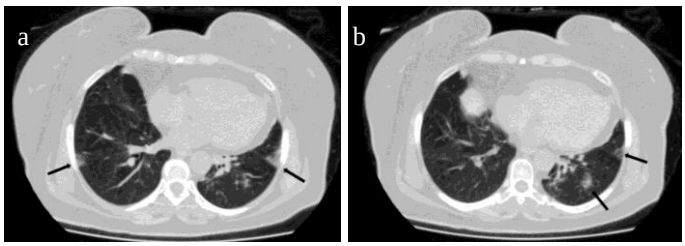

Figure 3: 61-year-old female patient who presented with nausea and gastric pain. Axial abdominopelvic CT images with lung windows (a, b) demonstrate bilateral peripheral located ground-glass opacities and nodules (arrows). After abdominal CT findings raised concern for COVID-19, the patient was found positive for coronavirus disease.

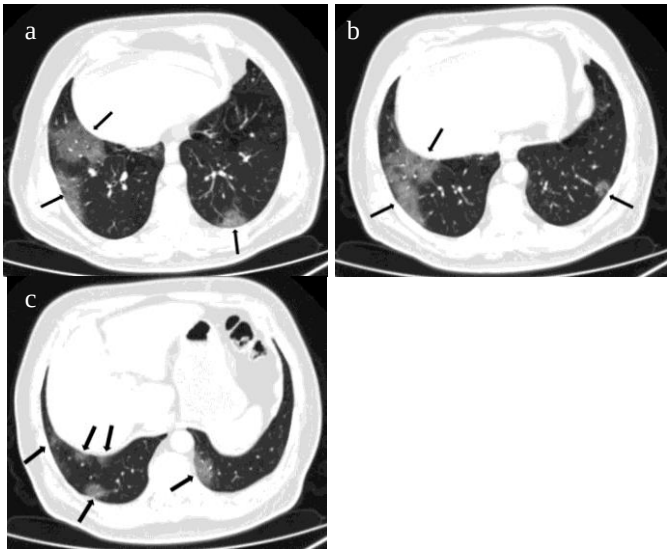

Figure 4: 63-year-old male patient who admitted with nausea, diarrhea, and abdominal pain. Axial abdominopelvic CT images with lung windows (a, b, c) show bilateral multifocal and peripheral distribution of ground-glass opacities and nodules (arrows). The patient was found positive for coronavirus disease after abdominopelvic CT findings raised concern for COVID-19.

SARS-CoV-2 PCR laboratory test was performed to confirm the diagnosis, and the results of eight patients came back positive at the first time. In the other 4 patients, the first tests were negative. Since the radiological findings were highly suspicious for SARS-CoV-2, the PCR test was repeated, and a positive result was confirmed in the second test.

All patients were hospitalized. Seven of these patients eventually developed respiratory symptoms such as dyspnea, cough, and fever. One patient with underlying lung cancer was admitted to the intensive care unit due to severe shortness of breath and hypoxia. He was intubated, but then lost. The remaining eleven patients were discharged after their symptoms regressed and their general condition improved. Median hospital stay (until death or discharge) was 8 days (4-20 days).

Chest CT was not performed on any patient simultaneously with abdominal CT. After abdominopelvic CT was performed, 10 patients underwent follow-up chest radiography, which confirmed the findings described on CT and showed regression of disease. Follow-up Chest CT was performed in only 2 patients after an average of 17 days. Follow-up CT showed progression in one and regression in the other patient. The patient with progression was intubated and died.

Discussion

The number COVID-19 diagnosed cases is increasing significantly. In the current global pandemic, typical symptoms of COVID-19 are well known, however, it may also present with nonspecific gastrointestinal symptoms. Early detection of the disease is the main challenge in patients with nonspecific abdominal complaints [4].

Early studies on COVID-19 reported that the rate of patients presenting with asymptomatic gastrointestinal complaints was low [5]. On the contrary, Pan et al. [3] evaluated 204 COVID-19 patients and reported that 50.5 % of patients presented with gastrointestinal symptoms as their chief complaint. Most common gastrointestinal symptoms included lack of appetite (78.6%), diarrhea (34%), vomiting (3.9%) and abdominal pain (1.9%).

To the best of our knowledge, there are very few studies reporting diagnosis of COVID-19 from unexpected lung base findings on abdominopelvic CT [2,4,6-9]. Most of these are case reports or case series [2,7-9]. King et al. [2] evaluated abdominal CT scans of 76 patients presenting with abdominal symptoms and found that the most common abdominal complaints were pain (83.9%) and nausea-vomiting-anorexia (46.8%). They also found CGOs (95.2%) in a peripheral (66.1%) and multifocal (95.2%) dispersion pattern on the lung bases in CT images. Dane et al. [6] reported 23 patients who underwent abdominopelvic CT for abdominal complaints, and according to CT lung base findings, COVID-19 was suspected. Abdominal pain was the most common complaint in 19 patients. COVID-19 PCR test was positive in 17 patients. CGOs were the most common lung base findings they found on abdominal CT.

The mechanism by which SARS-CoV-2 causes abdominal complaints is interesting. Probable causes include co-infection with another pathogen, direct viral infection of genitourinary and/or gastrointestinal tracts, or reflection of the pain from lung base infection [2, 10]. In humans, SARS-CoV-2

infection occurs according to the ability of the virus to bind to the angiotensin converting enzyme 2 (ACE2) receptor. It has much higher affinity than the 2003 coronavirus SARS-CoV [2,11,12]. ACE2 is released from the lung, gastrointestinal and genitourinary tracts (i.e. ileum, colon, upper esophagus, renal proximal tubules and urinary bladder) and provides a reasonable clarification for involvement in these areas [2,13,14]. Viral infection of enterocytes causes changes in intestinal permeability and can lead to various gastrointestinal symptoms such as abdominal pain, diarrhea, nausea, and vomiting [2,15].

Characteristic lung CT imaging features that have been widely described in COVID-19 are CGOs in the lung bases, peripheral distribution, rounded morphology, and basilar predominance. In case of more severe lung disease or longer infection duration, consolidative opacities may be seen [8,16-18]. Kim et al. [19] reported the sensitivity and specificity of chest CT as 94% and 37%, respectively, in their meta-analysis. The combination of consolidative opacities and GGOs are the most common CT findings, occurring in 88% of COVID-19 cases [20-22].

Limitations

Our study has some limitations. First, it is a retrospective study with a small sample size. This may cause bias and limit the generalizability or reliability of our results. Second, the follow-up period was not long. We believe that future studies should include larger patient populations and longer follow-up periods.

Conclusion

Considering that some patients present with nonspecific abdominal complaints, identifying the characteristic involvement of COVID-19 in the lung bases included on abdominal CT is important for early diagnosis, the protection of health professionals and in reducing the spread of disease. When examining abdominopelvic CT, radiologists should also evaluate lung bases included in the examination. If such findings are detected, they should promptly alert the referring clinician about COVID-19.

References

1. Lenzen M, Li M, Malik A, Pomponi F, Sun Y, Wiedmann T, et al. Global socio-economic losses and environmental gains from the Coronavirus pandemic. PLoS One. 2020;15(7):e0235654. doi: 10.1371/journal.pone.0235654
2. King MJ, Lewis S, El Homsi M, Meza GH, Bernheim A, Jacobi A, et al. Lung base CT findings in COVID-19 adult patients presenting with acute abdominal complaints: case series from a major New York City health system. Eur Radiol. 2020;1-9. doi: 10.1007/s00330-020-07040-z
3. Pan L, Mu M, Yang P, Sun Y, Wang R, Yan J, et al. Clinical Characteristics of COVID-19 Patients With Digestive Symptoms in Hubei, China: A Descriptive, Cross-Sectional, Multicenter Study. Am J Gastroenterol. 2020;115(5):766-73. doi: 10.14309/ajg.0000000000000620
4. Sendi AA, Saggat DF, Alzahrani SJ. Incidental typical COVID-19 appearance on the lung bases, visualized at abdominal CT for a patient that presented with abdominal pain and nausea. Radiol Case Rep. 2020;15(8):1238-41. doi: 10.1016/j.radcr.2020.05.039
5. Wan Y, Li J, Shen L, Zou Y, Hou L, Zhu Li, et al. Enteric involvement in hospitalised patients with COVID-19 outside Wuhan. Lancet Gastroenterol Hepatol. 2020;5(6):534-5. doi: 10.1016/S2468-1253(20)30118-7
6. Dane B, Brusca-Augello G, Kim D, Katz DS. Unexpected Findings of Coronavirus Disease (COVID-19) at the Lung Bases on Abdominopelvic CT. AJR Am J Roentgenol. 2020;1-4. doi: 10.2214/AJR.20.23240
7. Siegel A, Chang PJ, Jarou ZJ, Paushter D, Harmath C, Arevalo B, et al. Lung Base Findings of Coronavirus Disease (COVID-19) on Abdominal CT in Patients With Predominant Gastrointestinal Symptoms. AJR Am J Roentgenol. 2020;1-3. doi: 10.2214/AJR.20.23232
8. Voutsinas N, Toussie D, Jacobi A, Bernheim A, Chung M. Incidental CT findings in the lungs in COVID-19 patients presenting with abdominal pain. Clin Imaging. 2020;67:1-4. doi: 10.1016/j.clinimag.2020.05.021
9. Kim J, Thomsen T, Sell N, Goldsmith AJ. Abdominal and testicular pain: An atypical presentation of COVID-19. Am J Emerg Med. 2020;38(7):1542.e1-3. doi: 10.1016/j.ajem.2020.03.052
10. Minodier L, Masse S, Capai L, Blanchon T, Ceccaldi PE, Werf S, et al. Clinical and virological factors associated with gastrointestinal symptoms in patients with acute respiratory infection: a two-year prospective study in general practice medicine. BMC Infect Dis. 2017;17(1):729. doi: 10.1186/s12879-017-2823-9
11. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol. 2020;94(7):e00127-20. doi: 10.1128/JVI.00127-20
12. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. Clin Gastroenterol Hepatol. 2020;18(8):1663-72. doi: 10.1016/j.cgh.2020.04.001
13. Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci. 2020;12(1):8. doi: 10.1038/s41368-020-0074-x
14. Zou X, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front Med. 2020;14(2):185-92. doi: 10.1007/s11684-020-0754-0
15. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. Gastroenterology. 2020;158(6):1518-9. doi: 10.1053/j.gastro.2020.02.054
16. Chung M, Bernheim A, Mei X, Zhang N, Huang M, Zeng X, et al. CT Imaging Features of 2019 Novel Coronavirus (2019-nCoV). Radiology. 2020;295(1):202-7. doi: 10.1148/radiol.2020200230
17. Bernheim A, Mei X, Huang M, Yang Y, Fayad Z, Zhang N, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology. 2020;295(3):200463. doi: 10.1148/radiol.2020200463
18. Wang Y, Dong C, Hu Y, Li C, Ren Q, Zhang X, et al. Temporal Changes of CT Findings in 90 Patients with COVID-19 Pneumonia: A Longitudinal Study. Radiology. 2020;296(2):E55-64. doi: 10.1148/radiol.2020200843
19. Kim H, Hong H, Yoon SH. Diagnostic Performance of CT and Reverse Transcriptase-Polymerase Chain Reaction for Coronavirus Disease 2019: A Meta-Analysis. Radiology. 2020;201343. doi: 10.1148/radiol.2020201343
20. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20. doi: 10.1056/NEJMoa2002032
21. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020;296(2):E32-40. doi: 10.1148/radiol.2020200642
22. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. AJR Am J Roentgenol. 2020;215(1):87-93. doi: 10.2214/AJR.20.23034

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):994-997.
DOI: 10.28982/josam.780138

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Mortality analysis of hospitalized trauma patients in the intensive care unit

Yoğun bakım ünitesinde yatan travma hastalarının mortalite analizi

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Ethics Committee Approval: Approval was obtained from Adıyaman University Medicine Faculty Ethics Committee (3/23/2016-2016/2-21). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Adıyaman Üniversitesi Tıp Fakültesi Etik Kurulu'ndan onay alındı (23.03.2016-2016/2-21). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Trauma accounts for around five million deaths a year and constitutes a serious threat to public health globally. We examined the characteristics of patients admitted to the intensive care unit (ICU) due to trauma in 2015 and investigated the mortality rate and affecting factors.

Methods**:** In this retrospective cohort study, the data of 101 trauma patients who were followed up at the general ICU in Adıyaman University Training and Research Hospital between January 2015 and December 2015 were analyzed. Patients' demographic data, regions and causes of trauma, hospitalization durations, Glasgow Coma Scale (GCS) scores, whether blood products were transfused, mechanical ventilation support, operations, and duration of stay in ICU were noted. We then divided the patients into two groups as survivors and non-survivors and examined the mortality rates and the effective factors.

Results: Mortality rates of the patients were 15.8%. The mean age of the patients included in the study was 30.73 (25.188) years. Among all, there were 71 males and 30 females. The most common causes of trauma were in-vehicle traffic accidents (33.7%), falls (28.7%) and extravehicular traffic accidents (24.8%). The patients were often admitted to the ICU because of head trauma. The ICU length of stay was significantly higher in the non-survivor group compared to the discharged group (12.81 (23.49) vs. 3.78 (2.84) days, $P<0.001$), along with the duration of mechanical ventilation (2.49 (8.85) vs. 0.74 (1.30), $P<0.001$). GCS scores at admission were significantly lower in the non-survivor group (5.88 (3.12) vs. 11.98 (2.70), $P<0.001$).

Conclusion: Direct exposure to trauma as a pedestrian, duration of mechanic ventilation, and low GCS scores during admission increase mortality in patients admitted to the ICU due to trauma.

Keywords: Intensive care unit, Mortality, Trauma

Öz

Amaç: Travma nedeni yılda yaklaşık beş milyon kişi ölmektedir ve bu durum küresel olarak halk sağlığı için ciddi bir tehdittir. Bu çalışmada 2015 yılı travma nedeniyle yoğun bakım ünitesine kabul edilen hastaların genel özelikleri incelenmiş olup mortalite oranı ve mortaliteye etki eden nedenleri inceledik.

Yöntemler: Çalışmamızda retrospektif kohort yöntemi kullanıldı. Adıyaman Üniversitesi Eğitim ve Araştırma Hastanesi'nde Ocak 2015-Aralık 2015 tarihleri arasında genel YBÜ'de takip edilen 101 travma hastasının verileri retrospektif olarak incelendi. Hastaların demografik verileri, travma nedenleri, travma bölgeleri, yatış süreleri, Glasgow Koma Skoru (GKS), Kan transfüzyon yapılıp yapılmadığı, Mekanik Ventilasyon Desteği, ameliyat geçirip geçirmediği, YBÜ kalış süresi kaydedilmiştir. Daha sonra hastalar yoğun bakım sonuçlarına göre sağ kalan ve ölen hastalar olarak iki gruba ayrılarak mortalite oranları ve mortaliteye etki eden faktörler incelenmeye alındı.

Bulgular: Hastaların mortalite oranları %15.8 olarak tespit edildi. Çalışmaya alınan hastaların yaş ortalaması 30,73 (25,188) yıl idi. Hastaların 71 erkek, 30 kadındı. Travmanın en sık nedenleri araç içi trafik kazaları (%33.7), düşme (28.7) ve araç dışı trafik kazaları (%24,8) idi. Hastalar en sık kafa travması nedeniyle YBÜ yatırılmıştır. YBÜ kalış süresi; ex olan grupta taburcu olan gruba göre istatiksel olarak anlamlı bir şekilde fazlaydı (12,81 (23,49) ve 3,78 (2,84) gün, $P<0,001$). Mekanik ventilasyon süresi ex grubunda istatiksel olarak daha uzun (2,49 (8,85) ve 0,74 (1,30), $P<0,001$). YBÜ yatışındaki GKS ex grubunda istatistiksel olarak anlamlı düşük bulunmuştur (5,88 (3,12) ve 11,98 (2,70), $P<0,001$).

Sonuç: Travmaya bağlı YBÜ'ne yatan hastalarda, yaya olarak travmaya direk maruziyet, mekanik ventilasyon süresi uzunluğu ve hastaneye kabul sırasında GKS puanı düşüklüğü mortalitesi artırmaktadır.

Anahtar kelimeler: Yoğun bakım ünitesi, Mortalite, Travma

How to cite/Atıf için: Duran M, Uludağ Ö. Mortality analysis of hospitalized trauma patients in the intensive care unit. J Surg Med. 2020;4(11):994-997.

Introduction

The development of technology and an increase in individual armament, accidents, and violence have caused a significant increase in morbidity and mortality attributable to traumatic injuries. These injuries have become a serious public health concern as they place an economic burden and lead to disability [1,2]. One person dies of injury every six seconds around the world, which amounts to approximately 14,000 people a day and to 5 million people a year. These figures are higher than the number of deaths due to HIV, tuberculosis, and malaria, as well as the number of maternal deaths. It is expected to increase to the 7th rank in 2030 while death due to traffic accidents ranked 9th across the world in 2012 [3-5]. Even though car drivers are always at risk of injury or death, there are significant differences in mortality rates in different driving categories. Pedestrians and drivers of two-wheeled vehicles are at high risk. Especially riding a motorcycle has a bad reputation [6,7]. Intensive care units are multidisciplinary structures struggling with life-threatening diseases, where airway support, mechanical ventilation, current treatment modalities, effective administration of drugs and monitoring techniques are provided for survival [8]. Since trauma is a problem that increases mortality and morbidity significantly, these patients are usually followed up in intensive care units (ICU) [9].

We aimed to investigate the mortality rates of trauma patients hospitalized in ICU and the affecting factors.

Materials and methods

Approval was obtained from Adıyaman University Medicine Faculty Ethics Committee (23.03.2016-2016/2-21). The data of 101 trauma patients who were followed up at the general ICU in Adıyaman University Training and Research Hospital between January and December 2015 were analyzed retrospectively. We divided the patients into two groups as survivors and non-survivors. Patients' demographic data, causes and regions of trauma, hospitalization durations, Glasgow Coma Scores (GCS), whether blood and products were transfused, mechanical ventilation support and duration, operations, duration of stay in ICU, mortality and the affecting factors were examined.

Statistical analysis

Descriptive statistics of all trauma patients were performed using SPSS Inc., Chicago, IL, USA (SPSS v15.0) program. The numerical data were expressed as median (interquartile range) and categorical data as percentages. These patients were divided into two groups as survivors and non-survivors. Chi-square and Independent sample t tests were used for comparing categorical and numerical data, respectively. Multivariate logistic regression analysis was performed for significant data (cause of trauma, duration of stay in ICU, trauma site, mechanical ventilation time, GCS, blood transfusion) as indicated by univariate analysis to determine independent risk factors affecting mortality. *P*-value <0.05 was considered statistically significant.

Results

A total of 124 (11%) out of 1120 patients admitted to the ICU of our hospital were hospitalized due to trauma between January and December 2015. Full data of 101 of these patients were obtained. Among all, 84.2% (n=85) were discharged while 15.8% (n=16) died. Descriptive statistics of the study are presented in Table 1. The mean ages of the discharged and dying patient groups were similar (P=0.929). The most common cause of trauma was in-vehicle traffic accidents in the discharged group (36.5%), and extravehicular (56%) accidents among non-survivors.

Duration of stay in the ICU was 3.87 (2.84) days in the discharged group and 12.81 (23.49) days among non-survivors (P<0.001). Head trauma (36.5%) was the most common trauma site in the discharged group, while multiple traumas and head-thoracic traumas were the most common sites in the dying group. The duration of mechanical ventilation was significantly longer among non-survivors (P<0.001). GCS values during hospitalization in the ICU were 11.98 (2.70) and 5.88 (3.12) (3-13) in survivors and non-survivors, respectively (P<0.001). Multiple regression analysis was performed for variables associated with death. Significant variables included mechanical ventilation, cause of trauma and Glasgow coma scale score. The Glasgow coma scale score was the most effective (Table 2).

Table 1: Descriptive statistics

	Total	Discharge (n=85)	Death (n=16)	*P*-value
Age (year)	30.73(25.1)	30.64(25.33)	31.25(25.25)	0.929
Gender (F/M)	30/71	23/62	7/9	0.233
Cause of trauma				0.008*
In-vehicle	34(33.7%)	31 (36.5%)	3(18.8%)	
Extravehicular	25(24.8%)	16 (18.8%)	9(56.3%)	
Motorcycle	10(9.9%)	8 (9.4%)	2(12.5%)	
Direct head trauma	2(2%)	1 (1.2%)	1(6.3%)	
Falling from height	29(28.7%)	28 (32.9%)	1(6.3%)	
Exposure to explosive substance	1(1%)	1 (1.2%)	0	
Duration of stay in ICU (days)	5.21(10.02)	3.78(2.8417)	12.81(23.49)	<0.001*
Trauma site				0.013*
Head trauma	35(34.7%)	31(36.5%)	4(25%)	
Thorax trauma	3(3%)	3(3.5%)	0	
Abdominal trauma	7(6.9%)	7(8.2%)	0	
Extremity trauma	5(5%)	5(5.9%)	0	
Head-Thorax Trauma	20(19.8%)	14(16.5%)	6(37.5%)	
Head- Extremity trauma	17(16.8%)	17(20%)	0	
Multiple trauma	14(13.9%)	8(9.4%)	6(37.5%)	
Duration of mechanical ventilation (days)	2.49(8.85)	0.74(1.30)	11.75(20.11)	<0.001*
GCS	11.01(3.54)	11.98(2.70)	5.88(3.12)	<0.001*
Undergoing a surgery	45(44.6%)	39 (45.9%)	6 (37.5%)	0.594
Blood transfusion	53(52.5%)	40 (47.1%)	13 (81.3%)	0.014*

Table 2: Results of multiple regression analysis of variables related to death

	Beta	OR (95% CI)	*P*-value
Mechanical ventilation	0.421	1.524 (1.064 – 2.183)	0.022*
Cause of trauma	-1.099	0.333 (0.116 – 0.957)	0.041*
Glasgow coma scale	-0.659	0.517 (0.360 – 0.744)	<0.001*

*P<0.05

Discussion

The age group most exposed to trauma was children and young adults. Mortality increased in patients with multiple and head and thoracic traumas, and in patients who received blood transfusions. Trauma-related mortality is directly affected by exposure to trauma as a pedestrian, duration of mechanical ventilation and GCS scores during hospital admission.

The development of technology and an increase in individual armament, accidents, and violence have significantly increased morbidity and mortality attributable to traumatic

injuries. High mortality in traumas and the development of post-traumatic physical and psychosocial disorders significantly affect the quality of life and these patients should, therefore, be followed up in the ICU [9-11].

Data of the Turkish Statistical Institute in 2015 showed that external injuries and poisoning rank fifth among death causes [11,12]. Of the 1120 patients followed up in our intensive care unit during this period, 124 were traumatic (11%). In the USA, 15% of stays in ICU constitute major traumas [13]. In a study in Turkey, this rate ranged from 10 to 22% [14,15].

Early detection and good management of these patients having a substantial risk of death can provide positive results. In the recent three decades, the mortality of these patients has decreased by 15-45% due to improvements in structural and personnel conditions. Although the chance of survival of seriously injured patients has increased continuously in recent years, the trauma-related mortality rates increased by 22.8% while the population of US increased by 9.7% from 2000 to 2010 [16-18]. In Turkey, Kara et al. [14] found the mortality rate to be 19.4% and Ünlü et al. [15] reported it as 35.8%. However, we found it as low as 15.8%. The reason is that our hospital is the only center in the province where all trauma patients, including mild, moderate, and severe patients, are admitted. We consider that this has an impact on our results.

Trauma studies conducted so far in Turkey have found that the average age was within the range of 31 to 44 years [14,15,20,21]. The average age ranged between 33 and 37 years in studies conducted in different countries [23]. The results of our study showed that the mean age of the trauma patients was 30.7 years. In accordance with the literature, the trauma rates were higher among young patients.

Among all, 70.3% (n = 71) of the traumatized patients were male in our study. Rüden et al. [16] reported a male dominance over females in trauma. Durdu et al. [23] found a high rate of male gender, similar to our results, which are consistent with the literature. We consider that the reason male gender is higher in number than females is that men take a more active role in daily life than women and they spend more time in risky environments.

The most common causes of trauma are in-vehicle traffic accidents, falls, pedestrians, motorcycle accidents and sharp object injuries [15,24-27]. In our study, the most common causes were in-vehicle traffic accidents (33.7%), falls (28.7%) and extravehicular traffic accidents (24.8%). Özkayın et al. [26] indicated that the rate of injuries arising from motorcycle accidents increased from 2002 to 2007. The reason we found a low rate of injuries due to motorcycle accidents may be associated with the low rates of motorcycle use in our region.

Christopher et al. [4] reported that mortality rates dependent on traffic-related injuries increased in low- and middle-income countries. The literature shows that pedestrians were more likely to encounter traffic-related injuries, followed by car users and motorcycle riders, while deaths due to traffic-related injuries reduced in high-income countries [4,7,8]. The high mortality rate of motorcycle riders results from increased trauma severity and insufficient use of protective equipment. Wearing a helmet is highly beneficial to both the motorcycle riders and the community. The literature reported the protective effect of motorcycle helmets, which not only reduces mortality but also traumatic brain injury, duration of stay in the hospital and hospital charge [24,25]. In our study, the mortalities consisted of the extravehicular traffic accidents (56.3%), in-vehicle traffic accident (18.8%) and motor accident (12.5%). We think that high mortality in extravehicular traffic accidents is due to elevated trauma severity. The highest mortality rate was seen in patients with multiple and head - thoracic traumas. When mortality is evaluated in terms of whether the patient underwent operations, it is seen that surgery has no effect on mortality. However, we found that the need for blood transfusion was high in non-survivors. These results indicate that the patients who died were exposed to major traumas and needed a blood transfusion.

The regions exposed to trauma are divided into four, including the head, chest, abdomen, and extremities. Injuries to more than two sites were considered multiple traumas. Ünlü et al. [15] reported that the head, extremities, and thorax were the most injured sites during traumas. Trauma-related injuries vary regionally. Consistent with the literature, we found that patients were frequently admitted to ICU due to head trauma (34,7%).

Many scoring systems are used to measure the severity of trauma and estimate mortality [5,11]. Studies indicate that low GCS in trauma is important in predicting mortality and the best predictive power would be 5.5 [1,6]. In similar studies, Mpe et al. [27] reported that GCS values of 4 or less at admission to the intensive care unit were poor prognosis. Our mean GCS scores in the surviving group was higher, similar to the reports in the literature. Low GCS values were correlated with the severity of trauma and are accompanied by the need for mechanical ventilation. Our study revealed that dying patients received mechanical ventilation support for a longer period. Mechanical ventilation support and its increased duration are risk factors for mortality in trauma patients, as is the case with GCS scores. Related literature reported that the mortality rate was about 50% in patients receiving mechanical ventilatory support [1,8,28]. Increased duration of mechanical ventilation leads to the prolonged hospital stay. In our study, the duration of stay in the hospital was 3.78 (2.84) in the discharged group and 12.8 (23.49) among non-survivors.

Limitations

The limitations of our study include its retrospective and single-centered nature, and sparse number of cases. Failure to access the trauma scores of the patients at admission also weakens our results.

Conclusion

Direct exposure to trauma as a pedestrian, duration of mechanic ventilation, blood transfusion and low GCS scores at admission increase mortality in patients admitted to ICU due to trauma.

References

1. Jennett B. Epidemiology of head injury. J Neurol Neurosurg Psychiatry. 1996;362–9.
2. Guven C, Kafadar H. Evaluation of extremity vascular injuries and treatment approaches. Niger J Clin Pract. 2020 Sep;23(9):1221-8. doi: 10.4103/njcp.njcp_656_18. PMID: 32913160.
3. WHO. Injuries and violence: the facts 2014
4. Christopher P, Murray JL. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015:10;385(9963):117–71.
5. Murray CJL, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Articles Global, regional , and national incidence and mortality for HIV, tuberculosis ,and malaria during 1990 – 2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;6736(14):1–66.

6. Colburn TN, Meyer DR. Sports Injury or Trauma? Injuries of the competetion off-road motorcyclist. Injury. 2003;34:207-14.
7. Yan-Hong L, Rahim Y, Wei L, Gui-Xiang S, Yan Y, De Ding Z, et al. Pattern of traffic injuries in Shangai :implications for control. Injury Control and Safety Promotion. 2006;13:217-25.
8. Morgan GE. Clinical Anesthesiology. 4th ed. McGraw-Hill Medical; 2005
9. Hefny AF, Idris K, Eid HO, Abu-Zidan FM. Factors affecting mortality of critical care trauma patients. African Health Sciences. 2013;13:731-5.
10. Dur A, Koçak S, Cander B, Sönmez E, Civelek C. Factors affecting mortality in patients with multitrauma which were treated in intensive care unit. Dicle Medical Journal. 2013;40:177-82.
11. Banerjee M, Bouillon B, Shafizadeh S, Paffrath T, Lefering R, Wafaisade A, et al. Epidemiology of extremity injuries in multiple trauma patients. Injury. 2013;10:15-21.
12. Türkiye İstatistik Kurumu, Ölüm Nedeni İstatistikler, 2016 Sayı: 24572 27 Nisan 2017
13. Podoll AS, Kozar R, Holcomb JB, Finkel KW. Incidence and Outcome of Early Acute Kidney Injury in Critically-Ill Trauma Patients. Plos One. 2013;8:77376
14. Kara İ, Altınsoy S, Gök U, Onur A, Sarıbapıççı R. Bir Numune Hastanesi Genel Yoğun Bakım Ünitesinde Travma Hastalarının Mortalite Analizi. Türk Yoğun Bakım Derneği Dergisi. 2015;13:68-74.
15. Ünlü AR, Ülger F, Dilek A, Barış S, MuratN, Sarıhasan B. Yoğun Bakımda İzlenen Travma Hastalarında "Revize Travma Skoru" ve "Travma ve Yaralanma Şiddeti Skoru''nun Prognoz ile İlişkisinin Değerlendirilmesi. Türk Anest Rean Der Dergisi. 2012;40:128-35.
16. Rüden CV, Woltmann A, Röse M, Wurm S, Rüger M, Hierholzer C, et al. Outcome after severe multiple trauma: a retrospective analysis. J Trauma Manag Outcomes 2013;7:4.
17. Dresing K. Recommended guidelines for diagnostics and therapy in trauma surgery. Eur J Trauma. 2002; 27:137–50.
18. Barie PS, Hydo LJ, Fischer E. A prospective comparison of two multiple organ dysfunction/failure scoring systems for prediction of mortality in critical surgical illness. J Trauma. 1994;37:660–6.
19. Rhee P, Joseph B, Pandit V, et al. Increasing trauma deaths in the United States. Ann Surg. 2014;260:13-21.
20. Akoğlu H, Denizbaşı A, Ünlüer E, Güneysel Ö, Onur Ö. Marmara Üniversitesi Hastanesi Acil Servisine Başvuran Travma Hastalarının Demografik Özellikleri. Marmara Medical Journal. 2005;18;113-22.
21. Varol O, Eren ŞH, Oğuztürk H, Korkmaz İ, Beydilli İ. Acil servise trafik kazası sonucu başvuran hastaların incelenmesi. CÜ Tıp Fakültesi Derg. 2006;28:55-60.
22. Guenther S, Waydhas C, Ose C, Nast-Kolb D. Quality of multiple trauma care in 33 German and Swiss trauma centers during a 5-year period: regular versus on-call service. J Trauma. 2003;54:972–8.
23. Durdu T, Kavalci C, Yilmaz MS, Karakilic ME, Arslan ED, Ceyhan ME. Analysis of Trauma Cases Admitted to the Emergency Department. J Clin Anal Med 2013;
24. Çırak B, Güven MB, Işık S, Kıymaz N, Demir Ö. Acil servise başvuran travma hastaları ile ilgili epidemiyolojik bir çalışma. Ulusal Travma Derg. 1999;5(3):157-9.
25. Köksal Ö, Çevik Ş, Akköse Aydın Ş, Özdemir F. Acil servise başvuran travma hastalarında rutin testlerin gerekliliğinin analizi. Ulus Travma Acil Cerrahi Derg. 2012;18(1):23-30.
26. Ozkayin N, Kaan E, Aktuglu K. The state and importance of motorcycle injuries in progression with trauma etiologies. Medical Science and Discovery. 2016;3:219-24.
27. Mpe MJ, Mathekga K, Mzileni MO. The outcome of neuro-trauma. A 1 year retrospective study in an intensive care unit. In Critical Care BioMed Central. 2001 March;5(1):1-2.
28. Kuo SCH, Kuo PJ, Rau CS, Chen YC, Hsieh HY, Hsieh CH. The protective effect of helmet use in motorcycle and bicycle accidents: a propensity score-matched study based on a trauma registry system. BMC Public Health. 2017 Aug 7;17(1):639. doi: 10.1186/s12889-017-4649-1.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):998-1002.
DOI: 10.28982/josam.811915

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Assessment of the efficacy of endovascular treatment in chronic limb-threatening ischemia in diabetic and non-diabetic patients

Diyabetik ve non-diyabetik hasta gruplarında kronik ekstremite tehdit eden iskemide endovasküler tedavi etkinliğinin değerlendirilmesi

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Abstract

Aim: Peripheral artery diseases are a very common manifestation of atherosclerosis. We assessed the clinical outcomes of diabetic versus non-diabetic patients with chronic limb-threatening leg ischemia who underwent Peripheral Transluminal Angioplasty (PTA).

Methods: The patients (84 diabetic/66 non-diabetic) who underwent percutaneous transluminal angioplasty (PTA) in the lower extremity arterial lesions (stenosis/occlusion) because of chronic limb-threatening leg ischemia (Rutherford class 4 and above) between June 2013 and March 2020 were included in the study.

Results: Six-month primary patency rates were 86.5% and 93.3% in the diabetic and non-diabetic group, respectively. The 12-month primary patency rates were 73.0% and 73.3%; and 12-month secondary patency rates were 66.7% and 77.8%. No differences were detected between the groups in terms of patency rates. Major amputation and total amputation rates were higher at statistically significant levels in the diabetic patient group (%16.7% vs. 6.1%; *P*=0.003) (34.6% vs. 22.8%); *P*=0.004)

Conclusion: When patency and amputation rates are evaluated in diabetic and non-diabetic patient groups with limb-threatening chronic leg ischemia after endovascular treatment, good clinical results were reported in these two groups. Current results suggest that endovascular treatment can be used safely and effectively in both patient groups.

Keywords: Limb-threatening ischemia, Endovascular intervention, Diabetes mellitus

Öz

Amaç: Periferik arter hastalıkları, aterosklerozun neden olduğu günümüzde giderek yaygınlaşan hastalıklardır. Çalışmamızda Periferik Transluminal Anjiyoplasti (PTA) uygulanan kronik ekstremite tehdit eden bacak iskemisi olan, diyabetik ve non-diyabetik hasta gruplarının, klinik sonuçlarını değerlendirmeyi amaçladık.

Yöntemler: Haziran 2013 - Mart 2020 tarihleri arasında kronik ekstremite tehdit eden bacak iskemisi (Rutherford sınıf 4 ve üzeri) nedeniyle alt ekstremite arteriyel lezyonlarına (darlık / tıkanıklık) perkütan transluminal anjiyoplasti (PTA) işlemi uygulanan 150 hasta (84 diyabetik / 66 non-diyabetik) çalışmaya dahil edilmiştir.

Bulgular: Altı aylık primer açıklık oranları diyabetik ve diyabetik olmayan grupta sırasıyla %86,5 ve %93,3 idi. 12 aylık primer açıklık oranları %73,0 ve %73,3 iken; 12 aylık sekonder açıklık oranları ise %66,7 ve %77,8 idi. Açıklık oranları açısından gruplar arasında farklılık tespit edilmedi. Diyabetik hasta grubunda majör ampütasyon (%16,7-%6,1; *P*=0,003) ve toplam amputasyon oranları (%34,6-%22,8; *P*=0,004) istatistiksel olarak anlamlı düzeylerde daha yüksekti.

Sonuç: Endovasküler tedavi sonrası ekstremite tehdit eden kronik bacak iskemisi olan diyabetik ve diyabetik olmayan hasta gruplarında açıklık ve amputasyon oranları değerlendirildiğinde, her iki grupta da başarılı klinik sonuçlar bildirilmiştir. Güncel sonuçlarımız, endovasküler tedavinin ekstremite tehdit eden iskemide her iki hasta grubunda da etkili bir şekilde kullanılabileceğini göstermektedir.

Anahtar kelimeler: Ekstremite tehdit eden iskemi, Endovasküler girişim, Diabetes mellitus

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Ethics Committee Approval: The study was approved by Adiyaman University Ethics Committee (05/18/2020-220/5-29). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Adıyaman Üniversitesi girişimsel olmayan araştırmalar etik kurulu (18.05.2020-220/5-29) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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How to cite/Atıf için: Urcun YS, Pala AA. Assessment of the efficacy of endovascular treatment in chronic limb-threatening ischemia in diabetic and non-diabetic patients. J Surg Med. 2020;4(11):998-1002.

Introduction

Peripheral artery diseases are a very common manifestation of atherosclerosis. Its incidence increases in the presence of advanced age and cardiovascular risk factors [1,2]. Peripheral artery diseases are more common in diabetic patients, and their prevalence ranges from 9.5% to 13.6% in this group [3,4], while it is approximately 4% in the general population [1].

The atherosclerotic plaques in the lower extremity cause stiffness in wrist arteries, reduce vascular resistance, and decrease blood flow, creating ischemic symptoms, which, eventually, leads to clinical conditions that range from claudication to limb-threatening leg ischemia and can result in tissue loss. This critical leg ischemia can be defined with ischemic rest pain and nocturnal recumbent pain as well as ischemic skin lesions, ulcers, and frank gangrene [5]. In these patients, medical treatment results do not provide the expected clinical recovery [6]. In recent times, the encouraging and successful results of the endovascular treatment option [7] have made the endovascular treatment the first-line treatment option in peripheral vascular diseases in our clinic.

We assessed the clinical outcomes of diabetic versus non-diabetic patients with chronic limb-threatening leg ischemia who underwent Peripheral Transluminal Angioplasty (PTA).

Materials and methods

A total of 150 patients (84 diabetic/66 non-diabetic) were included in the study. The patients underwent percutaneous transluminal angioplasty (PTA) in the lower extremity arterial lesions (stenosis/occlusion) because of chronic limb-threatening leg ischemia (Rutherford class 4 and above) between June 2013 and March 2020. The study was commenced after approval was obtained from Adıyaman University Ethics Committee (Approval number: 2020/5-29). The exclusion criteria included having aortoiliac endovascular reconstruction and advanced endovascular procedures like atherectomy and mechanical thrombectomy, acute critical ischemia and functionally unsalvageable limb. The demographic, clinical and procedural data of the patients were obtained from patient files and clinical records. Patients who were Class 4 and above according to Rutherford Qualification were included in the study [8].

The measurement of Ankle Brachial Index (ABI) was performed after 5 min resting in supine position to all patients routinely in our clinic after the diagnosis of peripheral artery disease. Again, all patients who are scheduled for intervention undergo 3D Computed Tomography Angiography (3D-CTA) from abdominal aorta to tiptoe. All interventions are performed by the same cardiovascular surgery team in the cardiac catheterization laboratory.

All interventions are carried out under local anesthesia. Vascular access is often provided with Retrograde 6 F or 7 F sheath from the counter-lateral femoral artery. However, access can also be provided by placing antegrade sheath (4 F) in cases with isolated popliteal or tibial artery lesions through the ipsilateral femoral artery. The location and degree of the lesion are determined after the angiography process. Anticoagulation is administered to all patients with intravenous heparin (5.000 units) with an activated clotting time value of 200-250 sec. All lesions are passed by using hydrophilic guidewires (0.014-, 0.018-, 0.035-inch) through endoluminal or subintimal routes, and it is checked whether they are in the endoluminal location after a subsequent angiography. The healthy distal part of the vessel that will undergo the intervention is taken as the reference for the balloon measure. A balloon (2.5-8.0 mm) in appropriate size is selected and inflated in a time interval of 120-180 sec with 6-12 atmospheric pressure; an angiogram is performed again after the process, and technical results are evaluated. The stent is applied to all patients with current-restricting dissection, residual stenosis above 30%, intimal flap and acute occlusion; and the detection of residual stenosis under 30% is considered a technical success after PTA and stent application.

Following the procedure, 100-mg aspirin a day is started in patients without contraindications, and is continued for life. For the patient group with stents, 75 mg clopidogrel is administered once a day after an additional 300 mg clopidogrel loading dose following the intervention to be continued for 1 year.

After discharge, patients are called for clinical follow-ups, first in the 4th week, with 3-month intervals. The follow-ups are carried out with non-invasive techniques like pulse examination and hand doppler ultrasonography. In case a lack of pulse, claudication or resting pain are detected, 3D Computed Tomography Angiography (3D-CTA) from abdominal aorta to tiptoe is performed. If necessary, angiography is performed again, and a new endovascular intervention is planned if ≥50% angiographic stenosis is detected in the vascular segment that was treated.

In our study, primary patency was defined as a permanent opening in the vascular segment treated, for which no new endovascular or surgical intervention was required. Secondary patency, on the other hand, was defined as permanent opening after a reintervention for the lesion. Partial amputations of the heel and foot were defined as minor amputations, and all amputations above the ankle were defined as major amputations.

Statistical analysis

The SPSS 11.5 Program was used in the analysis of the data. Mean (standard deviation) and median (minimum-maximum) were used descriptively for quantitative variables; and number of patients (percent) was used for qualitative variables. In quantitative variables, the qualitative variable with two categories was tested with the Mann-Whitney U-test since there were no differences between the categories, and normal distribution assumptions were not met. The Chi-Square test was used to examine the relationship between two qualitative variables. The statistical significance limit was 0.05.

Results

A total of 150 patients who underwent endovascular intervention because of chronic limb-threatening leg ischemia were included in the study. A total of 56% (n:84) of the patients included in the study were in the Diabetic Group, and 44% (n:66) were in the Non-Diabetic Group. The mean age was 65.02 (11.59) in the diabetic patient group, and 68.58 (7.43) in the non-diabetic group (Table 1). The mean follow-up duration of the diabetic patient group was 14.76 (2.72) months, and that of the non-diabetic group was 13.94 (2.54) months (Table 1). When

compared with non-diabetic patients, diabetic patients had a higher percentage of coronary artery disease (92.9% vs. 78.8%; *P*=0.012) (Table 2). Other demographic data and additional diseases of the patients are given in Tables 1 and 2. Although pure SFA (superficial femoral artery) lesion was not detected in the diabetic patients, pure popliteal diseases were observed in 16.7% (n:14) of the patients, pure tibial, in 16.7% (n:14), SFA+distal, in 23.7% (n:20), popliteal+distal, in 28.6% (n:24), and tibial+distal artery diseases, in 14.3% (n:12). In the non-diabetic group, on the other hand, pure SFA lesion was detected in 6.1% (n:4) of the patients, pure popliteal disease, in 24.2% (n:16), pure tibial disease, in 18.2% (n:12), femoral+distal, in 24.2% (n:16), popliteal+ distal, in 21.2% (n:14), and tibial+distal artery diseases, in 6.1% (n:4). Distal disease was detected relatively more frequently in the diabetic patient group; however, this did not cause a statistically significant difference (*P*<0.05) (Table 2). Among the patients who underwent intervention in the diabetic patient group, 40.5% (n:34) were classified as Category 4 according to the Rutherford Qualification, 38.1% (n:32) were Category 5, and 21.4% (n:18) were Category 6. Among the patients who underwent intervention in the non-diabetic patient group, 42.4% (n:28) were classified as Category 4, 42.4% (n:28), as Category 5, 15.2% (n:10) as Category 6 according to the Rutherford Qualification. Although patients with Rutherford Classification Category 6 were relatively higher in the diabetic patient group, this did not cause a statistically significant difference (*P*<0.05) (Table 2).

Table 1: Preoperative data 1

Variables	Group				
	Diabetic		Non-Diabetic		
	Mean(SD)	Med (Min-Max)	Mean(SD)	Med (Min-Max)	*P*-value
Age	65.02(11.59)	65.00 (27.00-87.00)	68.58(7.43)	67.00 (55.00-87.00)	0.067
Hba1c	10.15(1.37)	10.00 (7.90-13.50)	4.17(0.97)	4 (3.90-5.50)	<0.001
ABI	0.37(0.09)	0.38 (0.11-0.54)	0.36(0.08)	0.37 (0.19-0.48)	0.306
Follow-Up Time (months)	14.76(2.72)	14.00 (10.00-24.00)	13.94(2.54)	14.00 (9.00-14.00)	0.121

ABI: Ankle Brachial Index

Table 2: Preoperative data 2

Variables		Group				
		Diabetic		Non-Diabetic		
		n	%	N	%	*P*-value
Gender	Male	66	78.6	50	75.8	0.683
	Female	18	21.4	16	24.2	
Smoking		60	71.4	52	78.8	0.304
HT		44	52.4	40	60.6	0.314
HL		62	73.8	50	75.8	0.785
CKD		14	16.7	8	12.1	0.435
ASA		76	90.5	60	90.9	0.928
CAD		78	92.9	52	78.8	0.012
	Sfa	0	0.0	4	6.1	0.096
Lesion location	Popliteal artery	14	16.7	16	24.2	
	Tibial+distally arteries	14	16.7	12	18.2	
	Sfa+distally arteries	20	23.7	16	24.2	
	Popliteal+distally arteries	24	28.6	14	21.2	
	Tibial+distally arteries	12	14.3	4	6.1	
Rutherford classification	4	34	40.5	28	42.4	0.610
	5	32	38.1	28	42.4	
	6	18	21.4	10	15.2	

HT: Hypertension, HL: Hyperlipidemia, CCD: Chronic Kidney Disease, ASA: Acetylsalicylic Acid, CAD: Coronary Artery Diease, Sfa: Superior Femoral Artery

Our technical success rate was 85.7% in the diabetic group and 90.9% in non-diabetic group (*P*=0.331). No significant differences were detected in technical complications in terms of dissection (11.9% vs 9.1%) and acute embolization (9.5% vs. 6.1%) (*P*>0.05). The reintervention rates among groups were similar (26.2% vs. 15.2%; *P*=0.101) (Table 3).

The clinical results of the patients are given in Tables 4 and 5. Six-month primary patency rates were 86.5% and 93.3% in the diabetic and non-diabetic groups, respectively. The 12-month primary patency rates were 73.0% and 73.3%; and 12-month secondary patency rates were 66.7% and 77.8%. No differences were detected between the groups in terms of patency rates (Table 4).

There were no differences between the groups in terms of minor amputation rates (17.9% vs. 16.7%; *P*=0.761). Major amputation and total amputation rates, on the other hand, were significantly higher in the diabetic patient group (%16.7% vs. 6.1%; *P*=0.003) (34.6% vs. 22.8%); *P*=0.004) Wound healing rates were lower in the diabetic patient group (64.0% vs. 86.8%); *P*=0.005). No differences were detected between the groups in terms of mortality rates during the follow-ups (21.4% vs. 21.2%); *P*=0.974) (Table 5).

Table 3: Angiographic results

Variables	Group				
	Diabetic		Non-Diabetic		
	n	%	N	%	*P*-value
Technical Failure	12	14.3	6	9.1	0.331
Dissection	10	11.9	6	9.1	0.579
Embolization	8	9.5	4	6.1	0.438
Reintervention	22	26.2	10	15.2	0.101

Table 4: Primer patency and secondary patency rates

Variables		Group				
		Diabetic		Non-Diabetic		
		n	%	n	%	*P*-value
SP	Yok	10	33.3	4	22.2	0.412
	Var	20	66.7	14	77.8	
6 months PP	Yok	10	13.5	4	6.7	0.198
	Var	64	86.5	56	93.3	
12 months PP	Yok	20	27.0	16	26.7	0.963
	Var	54	73.0	44	73.3	

SP: Secondary Patency, PP: Primer Patency

Table 5: Clinical results

Variables	Group				
	Diabetic		Non-Diabetic		
	n	%	n	%	*P*-value
Minor Amputation	15	17.9	11	16.7	0.761
Major Amputation	14	16.7	4	6.1	0.003
Minor+Major Amputation	29	34.6	15	22.8	0.004
Wound Healing	32	64.0	33	86.8	0.005
Mortality	18	21.4	14	21.2	0.974

Discussion

Amputation and mortality risks are high in patients with limb-threatening leg ischemia. Major amputation and mortality are observed in 30% of these cases within 1 year after the diagnosis [9]. Successful revascularization is required to reduce amputation rates, accelerate wound healing and reduce mortality rates. As a less invasive method, percutaneous intervention is preferred with the improvements in percutaneous treatment methods in many healthcare centers as a priority for these patients, since bypass surgery is a risky surgical intervention because of advanced age and cardiac comorbidities [10]. In our study, the purpose was to determine the effect of percutaneous interventions on wound healing, minor and major amputation rates in the diabetic and non-diabetic patient group with limb-threatening chronic ischemia in lower extremities and compare the re-intervention rates with primary and secondary patency rates.

Among other objective and non-invasive tests, Ankle-Brachial Index (ABI) can be used in the diagnosis of peripheral artery disease in lower extremities. ABI values are also among

the independent variables of mortality and morbidity [11,12]. ABI values being at or below 0.9 confirms the peripheral artery disease diagnosis, and values below 0.4 show limb-threatening leg ischemia [5]. In diabetic patient group, ABI values may not always yield accurate values because of the inability of the arteries to compress due to medial arterial sclerosis [13]. For this reason, there are no significant correlations between the stenosis degree and ABI values in these patients [14]. In diabetic and non-diabetic patient groups with chronic limb-threatening leg ischemia included in our study, the ABI values were 0.37(0.09) and 0.36(0.08), respectively, and the differences were not significant. In their study, Santos et al. [15] also showed that the falsely elevated ABI was in high prevalence in diabetic patients with limb-threatening leg ischemia, and they did not find any differences in terms of ABI values in the diabetic and non-diabetic group when the false-positive ABI values were excluded from the study.

In the present study, after the intervention, 30% or more residual stenosis patients were considered a technical failure, which was observed as 14.3% and 9.1% in the diabetic and non-diabetic group, respectively, and there were no differences between the groups in this regard. The fact that there were excessive calcified lesions in diabetic patients caused relatively high results compared to the non-diabetic group without significance. In their study, Kahraman et al. [16] evaluated the results of endovascular intervention in limb-threatening leg ischemia, and reported the technical failure rate as 27%, and complication rates as 17% during the procedure. In their study, the TASC Group reported the technical success rate as 90% and 1-year primary patency rate as 61% in patients with femoropopliteal lesions that were admitted with claudication complaints [17]. In our study, no differences were detected between the groups in terms of complications like dissection and embolization during the procedure. The process complication rate in the diabetic group was 21.4%, and 15.1% in the non-diabetic group. Likewise, Hanna et al. [18] reported the procedural complication rate as 21% in diabetic patients with limb-threatening leg ischemia who underwent balloon angioplasty [18].

Chronic limb-threatening leg ischemia is more common in diabetic patient group than in non-diabetic patient group, and is associated with higher restenosis and amputation rates [19]. No differences were observed between the groups in our study in terms of 6-month and 1-year primary patency, secondary patency, and minor amputation rates. However, it was found that the major amputation and total amputation rates were statistically and significantly higher in the diabetic group.

Atherosclerosis is diagnosed more frequently in diabetic patients, and progresses in diffuse form. It is already known that chronic high blood glucose values cause abnormalities in vascular endothelium and prepare the ground for hypercoagulability and atherogenesis [20]. In our study, the mean Hba1c value in the diabetic group was 10.15(1.37), which suggested that the patient population had a poor long-term blood glucose control. This may explain why the major and total amputation rates are high with the damage done by diabetes mellitus at microvascular level compared to the non-diabetic group in our study. Also, because of peripheral neuropathy, diabetic patients being asymptomatic for longer durations and applying to the hospital at later stages might be another cause of poor clinical outcomes. In the study conducted by Levigne et al. [21], it was found that there were higher amputation rates after endovascular interventions in the diabetic patient group, which was associated with hyperglycemia, reducing the tolerance of tissue ischemia. Xiao et al. [22] conducted a study and evaluated the effectiveness of endovascular treatment in limb-threatening leg ischemia, and reported that there were no differences between the diabetic and non-diabetic patient groups in terms of 12-month primary and secondary patency and limb recovery rates. In the literature, up to 70% amputation rates were reported in limb-threatening leg ischemia patients, which were 5 times more common in diabetic patients [23, 24]. In our study, the total amputation rates being 34.5% in the diabetic group, and 22.7% in the non-diabetic group shows that endovascular treatment is an effective method reducing amputation rates in both patient groups.

The risk of developing feet wounds in patients with diabetes is up to 25%, and feet lesion is one of the most important risk factors for limb amputation [25]. Diabetes Mellitus and the infection of the wound in the feet are considered predictors of delayed wound healing after endovascular interventions [26]. The 1-year wound healing rate ranges from 54% to 86% after endovascular interventions [27, 28]. In our study, the wound healing rate was 64.0% in the diabetic group and 86.8% in the non-diabetic group. In our study, the delay in wound healing was significantly higher in the diabetic group, which may be a reason of higher amputation rates in the diabetic group despite similar patency rates due to increased metabolic demand in the feet.

Limitations

The retrospective, single-center design of this study, and low patient count can be listed as the disadvantages of this study. The significantly higher rate of preoperative coronary artery disease in the diabetic group might have affected the mortality rates between the two groups. The short mean follow-up duration in the study can also be mentioned as one of the limitations of the study.

Conclusion

When patency and amputation rates are evaluated in diabetic and non-diabetic patient groups with limb-threatening chronic leg ischemia after endovascular treatment, good clinical results were reported in these two groups. Current results suggest that endovascular treatment can be used safely and effectively in both patient groups. However, further prospective studies are required to be conducted with a higher patient population to determine optimal treatment options in especially diabetic patient populations with limb-threatening leg ischemia.

References

1. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999-2000. Circulation. 2004 Aug 10;110(6):738-43.
2. Pasternak RC, Criqui MH, Benjamin EJ, Fowkes FG, Isselbacher EM, McCullough PA, et al. American Heart Association. Atherosclerotic Vascular Disease Conference: Writing Group I: epidemiology. Circulation. 2004 Jun 1;109(21):2605-12.
3. Gregg EW, Sorlie P, Paulose-Ram R, Gu Q, Eberhardt MS, et al. 1999-2000 national health and nutrition examination survey. Prevalence of lower-extremity disease in the US adult population >=40 years of age with and without diabetes: 1999-2000 national health and nutrition examination survey. Diabetes Care. 2004 Jul;27(7):1591-7.
4. Norman PE, Davis WA, Bruce DG, Davis TM. Peripheral arterial disease and risk of cardiac death in type 2 diabetes: the Fremantle Diabetes Study. Diabetes Care. 2006 Mar;29(3):575-80.

5. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II). J Vasc Surg. 2007 Jan;45 Suppl S:S5-67.
6. Adam DJ, Bradbury AW. TASC II document on the management of peripheral arterial disease. Eur J Vasc Endovasc Surg. 2007 Jan;33(1):1-2.
7. Bosiers M, Hart JP, Deloose K, Verbist J, Peeters P. Endovascular therapy as the primary approach for limb salvage in patients with critical limb ischemia: experience with 443 infrapopliteal procedures. Vascular. 2006 Mar-Apr;14(2):63-9.
8. Rutherford RB, Baker JD, Ernst C, Johnston KW, Porter JM, Ahn S, et al. Recommended standards for reports dealing with lower extremity ischemia: revised version. J Vasc Surg. 1997 Sep;26(3):517-38. doi: 10.1016/s0741-5214(97)70045-4. Erratum in: J Vasc Surg 2001 Apr;33(4):805.
9. Feiring AJ, Krahn M, Nelson L, Wesolowski A, Eastwood D, Szabo A. Preventing leg amputations in critical limb ischemia with below-the-knee drug-eluting stents: the PaRADISE (PReventing Amputations using Drug eluting StEnts) trial. J Am Coll Cardiol. 2010 Apr 13;55(15):1580-9.
10. Romiti M, Albers M, Brochado-Neto FC, Durazzo AE, Pereira CA, De Luccia N. Meta-analysis of infrapopliteal angioplasty for chronic critical limb ischemia. J Vasc Surg. 2008 May;47(5):975-981.
11. O'Hare AM, Katz R, Shlipak MG, Cushman M, Newman AB. Mortality and cardiovascular risk across the ankle-arm index spectrum: results from the Cardiovascular Health Study. Circulation. 2006 Jan 24;113(3):388-93.
12. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA. 2008 Jul 9;300(2):197-208.
13. Coutinho T, Rooke TW, Kullo IJ. Arterial dysfunction and functional performance in patients with peripheral artery disease: a review. Vasc Med. 2011 Jun;16(3):203-11.
14. Englund EK, Langham MC, Ratcliffe SJ, Fanning MJ, Wehrli FW, Mohler ER 3rd, et al. Multiparametric assessment of vascular function in peripheral artery disease: dynamic measurement of skeletal muscle perfusion, blood-oxygen-level dependent signal, and venous oxygen saturation. Circ Cardiovasc Imaging. 2015 Apr;8(4): doi: 10.1161/CIRCIMAGING.114.002673 e002673.
15. Santos VPdA, Alves CAS, Fidelis Ronald José Ribeiro, Fidelis Cícero, Araújo Filho José Siqueira de. Estudo comparativo do Índice Tornozelo-Braquial em diabéticos e não diabéticos com isquemia crítica. J Vasc Bras. 2015 Dec;14(4):305-10.
16. Şırlak M, Kahraman D. Infrapoplıteal Angioplasty In Critical Limb Ischemia. Damar Cerrahi Dergisi.2016;25:11-6. doi: 10.9739/uvcd-51827.
17. Dormandy JA, Rutherford RB. Management of peripheral arterial disease (PAD). TASC Working Group. TransAtlantic Inter-Society Consensus (TASC). J Vasc Surg. 2000 Jan;31(1 Pt 2):S1-S296.
18. Hanna GP, Fujise K, Kjellgren O, Feld S, Fife C, Schroth G, et al. Infrapopliteal transcatheter interventions for limb salvage in diabetic patients: importance of aggressive interventional approach and role of transcutaneous oximetry. J Am Coll Cardiol. 1997 Sep;30(3):664-9.
19. Lee MS, Rha SW, Han SK, Choi BG, Choi SY, Ali J, et al. Comparison of diabetic and non-diabetic patients undergoing endovascular revascularization for peripheral arterial disease. J Invasive Cardiol. 2015 Mar;27(3):167-71.
20. American Diabetes Association. Peripheral arterial disease in people with diabetes. Diabetes Care. 2003 Dec;26(12):3333-41.
21. Lévigne D, Tobalem M, Modarressi A, Pittet-Cuénod B. Hyperglycemia increases susceptibility to ischemic necrosis. Biomed Res Int. 2013;2013:490964.
22. Xiao L, Huang DS, Tong JJ, Shen J. Efficacy of endoluminal interventional therapy in diabetic peripheral arterial occlusive disease: a retrospective trial. Cardiovasc Diabetol. 2012 Feb 28;11:17.
23. Jude EB, Oyibo SO, Chalmers N, Boulton AJ. Peripheral arterial disease in diabetic and nondiabetic patients: a comparison of severity and outcome. Diabetes Care. 2001 Aug;24(8):1433-7.
24. Wolfe JH, Wyatt MG. Critical and subcritical ischaemia. Eur J Vasc Endovasc Surg. 1997 Jun;13(6):578-82.
25. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcers in patients with diabetes. JAMA. 2005 Jan 12;293(2):217-28.
26. Kawarada O, Fujihara M, Higashimori A, Yokoi Y, Honda Y, Fitzgerald PJ. Predictors of adverse clinical outcomes after successful infrapopliteal intervention. Catheter Cardiovasc Interv. 2012 Nov 1;80(5):861-71.
27. Rocha-Singh KJ, Jaff M, Joye J, Laird J, Ansel G, Schneider P; et al. Major adverse limb events and wound healing following infrapopliteal artery stent implantation in patients with critical limb ischemia: the XCELL trial. Catheter Cardiovasc Interv. 2012 Nov 15;80(6):1042-51.
28. Iida O, Nakamura M, Yamauchi Y, Kawasaki D, Yokoi Y, Yokoi H, et al. OLIVE Investigators. Endovascular treatment for infrainguinal vessels in patients with critical limb ischemia: OLIVE registry, a prospective, multicenter study in Japan with 12-month follow-up. Circ Cardiovasc Interv. 2013 Feb;6(1):68-76.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1003-1007.
DOI: 10.28982/josam.812679

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Novel markers in predicting non-alcoholic liver fatty and metabolic syndrome in obese children and adolescents: Atherogenic index of plasma and monocyte / high-density lipoprotein cholesterol ratio

Obez çocuk ve adölesanlarda metabolic sendrom ve non-alkolik karaciğer yağlanmasını öngörmede yeni belirteçler: Plazma aterojenik indeks ve monosit / yüksek dansiteli lipoprotein kolesterol oranı

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Ethics Committee Approval: This study was approved by Ethics Committee of Dicle University Medicine of Faculty (Document number: 25.03.2016/158). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Dicle Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylandı (Belge no: 25.03.2016/158). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: The aim of this study is to investigate the relationship between metabolic syndrome (MetS), insulin resistance, waist circumference (WC) and non-alcoholic fatty liver disease (NAFLD) with atherogenic index of plasma (AIP) and monocyte/ high-density lipoprotein cholesterol ratio (MHR) among obese children and adolescents.

Methods: The cross-sectional study consisted of 172 obese and 63 healthy children. Anthropometric and biochemical parameters [Weight, height and BMI SDS, WC, Complete blood count, aspartate-aminotransferase (AST), alanine-aminotransferase (ALT), insulin, glucose, total cholesterol (TC), high-density lipoprotein (HDL-C), triglyceride (TG) and low-density lipoprotein (LDL-C), homeostasis model assessment-insulin resistance (HOMA-IR), AIP, MHR] were assessed. The AIP was classified into three groups: Low (<0.11), intermediate (0.11–0.21) and high (>0.21) risk. The MetS definition proposed by the International Diabetes Federation was adopted.

Results: BMI SDS, WC, HOMA-IR, TC, TG, LDL-C, AST, ALT, AIP, and MHR parameters were significantly higher among the obesity group (P<0.05 for each). The MetS was analyzed in 146 obese children older than 10 years of age and found positive in 49 (33.6%) children. The mean AIP and median MHR were significantly higher in the group with MetS than in the group without (P<0.001, P=0.017, respectively). A significant positive correlation was determined between AIP and WC, HOMA-IR, TG, ALT, MHR, and steatosis degree (r=0.34, P<0.001, r=0.289, P<0.001, r=0.863, P<0.001, r=0.292 P<0.001, r=0.447, P<0.001, r=0.298, P<0.001 respectively).

Conclusion: Both AIP and MHR are simple, cheap, and easily calculable parameters. The AIP might be used as an effective marker to predict MetS, abdominal obesity, NAFLD and IR in obese children. In addition, the high MHR in obese children may be associated with an increased risk of cardiovascular disease and MetS.

Keywords: Atherogenic index of plasma, Monocyte to HDL cholesterol ratio, Obesity, Metabolic syndrome, Children

Öz

Amaç: Bu çalışmada obezitesi olan çocuk ve adölesan hastalarda plazma aterojenik indeks (PAİ) ve monosit / HDL oranı (MHO) ile metabolik sendrom (MS), insülin direnci (İD), bel çevresi (BÇ) ve non-alkolik karaciğer yağlanması (NAKY) arasındaki ilişkinin araştırılması amaçlanmıştır.

Yöntemler: Çalışma kesitsel olup, 172 obez çocuk hasta ile 63 sağlıklı kontrol hastası içermekteydi. Antropometrik ve biyokimyasal parametreler [ağırlık, boy, beden kitle indeksi (BKİ) standart deviasyon skoru (SDS), BÇ, hemogram, aspartat transaminaz (AST), alanin transaminaz (ALT), insulin, glukoz, total kolesterol (TC), yüksek-dansiteli lipoprotein kolesterol (HDL-C), trigliserid (TG), düşük-dansiteli lipoprotein kolesterol (LDL-C), HOMA-IR, PAİ ve MHO] değerlendirildi. Plazma aterojenik indeks; düşük (<0,11), orta (0,11–0,21) ve yüksek (>0,21) risk diye üç gruba ayrıldı. Metabolik sendrom tanımı Uluslararası Diyabet Fedarasyonuna göre yapıldı.

Bulgular: Obez hasta grubunda BKİ SDS, BÇ, HOMA-IR, TC, TG, LDL-C, AST, ALT, PAİ değeri ve MHO anlamlı ölçüde yüksek saptandı (her biri için P<0,05). On yaş üzeri 146 hastada MS araştırıldı ve 49 hastada (%33,6) pozitif saptandı. Ortalama PAİ ve ortanca MHO değeri obez ve MS'u olanlarda, obez ve MS'u olmayanlara göre anlamlı ölçüde yüksek saptandı (p değeri sırasıyla; <0,001, 0,017). Plazma aterojenik index ile BÇ, HOMA-IR, TG, ALT, MHO ve karaciğerin yağlanma derecesi arasında anlamlı pozitif korelasyon saptandı (r=0,34, P<0,001, r=0,289, P<0,001, r=0,863, P<0,001, r=0,292, P<0,001, r=0,447, P<0,001, r=0,298, P<0,001 sırasıyla).

Sonuç: Hem PAİ hem de MHO basit, ucuz ve kolay hesaplanabilen parametrelerdir. Obez çocuklarda PAİ değerinin, abdominal obezite, NAKY, İD ve MS'u öngörmede bir belirteç olarak kullanılabilir. Ayrıca obez çocuklarda yüksek MHO'nın artmış kardiyovasküler hastalık riski ve MS ile ilişkili olduğu düşünülebilir.

Anahtar kelimeler: Plazma aterojenik indeks, Monosit/HDL-C oranı, Obezite, Metabolik sendrom, Çocuklar

Introduction

Childhood obesity is one of the most serious public health issues of the 21st century, with rapidly increasing worldwide prevalence. According to 2016 World Health Organization (WHO) data, there are more than 42 million overweight children under the age of 5 years. Obesity increases the risk for both diabetes and cardiovascular diseases (CVD) by provoking insulin resistance and impaired glucose tolerance, leading to hypertension, dyslipidemia, and Non-alcoholic fatty liver disease (NAFLD) [1]. One of the most important risk factors for CVD is dyslipidemia. It has been shown that both a decrease in high density lipoprotein cholesterol (HDL-C) and an increase in total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels contribute to the progression of atherosclerosis [2]. The atherogenic index of plasma (AIP) value is a proven good marker to determine the risk of atherosclerosis and CVD [3,4]. The AIP value is calculated through logarithmic transformation of the number obtained from the division of the plasma TG level by the HDL-C level.

Similar to the AIP value, the Monocyte/HDL Ratio (MHR) has also been proven as a useful prognostic marker, especially for atherosclerotic cardiovascular diseases, hypertension and metabolic syndrome, as the value is elevated in those diseases [5-8]. Monocytes and macrophages play a significant role during atherosclerotic plaque development and monocytes in large numbers are known to trigger the development of plaque. It has also been previously reported that HDL-C inhibits the expression of inflammation adhesion molecules in endothelial cells [9].

Most studies that have evaluated the relationship of both AIP and MHR with CVD have been conducted on adults [3,4]. The aim of this study is to investigate the relationship between metabolic syndrome (MetS), insulin resistance (IR), waist circumference (WC) and NAFLD with AIP and MHR among children and adolescents with obesity.

Materials and methods

The study included patients aged 7-18 years, who presented at the Pediatric Endocrinology Polyclinic of Dicle University Medical Faculty. Patients were excluded from the study if obesity was associated with hypothyroidism, Cushing syndrome, growth hormone deficiency, chronic corticosteroid drug usage, genetic or neuromuscular reasons. Body weight, weight standard deviation scores (SDS), height, height SDS, Body Mass Index (BMI), BMI SDS and WC measurements were obtained and recorded for all patients. Height was measured using a Harpenden stadiometer with sensitivity of 0.1 cm and weight was measured using scales with sensitivity of 0.1 kg (SECA, Hamburg, Germany).

Venous blood samples were obtained from all patients after 12 hours of fasting. Complete blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), insulin, fasting blood glucose, TC, HDL-C, TG and LDL-C levels were examined from the blood samples.

Steatosis was investigated in all patients on abdomen ultrasonography (USG) performed by a single experienced radiologist. The diagnosis of hepatic steatosis was based on the criteria defined by Saverymuttu et al. [10] and the severity was classified as grade 1: mild, grade 2: moderate, and grade 3: severe, according to the degree of fatty infiltration. Control group was assembled from individuals visiting the outpatient clinics for routine check-up, who were not diagnosed with obesity and had normal results for physical examination.

Written informed consent was obtained from the parents of the patients for publication of this paper. This study was approved by Ethics Committee of Dicle University Medicine of Faculty (Document number: 25.03.2016/158).

Definitions

Body mass index was calculated with the formula: Body weight/height^2. Body Mass Index values >95% according to age and sex were considered obesity. Acquired BMI values were compared with the normal reference values in Turkish public society [11]. The waist circumference was measured at the level of the midpoint between the spina iliaca anterior superior and arcus costalis and then compared with the age-related reference values for Turkish children [12].

Metabolic syndrome was defined according to the International Diabetes Federation (IDF) criteria which was adapted for children and adolescents [13]. It is suggested that MetS cannot be diagnosed children below the age of 10 years by the IDF. For children between 10 and 16 years of age, the diagnosis of MetS required the presence of abdominal obesity and the two or more of the following factors: (a) hypertriglyceridemia (>150 mg/dL); (b) low HDL-C (<40 mg/dL); (c) increased fasting glucose (≥ 100 mg/dL); (d) elevated blood pressure (the online calculator program was developed by Demir et al [14] and it was used for evaluation of blood pressure). The percentile curves established for Turkish children were used for waist circumference. A waist circumference ≥90th percentile was considered abdominal obesity [12].

The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value was calculated with the formula of fasting insulin (mcU/ml) X fasting glucose (mg/dl) / 405. The HOMA-IR values were considered positive at >2.67 in prepubertal boys, >2.22 in prepubertal girls, >5.22 in pubertal boys and >3.82 in pubertal girls [15]. Monocyte/HDL ratio was calculated by division of total monocyte number acquired by complete blood count to serum HDL value. The AIP value was calculated by logarithmic transformation of the number acquired by division of plasma TG value to HDL value. The AIP value was considered low risk at values <0.11, moderate risk at values between 0.11 and 0.21 and high risk at values >0.21 according to the references of previous studies [16,17].

Statistical analysis

SPSS 20.0 statistical package program was used to analyze the data of this study. Measured variables were stated as mean (standard deviation (SD)) values, and categorical variables as number (n) and percentage (%). Conformity of the data to normal distribution was assessed with the Kolmogorov Smirnov and Shapiro Wilk tests. For numerical comparisons, the independent sample t-test, or Mann-Whitney U-test were used according to normality of distribution of the measured parameters. Spearman or Pearson correlation analysis was used

to identify the associations between variables. The patient group was separated into three subgroups as low, moderate, and high according to the AIP values and ANOVA test was used to compare the data of those three groups. The Kruskal-Wallis test was used for non-normally distributed parameters (TG, HDL-C, BMI, ALT and MHR). A receiver operating characteristics (ROC) curve analysis was performed for determination of the best cut-off value for AIP in prediction of MetS. In addition, ROC analysis was performed for AIP, TG and HDL-C to differentiate which parameter is more useful in predicting MetS in obese patients. The AIP-HDL, AIP-TG and HDL-TG ROC curves were compared using pROC package analysis in R version 4.0.0 Arbor Day program. In all statistical tests, $P<0.05$ was considered statistically significant.

Results

A total of 235 children including 172 obese patients and 63 normal weight healthy control subjects were included in this study. No statistically significant difference was determined between the patient and control groups with respect to age and gender. The BMI SDS, WC, systolic blood pressure, HOMA-IR, TC, TG, LDL-C, AST, ALT, AIP value and MHR ratio parameters were significantly higher in the obese patient group compared to the control group ($P<0.05$ for each), and HDL-C was significantly lower ($P<0.001$). The anthropometric data and laboratory test results of the patient and control groups are presented in Table 1. According to the AIP value, 113 (65.7%) children in the patient group were classified as having low risk, 21 (12.2%) as moderate risk and 38 (22.1%) as high risk. The three groups were similar in terms of BMI SDS, systolic blood pressure, TC, LDL-C and AST (p values: 0.072, 0.225, 0.213, 0.253, 0.233, and 0.180, respectively), but significantly different with regards to WC, HOMA-IR, TG, HDL-C, ALT and MHR (p values: <0.001, <0.001, <0.001, <0.001, 0.004, and <0.001, respectively) (Table 2).

The International Diabetes Federation criteria for MetS were analyzed in 146 obese children older than 10 years of age. Metabolic syndrome was diagnosed in 49 children, which accounted for 33.6% of the group. While the mean AIP value was 0.25 (0.23) and the median MHR value was 13.6 in the group with MetS, the mean AIP value was -0.76 (0.20) and the median MHR value was 12.52 (4.62-25.6) in the non-MetS group ($P<0.001$, $P=0.017$, respectively).

In the ROC analysis, the optimum cut-off value for AIP in predicting MetS was 0.065 (AUC: 0.884, sensitivity 85%, specificity 75%, $P<0.001$) (Figure 1). In predicting the development of MetS, AUC values for AIP, TG and HDL-C were 0.884 (95% Cl: 0.824-0.943, $P<0.001$), 0.815 (95% Cl: 0.742-0.887, $P<0.001$), and 0.787 (95% Cl: 0.701-0.873, $P<0.001$), respectively. There was a significant difference between AIP-HDL and AIP-TG ROC curves ($P=0.01$, $P=0.02$, respectively), while HDL-TG ROC curves were similar ($P=0.65$) (Figure 2).

A significant positive correlation was detected between the AIP value and WC, HOMA-IR, TG, ALT, MHR, and steatosis degree (r=0.34, $P<0.001$, r=0.289, $P<0.001$, r=0.863, $P<0.001$, r=0.292 $P<0.001$, r=0.447, $P<0.001$, r=0.298, $P<0.001$ respectively). A significant negative correlation was detected between AIP and HDL-C (r=-0.650, $P<0.001$). No significant correlation existed between the AIP value and BMI SDS, systolic blood pressure, diastolic blood pressure, TC, LDL-C, and AST (r=0.067, $P=0.381$, r=0.073, $P=0.339$, r=0.124, $P=0.118$, r=0.112, $P=0.144$, r=0.660, $P=0.391$, r=0.144, $P=0.06$ respectively) (Table 3).

Table 1: Comparison of anthropometric and laboratory data of obese patients and healthy control group

	Patient Group (n:172)	Control Group (n:63)	*P*-value
Age (month)	159.77 (30.05)	161.23 (24.60)	0.074*
BMI (kg/m^2)	29.55 (21.1-46.6)	19.36 (14.2-25.48)	<0.001**
BMI SDS	2.58 (0.62)	-0.30 (1.05)	<0.001*
WC (cm)	97.35 (11.79)	70.44 (9.06)	<0.001*
SBP (mmHg)	118.35 (14.68)	114.21 (7.83)	0.034 *
DBP (mmHg)	76.55 (11.89)	75.95 (5.66)	0.751*
Glucose (mg/dl)	89.61 (6.63)	90.33 (8.47)	0.498*
Insulin (µIU/mL)	23.43 (11.35)	11.84 (4.47)	<0.001*
HOMA-IR	5.17 (2.62)	2.66 (1.02)	<0.001*
TC (mg/dl)	165.41 (29.91)	152.88 (24.22)	0.003*
TG (mg/dl)	114.5 (38-324)	81 (36-130)	<0.001**
LDL (mg/dl)	91.19 (27.20)	79.78 (21.35)	0.003*
HDL (mg/dl)	48.35 (27.7-90)	55.6 (34.5-91.70)	<0.001**
AST (U/L)	23.42 (8.40)	19.9 (6.36)	0.003*
ALT (U/L)	21 (7-109)	13 (6-29)	<0.001**
AIP	0.04 (0.27)	-0.20 (0.20)	<0.001*
MHR	12.66 (4.66-29.8)	10.6 (4.20-22.60)	0.003**

BMI-SDS: body mass index-standard deviation score, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, HOMA-IR: homeostasis model assessment of insulin resistance, TC: total cholesterol, TG: triglyceride, LDL: low density lipoprotein, HDL: high density lipoprotein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, AIP: atherogenic index of plasma, MHR: monocyte to high-density lipoprotein cholesterol ratio, *independent t test, **Mann–Whitney U test; data are given as mean (SD) or median (Interquartile Range 25th–75th percentile)

Table 2: Comparison of anthropometric and laboratory characteristics of low, moderate and high-risk AIP groups

Parameters	Low risk (group 1), mean (SD)	Moderate risk, (group 2) mean (SD)	High risk (group 3) mean (SD)	*P*-value
Age (month)	157.82 (30.06)	159.66 (29.20)	161.84 (27.84)[b]	0.084*
BMI SDS	2.50 (0.58)	2.69 (0.58)	2.75 (0.71)	0.072*
WC (cm)	94.53 (9.67)	100.90 (12.63)[a]	104.68 (13.66)[b]	<0.001*
SBP (mmHg)	117.23 (14.54)	117.86 (11.24)	121.97 (16.42)	0.225*
DBP (mmHg)	75.83 (11.68)	74.52 (12.23)	79.34 (12.11)	0.213*
HOMA-IR	4.62 (2.37)	5.84 (2.52)	6.45 (2.93)[b]	<0.001*
TC (mg/dl)	163.32 (26.06)	175.04 (38.20)	166.28 (34.98)	0.253*
TG (mg/dl)	91.77 (33.27)	152.14 (28.58)[a]	214.97 (103.06)[b,c]	<0.001**
LDL (mg/dl)	89.94 (24.95)	100.69 (32.74)	89.66 (29.93)	0.233*
HDL (mg/dl)	53.76 (11.11)[a,b]	45.70 (8.74)[c]	38.76 (7.22)	<0.001**
AST (U/L)	22.69 (7.63)	26.24 (12.32)	24.05 (7.83)	0.180*
ALT (U/L)	22.04 (10.46)	30.62 (23.51)[a]	29.82 (16.56)[b]	0.004**
AIP	-0.14 (0.18)	0.15 (0.03)[a]	0.35 (0.18)[b,c]	<0.001**
MHR	12.52 (4.07)	14.75 (5.32)	17.14 (6.06)[b]	<0.001**

[a]: between low risk and moderate risk, [b]: between low risk and high risk, [c]: between moderate risk and high risk, *One way Anova test, **Kruskal Wallis test

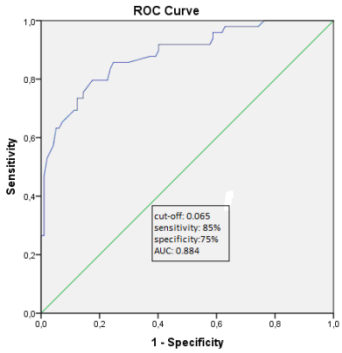

Figure 1: The ROC analysis for AIP in prediction of the metabolic syndrome

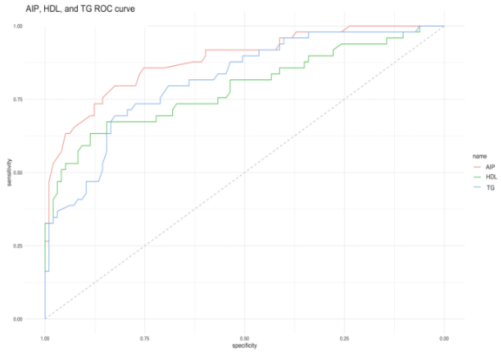

Figure 2: Comparison of AIP-HDL, AIP-TG and HDL-TG ROC curves

Table 3: Pearson correlation analysis between AIP and other parameters

Parameters	r	*P*-value
Age (month)	0.213	0.05
BMI SDS	0.067	0.381
WC (cm)	0.341	<0.001
SBP (mmHg)	0.073	0.339
DBP (mmHg)	0.124	0.118
HOMA-IR	0.289	<0.001
TC (mg/dl)	0.112	0.144
TG (mg/dl)	0.863	<0.001
LDL (mg/dl)	0.660	0.391
HDL (mg/dl)	-0.650	<0.001
AST (U/L)	0.144	0.060
ALT (U/L)	0.292	<0.001
MHR	0.447	<0.001
Liver steatosis degree	0.298	<0.001

A significant positive correlation was detected between MHR value and TC, TG and ALT (r=0.212, *P*=0.008, r=0.216, *P*=0.007, r=0.167, *P*=0.038 respectively). On the other hand, MHR and HDL-C were significantly negatively correlated (r=-0.650, *P*<0.001) (Table 4).

Steatosis was determined in 64 (37.2%) patients in the obesity group. The mean AIP value was 0.084 (0.038) in the subjects with steatosis and -0.043 (0.022) in those without. The difference between those two groups was statistically significant (*P*=0.003). Steatosis was grade 1 in 45 (70.3%) of the 64 steatotic subjects, grade 2 in 16 (25%) and grade 3 in 3 (4.7%). A significant positive correlation was determined between AIP value and steatosis grade (r=0.298, *P*<0.001).

Table 4: Spearman correlation analysis between MHR and other parameters

Parameters	r	*P*-value
Age (month)	0.033	0.679
BMI SDS	-0.053	0.510
WC (cm)	0.119	0.138
SBP (mmHg)	-0.050	0.535
DBP (mmHg)	0.011	0.889
HOMA-IR	0.059	0.473
TC (mg/dl)	0.212	0.008
TG (mg/dl)	0.216	0.007
LDL (mg/dl)	-0.047	0.561
HDL (mg/dl)	-0.650	<0.001
AST (U/L)	0.069	0.393
ALT (U/L)	0.167	0.038
Liver steatosis degree	0.153	0.056

Discussion

Clinical and epidemiological studies conducted on children, adolescents and adults have revealed that body fat distribution is associated with cardiovascular risk factors. Various parameters are used to evaluate fat distribution of body. One of those parameters is BMI, which is recommended for use in defining obesity and overweight status in children aged >2 years and adolescents. However, BMI is not an accurate reflection of the composition and distribution of fat throughout the body. Waist circumference has been reported to be a better marker than BMI for cardiovascular risk factors and visceral fat tissue [18]. In the current study, no significant difference was determined between the low, moderate, and high-risk groups according to the AIP value in terms of BMI SDS, whereas a significant difference was detected in WC. Moreover, there was no significant correlation between AIP and BMI SDS, whereas a positive significant correlation was determined between AIP and WC. Based on this correlation between AIP and WC in our study, it can be suggested that AIP might be used as an efficient marker for cardiovascular risk factors and abdominal obesity predictions in obese children and adolescents. There are very few studies that have investigated the relationship between AIP values and abdominal obesity in children. Nonetheless, a previous study conducted with children reported comparable results with our study, which stated elevated levels of AIP values among obese cases and a positive significant correlation between AIP and WC [19]. In addition, a study conducted on adults have also revealed a positive correlation between AIP and WC [20].

Some studies in adults have shown that AIP can be used as a marker to predict the development of MetS [21,22]. However, to the best of our knowledge, there is no study evaluating the relationship between AIP and MetS in pediatric patients. In our study, it was shown that the AIP value was significantly higher in the group with MetS. In ROC analysis, the optimum cut-off value for AIP in predicting metabolic syndrome was 0.065 (AUC: 0.884; sensitivity 85%; specificity 75%; *P*<0.001). In addition, we showed that the AUC value for AIP was greater in predicting MS development and AIP could be more meaningful than TG and HDL-C in predicting MS with respect to ROC curves.

Previous studies have shown dyslipidemia to be a risk factor for CVD. Furthermore, the relationship between CVD and lipid parameters such as TC, LDL-C and TG is well known. Moreover, it is also accepted that lipid ratios such as TC/HDL-C and LDL-C/HDL-C are predictors for CVD [2,3]. Because of small particle size, small density LDL particles (sdLDL) can penetrate the arterial walls, easily accumulate to be stored and oxidized to turn into OxLDL, when compared to LDL particles. When OxLDL is phagocyted with macrophages, macrophages turn into foam cells and cause atherosclerosis and cardiovascular disease. Recent studies have suggested the clinical utilization of sdLDL particles as a marker to predict atherosclerosis [4]. However, because of the complicated detection method and expensive costs, the detection of sdLDL is limited in clinical applications. AIP was first defined as a strong sensitive index that reflects the interaction between atherogenic and protective lipoproteins by Dobiasova and Frohlich in 2001 [17]. In that study, AIP value was inversely correlated with the circumference of LDL-C particles and reflected the size of the sdLDL particles [17]. Likewise, previous studies conducted with adults revealed that AIP value is a more reliable marker for CVD risk factors compared to traditional lipid parameters and lipid ratios [4,23]. However, there are not adequate studies on this issue in children. In our study, TC, LDL-C, TG, AIP values were significantly higher, and HDL-C was significantly lower in obese patients compared to the control group.

The parameter of IR in obese children is related to cardiovascular and metabolic risk, and IR is known to have a role in the development of endothelial dysfunction metabolism [24]. In the current study, the AIP value of the patient group was higher than that of the control group. Moreover, the HOMA-IR value was significantly higher in the high-risk group according to AIP value compared to the low-risk group and a positive correlation was determined between AIP and HOMA-IR. There are very few studies which have evaluated the relationship between AIP and IR in children. Two previous studies conducted on obese children reported a positive correlation between AIP and HOMA-IR, similar to the current study [19,25]. The detection of a positive correlation between AIP and HOMA-IR in both the current study and the two previous studies indicates that AIP might be used as a marker to predict insulin resistance in childhood obesity.

Non-alcoholic fatty liver disease is the most frequent chronic liver disease seen in children. NAFLD prevalence has been reported to vary between 1.7% and 85% in studies conducted on obese children [26]. It is thought to be caused by primary metabolic dysfunctions which are triggered by prevalent symptoms such as oxidative stress, insulin resistance and inflammatory cytokines [27]. Very few studies in literature have evaluated the relationship between AIP value and NAFLD in obese patients [20, 28]. One of the previous studies of adults with NAFLD revealed a significantly higher AIP value in the patient group than in the control group and a positive correlation between AIP value and Carotis intima media thickness of the patients [28]. Another study of adults separated the obese patients into three groups as low, moderate, and high-risk according to the AIP value. That study reported a significant difference in ALT values between the groups and higher steatosis prevalence in the moderate and high-risk groups [20]. In the current study, NAFLD was detected in 37.2% of the obese patients, and AIP values were significantly higher in the obese patients with NAFLD than those without. Moreover, a significant positive correlation was detected between the AIP value, steatosis degree and ALT level. Therefore, AIP value can be considered for use as a marker for NAFLD in obese children. To the best of our knowledge, this is the first study which evaluated the relationship between NAFLD and AIP in obese children.

Monocyte activation is a factor known to play a role in chronic inflammation and cardiovascular diseases [5]. It has also been reported that HDL-C might prevent macrophage migration as it has anti-inflammatory, antioxidant, and antithrombotic effects [5]. Previous studies have suggested that MHR might be used to predict the development and prognosis of CVD [29, 30]. However, all those studies were conducted on adults. To the best of our knowledge, there is no study in literature which has investigated the relationship between obesity and MHR in children. Monocyte/HDL ratio was significantly higher in obese patients in the current study. In the group with MetS, the median MHR was significantly higher than those without MetS. MHR was high in the AIP high-risk group and a positive correlation was detected between AIP value and MHR, MHR, TC, and TG, whereas a negative correlation was found between MHR and HDL-C. An elevated MHR value can be related with CVD risk in obese children.

Limitations

This study had some limitations. First, it was a cross-sectional study, and the study population was small. Second, the results of the study could not definitively provide a causal relationship between AIP and NAFLD. In addition, the monocyte count was calculated automatically from the peripheral blood sample, and it was not compared with other inflammatory biomarkers.

Conclusion

Both AIP and MHR are simple, cheap, and easily calculated parameters, and AIP might be an effective marker to predict MetS, abdominal obesity, NAFLD and IR in obese children. The AIP and MHR calculations might also be beneficial in the determination of the CVD risk, as MHR was significantly high in obese children and a significant correlation existed between AIP and MHR. However, the findings of this study must be supported by future studies, as there are very few studies on this subject, and this was the first such study for some of the findings.

References

1. World Health Organization (2016). Childhood overweight and obesity. World Health Organization.
2. Goliasch G, Wiesbauer F, Blessberger H, Demyanets S, Wojta J, Huber K, et al. Premature myocardial infarction is strongly associated with increased levels of remnant cholesterol. J Clin Lipidol. 2015;9:801–6.
3. Zhu L, Lu Z, Zhu L, Ouyang X, Yang Y, He W, et al. Lipoprotein ratios are better than conventional lipid parameters in predicting coronary heart disease in Chinese Han people. Kardiol Pol. 2015;73:931–8.
4. Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine (Baltimore). 2017 Sep;96(37):e8058. doi: 10.1097/MD.0000000000008058
5. Akboga MK, Balci KG, Maden O, Ertem AG, Kirbas O, Yayla C, et al. Usefulness of monocyte to HDL-cholesterol ratio to predict high SYNTAX score in patients with stable coronary artery disease. Biomark Med. 2016;10(4):375–83.
6. Aydin E, Ates I, Fettah Arikan M, Yilmaz N, Dede F. The ratio of monocyte frequency to HDL cholesterol level as a predictor of asymptomatic organ damage in patients with primary hypertension. Hypertens Res. 2017;40:758–64.
7. Demir V, Samet Y, Akboga MK. Assessment of monocyte to high density lipoprotein cholesterol ratio and lymphocyte-to-monocyte ratio in patients with metabolic syndrome. Biomark Med. 2017 Jul;11(7):535-40.
8. Uslu AU, Sekin Y, Tarhan G, Canakcı N, Gunduz M, Karagulle M. Evaluation of Monocyte to High-Density Lipoprotein Cholesterol Ratio in the Presence and Severity of Metabolic Syndrome. Clin Appl Thromb Hemost. 2018 Jul;24(5):828-33.
9. Johnsen SH, Fosse E, Joakimsen O, Mathiesen EB, Stensland-Bugge E, Njølstad I, et al. Monocyte count is a predictor of novel plaque formation: a 7 year follow-up study of 2610 persons without carotid plaque at baseline the Tromso Study. Stroke. 2005;36 (4):715–9.
10. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. Br Med J (Clin Res Ed). 1986;292:13–5.
11. Neyzi O, Günöz H, Furman A, Bundak R, Gökçay G, Darendeliler F, et al. Weight, height, head circumference and body mass index references for Turkish children. Journal of Child Health and Diseases. 2008;51:1-14.
12. Hatipoğlu N, Öztürk A, Mazicioğlu M, Kurtoglu S, Seyhan S, Lokoglu F. Waist circumference percentiles for 7- to 17-year–old Turkish children and adolescents. Eur J Pediatr. 2008;167:383-9.
13. Zimmet P, Alberti KG, Kaufman F. The metabolic syndrome in children and adolescents – an IDF consensus report. Pediatr Diabetes. 2007;8:299–306.
14. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A Comprehensive Online Calculator for Pediatric Endocrinologists: ÇEDD Çözüm/TPEDS Metrics. J Clin Res Pediatr Endocrinol. 2017;9:182-4.
15. Kurtoglu S, Hatipoglu N, Mazıcıoglu M, Kendirci M, Keskin M, Kondolot M. Insulin resistance in obese children and adolescents: HOMA-IR cut-off levels in the prepubertal and pubertal periods. J Clin Res Ped Endo. 2010;2:100-6.
16. Akbas EM, Timuroglu A, Ozcicek A, Ozcicek F, Demirtas L, Gungor A, et al. Association of uric acid, atherogenic index of plasma and albuminuria in diabetes mellitus. Int J Clin Exp Med. 2014;7(12):5737–43.
17. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER (HDL)). Clin Biochem. 2001;34(7):583–8.
18. Sousa NPS, Salvador EP, Barros AK, Polisel CG, Carvalho WRG. Anthropometric Predictors of Abdominal Adiposity in Adolescents. Journal of Exercise Physiologyonline. 2016;19:66-76
19. Sapunar J, Aguilar-Farías N, Navarro J, Araneda G, Chandía-Poblete D, Manríquez V, et al. High prevalence of dyslipidemia and high atherogenic index of plasma in children and adolescents. Rev Med Chil. 2018 Dec;146(10):1112-22
20. Wang Q, Zheng D, Liu J, Fang L, Li Q. Atherogenic index of plasma is a novel predictor of non-alcoholic fatty liver disease in obese participants: a cross-sectional study. Lipids Health Dis. 2018 Dec 13;17(1):284. doi: 10.1186/s12944-018-0932-0
21. Luptáková L, Siváková D, Cvíčelová M, Wsólová L, Danková Z, Michnová A, et al. Power of biomarkers and their relative contributions to metabolic syndrome in Slovak adult women. Ann Hum Biol. 2013 Mar;40(2):132-38. doi: 10.3109/03014460.2012.748828.
22. Zhang X, Zhang X, Li X, Feng J, Chen X. Association of metabolic syndrome with atherogenic index of plasma in an urban Chinese population: A 15-year prospective study. Nutr Metab Cardiovasc Dis. 2019 Nov;29(11):1214-9. doi: 10.1016/j.numecd.2019.07.006.
23. Mudhaffar Sami Khazaál. Atherogenic index of plasma (AIP) as a parameter in predicting cardiovascular risk in males compared to the conventional dyslipidemic indices (Cholesterol ratios). Karbala J Med. 2013 Jun;6 (1):1506-13.
24. Giannini C, de Giorgis T, Scarinci A, Ciampani M, Marcovecchio ML, Chiarelli F, et al. Obese related effects of inflammatory markers and insulin resistance on increased carotid intima media thickness in pre-pubertal children. Atherosclerosis. 2008;197:448–56. doi:10.1016/j.atherosclerosis.2007.06.023
25. Vrablík M, Dobiášová M, Zlatohlávek L, Urbanová Z, Češka R. Biomarkers of cardiometabolic risk in obese/overweight children: effect of lifestyle interven-tion. Physiol Res. 2014;63(6):743–52.
26. Jimenez-Rivera C, Hadjiyannakis S, Davila J, Hurteau J, Aglipay M, Barrowman N, et al. Prevalence and risk factors for non-alcoholic fatty liver in children and youth with obesity. BMC Pediatr. 2017;17:113.
27. Westerbacka J, Lammi K, Hakkinen AM, Rissanen A, Salminen I, Aro A, et al. Dietary fat content modifies liver fat in overweight nondiabetic subjects. J Clin Endocrinol Metab. 2005;90:2804-9.
28. Fadaei R, Meshkani R, Poustchi H, Fallah S, Moradi N, Panahi G, et al. Association of carotid intima media thickness with atherogenic index of plasma, apo B/apo A-Iratio and paraoxonase activity in patients with non-alcoholic fatty liver disease. Arch Physiol Biochem. 2019;Feb;125(1):19-24. doi: 10.1080/13813455.2018.1429475.
29. Rohatgi A. High-density lipoprotein function measurement in human studies: focus on cholesterol efflux capacity. Prog Cardiovasc Dis. 2015;58(1):32-40.
30. Van de Woestijne AP, van der Graaf Y, Liem AH, Cramer MJ, Westerink J, Visseren FL. SMART Study Group. Low high-density lipoprotein cholesterol is not a risk factor for recurrent vascular events in patients with vascular disease on intensive lipid lowering medication. J Am Coll Cardiol. 2013;62(20):1834-41.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1008-1012.
DOI: 10.28982/josam.812077

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Prospective evaluation of patients with small cell lung cancer: A single center study

Küçük hücreli akciğer kanseri tanısı alan hastalarımızın prospektif incelemesi: Tek merkezli çalışma

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Ethics Committee Approval: The study was approved by Onokuz Mayıs University Ethics Committee (OMU KAEK, 2007/48). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Ondokuz Mayıs Üniversitesi Etik Kurulu (OMU KAEK, 2007/48) tarafından onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Small cell lung cancer (SCLC) is the most aggressive form of lung cancer. No major treatment advances have occurred for SCLC over the past 30 years, unlike non-small cell lung cancer (NSCLC). We aimed to prospectively examine demographic, clinical, radiological properties, its association with cigarette smoking, delays in diagnosis, treatment responses, toxicities, prognostic factors, and survivals.

Methods: Patients diagnosed with small cell lung cancer during 4 years in Ondokuz Mayıs University, Department of Chest Diseases were included in our prospective cohort study. The demographic characteristics of the patients, symptoms, performance status, laboratory, radiologic, bronchoscopy findings, staging procedures, periods from the initiation of the symptoms to the admission of the patients to our department and definitive diagnosis, chemotherapy responses and toxicities were recorded. Follow-ups were performed in our clinic. Dates of deaths of patients who died outside our hospital were followed up from the records of census directorate. Patients that we lost to follow up, with missing data, or those who did not give consent for participation in the study were excluded.

Results: The study group consisted of 88 patients (82 males, 6 females). The mean age was 61.16 years. The main symptoms on admission were cough (77%), fatigue (62%), dyspnea (60%). Among all, 39% of patients had limited disease whereas the remaining 61% were extensive. The median delay between the occurrence of first symptom and the patient's presentation to our clinic was 30 days and the median delay before diagnosis was 10 days. Seventy-seven patients were given cisplatin/carboplatin-etoposide as the first line and irinotecan as second line chemotherapy. Overall median survival was 355 (30.8) days, 416 (47) days in limited stage and 296 (48) days in the extensive stage (P=0.003). Six-month cumulative survival was 76%, and 12-month cumulative survival was 44%. Univariate analysis showed that increased LDH levels, performance score >1, extensive stage and weight loss were poor prognostic factors (P=0.042, 0.001, 0.003, 0.022). In multivariate analysis, serum LDH levels, performance score >1 and extensive disease were independent poor prognostic factors.

Conclusion: The ratio of our female patients is still much lower than the world average. Time from the admission of our patients to diagnosis was shorter than most of the developed countries. However, treatment response rates and survival periods were within lower limits of world reports. Stage, PS, LDH can be used as independent prognostic factors.

Keywords: Small cell lung cancer, Chemotherapy, Prognosis, Survival

Öz

Amaç: Küçük hücreli akciğer kanseri en saldırgan akciğer kanseri türüdür. Küçük hücreli dışı akciğer kanserinin aksine son 30 yılda tedavide kaydadeğer bir ilerleme gösterilememiştir. Biz bu çalışmada SCLC hastalarının demografik, klinik, radyolojik özelliklerini, sigara ile ilişkisini, tedavi gecikmelerini, tedavi yanıtları, toksisiteleri, prognoza etki eden faktörleri ve yaşam sürelerini incelemeyi amaçladık.

Yöntemler: Samsun Ondokuz Mayıs Üniversitesi Tıp Fakültesi Göğüs Hastaıklarında 4 yıllık sürede küçük hücreli akciğer kanseri tanısı alan hastalar prospektif kohort çalışmamıza dahil edildi. Hastaların demografik özellikleri, semptomları, performans durumları, laboratuvar, radyolojik, bronkskopik bulguları, evreleme tetkikleri, semptom başlangıcından bölümümüze müracat, müracattan tanıya kadar geçen süreler, kemoterapi yanıt ve toksisiteleri kaydedildi. Takipler bölümümüzde yapıldı. Hastanemiz dışında vefat eden hastaların ölüm tarihleri nüfus müdürlüğünden alındı. Takipten çıkan, eksik verisi olan veya onam vermeyen hastalar çalışmadan çıkarıldı.

Bulgular: Çalışma grubu 88 hastadan oluşuyordu. Bu hastaların 82'si erkek, 6'sı kadındı. Ortalama yaş 61,16 idi. Başvuru anındaki esas semptomlar öksürük (%77), yorgunluk (%62), dispne (%60) olarak tespit edildi. Tanı anında hastaların %39'u sınırlı hastalık iken %61'i yaygın evrede idi. İlk semptomdan kliniğimize başvurana kadar geçen sure ortalama 30 gün, tanı konulmasına kadar geçen süre ise 10 gündü. 77 hastaya birinci basamak tedavi olarak cisplatin/carboplatin-etoposide, ikinci basamak tedavi olarak da irinotecan uygulandı. Genel ortalama yaşam süresi 355 (30,8) gün olup sınırlı hastalıkta 416 (47) gün, yaygın hastalıkta 29 (48) gün olarak bulundu (P=0,003). 6 aylık kümülatif survival %76 iken, 12 aylık kümulatif survival %44 idi. Tek değişkenli analalizlerde LDH seviyeleri artışı, performans skoru (PS) >1, yaygın hastalık ve kilo kaybı kötü prognostik faktörlerdi (P=0,042, 0,001, 0,003, 0,022). Çok değişkenli analizlerde ise serum LDH seviyeleri, performans skoru >1 ve yaygın hastalık bağımsız kötü prognostik faktörler olarak belirlendi.

Sonuç: Kadın hasta oranımız halen dünya ortalaması altında. Hastaların kabulünden tanı konulana kadar geçen süre çoğu gelişmiş ülkeden daha kısa olmasına rağmen tedaviye yanıt oranları ve yaşam süreleri dünyada bildirilenlerin alt sınırındaydı. Evre, PS, LDH bağımsız prognostik faktor olarak kullanılabilir.

Anahtar kelimeler: Küçük hücreli akciğer kanseri, Kemoterapi, Prognoz, Yaşam süresi

How to cite/Atıf için: Tuna T, Erkan L, Uzun O. Prospective evaluation of patients with small cell lung cancer: A single center study. J Surg Med. 2020;4(11):1008-1012.

Introduction

Lung cancer is the most prevalent and preventable cancer type. Small cell lung cancer (SCLC) is the most aggressive form among all types associated with smoking [1].

SCLC accounts for 15% of all new lung cancers [2]. Small cell lung cancer (SCLC) is distinguished from non-small cell lung cancer by its rapid doubling time, high growth fraction, central localization, and the early development of widespread metastases. It has different histological, clinical and treatment features among lung cancers. Although the cancer is initially highly responsive to chemotherapy and radiotherapy, most patients will relapse with broadly resistant disease within a few months to a year from initial therapy. Consequently, most patients (60-70%) will have extensive stage disease at the time of diagnosis. The 5-year survival rate remains low at <7% overall, and most patients survive for only 1 year or less after diagnosis. [3] In contrast to NSCLC where significant improvements are observed with targeted agents and immunotherapies, no major treatment advances have occurred for SCLC over the past 30 years. [4] The major treatment of SCLC is still systemic chemotherapy or chemotherapy combined with radiotherapy.

In this study, we aimed to prospectively examine demographic, clinic, radiological properties of our patients diagnosed with SCLC, its association with cigarette smoking, delays in diagnosis, treatment results, side effects, prognostic factors, and survival.

Materials and methods

Patients who were diagnosed with small cell lung cancer were followed up for a period of 4 years in Ondokuz Mayıs University Faculty of Medicine, Department of Chest Diseases. The patients that we lost to follow up or have missing data, those not giving consent for inclusion into the study were excluded. This is a prospective, single center, cohort study that was approved by Ondokuz Mayıs University Ethics Committee (OMU KAEK, 2007/48)

After obtaining the histories of the patients, their physical examinations were performed. Age, gender, smoking status, weight loss, and other symptoms were recorded. Performances of the patients were determined in accordance with "European Cooperative Oncology Group (ECOG)" criteria [5]. Periods starting from the initiation of the symptoms until admission to our department and getting diagnosed were recorded. In the first admission, laboratory examinations (complete blood count, urea, lactate dehydrogenase (LDH), serum glutamate oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), serum albumin were performed. Chest radiography and thoracic Computed Tomography (CT) were obtained from patients. For staging, Magnetic Resonance Imaging of the brain, upper abdomen CT and bone scintigraphy or Positron Emission Tomography (PET/CT) were performed. Bronchoscopy findings, and if present, other methods of diagnosis were recorded. Histopathological assessment was performed in the pathology department of our hospital, in accordance with histological and cytological criteria of SCLC. Staging was performed according to Veterans' Affairs Lung Study Group (VALG) classification [6].

Chemotherapy was administered to patients who were diagnosed during the limited stage, and simultaneous thoracic Radiotherapy (RT) was administered to patients with favorable general conditions. Only chemotherapy was administered to patients who were in the extensive stage. Platinum-based (cisplatin or carboplatin) and etoposide protocol was administered as first-line, and irinotecan or topotecan was administered as second-line chemotherapy. Chemotherapy toxicities were recorded in accordance with "Common Terminology Criteria for Adverse Events (CTCAE)" criteria. Chemotherapy responses were assessed with "Response Evaluation Criteria in Solid Tumors (RECIST)" [7] criteria.

At the end of the treatment, prophylactic cranial RT was administered to patients having full response. After the treatment, follow-ups were performed in our clinic. Dates of deaths of patients who died outside our hospital were followed up from the records of census directorate.

Statistical analysis

Data were presented as frequency in categorical variables, mean (standard deviation, SD) for normally distributed continuous variables and as median (25-75%) for those that do not comply with normal distribution. Survival times were given as median (SD).

In the comparison of continuous variables, "student t test" was used for variables complying with normal distribution, and "Mann-Whitney U" test was used for those that do not comply. In the comparison of categorical variables, chi-square and Fisher exact test were used. Kaplan Meier survival analysis and Log Rank analysis were used in the comparison of groups with respect to survival time. Impact of independent variables on survival was assessed with Cox regression analysis. Level of statistical relevance was $P<0.05$.

Results

A total of 493 patients were diagnosed with lung cancer in our clinic. The number of patients diagnosed with SCLC and NSCLS were 97 (19.67%), and 388 (78.7%), respectively. Other 8 (4.15%) patients were diagnosed with carcinoid tumor, lymphoma, and sarcoma.

Nine out of 97 SCLC patients were lost to follow up. Remaining 88 patients were included in this study. Six (6.8%) were female, 82 (93.2%) were male (M/F=14.7/1). The overall mean age was 61.16 (10.7) years (61.5 (10.3) years in males and 55.3 (14.9) years in females). There was no significant difference between the mean ages of males and females (p>0.05). The age groups that had the highest incidence of cancer in both genders was over the age of 65 years.

All patients except 2 non-smoker women were smokers. One was subjected to passive smoking for 25 years due to her husband. Fifty-one (58%) of the patients smoked more than 40 package/years. Fifty-nine (67%) were still smoking.

Main symptoms of the patients were examined (Table 1). Cough was the most frequent symptom in 24 (27.3%) patients. Shortness of breath ranked number two in 22 (25%) patients.

We detected paraneoplastic syndromes in 14 (15.9 %) patients, "Syndrome of inappropriate antidiuretic hormone secretion" (SIADH) in 9 (10.2%) patients, hypercalcemia in 4 (4.5%) patients, and gynecomastia in 1 (1.1%) patient.

Median time from the initiation of complaints of the patients to their admission to our department was 30 days (15–60 days), median time from admission to diagnosis was 10 days (7-16 days) (Table 2).

Chest radiography results of our patients are given in Table 3. None were normal. The most frequent abnormality was the hilar enlargement in 72 patients (81.8%).

Bronchoscopy was performed to all patients except 1, who refused the procedure. Sixty-nine patients (78.4 %) were diagnosed by bronchoscopy, thirteen patients (14.7 %) by CT guided transthoracic biopsy, two patients (2.3 %) by thoracoscopy, mediastinoscopy and lymph node biopsy each. Bronchoscopic findings of the patients are presented in Table 4.

Performance status of the patients were as follows: 28 (31.8%) ECOG 0, 19 (21.6%) ECOG 1, 26 (29.5%) ECOG 2, 12 (13.6%) ECOG 3 and 3 (3.4%) ECOG 4. Two ECOG 4 patients died before the initiation of chemotherapy. The remaining patient who was in the limited stage despite being ECOG 4 fully responded to chemotherapy. The patient who rejected prophylactic cranial RT died 6 months later due to brain metastasis and progression in the primary mass.

Majority of the patients were in the extensive stage 53 (60.2%), 35 (39.7%) patients were in the limited stage. Locations of metastasis detected during extensive stage are given in Table 5 in detail.

Table 1: Symptoms of small cell lung cancer patients

Symptoms	Number	%
Cough	24	27.3
Shortness of breath	22	25.0
Extra-thoracic pain	13	14.8
Hemoptysis	9	10.2
Chest pain	8	9.1
Swelling of the head and neck	3	3.4
Fatigue, weakness	3	3.4
Hoarseness	2	2.3
Loss of appetite-weight loss	2	2.3
Numbness, tingling	2	2.3
Total	88	100.0

Table 2: Time from the first symptoms of the patient to diagnose

	Time (day) Mean	Median	Min-Max
Symptom - admission	53 (66)	30 (15-60)	1-365
Admission - diagnosis	13.6 (11.1)	10 (7-16)	2-60
Symptom-diagnosis	67 (69)	39.5 (27-71)	8-38

Table 3: Distribution of chest radiography findings of SCLC patients

Abnormal findings	Number*	%
Hilar enlargement	72	81.8
Consolidation	21	23.9
Atelectasis	20	22.7
Pleural effusion	18	20
Enlargement in mediastinum	15	17
Peripheral nodule or mass	13	14.8
Normal	0	0

(*) More than one finding is present in some of the cases

Table 4: Bronchoscopic findings of SCLC patients

Findings		Number*	%
Vocal cord paralysis		9	10
Trachea	External Pressure	5	5.7
	Infiltrated	7	8
Carina	Blunt	15	17
	Infiltrated	8	9.1
Bronchus	Endobronchial lesion	35	39.8
	External pressure	54	61.4
	Infiltrated	39	44.3
Normal		11	12.6

(*) More than one finding is present in some of the cases

Table 5: Locations of metastasis detected during the extensive stage

Location of metastasis (*)	Number	%
Liver	26	31
Bone	23	27.4
Brain	16	19
Adrenal	9	10.7
Abdomen (liver except for adrenal)	5	6
Opposite lung	1	1.2

(*) More than one metastatic involvement might be present in a patient

While rate of weight loss was 72.5% in extensive stage, it was 39.4% in limited stage. A significant difference was present between the two stages in terms of weight loss [(x^2=7.8, sd=1, P<0.01), (OR=4.1, %95 GA 1.6<OR<10.3)] and survival (P=0.022).

Survival times were similar when compared according to laboratory parameters such as hemoglobin, white blood cell, thrombocyte counts, urea, SGOT, SGPT, ALP and serum albumin. Serum LDH level significantly impacted survival. Median LDH level was 424.5 (332-516) U/L in the limited stage, and 491 (385.7–696.5) U/L in the extensive stage (P=0.044).

Eleven (12.5%) out of 88 patients could not receive chemotherapy. Five died during the initial period after diagnosis. Six patients refused treatment. Seventy-seven (87.5%) patients received platinum-based treatment, thirty-three (42.9%) of which were in limited, and 44 (57.1%) of which were in extensive stage. Twelve patients (15.6%) died after 1-2 cycles. Thirteen patients (16.9%) received 3-4 cycles, and 52 patients (67.5%) received 5-6 cycles of "first line" chemotherapy. Neutropenic fever developed in 16 of the patients (20.8%). One patient died due to pancytopenia and neutropenic fever, 1 patient died due to pneumocystis carinii pneumonia and gastric perforation. Twelve patients (15.6%) developed Grade 1 nephrotoxicity; 1 patient (1.3%) had Grade 2 hepatotoxicity. None of the patients had advanced nephro- or hepatotoxicity. Six patients had stable, 30 patients had partial and 13 patients had complete response. 19 patients had (27.9%) progression. 9 patients who were lost to follow-up were not included in this assessment.

Progression occurred in the primary lesion of the thorax (32.5%) most. The second progression location was brain metastasis (11.7%). Sixteen patients who were found to have progressed after 3 months were administered the same protocol for a second time. Three developed stable disease, 2 had partial response and 6 had progression. Four patients died following chemotherapy and the other patient died 3 weeks later.

A total of 41 patients (53.2%) received RT, 22 of which (28.6%) received RT for curative purposes and 19 (24.7%), for palliative purposes. Palliative RT was applied mostly to the brain (%18.2).

Twenty-five patients were administered second line chemotherapy due to relapse or resistance to treatment; from these, 3 patients had stable disease, 2 had partial disease and 9 had progression. Five patients died after the first cycle; 3 patients died during the early period following the second cycle. One patient had to discontinue treatment due to acute abdomen. Two patients (2.6%) developed neutropenic fever due to second line chemotherapy, 3 patients developed (3.9%) grade 1 nephrotoxicity, 5 patients had (6.5%) grade 1, 1 patient (1.3%) had grade 2 hepatotoxicity. Median survival period of patients who received "second line" chemotherapy due to progression was 106 (34) days. Chemotherapy responses in accordance with stage were assessed, and statistically significant differences were

found between the stages (P=0.034). Response rates to platinum-based and etoposide in the limited and extensive stage were evaluated (Table 6).

Table 6: Response rates to platinum-based and etoposide due to stages

Response	Limited	Extensive
Stable	1(3.2%)	5(13.5%)
Partial	14(45.2%)	16(43.2%)
Complete	10(32.3%)	3(8.1%)
Progression	6(19.4%)	13(35.1%)
Total	31	37

When all patients were evaluated, median survival was 355 (30.8) days, 6-month cumulative survival was 76%, and 12-month cumulative survival was 44% (Figure 1).

Median survival was 416 (47.2) days in the limited stage and 296 (48.4) days in the extensive stage (P=0.003) (Figure 1). As a result of multivariate analyses, stage was concluded to be an independent prognostic factor [OR=2.1, (95% C.I. 1.1 – 3.8), P=0.019] (Figure 2).

In univariate analyses, ECOG 0 and 1 patients were compared with ECOG 2, 3 and 4 patients according to PS. Median survival time was 364 (25.4) days in ECOG 0 and 1 patients, and 134 (76) days in other patients (P=0.001). PS was an independent prognostic factor based on multivariate analyses [OR=2.8, (95% C.I. 1.4 – 5.3), P=0.004].

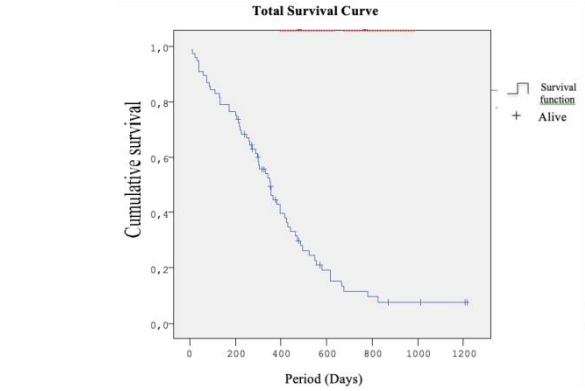

Figure 1: Overall median survival

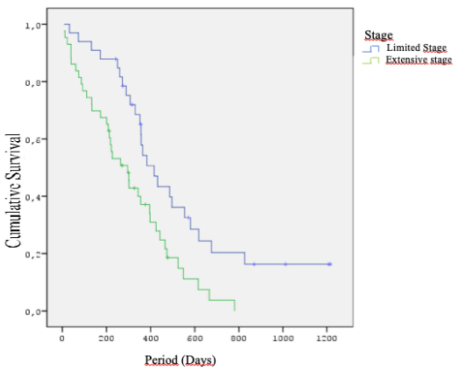

Figure 2: Survival curve in patients with small cell lung cancer according to stages

Discussion

SCLC is still at the top of the list of lung cancer related deaths among both genders in many countries of the world. Our male/female patient ratio is higher than other centers from Turkey, and much higher than other European countries and USA [8-10].

When we consider the fact that most of our patients came from rural areas, we can say that women smoke less than men and they might have developed less cancer. In the reports of big cities like Ankara, İstanbul and İzmir, female ratios are higher than ours. Though we do not have smoking ratios, smoking might be more common in women living in big cities.

The risk increases with increasing package/years ratio [11]. In a study performed in California with 4782 SCLC patients, only 2.5% of the patients were non-smokers [12] In a study of Mayo Clinic performed on 5628 patients with lung cancer, only 16 out of 635 SCLC patients (2.5%) had never smoked [13]. In our patient group, smoking ratio was 97.7%. All the men were smokers, only 2 women had never smoked. These findings support the fact that smoking is quite effective in etiology, and it especially reminds us that although significantly fatal, SCLC is almost completely preventable by not smoking.

The most frequent symptom was cough followed by shortness of breath, extrathoracic pain and hemoptysis, which are consistent with the literature [14].

Many studies report that diagnosis and treatment delays might negatively affect the tumor stage and prognosis [15]. Our results show that time from the admission of the patients to our clinic to diagnosis is shorter than many studies carried out throughout the world [16] and in our country [17-19]. When we consider the above-mentioned data, delays in world occur in places where primary care implementations are mandatory. Data on hand reveals this drawback of primary care implementations, and points to the fact that physicians must be more careful when they are examining their patients to not cause delays.

Most of SCLC disease is centrally located and hilar enlargement is the major radiologic anomaly [20]. Therefore, the rate of bronchoscopic diagnosis is higher than that in literature. [21].

Cohen et al [22] suggested for the first time that some laboratory values during the admission of SCLC patients might be prognostic factors with their studies in 1981 and found out that albumin and hemoglobin values were especially related to survival. Some studies found that low levels of hemoglobin, thrombocyte, increase in white cell, and neutrophil count were effective on survival [23,24]. However, they were ineffective in some other studies [25]. In our study, increase in white cell and neutrophil count, low levels of hemoglobin, and thrombocyte were ineffective on survival, contrary to some other studies [23,25]. Serum LDH level is the most studied parameter among laboratory values and the one which affects survival. In most studies, LDH value above the normal limit is indicative of poor prognosis. [23-26]. There are rare studies stating that it has no effect on survival [27,28]. In our study, LDH increase was an independent prognostic factor.

In a study by Rawson et al. [29] PS, stage, Na, ALP, SGOT and LDH were important prognostic factors. Among the laboratory tests that we evaluated, hemoglobin, white blood cell, thrombocyte counts, urea, SGOT, SGPT, ALP and serum albumin were not effective on survival.

There are many studies demonstrating that weight loss is a prognostic factor that affects survival [23,30]. In our study, weight loss was effective on survival only in univariate analyses. In the study by Arınç et al. [31], age (under and over the age 60 years), weight loss, gender, Hb, thrombocyte and albumin values, pleural effusion, having a mass with a size over or under 4 cm, liver and brain metastasis were ineffective on survival; stage, PS and SVCS were independent prognostic factors.

When we consider all our patients (limited and extensive stages), 19% had complete and 44% of the patients had partial response to chemotherapy, 8% had stable disease. Progression developed at a ratio of 27.9%. While our general response rate in limited stage was 77.5%, and complete response rate was 32.3%, these values were 51.3% and 8.12% in the extensive stage, respectively. The reason for our lower complete response rates compared to references might be related to living conditions, general conditions, and nutrition problems of our patients. Indeed, in Canada, lung cancer risk was inversely proportional with income, education, and social class in both sexes [32].

Death ratio due to chemotherapy complications in SCLC is below 5% [33]. Eight of our patients died right after chemotherapy (6 patients after the first and 2 patients after 2 cycles). However, these patients had multiple metastases during diagnosis and 3 of them were ECOG 3. It is difficult to say whether the reasons of their death were due to primary disease or chemotherapy complications. Since all these patients received chemotherapy, ethically, carrying out controlled studies seems impossible. Though chemotherapy must be administered in SCLC irrespective of performance score, we should also keep in mind the fact that these patients might prematurely die following chemotherapy.

Since 1970, disease stage and performance status of the patients have traditionally been used to predict survival periods of patients with SCLC. The prognostic factor that is supported by studies is performance status [23,25,34]. In our study, median survival was longer in the limited stage. Performance status of the patients were also effective on survival in line with references [25,34]. Stage and PS were independent prognostic factors.

Limitations

Our limitations include small sample size, short study period, and the fact that evaluation of laboratory and clinical parameters simultaneously may have caused complexity.

Conclusions

We would like to emphasize that the ratio of our female patients is still much lower than the world data; SCLC is causally related to smoking, and the time from the admission of our patients to diagnosis is shorter when compared with the data obtained in our country and many western countries. However, treatment response rates and survival periods are within but closer to lower limits. Contrary to widespread belief, side effects of second line chemotherapy are tolerable. Weight loss, stage, PS, LDH can be used as prognostic factors, and we also would like to emphasize strongly that development of novel medications are necessary in the treatment of SCLC with future studies.

References

1. Ettinger DS, Aisner J. Changing face of small-cell lung cancer: real and artifact. J Clin Oncol. 2006; 24:4526–7. doi: 10.1200/JCO.2006.07.3841.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA Cancer J Clin. 2012;62(1):10-29. doi: 10.3322/caac.20138.
3. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? Cancer.2015;121:664-72. doi: 10.1002/cncr.29098.
4. Oronsky B, Reid TR, Oronsky A, Carter CA. What's New in SCLC? A Review. Neoplasia. 2017;19(10):842–7. doi: 10.1016/j.neo.2017.07.007.
5. WHO, Handbook for reporting results of cancer treatment, in WHO Offset publication No.48. 1979; 745.Geneva.
6. Zelen M. Keynote address on biostatistics and data retrieval. Cancer Chemother Rep 3. 1973;4 (2):31-42.
7. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Dancey J, Arbuck S, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal Of Cancer. 2009;45:228–47. doi: 10.1016/j.ejca.2008.10.026.
8. Bozkurt B, Selçuk T, Fırat P, Kalyoncu AF, Artvinli M. 1972–2002 döneminde Hacettepe Üniversitesi Tıp Fakültesi Hastanesi'nde akciğer kanseri tanısı konulan hastaların histolojik ve epidemiyolojik değerlendirmesi. Toraks Dergisi. 2004;5(3):143-8.
9. Ferlay J, Autier P, Boniol M, , Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Annals of Oncology. 2007;18(3):581-92. doi: 10.1093/annonc/mdl498.
10. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T et al. Cancer statistics, 2008. CA Cancer J Clin. 2008;58:71. doi: 10.3322/CA.2007.0010.
11. Bernhardt EB, Jalal SI. Small cell lung cancer Cancer Treat Res. 2016;170:301-22. doi: 10.1007/978-3-319-40389-2_14.
12. OU SH, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. J Thorac Oncol. 2009 Jan;4(1):37-43. doi: 10.1097/JTO.0b013e31819140fb.
13. Yang P, Allen M, Aubry M, Wampfler J, Marks RS, Edell ES, et al. Clinical Features of 5,628 Primary Lung Cancer Patients. Chest. 2005;128:452-62. doi: 10.1378/chest.128.1.452
14. Wang S, Zimmermann S, Parikh K, Mansfield AS, Adjei AA. Current Diagnosis and Management of Small-Cell Lung Cancer Mayo Clin Proc. 2019 Aug;94(8):1599-1622. doi: 10.1016/j.mayocp.2019.01.034.
15. Salomaa ER, Sällinen S, Hiekkanen H, Lippo K. Delays in the diagnosis of lung cancer. CHEST 2005;128: 2282-88. doi: 10.1378/chest.128.4.2282.
16. Koyi H, Hillerdal G, Branden E. Patient's and doctor's delays in the diagnosis of chest tumors. Lung Cancer. 2002;35:53-7. doi: 10.1016/s0169-5002(01)00293-8.
17. Erbaycu AE, Özsöz A, Çakan A. Akciğer kanserinde tanı gecikmesine hastanın ve hekimin etkisi. Solunum Hastalıkları. 2005;16:161-65.
18. Özlü T, Bülbül Y, Öztuna F, Çan G. Akciğer kanseri tanısını ne kadar sürede koyabiliyoruz? Tüberküloz ve toraks dergisi. 2002;50:288-91.
19. Yılmaz A, Aybatlı A. Akciğer kanseri tanı ve tedavisinde gecikmeler. Toraks Dergisi. 2005;6(1):68-72.
20. Webb RW, Higgins CB, ed. Lung cancer and bronchopulmonary neoplasms. In:Thoracic imaging Pulmonary and cardiovascular radiology. Lippincott Williams and Wilkins: Philadelphia. 2005;3:75-9.
21. Rivera MP, Mehta AC; American College of Chest Physicians. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition) Chest. 2007 Sep;132(3 Suppl):131S-148S. doi: 10.1378/chest.07-1357.
22. Cohen MH, Makuch R, Johnston-Early A, Ihde DC, Bunn PA Jr, Fossieck BE Jr et al. Laboratory parameters as an alternative to performance status in prognostic stratification of patients with small cell lung cancer. Cancer Treat Rep. 1981;65:187-95.
23. Bremnes M, Sundstrom S, Aasebø U, Kaasa S, Hatlevoll R, Aamdal S. The value of prognostic factors in small cell lung cancer: results from a randomised multicenter study with minimum 5 year follow-up. Lung Cancer. 2003;39:303–13. doi: 10.1016/s0169-5002(02)00508-1.
24. Quoix E, A Purohit, M Faller-Beau M, Moreau L, Oster JP, Pauli G. Comparative prognostic value of lactate dehydrogenase and neuron-specific enolase in small-cell lung cancer patients treated with platinum-based chemotherapy. Lung Cancer. 2000;30:127–34. doi: 10.1016/s0169-5002(00)00131-8.
25. Paesmans M, Sculier JP, Lecomte J, Thiriaux J, Libert P, Sergysels R,et al. Prognostic factors for patients with small cell lung carcinoma: analysis of a series of 763 patients included in 4 consecutive prospective trials with a minimum follow-up of 5 years. Cancer 2000;89:523–33. doi: 10.1002/1097-0142(20000801)89:3<523:aid-cncr7>3.0.co;2-6.
26. Deng T, Zhang J, Meng Y, Zhou Y, Li W. Higher pretreatment lactate dehydrogenase concentration predicts worse overall survival in patients with lung cancer. Medicine Baltimore). 2018 Sep;97(38):e12524. doi: 10.1097/MD.0000000000012524.
27. Osterlind K, Hansen HH, Hansen M, Dombernowsky P, Andersen PK. Long-term disease-free survival in small-cell carcinoma of the lung: a study of clinical determinants. J Clin Oncol. 1986;4:1307–13. doi: 10.1200/JCO.1986.4.9.1307.
28. Li J, Dai CH, Chen P, Wu JN, Bao QL, Qiu H, et al. Survival and prognostic factors in small cell lung cancer. J Med Oncol. 2010 Mar,27(1):73-81. doi: 10.1007/s12032-009-9174-3.
29. Rawson N, Peto J, An overview of prognostic factors in small cell lung cancer. A report from the Subcommittee for the Management of Lung Cancer of the United Kingdom Coordinating Committee on Cancer Research. Br J Cancer. 1990;61(4):597-604. doi: 10.1038/bjc.1990.133.
30. Tamura M, Ueoka H, Kiura K, Tabata M, Shibayama T, Miyatake K et al. Prognostic factors of small-cell lung cancer in Okayama Lung Cancer Study Group Trials. Acta Med Okayama. 1998;52(2):105–11. doi: 10.18926/AMO/31310.
31. Arınç S, Gönlügür U, Devran O, Erdal N, Ece F, Ertugrul M et al. Prognostic factors in patients with small cell lung carcinoma. Med Oncol. Apr 2010. doi: 10.1007/s12032-009-9198-8.
32. Mao Y, Hu J, Ugnat AM, Semenciw R, Fincham S. Socioeconomic status and lung cancer risk in Canada. Int J Epidemiol. 2001;30:809–817. doi: 10.1093/ije/30.4.809.
33. Jackman DM, Johnson BE. Small cell lung cancer. Lancet. 2005;366:1385-96. doi: 10.1016/S0140-6736(05)67569-1.
34. Buccheri G, Ferrigno D. Prognostic factors in lung cancer: tables and comments. Eur Respir J. 1994;7(7):1350–64. doi: 10.1183/09031936.94.07071350.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1013-1017.
DOI: 10.28982/josam.826501

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Evaluation of potential early life risk factors for ulcerative colitis

Ülseratif kolit için potansiyel erken yaşam risk faktörlerinin değerlendirilmesi

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Ethics Committee Approval: The study was approved by the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (date: 20.10.2020, decision no: 409). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi Etik Kurulu tarafından onaylandı (tarih: 20.10.2020, karar no: 409). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: It has been suggested that early life factors may affect the risk of inflammatory bowel disease by affecting the gut microbiome. Delivery type, breast milk, and parental smoking are the most important environmental factors. There are limited studies on the effects of these factors on the location of the disease and age at diagnosis. In addition, the effects of these factors on medical treatments and bowel involvement are unknown. We examined the relationship between potential early-life risk factors experienced in the first years of life and ulcerative colitis (UC).

Material and Method: This study is a prospective case-control study. Sixty-nine UC patients were compared with 44 age- and sex-matched healthy controls (HC). We investigated delivery type, breastfeeding, maternal age at birth, and parents' smoking status, which may be potential early-life risk factors. Our analysis involved the relationship of these potential factors with the age at diagnosis and medical treatments in UC patients.

Results: UC and HC groups were compared in terms of delivery type, breastfeeding, and parents' smoking status: There was no statistical difference between the groups. In terms of the duration of breastfeeding, we found that 6-12 months of breastfeeding was lower in the UC group (P=0.046). In addition, the age at diagnosis of the disease was lower in UC patients who were not breastfed and whose mothers smoked (P=0.031, P=0.016, respectively).

Conclusions: The duration of breastfeeding is important for the development of UC. We recommend breastfeeding for longer than six months to prevent UC. Maternal smoking cessation has a protective role in the risk of early-onset UC.

Keywords: Ulcerative colitis, Early life factors, Breastfeeding, Delivery

Öz

Amaç: Erken yaşam faktörlerinin bağırsak mikrobiyomunu etkileyerek iltihaplı bağırsak hastalığı riskini etkileyebileceği öne sürülmüştür. Doğum şekli, anne sütü ve ebeveynlerin sigara içmesi en önemli çevresel faktörlerdir. Bu faktörlerin hastalığın yeri ve tanı anındaki yaş üzerindeki etkileri konusunda sınırlı sayıda çalışma bulunmaktadır. Ayrıca bu faktörlerin medikal tedavilere ve barsak tutulum yerine etkisi de bilinmemektedir. Yaşamın ilk yıllarında yaşanan potansiyel erken yaşam risk faktörleri ile ülseratif kolit (ÜK) arasındaki ilişkiyi inceledik.

Yöntemler: Bu çalışma prospektif bir vaka kontrol çalışmasıdır. Atmış dokuz ÜK hastası yaş ve cinsiyet bakımından benzer 44 sağlıklı kontrol ile karşılaştırıldı. Potansiyel erken yaşam risk faktörü olabilecek doğum şekli, anne sütü ile beslenme, anne doğum yaşı, anne ve baba sigara kullanım durumları araştırıldı. ÜK hastalarında bu potansiyel faktörlerin hastalık tanı yaşı, medikal tedavilerle ilişkisi incelendi.

Bulgular: ÜK ve kontrol grubu, doğum şekilleri, anne sütü ile beslenme, anne-baba sigara kullanma durumları bakımından karşılaştırıldığında gruplar arasında istatistiksel farklılık izlenmedi. Anne sütü alma süreleri bakımından karşılaştırıldığında ise 6-12 ay arası anne sütü alanlar, ÜK grubunda daha düşük saptanmıştır (P=0,046). Ayrıca anne sütü almayan ÜK hastaları ile annesi sigara kullanan ÜK hastalarının hastalık tanı yaşları daha düşük bulunmuştur (sırasıyla: P=0,031, P=0,016).

Sonuçlar: ÜK gelişimi açısından emzirmenin süresi önemlidir. ÜK'den korunmak için 6 aydan daha uzun anne sütü ile beslenme önermekteyiz. Erken başlangıçlı ÜK riski açısından annenin sigarayı bırakmasının koruyucu rolü vardır.

Anahtar kelimeler: Ülseratif kolit, Erken yaşam faktörleri, Anne sütü, Doğum

How to cite/Atıf için: Gökden Y, Koç DÖ. Evaluation of potential early life risk factors for ulcerative colitis. J Surg Med. 2020;4(11):1013-1017.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of inflammatory bowel disease (IBD), a chronic inflammatory disease of the gastrointestinal system of unknown cause. Its etiology is not yet fully known; however, it is thought to be caused by an exaggerated immunological response triggered by environmental and genetic factors [1]. The perinatal period is the period of first exposure to many antigenic stimuli. During this period, many factors act as markers by affecting the composition of the gut microbiome and its composition [2]. Increasing evidence suggests that early-life factors are determinants of a person's health and disease status in their future life. There are also epidemiological studies reporting that perinatal or childhood events play a role in the etiology of IBD [3,4].

It is thought that some factors affecting the gut microbiome in the perinatal period and the first years of life may also be related to immune-mediated diseases, including UC [5,6,7]. However, the triggers to develop UC remain unknown.

The present study investigated whether critical events experienced at birth or in the first years of life and those thought to cause changes in the gut microbiome in individuals, such as delivery type, breastfeeding, and maternal age at birth could be a risk for UC. Our evaluation included the relationship of these factors with the age at UC diagnosis, the site of intestinal involvement, and medical treatments. Considering that parents' smoking might cause passive nicotine exposure in the first years of life, whether this is a risk for UC and affects the age of diagnosis and medical treatments were also included in the analysis.

Materials and methods

Ethics committee approval was obtained for this prospective case-control study. In this study, informed consent was obtained from all participants whose data could be analyzed and published for scientific purposes. A detailed questionnaire was then administered by telephone. The study included patients >18 years of age, with definite endoscopic, pathological, and radiological diagnosis of UC, followed at the Prof. Dr. Cemil Taşcıoğlu Gastroenterology outpatient clinic. Those <18 years of age, with incomplete answers, and an unclear diagnosis of UC were excluded.

Healthy controls (HC) matching in age and gender were also included in the study. They were selected among those who visited our hospital for their routine check-up and did not have any known diseases, malignancy, or drug history. UC and HC groups were asked about the maternal age of birth, type of delivery (vaginal or cesarean section), parental smoking, and whether they were breastfed, and if so, its duration (0-6 months, 6-12 months, and >12 months). In addition, from the hospital records of UC patients, the year of disease diagnosis, medical treatment, and disease locations in the intestine were recorded. Endoscopic involvement sites were grouped as rectal, distal, left colon, and pancolitis.

Statistical analysis

Number Cruncher Statistical System (NCSS) program was used for statistical analysis. The study data were analyzed using descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, and maximum). The suitability of quantitative data to normal distribution was tested by the Shapiro-Wilk test and graphical analyses. Student's t-test was used for comparing two groups of normally distributed quantitative variables and the Mann-Whitney U test for comparisons of quantitative variables that did not show normal distribution. The Kruskal-Wallis test was used to compare more than two groups of quantitative variables that did not show normal distribution. Pearson's chi-square test, Fisher's exact test, and the Fisher-Freeman-Halton exact test were used to compare qualitative data. The Pearson correlation coefficient was used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $P<0.05$.

Results

In total, 113 subjects (69 UC patients and 44 HCs) between the ages of 18–72 years [59 females (52.2%) and 54 males (47.6%)] were included in the study. UC and HC groups were similar in terms of average age and gender ratios.

UC and HC groups were compared regarding the type of delivery, breastfeeding (no or yes), and the parents' smoking status: there was no statistical difference between the groups. When the breastfed UC and HC groups were compared in terms of the duration of breastfeeding, the number of those who received breast milk between 6-12 months was lower in the UC group ($P=0.046$). Maternal age at birth was also significantly lower in the UC group than in the HC group ($P=0.032$) (Table 1).

Table 1: Evaluation of descriptive features according to groups

		Total	UC (n=69)	HC (n=44)	*P*-value
Age	Min-Max (Median)	18-72 (38)	18-72 (37)	18-67 (41)	[a]0.627
	mean(Sd)	39.23(13.46)	39.72(13.26)	38.45(13.90)	
Gender	Male	54 (47.80)	35 (50.7)	19 (43.2)	[b]0.434
	Female	59 (52.2)	34 (49.3)	25 (56.8)	
BMI (kg/m^2)	Min-Max (Median)	17.3-36.3 (24.7)	17.3-36.3 (24.6)	17.6-30.1 (25.2)	[a]0.768
	mean(Sd)	24.64(3.91)	24.73(4.33)	24.51(3.20)	
Father's smoking	No	47 (41.6)	26 (37.7)	21 (47.7)	[b]0.291
	Yes	66 (58.4)	43 (62.3)	23 (52.3)	
Mothers' smoking	No	94 (83.2)	56 (81.2)	38 (86.4)	[b]0.471
	Yes	19 (16.8)	13 (18.8)	6 (13.6)	
Delivery Type	Vaginal	106 (93.8)	65 (94.2)	41 (93.2)	[c]1.000
	Cesarean section	7 (6.2)	4 (5.8)	3 (6.8)	
Breastfeeding	No	17 (15.0)	12 (17.4)	5 (11.4)	[b]0.382
	Yes	96 (85.0)	57 (82.6)	39 (88.6)	
Breastfeeding time	0-6 mount	19 (19.8)	15 (26.3)	4 (10.3)	[b]0.046*
	6-12 mount	24 (25.0)	10 (17.5)	14 (35.9)	
	>12 mount	53 (55.2)	32 (56.1)	21 (53.8)	
Maternal age at birth	Min-Max (Median)	14-44 (25)	14-42 (24)	19-44 (26)	[a]0.032*
	mean(Sd)	25.83(6.35)	24.81(6.13)	27.43(6.41)	

[a] Student-t Test, [b] Pearson Chi-Square Test, [c] Fisher's Exact Test, * $P<0.05$, UC: ulcerative colitis, HC: healthy controls

The age at the diagnosis of the disease ranged from 11 to 64 years, with an average age of 34.28 ± 12.52 in the UC group. The disease involvement sites were as follows: Rectal in 10.1% (n=7), distal in 26.1% (n=18), left colon in 20.3% (n=14), and pancolitis in 43.5% (n=30). In the same group, 71% (n=49) of the patients received single medication, 29% (n=20) received two medications or more: 95.7% (n=66) received mesalazine, 13% (n=9), azathioprine, 11.6% (n=8), anti-TNF, and 11.6% (n=8) received steroid therapy.

When the UC group is evaluated in terms of age at the time of diagnosis, no statistical relationship was found in terms

of gender, maternal age at birth, mode of delivery, father's smoking, and medical treatments (Table 2).

The UC diagnosis ages of patients whose mothers smoked were significantly lower than those whose mothers did not smoke (P=0.016). The diagnosis ages were also significantly lower in UC patients who were not breastfed than those who were (P=0.031) (Figure 1).

Table 2: Evaluations regarding the age at diagnosis of the ulcerative colitis patient

		Patient Diagnosis Age		
		r	*P*-value	
BMI (kg/m^2)		0.387	0.001**	
Maternal age at birth		0.173	0.155	
		Min-Max (Median)	Mean(Sd)	*P*-value
Gender	Male (n=35)	15-64 (34)	36.66(12.21)	[a]0.110
	Famale (n=34)	11-59 (30)	31.82(12.54)	
Father's smoking	No (n=26)	15-64 (34)	36.31(12.77)	[a]0.298
	Yes (n=43)	11-59 (32)	33.05(12.36)	
Mothers' smoking	No (n=56)	15-64 (34.5)	36.02(12.43)	[d]0.016*
	Yes(n=13)	11-50 (26)	26.77(10.26)	
Mesalazine	No (n=3)	20-43 (38)	33.67(12,1)	[d]0.930
	Yes (n=66)	11-64 (32.5)	34.30(12.63)	
Azathioprine	No (n=60)	11-64 (33.5)	35.12(12.44)	[d]0.130
	Yes (n=9)	14-54 (28)	28.67(12.3)	
Anti-TNF	No (n=61)	14-64 (33)	34.31(12.31)	[d]0.955
	Yes (n=8)	11-49 (36.5)	34.00(14.97)	
Steroid	No (n=61)	11-64 (33)	34.38(12,43)	[d]0.837
	Yes(n=8)	14-54 (31.5)	33.5(14.08)	
	Vaginal (n=65)	14-64 (33)	34.89(12.32)	[d]0.182
Delivery Type	Cesarean (n=4)	11-37 (24.5)	24.25(13.15)	
	No (n=12)	11-55 (26)	27.42(13.68)	[d]0.031*
Breastfeeding	Yes (n=57)	15-64 (34)	35.72(11.9)	
	0-6 mount (n=15)	21-64 (37)	37.07(11.83)	[e]0.638
Breastfeeding time	6-12 mount(n=10)	28-55 (33)	37.70(9.89)	
	>12 mount(n=32)	15-59 (33)	34.47(12.66)	

[a] Student-t Test, [d] Mann Whitney U Test, [e] Kruskal Wallis Test, * P<0.05, ** P<0.01, r= Pearson Correlation Coefficient

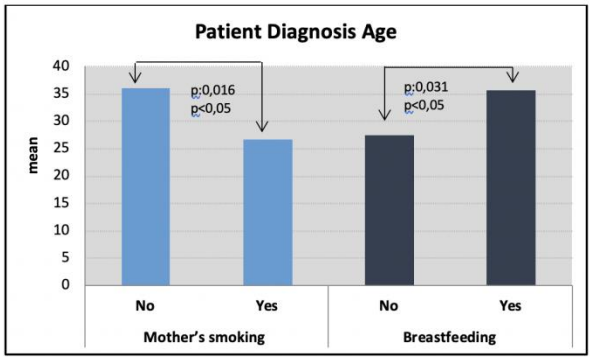

Figure 1: Age of diagnosis of ulcerative colitis according to mother's smoking and breastfeeding

There was no statistically significant difference in the disease involvement site and anti-TNF use in the UC group in terms of age, gender, parental smoking, type of delivery, breastfeeding and its duration, and maternal birth age (Table 3, 4).

Table 3: Evaluation according to disease degree in patients with ulcerative colitis

		Disease location				
		Proctitis (n=7)	Distal (18)	left side (n=14)	Pancolitis (n=30)	*P*-value
Age	Min-Max (Median)	27-60 (40)	18-72 (37.5)	22-70 (36)	18-64 (36)	[e]0.745
	Mean(Sd)	43.29(11.19)	40.17(14.77)	39.86(13.84)	38.57(12.95)	
Gender	Male	3 (42.9)	11 (61.1)	9 (64.3)	12 (40.0)	[f]0.363
	Female	4 (57,1)	7 (38.9)	5 (35.7)	18 (60.0)	
BMI (kg/m^2)	Min-Max (Median)	19.7-35.2 (25.4)	18.9-36.3(24.4)	17.3-29.6(23.8)	18.4-33.7 (25.2)	[e]0.916
	Mean(Sd)	26.05(5.55)	25.22(5.33)	24.04(3.81)	24.45(3.67)	
Father's smoking	No	2 (28.6)	8 (44.4)	6 (42.9)	10 (33.3)	[f]0.822
	Yes	5 (71.4)	10 (55.6)	8 (57.1)	20 (66.7)	
Mothers' smoking	No	6 (85.7)	15 (83.3)	11 (78.6)	24 (80.0)	[f]1.000
	Yes	1 (14.3)	3 (16.7)	3 (21.4)	6 (20.0)	
Mesalazine	No	0 (0.0)	1 (5.6)	0 (0.0)	2 (6.7)	[f]1.000
	Yes	7 (100.0)	17 (94.4)	14 (100.0)	28 (93.3)	
Azathioprine	No	7 (100.0)	16 (88.9)	13 (92.9)	24 (80.0)	[f]0.655
	Yes	0 (0.0)	2 (11.1)	1 (7.1)	6 (20.0)	
Anti-TNF	No	7 (100.0)	16 (88.9)	12 (85.7)	26 (86.7)	[f]0.901
	Yes	0 (0.0)	2 (11.1)	2 (14.3)	4 (13.3)	
Steroid	No	7 (100.0)	18 (100.0)	13 (92.9)	23 (76.7)	[f]0.072
	Yes	0 (0.0)	0 (0.0)	1 (7.1)	7 (23.3)	
Delivery Type	Vaginal	6 (85.7)	17 (94.4)	13 (92.9)	29 (96.7)	[f]0.505
	Cesarean	1 (14.3)	1 (5.6)	1 (7.1)	1 (3.3)	
Breastfeeding	No	0 (0.0)	4 (22.2)	3 (21.4)	5 (16.7)	[f]0.647
	Yes	7 (100.0)	14 (77.8)	11 (78.6)	25 (83.3)	
Breastfeeding time	0-6 mount	1 (14.3)	2 (14.3)	4 (36.4)	8 (32.0)	[f]0.811
	6-12 mount	1 (14.3)	3 (21.4)	1 (9.1)	5 (20.0)	
	>12 mount	5 (71.4)	9 (64.3)	6 (54.5)	13 (48.0)	
Maternal age at birth	Min-Max (Median)	21-40 (25)	14-36 (22)	19-30 (23.5)	16-42 (23.5)	[e]0.570
	Mean(Sd)	27.14(6.01)	23.83(6.22)	24.29(3.54)	25.10(7.08)	

[e] Kruskal Wallis Test, [f] Fisher Freeman Halton Test

Table 4: Comparisons for Anti TNF Use in Ulcerative Colitis Patients

		Anti- TNF		
		No (n=61)	Yes (n=8)	*P*-value
Age	Min-Max(Median)	18-72 (37)	18-58 (40.5)	[d]0.910
	Mean(Sd)	39.79(13.18)	39.25(14.72)	
Gender	Male	33 (54.1)	2 (25.0)	[c]0.151
	Female	28 (45.9)	6 (75.0)	
BMI (kg/m^2)	Min-Max (Median)	17.3-36.3 (25.1)	18.9-36.3 (22.5)	[d]0.494
	Mean(Sd)	24.78(4.21)	24.27(5.40)	
Father's smoking	No	21 (34.4)	5 (62.5)	[c]0.143
	Yes	40 (65.6)	3 (37.5)	
Mothers' smoking	No	49 (80.3)	7 (87.5)	[c]1.000
	Yes	12 (19.7)	1 (12.5)	
Delivery Type	Vaginal	59 (96.7)	6 (75.0)	[c]0.063
	Cesarean	2 (3.3)	2 (25.0)	
Breastfeeding	No	10 (16.4)	2 (25.0)	[c]0.621
	Yes	51 (83.6)	6 (75.0)	
Breastfeeding time	0-6 ay	13 (14.3)	2 (33.3)	[f]0.852
	6-12 ay	9 (17.6)	1 (16.7)	
	>12 ay	29 (56.9)	3 (50.0)	
Maternal age at birth	Min-Max(Median)	14-42 (24)	18-38 (24)	[d]0.403
	Mean(Sd)	24.61(6.12)	26.37(6.36)	

[b] Pearson Chi-Square Test, [c] Fisher's Exact Test, [d] Mann Whitney U Test, [f] Fisher Freeman Halton Test

Discussion

Critical events experienced at birth or in the first year of life can increase IBD risk by causing changes in the gut microbiome. Delivery type and breastfeeding are among the critical factors that can affect the gut microbiome. Exposure to bacteria from both the mother and the environment is decisive on an infant's intestinal flora. Breast milk is one of the earliest environmental factors a baby is exposed to. The microbiota of breastfed babies contains higher concentrations of bifidobacteria and less anaerobic bacteria than that of bottle-fed babies. Besides, fecal flora can change up to the age of 1-2 years [8-10].

The relationship between breastfeeding and UC is complex. A study by Klement et al. [7] reported that breastfeeding is protective for UC. Again, a systematic review and meta-analysis showed a strong inverse relationship between breastfeeding in infancy and the development of pediatric- and adult-onset IBD. One of the most important results from this analysis is the time-response effect of breastfeeding on both CD and UC development. While even three months of breastfeeding

is protective compared to no breastfeeding at all, it is emphasized that it has an even greater effect when occurred for >12 months [11].

There are also studies reporting that breastfeeding does not affect the development of UC and CD [12-15]. In these studies, the mean breastfeeding duration is generally short or its relationship with duration has not been investigated. The common feature of the studies advocating the protective effect of breast milk on UC and CD is the emphasis on breastfeeding for longer than three months [16].

It was concluded in our study that the duration of breastfeeding is important to prevent UC. While there was no difference between UC and HC regarding breastfeeding during the first six months, breastfeeding between 6-12 months was lower in the UC group. In addition to the duration of breastfeeding, there is a need for studies on the extent of breastfeeding, that is, the quality of breastfeeding, how much formula and supplementary foods are included in the first years of life, and whether this affects the UC development.

A study on the role of breastfeeding in the development of early-onset IBD showed that breast milk has a protective effect on its development [17]. Similarly, we observed that UC started at an earlier age in patients who did not receive breast milk.

A study by Rigars et al. [18] did not find any relationship between the maternal age at birth, the number of children the mother had, the mother's smoking status, or the birth season and UC. Robert et al [19] found higher CD incidence among mothers >35 years of age. However, they reported that there was no such relationship between UC and maternal age. In our study, the maternal age at birth was lower in UC patients compared to that in HCs. This difference may have resulted from our society's younger age at marriage due to cultural and social differences and having children at earlier ages.

The role of the gut microbiome in the pathogenesis of IBD has not yet been fully defined. However, the specific structure and/or change of the gut microbiome may affect the risk of developing IBD in genetically susceptible individuals. Delivery type is one of the most important risks in early-life and is the main determinant of neonatal intestinal colonization. While babies born vaginally show a microbiota composition closer to their mothers' vaginal and intestinal microbiota, babies born by cesarean section show a microbiota composition similar to maternal skin [20].

According to the delivery method, the IBD risk has not yet been identified. Studies evaluating the relationship between the cesarean section and IBD have conflicting results [12,21]. Bager et al. [21] reported that cesarean delivery caused a moderate increase in the risk of childhood-onset IBD.

A study by Berstein et al. [12] claims that cesarean delivery is not a risk for developing UC. They found that the first years of life are critical for gut microbiome development, and infection and the use of antibiotics during this period are associated with the development of UC in later life. Gomes et al. [15] reported that cesarean section performed under both emergency and elective conditions was not related to an increased UC risk. In our study, there was no statistical difference between UC and HC groups in terms of delivery type. In addition, there was no relationship in terms of delivery type and age at diagnosis, intestinal involvement and medical treatments in UC patients.

Living in rural areas and having spent the first five years of life in rural areas is reportedly a protective factor for UC development [22]. The region where both our UC and HC groups lived is an area receiving high immigration from rural areas. Therefore, it was not possible for us to interpret the results in this respect since there was no group diversity.

It is still unclear what is triggers UC development and gut inflammation. There are also studies on various inflammatory markers, disease behavior and intestinal involvement [23,24]. However, the mystery remains.

Limitations

This study is the first to report that early-life risk factors have no effect on the intestinal involvement sites, medical treatments, and anti-TNF requirement in UC patients. However, our study has some limitations worth mentioning: Potential early-life risk factors in UC patients such as birth weight, preterm birth, infections in infancy, and early exposure to antibiotics were not included in our study. These could affect UC risk. However, we thought that it would not be very reliable to obtain this information by only retrospective questioning of UC patients without official records, which is the reason we chose not to. Another limitation of the study is that childhood vaccines and cow's milk allergy were not included in the study.

Conclusions

In this study, it was emphasized that the mother's passive smoking brings the age of the diagnosis of UC earlier. This reveals the protective role of maternal smoking cessation in the early development of UC. The duration of breastfeeding is important for UC development. We recommend breastfeeding for longer than six months to prevent UC. Additionally, breastfeeding is protective for the risk of early-onset UC.

References

1. Abraham C, Cho JH. Inflammatory bowel disease. N Engl J Med. 2009;361:2066–78. doi: 10.1056/NEJMra0804647.
2. Hutfless S, Heyman MB, Bayless TM, Abramson O, Lisa J. Herrinton LJ. Prenatal and Perinatal Characteristics Associated with Pediatric-Onset Inflammatory Bowel Disease. Dig Dis Sci (2012) 57:2149–56. doi: 10.1007/s10620-012-2128-1.
3. Loftus EV Jr. Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influences. Gastroenterology. 2004;126:1504–17. doi: 10.1053/j.gastro.2004.01.063.
4. Marshall JK, Hilsden RJ. Environment and epidemiology of inflammatory bowel diseases. In: Satsangi J, Sutherland RL, eds. Inflammatory bowel diseases. London: Churchill Livingston, 2003:17–28.
5. Metsala J, Kilkkinen A, Kaila M, Tapanainen H, Klaukka T, Gissler M, et al. Perinatal Factors and the Risk of Asthma in Childhood-A Population-based Register Study in Finland. Am J Epidemiol. 2008;168:170-8. doi: 10.1093/aje/kwn105.
6. Ievins R, Roberts SE, Goldacre MJ. Perinatal factors associated with subsequent diabetes mellitus in the child: record linkage study. Diabet Med. 2007;24(6):664-70. doi: 10.1111/j.1464-5491.2007.02147.x.
7. Klement E, Cohen RV, Boxman J, Joseph A, Reif S. Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysi. Am J Clin Nutr. 2004;80(5):1342-52. doi: 10.1093/ajcn/80.5.1342.
8. Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. Acta Paediatr Suppl. 2003;91(441):48–55. doi: 10.1111/j.1651-2227.2003.tb00646.x.
9. Midtvedt AC, Midtvedt T. Production of short chain fatty acids by the intestinal microflora during the first 2 years of human life. J Pediatr Gastroenterol Nutr. 1992;15:395–403. doi: 10.1097/00005176-199211000-00005.
10. Palmer C. Bik EM, Digiulio DB. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5:e177. doi: 10.1371/journal.pbio.0050177.
11. Xu L, Lochhead P, Ko Y, Claggett B Leong RW, Ananthakrishnan AN, Systematic review with meta-analysis: Breastfeeding and the risk of Crohn's disease and ulcerative colitis. Aliment Pharmacol Ther. 2017 Nov;46(9):780–9. doi: 10.1111/apt.14291.
12. Bernstein CN, Banerjee A, Targownik LE. Cesarean section delivery is not a risk factor for development of inflammatory bowel disease: a population-based Analysis. Clin Gastroenterol Hepatol. 2016;14:50–7. doi: 10.1016/j.cgh.2015.08.005.
13. Khalili H, Ananthakrishnan AN, Higuchi LM, Richter JM, Fuchs CS, Chan AT. Early Life Factors and Risk of Inflammatory Bowel Disease in Adulthood. Inflamm Bowel Dis. 2013 Mar;19(3):542-7. doi: 10.1097/MIB.0b013e31828132f8.
14. Wang Y-F, Ou-yang Q, Xia B, Liu L-N , Gu F, Zhou K-F, et al. Multicenter case-control study of the risk factors for ulcerative colitis in China. World J Gastroenterol. 2013 March 21;19(11):1827-33. doi: 10.3748/wjg.v19.i11.1827.

15.Gomes CF, Narula N, Morão B, Nicola P, Cravo M, Torres J. Mode of delivery does not afect the risk of infammatory bowel disease. Dig Dis Sci. 2020 Mar 21. doi: 10.1007/s10620-020-06204-7.
16.Gearry RB, Richardson AK, Frampton CM, Dodgshun AJ, Barclay ML. Population-based cases control study of inflammatory bowel disease risk factors. Journal of Gastroenterology and Hepatology. 2010;25:325-33. doi: 10.1111/j.1440-1746.2009.06140.x.
17.Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, Wilson DC. Systematic review: the role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediatr 2009 Sep;155(3):421-6. doi: 10.1016/j.jpeds.2009.03.017
18.Rigas A, Rigas B, Glassman M, Yen Y, Lan SJ, Petridou E, et al. Breast-feeding and maternal smoking in the etiology of Crohn's disease and ulcerative colitis in childhood. Ann Epidemiol. 1993 Jul;3(4):387-92.
19.Roberts SE, Clare J, Wotton CJ, Williams JG, Griffith M, Goldacre MJ. Perinatal and early life risk factors for inflammatory bowel disease. World J Gastroenterol. 2011 Feb 14;17(6):743-9. doi: 10.1016/1047-2797(93)90066-d.
20.Ley D, Desseyn JL, Mischke M, Knol J, Turck D, Gottrand F. Early-life origin of intestinal infammatory disorders. Nutr Rev. 2017;75:175–87. doi: 10.1093/nutrit/nuw061.
21.Bager P, Simonsen J, Nielsen NM, Frisch M. Cesarean section and ofspring's risk of infammatory bowel disease: a national cohort study. Infamm Bowel Dis. 2012;18:857–62. doi: 10.1002/ibd.21805.
22.Benchimol EI, Kaplan GG, Otley AR, Nguyen GC, Underwood FE, Guttmann A. Rural and urban residence during early life is associated with risk of inflammatory bowel disease: a population-based inception and birth cohort study. Am J Gastroenterol. 2017;112:1412–22. doi: 10.1038/ajg.2017.208.
23.Kalyon S, Gökden Y, Oyman F. A new biological marker in inflammatory bowel disease: Pentraxin 3. J Surg Med. 2020;4(10):875-8.
24.Gökden Y, Hot S, Gönen C, Kalyon S, Çetinkaya ZA. The value of adenosine deaminase level in assessing activation of inflammatory bowel disease. J Surg Med. 2020;4(8):654-9. doi: 10.28982/josam.791156.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1018-1022.
DOI: 10.28982/josam.765082

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Comparison of primipara women's pre-pregnancy, pregnancy, and postpartum sexual lives

Primipar kadınların gebelik öncesi, gebelik ve doğum sonrası cinsel yaşamlarının karşılaştırılması

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Ethics Committee Approval: Approval was obtained from the Ethics Committee of the Faculty of Health Sciences of Kafkas University (number: 81829502.903/48, date: 29.03.2019). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Onay Kafkas Üniversitesi Sağlık Bilimleri Fakültesi Etik Kurulu'ndan (sayı: 81829502.903 / 48, tarih: 29.03.2019) alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Sexual dysfunction can affect women's quality of life and marriage. This study compared the sexual lives of primipara women before, during pregnancy and in the postpartum period.

Methods: This descriptive follow-up research comprised 100 primipara women who agreed to participate in the study. Data were collected using the survey form and the Arizona Sexual Experiences Scale. Number, percentage, means, standard deviation, median, minimum, maximum values and Friedman analysis were used to analyze the data.

Results: Women's sexual desire and orgasm level before pregnancy were significantly better than their postpartum orgasm level. Our study results showed that the level of sexual arousal and lubrication before pregnancy was significantly better than that after birth. We also determined that women's postpartum orgasm satisfaction was significantly less than their pre-pregnancy and pregnancy orgasm satisfaction. Based on Arizona Sexual Experiences Scale average, the sexual dysfunction of women before pregnancy was significantly less than during the pregnancy and postpartum periods and the pregnancy period was better than the postpartum period (P<0.001).

Conclusion: This study has reported that sexual dysfunction in women is less during pre-pregnancy; however, it increases during pregnancy and the postpartum period.

Keywords: Primipara, Pre-Pregnancy period, Pregnancy period, Postpartum period, Sexual dysfunction

Öz

Amaç: Bu araştırmada, primipar kadınların gebelik öncesi, gebelik ve doğum sonrası cinsel yaşamlarının karşılaştırılması amacıyla yapılmıştır.

Yöntemler: Tanımlayıcı izlem araştırması olarak yapılan araştırmanın örneklemini araştırmaya katılmayı kabul eden 100 primipar kadın oluşturmuştur. Araştırmanın verileri; anket formu ve Arizona Sexual Experiences Scale kullanılarak toplanmıştır. Verilerin analizinde sayı, yüzde, ortalama, standart sapma, medyan, minimum, maksimum değerleri ve friedman analizi kullanılmıştır.

Bulgular: Çalışmamızda, kadınların gebelik öncesi cinsel istek ve orgazm düzeyi doğum sonrası orgazm düzeyinden anlamlı derecede daha iyi olduğu belirlenmiştir. Çalışmamızda, gebelik öncesi cinsel uyarılma ve lubrikasyon, düzeyinin doğum sonrası cinsel uyarılma ve lubrikasyon düzeyinden anlamlı derecede daha iyi düzeyde olduğu belirlenmiştir. Çalışmamızda kadınların doğum sonu orgazm tatminin, gebelik öncesi ve gebelik dönemi orgazm tatmininden anlamlı derecede daha kötü düzeyde olduğu belirlenmiştir. Arizona Cinsel Yaşantılar Ölçeği ortalamasına baktığımızda, kadınların gebelik öncesi dönemde cinsel disfonksiyonlarının gebelik ve doğum sonu dönemden, gebelik döneminin ise, doğum sonu dönemden anlamlı düzeyde daha iyi olduğu belirlenmiştir (P<0,001).

Sonuç: Kadınların gebelik öncesi dönemde daha az olmak üzere cinsel disfonksiyonun gebelik ve doğum sonu dönemlerde artarak devam ettiği belirlenmiştir.

Anahtar kelimeler: Primipar, Gebelik öncesi dönem, Gebelik dönemi, Doğum sonrası dönem, Cinsel disfonksiyon

How to cite/Atıf için: Delibalta RT, Çılgın H. Comparison of primipara women's pre-pregnancy, pregnancy, and postpartum sexual lives. J Surg Med. 2020;4(11):1018-1022.

Introduction

An individual's sexuality is determined before birth and shaped by many factors. These include the communities they live in, their values, beliefs, emotions, personalities, likes and dislikes, attitudes, behaviors, and physical appearance. It includes not only genitals, but one's whole body and mind [1,2]. Sexuality is influenced by the interaction of psychological, social, economic, political, cultural, legal, historical, religious, biological, and spiritual factors [3]. Sexual dysfunction is an important health problem that can be seen in every society [4]. Studies throughout the world and Turkey show a high prevalence of sexual dysfunction with rates between 22% and 93%, although it varies depending on the ages of the women [5,6].

Pregnancy, especially a first pregnancy, is one of the most important events in a woman's life [7,8]. The physical and emotional changes during this time, which are influenced by social and cultural factors, affect the woman's sex life and sexuality. These factors would include a couple's reaction to pregnancy, the idea of being a family, the sexual identity of women, their changed roles as wives and mothers, and various cultural norms and economic factors [7,9].

Pregnancy is also one of the most common periods in which women experience sexual dysfunction [10]. During this time, a woman may experience various physical ailments and her sexual interest and libido may decline. She may also fear that sexual activity could harm the baby. All these can affect a couple's sexual relationship.

The postpartum period is when couples adapt to their parenting roles and changes in the anatomy and hormones of the female reproductive organs. During this time, couples return to their sexual activities [11,12]. One study reported that active sexual intercourse in the postpartum period usually begins after the second week when the risk of bleeding and infection is reduced [13]. Sexual intercourse can resume six weeks after birth when uterine involution occurs, the woman returns to her normal physiology, the tissue repair of her episiotomy is completed, and lochia has ceased [14].

Studies have shown that most women experience a significant increase in sexual health-related problems during the postpartum period [15,16]. At the same time, it has been noted that health care professionals have difficulty assessing and diagnosing sexual dysfunction. This may be due to their own biases, lack of knowledge of sexuality, and their personal beliefs and attitudes [17]. Therefore, this study was conducted to compare the sexual life of primipara women before pregnancy, during pregnancy and the postpartum period. It is thought that the results will contribute to the development of more specialized training and counseling education. Such training would thus enable health professionals to offer up-to-date information regarding sexual health with a goal towards improving women's quality of life.

Materials and methods

Design

This study was conducted as a descriptive follow-up study.

Population

The population of the study included primipara women who visited the Obstetrics Clinic of Kafkas University Health Research and Practice Center. Power analysis performed at 0.05 revealed a sample size of 86 individuals. This research was completed with a total of 100 primipara women who were followed up in the second trimester and two months after birth.

Data collection tools and features

After reviewing the literature, data were collected using the survey form [18,19] prepared by the researcher, and the Arizona Sexual Experiences Scale (ASES).

Survey form

The survey form created by the researchers consisted of questions regarding the demographic, obstetric and sex life characteristics of women.

The Arizona Sexual Experiences Scale

The Arizona Sexual Experience Scale is a measurement tool for assessing sexual dysfunctions. This scale, developed by McGahuey et al. [20], was adapted to Turkish by Soykan [21]. It has separate forms for men and women. The form for women was used in this study. The scale is a 5-Item, 6-grade Likert type, self-assessment scale. It determines sex drive, arousal, vaginal wetness, the capacity to have orgasm and the sense of satisfaction as a result of orgasm. The lowest score that participants can obtain from the scale is 5 and the highest is 30. In Soykan's study, the cut-off score of the scale was determined as 11 (sensitivity = 100%, specificity = 52%). The sum of the points obtained from the scale items constitutes the total scale score. Low scores from the scale indicate that sexual response is strong, easy, and satisfying, while high scores indicate sexual dysfunction. In Soykan's study, the Cronbach alpha value of the scale was 0.90 and the test-retest reliability was 0.88 [21]. In this study, the Turkish version of the ASES was used. In our study, Cronbach alpha values of ASES for pre-pregnancy, pregnancy and postpartum periods were high, between 0.840 and 0.895.

Type of collection

The survey form and ASES were filled out by the primipara who came for their first prenatal checkup. These forms assessed the study participants' pre-pregnancy sexual activity. In order to evaluate sexual life during pregnancy, the ASES form was completed by women between 13-28 weeks of gestation. Two months after birth, postpartum questionnaire and ASES were filled out by women through home visits.

Ethical principles of research

Prior to beginning the research, approval number 81829502.903/48 dated 29.03.2019 was obtained from the Ethics Committee of the Faculty of Health Sciences of Kafkas University, and the necessary permission from the relevant institution was received. Adhering to the principles of "Informed Consent", "Confidentiality and Protection of Privacy", and "Respect for Autonomy", the purpose of the research was carefully explained to the women. The women who chose to participate voluntarily in the research were assured that all data and information obtained would be kept confidential [22].

Statistical analysis

The data were analyzed with the IBM SPSS Statistics 23 package program. In the analysis of the data, number and percentage were used for numerical variables, and mean,

standard deviation, median, minimum, and maximum values were used for categorical variables. For numerical variables, the Kolmogorov Smirnov normality test was applied, and it was determined that the data did not show normal distribution. Therefore, the differences between more than two dependent variables were analyzed using Friedman's analysis. $P<0.05$ indicated statistical significance.

Results

The research was eventually completed with 100 primipara women. The mean age of the women and their partners were 27 and 30 years, respectively. Among all, 74% of women had been married for 1-3 years; the majority of women and their spouses had a university education. Forty percent of the women were working, and 47.5% of these women were teachers. The majority of their spouses were also working, and 36.4% of them were employed as teachers/government employees. The income of 69% of the women covered their expenses; 50% had extended families and 50% had nuclear families (Table 1).

Table 1: Distribution of socio-demographic characteristics of women

Characteristics	n	%
Age (M=27 SD=4.987)		
18-29	74	74.0
30-49	26	26.0
Age of Spouse (M=30.68 SD=5.337)		
20-30	55	55.0
31-51	45	45.0
Length of Marriage		
Less than 1 Year	8	8.0
1-3 Year	74	74.0
More than 3 years	18	18.0
Education		
Primary school	7	7.0
Middle School	10	10.0
High school	33	33.0
University	46	46.0
Graduate	4	4.0
Spouse’s Education		
Primary school	4	4.0
Middle School	9	9.0
High school	24	24.0
University	59	59.0
Graduate	4	4.0
Employment Status		
Working	40	40.0
Not Working	60	60.0
Profession (n=40)		
Teacher	19	47.5
Public Official	11	27.5
Nurse-Midwives	5	12.5
*Other	5	12.5
Spouse’s Employment Status		
Working	99	99.0
Not Working	1	1.0
Spouse's Profession (n=99)		
Military /Staff-Police	25	25.3
Teacher/ Public Official	36	36.4
Self-employed / Worker	24	24.2
**Other	14	14.1
Income Level		
Income Less than Expenses	13	13.0
Income Expenses	69	69.0
Income More Than Expenses	18	18.0
Family Type		
Extended family	50	50.0
Nuclear family	50	50.0

* Occupational health and safety (1), Call center employee (1), Accountant (1), Psychologist (1), Secretary (1), ** Doctor (3), Tradesman (1), Income specialist (1), Security officer (1), Store Manager (1), Engineer (6) Technician (2)

Our study determined that 20% of women had experienced dyspareunia before pregnancy, 30% during pregnancy and 64% during the postpartum period. It was found that 60% of these women had not applied to any health care facility when they had problems with their sexual lives, because all considered it shameful or sinful to talk about these problems. About 80% of study participants had sought solutions to their sexual issues but had used the internet for answers (Table 2).

Table 2: Distribution of characteristics of women

Characteristics	n	%
Dyspareunia Problem in Pre-pregnancy Period		
Yes	20	20.0
No	80	80.0
Dyspareunia Problem in Pregnancy		
Yes	30	30.0
No	70	70.0
Postpartum Dyspareunia Problem		
Yes	64	64.0
No	36	36.0
Applying to a Health Institution for Sexuality Problems		
Yes	40	40.0
No	60	60.0
Reasons for Not Applying to a Health Institution for Sexuality Problems		
Talk of sexuality is shameful or sinful	60	100
Behavior Seeking Solution to Sexuality Problems		
Yes	80	80.0
No	20	20.0
Where Women Sought Solutions for Sexuality Problems		
Checked the Internet	80	100
Baby Breastfeeding Status		
Yes	100	100.0
Baby Slept in Separate Bed in Parents’ Bedroom after Birth		
Yes	100	100.0
Reason for Baby Sleeping in a Separate Bed in Parents’ Bedroom after Birth		
Fear that something could happen to baby during sleep	94	94.0
If the baby sleeps with the mother, she gets used to her smell, and refuses to sleep in its own bed	4	4.0
Sleeps more comfortably in its own bed	2	2.0
Postpartum Sexual Life Start Time		
40-50 Days	71	71.0
51-75 Days	29	29.0
Religious Belief on Postpartum Sexual Life Start Time		
Yes	65	65.0
No	35	35.0
Which Religious Opinion		
Based on religious belief, postpartum sexual intercourse starts after 40 days	65	100
Current Use of Any Method to Prevent Pregnancy		
Yes	43	43.0
No	57	57.0
Which Family Planning Method Used		
Withdrawal Method	39	90.7
Condom	4	9.3

In our study, women’s average sexual desire score before pregnancy was 2.71, which was significantly less during pregnancy (3.28) and the postpartum period (3.55). In addition, the average sexual desire score during pregnancy (3.28) was significantly less than the average sexual desire score during the postpartum period (3.55) ($P<0.001$). In our study, the average score of sexual arousal before pregnancy (3.08) was significantly less than the average score of sexual arousal after birth (3.32) ($P<0.001$). We determined that the average score of pre-pregnancy lubrication was significantly lower (2.80) than the mean of postpartum lubrication (3.09) ($P<0.001$). The average pre-pregnancy orgasm score (2.98) was less than the average pregnancy orgasm score (3.25), and the postpartum orgasm score (3.33). However, the average pre-pregnancy orgasm score (2.98) was significantly less than the postpartum orgasm score (3.33) ($P<0.001$). The average of the orgasm satisfaction score during the postpartum period (2.94) was significantly higher than the average of orgasm satisfaction before pregnancy (2.41) and the average of orgasm satisfaction during pregnancy (2.61) ($P<0.001$). In addition, the study results showed that the mean ASES was significantly lower in the pre-pregnancy period (13.98) than during pregnancy (15.29) and in the postpartum period (16.23). At the same time, it was determined that the mean ASES score during pregnancy (15.29) was significantly less than the mean of the ASES score during the postpartum period (16.23) ($P<0.001$) (Table 3) (Figure 1).

Table 3: Examination of differences between Arizona Sexual Experience Scale and lower dimensions according to women's pre-pregnancy, pregnancy and postpartum period

	Prepregnancy		During Pregnancy		Postpartum Period		*P*-value
	Mean(SD)	Median (Min.-Max.)	Mean(SD)	Median (Min.-Max.)	Mean(SD)	Median (Min.-Max.)	
Desire	2.71(1.15)	3(1-6)	3.28(1.42)	3(1-6)	3.55(1.00)	3(1-6)	<0.001* difference: 1-2.3 2-3
Arousal	3.08(0.92)	3(1-5)	3.18(1.00)	3(1-6)	3.32(0.92)	3(1-5)	0.007* difference: 1-3
Lubrication	2.80(0.95)	3(1-5)	2.97(1.00)	3(1-6)	3.09(0.91)	3(1-5)	<0.001* difference: 1-3
Orgasm	2.98(1.06)	3(1-6)	3.25(1.15)	3(1-6)	3.33(1.14)	3(1-6)	<0.001* difference: 1-3
Satisfaction	2.41(1.02)	2(1-6)	2.61(1.02)	3(1-5)	2.94(1.00)	3(1-5)	<0.001* difference: 3-1.2
Total	13.98(3.99)	15(5-24)	15.29(4.74)	15(5-29)	16.23(3.91)	16.5(8-26)	<0.001* difference: 1-2.3 2-3

SD: Standard deviation, *:*P*<0.05 (Statistically significant)

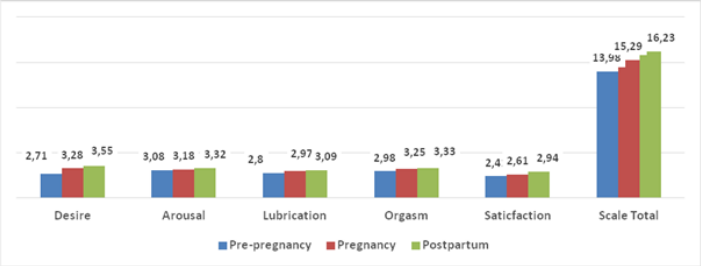

Figure 1: Examination of differences between Arizona Sexual Experience Scale and lower dimensions according to women's pre-pregnancy, pregnancy, and postpartum period

Discussion

Sexual health, which also includes reproductive health, is considered an important part of general health. Sexual dysfunctions are among the major health problems found in all societies [4]. The Word Health Organization has recommended that a research must be conducted on sexual health, because of its importance, independent of reproductive health because lack of awareness about sexual health is the underlying cause of many dysfunctions and diseases worldwide [23]. Female sexual dysfunction is a very common problem in 40-45% of women [24]. Hobbs and his colleagues noted that in order to appropriately evaluate pregnancy and postpartum processes, a woman's sexual history (pre-pregnancy period) should be disclosed [25]. This study therefore aimed to determine the problems that women experience during the pre-pregnancy, pregnancy, and postpartum periods.

Sexual dysfunction may lead to a general feeling of dissatisfaction with one's life and a decreased quality of life. It may also negatively affect women's physical, psychological, social and emotional health [26,27]. Studies have determined that between 28.6% and 48.3% of women have experienced sexual dysfunction [28,29]. Results of some studies have reported that most women who report a decline in sexual function during pregnancy continue to experience a decline in the postpartum period [30,31]. In contrast, other studies have determined that although sexual activity increased in the postpartum period compared to the pregnancy period, this increase remained lower than in the prenatal period [16,32].

Incidence data has shown that one of the most common sexual dysfunctions in women was sexual desire disorder [33]. Our study found that the women's level of sexual desire before pregnancy was significantly higher than during pregnancy and postpartum, and the level of sexual desire during pregnancy was significantly higher than postpartum levels. While one study showed similarity with ours in finding women's level of sexual desire before pregnancy higher than postpartum levels, it differs in reporting that sexual desire during pregnancy was less than during the postpartum period [34].

Many women experience low arousal as a result of decreased blood fluidity related to genital temperature and vaginal lubricity [35,36]. Incidence data has determined that another common sexual dysfunction in women is sexual arousal disorder [33]. A study found that 40.4% of women experienced sexual arousal disorder during the postpartum period [37]. In our study, the women's level of sexual arousal before pregnancy was significantly higher than the level of sexual arousal after childbirth. Another study also found that sexual arousal was higher in the pre-pregnancy period than in other periods [34]. This study finding is in accordance with our study.

However, in our study, the level of pre-pregnancy lubrication was significantly better than the level of postpartum lubrication. One study found that 39.2% of women experienced a lubrication problem during the postpartum period [38]. Another study determined that women had a better level of lubrication in the postpartum period than in the pre-pregnancy and pregnancy periods [34].

A study found that women experience more orgasm disorders during pregnancy than prior to pregnancy [38]. In a different study, women's pre-pregnancy orgasm level was determined to be better than during pregnancy and postpartum. These study findings correspond to ours [34]. Our study found women's pre-pregnancy orgasm level to be higher than their pregnancy and postpartum orgasm levels, but their pre-pregnancy orgasm level was significantly better than their postpartum orgasm level. Studies have shown that orgasm satisfaction was 76-79% before pregnancy, 75-84% during the second trimester and 40-41% during the third trimester [16,39,40]. One study determined that women had problems with orgasm satisfaction during the postpartum period [41]. In our study, it was determined that women's postpartum orgasm satisfaction was significantly less than their pre-pregnancy and pregnancy orgasm satisfaction. In a different study, which had similar results to ours, women's pre-pregnancy orgasm satisfaction was better than their postnatal orgasm satisfaction [34].

Based on the Arizona Sexual Experiences Scale average, the sexual dysfunction scores of our study participants before pregnancy were significantly less than during the pregnancy and postpartum periods. Sexual dysfunction during pregnancy was significantly less than postpartum dysfunction. The score of 11 scale cut-off of ASES used in our study shows that the women in our study experienced sexual dysfunction prior to pregnancy. This indicates that women continue to experience sexual dysfunction during pregnancy and postpartum. Some studies have reported that women have decreased sexual function during pregnancy compared to the pre-pregnancy period [34,38]. Other studies have shown that this decline in sexual activity during pregnancy continues for several months after birth [16,32]. These results are comparable our study.

Certain studies have reported that 14-27% of women had dyspareunia [42,43]. In a study, some women experience dyspareunia in the postpartum period because of the reduced vaginal lubrication resulting from decreased estrogen levels [44,45]. Our study determined that 20% of women experienced dyspareunia before pregnancy, 30% during pregnancy and 93.9% during the postpartum period. Another study reported that women's complaints of dyspareunia decreased significantly in the postpartum period, compared to pre-pregnancy and pregnancy periods [34]. The most difficult aspects of the study were in the follow up of women from the pre-pregnancy period to the postpartum period and in covering the economic costs of the study by the researchers. The limitation of the research was that it cannot be generalized to all of Turkey since it was conducted in Kars province in eastern Turkey.

Conclusion

In conclusion, the studies have reported that women experience sexual dysfunction during the pre-pregnancy, post-pregnancy, and postpartum periods. It has been determined that sexual dysfunction can be found in women prior to pregnancy, but it increases during pregnancy and postpartum periods. Therefore, it is significant that all health professionals, especially nurses, be able to identify the problems related to women's sexuality in the pre-pregnancy and postpartum periods and direct them to the proper health units for treatment.

References

1. Taylor TF. The origins of human sexual culture. Journal of Psychology&Human Sexuality. 2007;18(2):69-105. doi: 10.1300/J056v18n02_03.
2. Moseley A. Philosophy from A to Z. 2. Printing. Istanbul: NTV Publications; 2010. pp.55-8.
3. Bozdemir N, Özcan S. Sexuality and sexual health overview. Turkish Journal of Family Medicine and Primary Care. 2011;5(4):37-46.
4. Karakoyunlu F, Oncel S. Example of the nursing care process in women's sexual dysfunctions. Ataturk Univ J Nurs Stud. 2009;12(3):8-10.
5. Fiskin G, Beji N. Valuation of sexual function and role of nurse. i.u. florence nightingale faculty of nursing, department of women's health and diseases nursing. Androl Bull. 2010;73–6.
6. Oberg K, Fugl-Meyer AR, Fugl-Meyer KS. On categorization and quantification of women's sexual dysfunctions: an epidemiological approach. Int J Impot Res. 2004; 6:261–69.
7. Golbasi Z, Tugut, N Erenel A, Eroğlu K. Sexual dysfunction, prevalence and related factors in married women admitted to gynecology polyclinic. Repub Med J. 2014;36:1–10. doi: 10.7197/cmj.v36i1.1008002434.
8. Yarali S. Sexual dysfunction in married women and investigation of quality of sexual life. Department of Public Health Nursing [Master's Thesis]. Erzurum, Turkey, 2013.
9. Gökyıldız S, Beji NK. The moneffects of pregnancy on sexual life. Journal of Sex & Marital Therapy. 2005;31(3):201-15.
10. Incesu C. Sexual functions and sexual dysfunctions. Clinical Psychiatry. 2004;3:3-13.
11. Arslan F, Uzun İ. Examination of nursing postnatal training and counseling services. Turkey Clinics J Med Sci. 2008;28:736-742.
12. Rogers RG, Leeman LM, Migliaccio L, Albers LL. Does the severity of spontaneous genital tract trauma affect postpartum pelvic floor function?. Int Urogynecol J Pelvic Floor Dysfunct. 2008;19(3):429–35. doi: 10.1007/s00192-007-0458-x.
13. Blackburn ST. Maternal, fetal & neonatal physiology:A clinical perspective. 2 Ed., Saunders, New York. Nd; 2003, pp. 158-79,
14. Doganer, G, Bekar M. Determining the problems of women having vaginal delivery in the early postpartum period for the care of her and newborn. Health and Society. 2006;16(4):60-70.
15. Eryilmaz HY, Abali S, Dondar C, Kurnaz E. Sexual functions of women in postpartum period and affecting factors. 4th International Congress of Reproductive Health Book, Bilkent Hotel and Conference Center, Ankara, Turkey; 20-23 April, 2005, pp. 198,
16. Barrett G, Pendry E, Peacock J, Victor C, Thakar R, Manyonda I. Women's sexual health after childbirth. An International Journal of Obstetrics & Gynaecology. 2000;107(2):186-95. doi: 10.1111/j.1471-0528.2000.tb11689.x.
17. Demireloz Akyuz M, Ceber Turfan E, Cetintas Oner S, Sakar T, Mamik Aktay D. Sexual functions in pregnancy: different situations in near geography:a case study on Turkey, Iran and Greece. The Journal of Maternal-Fetal & Neonatal Medicine. 2020;33(2):222–9. doi: 10.1080/14767058.2018.1488164.
18. Akyüz EO. Postnatal sexual problems and investigation of affecting factors. Published Master Thesis. Adnan Menderes University Institute of Health Sciences Health and Obstetrics Nursing, Aydin, Turkey, 2009.
19. Yoruk F, Karacam Z. The effectiveness of PLISSIT model in solving sexual problems of postpartum women. Published Master's Thesis, Institute of Adnan Menderes University of Health Sciences Health and Obstetrics Nursing, Aydin, Turkey in 2014.
20. McGahuey AC, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL. The Arizona Sexual Experience Scale (ASEX): Reliability and validity. Journal of Sex & Marital Therapy. 2000;26:25–40. doi: 10.1080/009262300278623.
21. Soykan A. The reliability and validity of arizona sexual experiences scale in Turkish ESRD patients undergoing hemodialysis. International Journal of Impotence Research. 2004;16:531-4.
22. Bayık A. Cs in nursing research. (In) the first of nursing research, process and methods. the Focus Offset, Istanbul, Turkey; 2004,pp:27-48,
23. Kaviani M, Rahnavard T, Azima S, Emamghoreishi M, Asadi N, Sayadi M. The effect of education on sexual health of women with hypoactive sexual desire disorder: a randomized controlled trial. Int J Community Based Nurs Midwifery. 2014; 2(2):94.
24. Yeniel AO, Petri E. Pregnancy, childbirth and sexual function: perceptions and facts. Int Urogynecol J. 2014; 25(1):5–14. doi: 10.1007/s00192-013-2118-7.
25. Hobbs K, Bramwell R & May K. Sexuality, sexual behaviour and pregnancy. Sexual and Marital Therapy. 1999;4:371–83.
26. Fan D, Li S, Wang W, Tian G, Liu L, Wu S, et al. Sexual dysfunction and mode of delivery in chinese primiparous women: a systematic review and meta-analysis. BMC Pregnancy and Childbirth. 2017;17:408. doi: 10.1186/s12884-017-1583-2.
27. Banaei M, Tork Zahrani S, Pormehr-Yabandeh A, Ozgoli G, Azad M. Investigating the ımpact of counseling based on PLISSIT model on sexual ıntimacy and satisfaction of breastfeeding women. Int J Pharm Res Allied Sci. 2016;5(3):489–99.
28. Demir O, Parlakay N, Gök G, Esen AA. Sexual dysfunction in female hospital workers. Andrology. 2007;33 (2):156-60.
29. Ege E, Akın B, Yaralı Arslan, S, Bilgili N. Prevalence and risk factors of sexual dysfunction in healthy women. TÜBAV Journal of Science. 2010;3(1):137-44.
30. Brtnicka H, Weiss P, Zverina J. Human sexuality during pregnancy and the postpartum period. Bratislava Medical Journal 2009;110:427–31.
31. Johnson CE. Sexual health during pregnancy and the postpartum. Journal of Sexual Medicine. 2011;8:1267–84. doi: 10.1111/j.1743-6109.2011.02223.x.
32. Trutnovsky G, Haas J, Lang U, Petru E. Women's perception of sexuality during pregnancy and after birth. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2006;46:282–7.
33. McCabe MP, Sharlip ID, Lewis R, Atalla E, Balon R, Fisher A, et al. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth ınternational consultation on sexual medicine 2015. J Sex Med. 2015;13(2):144-52. doi: 10.1016/j.jsxm.2015.12.034.
34. Yıldız H. The relation between prepregnancy sexuality and sexual function during pregnancy and the postpartum period: a prospective study. Journal of Sex & Marıtal Therapy. 2015;41(1):49–59. doi: 10.1080/0092623X.2013.811452.
35. Komurcu N, Demirci N, Yildiz H, Gün C. Sexuality in Turkish journals of nursing: a literature review. J Train Res Nurs. 2014;11(1):9–17.
36. Sadi Z, Aksu H. Sexual life of partners during pregnancy and affecting factors. Anatolian J Nurs Health Sci. 2016;19(2).
37. Banael M, Morldl A, Dashti S. Sexual dysfunction and its associated factors after delivery: longitudinal study in iranian women. Mater Sociomed. 2018;30(3):198-203. doi: 10.5455/msm.2018.30.198-203.
38. Erenel AS, Eroglu K, Vural G & Dilbaz B. A pilot study: in what ways do women in turkey experience a change in their sexuality during pregnancy. Sexuality and Disability. 2011;29:207–16. doi: 10.1007/s11195-011-9200-1.
39. Glazener CM. Sexual function after childbirth: women's experiences, persistent morbidity and lack of professional recognition. British J Obstetr Gynaecol. 1997;104(3):330–5. doi: 10.1111/j.1471-0528.1997.tb11463.x.
40. Xu XY, Yao ZW, Wang HY, Zhou Q, Zhang W. Women's postpartum sexuality and delivery types. Zhonghua Fu Chan Ke Za Zhi. 2003;38(4):219–22.
41. Türk R, Erkaya R. An evaluatıon of the postpartum sexual lıves of prımıparous women. International Refereed Journal of Nursing Researches;T January / February / March / April 2019 Winter Spring Semester, Issue: 15. doi: 10.17371/UHD.2019.1.10.
42. Safarinejad MR. Female sexual dysfunction in a populationbased study in iran: prevalence and associated risk factors. Int J Impot Res. 2006;18:382. doi: 10.1038/sj.ijir.3901440.
43. Johnson SD, Phelps DL, Cottler LB. The association of sexual dysfunction and substance use among a community epidemiological sample. Arch Sex Behav. 2004 33:55. doi: 10.1023/B:ASEB.0000007462.97961.5a.
44. Wouda JC, Hartman PM, Bakker RM, Bakker JO, van de Wiel HBM & Schultz WCMW. Vaginal plethysmography in women with dyspareunia. The Journal of Sex Research. 1998;35:141–7. doi: 10.1080/00224499809551927.
45. Brauer M, ter Kuile MM, Janssen SA, Laanc E. The effect of painrelated fear on sexual arousal in women with superficial dyspareunia. European Journal of Pain. 2007;11:788–98. doi: 10.1016/j.ejpain.2006.12.006.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1023-1026.
DOI: 10.28982/josam.800727

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Comparison of intravenous lidocaine and intravenous lidocaine/paracetamol in prevention of postoperative sore throat after laryngeal mask insertion

Laringeal maske yerleşim sonrası postoperatif boğaz ağrısı sıklığının önlenmesinde intravenöz lidokain ve intravenöz lidokain/parasetamol kombinasyonunun karşılaştırılması

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Ethics Committee Approval: The study was conducted after receiving the approval from the Ethics Committee of Necmettin Erbakan University (2019/2037). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Necmettin Erbakan Üniversitesi Etik Kurulu'ndan (2019/2037) gerekli onay alındıktan sonra gerçekleştirildi. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Postoperative sore throat after general anesthesia with laryngeal mask airway is a common and undesirable complication. There are many agents and methods to prevent this complication. However, there is no study comparing intravenous lidocaine and lidocaine-paracetamol combination in the literature. The objective of this study was to compare the effects of systemic lidocaine and systemic lidocaine-paracetamol combination on postoperative sore throat in patients who underwent general anesthesia with laryngeal mask airway.

Methods: A total of 80 patients aged over 18 years with ASA I-III who underwent elective inguinal hernia surgery under general anesthesia with laryngeal mask airway were included in this cross-sectional study. Group LidoPara was administered 1 mg kg^{-1} lidocaine + 10 mg kg^{-1} paracetamol, and Group Lido, 1 mg kg^{-1} lidocaine. Resting and swallowing sore throat and hoarseness were evaluated with a 4-point scale at the postoperative 0^{th}, 2^{nd}, 4^{th}, and 24^{th} hours.

Results: Demographic data of the patients were similar (P>0.05). There was no statistically significant difference between the two groups in terms of resting and swallowing sore throat at the postoperative 0^{th}, 2^{nd}, 4^{th}, and 24^{th} hours. No hoarseness was found in both groups at the postoperative 4^{th} and 24^{th} hours.

Conclusion: Combined paracetamol and lidocaine was found to affect postoperative resting and swallowing sore throat similar to lidocaine alone.

Keywords: General anesthesia, Laryngeal mask airway, Lidocaine, Paracetamol, Sore throat

Öz

Amaç: Laringeal maske airway ile genel anestezi sonrası postoperatif boğaz ağrısı sık görülen ve istenmeyen bir komplikasyondur. Bu komplikasyonu önlemek için literatürde pekçok ajan ve metod vardır. Fakat lidokain ve lidokain-parasetamol kombinasyonunu karşılaştıran bir çalışma yoktur. Bu çalışmanın amacı laringeal maske airway ile genel anestezi uygulanan hastalarda, sistemik lidokain ile sistemik lidokain-parasetamol kombinasyonunun postoperatif boğaz ağrısı üzerine etkilerini karşılaştırmaktır.

Yöntemler: Kesitsel çalışmaya laringeal maske airway ile genel anestezi altında elektif inguinal herni cerrahisi olan, 18 yaşından büyük ASA fiziksel statüsü I-III olan 80 hasta dahil edildi. LidoPara grubuna 1mg/kg lidokain+10 mg/kg parasetamol, Lido grubuna 1mg/kg Lidokain uygulandı. Postoperatif 0, 2, 4 ve 24. saatlerde istirahat ve yutma boğaz ağrısı ve ses kısıklığı 4 puanlı bir skala ile değerlendirildi.

Bulgular: Hastaların demografik verileri benzerdi (P>0,05). İki grup arasında postoperatif 0, 2, 4 ve 24. saatlerde istirahat ve yutma boğaz ağrısı yönünden istatistiksel olarak anlamlı farklılık yoktu. Postoperatif 4. ve 24. saatte her iki grupta da ses kısıklığı yoktu.

Sonuç: Kombine parasetamol ve lidokainin postoperatif istirahat ve yutma esnasındaki boğaz ağrısını tek başına lidokain ile benzer şekilde etkilediği görüldü.

Anahtar kelimeler: Genel anestezi, Laryngeal maske airway, Lidokain, Parasetamol, Boğaz ağrısı

How to cite/Atıf için: Arıcan Ş, Yılmaz R, Hacıbeyoğlu G, Bilge A, Yaman R, Topal A, Tuncer S. Comparison of intravenous lidocaine and intravenous lidocaine/paracetamol in prevention of postoperative sore throat frequency after laryngeal mask insertion. J Surg Med. 2020;4(11):1023-1026.

Introduction

Supraglottic airway devices (SGDs) are a group of airway devices that can be inserted into the pharynx to allow ventilation, oxygenation, and administration of anesthetic gases, without the need for endotracheal intubation. The SGDs used most commonly in the operating room are the laryngeal mask airways (LMAs).

Postoperative sore throat (POST) is one of the most common and predictable complications in patients receiving general anesthesia [1]. The incidence of POST can reach 70% after administration of general anesthesia in patients with LMAs for the safety of airway [2]. POST symptoms peak postoperatively within 2 to 6 hours [3].

In the studies, it has been attempted to reduce the incidence and severity of POST with both non-pharmacological and pharmacological methods [4]. Lidocaine is an agent, used with different methods and concentrations against POST, in which it provides a significant reduction [5].

Paracetamol is a potent analgesic and antipyretic agent used for short-term treatment of acute postoperative pain both in adults and children [6]. It significantly decreases the postoperative need for opioids in pain management [7-9]. However, the number of studies investigating its effects on the incidence of POST is limited. In addition, no study investigating effects of the combination of intravenous lidocaine and paracetamol on the incidence of POST was found.

The objective of this study was to compare the effects of systemic lidocaine and systemic lidocaine-paracetamol combination on POST in patients who underwent general anesthesia with laryngeal mask airway.

Materials and methods

The study was conducted after receiving the necessary approval from the Ethics Committee of Necmettin Erbakan University (2019/2037). In this study, medical records of patients undergoing general anesthesia at the University Hospital between January 2018 and November 2018 were retrospectively reviewed. The eligible participants were accepted as adult patients aged over 18 years who had a physical status of ASA I-III, and underwent elective inguinal hernia surgery lasting shorter than 2 hours, under general anesthesia. Patients with a known allergy to lidocaine and paracetamol, pregnant women, patients who underwent emergency surgery, those have experienced sore throat, upper respiratory tract infection within the last month before the surgery, patients at a high risk for aspiration of gastric content (diabetes, gastroesophageal reflux, body mass index (BMI) > 35), and patients with expected airway difficulties requiring tracheal intubation were excluded from the study.

We calculated that a total of 80 patients (40 patients for each group) would be needed to compare the two groups with 80-90% power, 5% type I error level, and 25% effect size with the *F* test. The sample size needed was estimated from a pilot test. A total of 80 patients were included in the study. Demographic data of the patients (age, height, ASA, gender, weight, Mallampati scores) were recorded and the patients were divided into two groups. All patients were administered 1 mg kg^{-1} IV lidocaine after routine monitoring (peripheral blood pressure, electrocardiography, peripheral oxygen saturation). Both lidocaine (Group Lido) and lidocaine-paracetamol (Group LidoPara) groups were administered transversus abdominis plane block for postoperative analgesia. About 30 min before the end of surgery, patients in the LidoPara group received IV paracetamol (10 mg kg^{-1}). Anesthetic induction was provided with the infusion of propofol (2 mg kg^{-1}) and remifentanil (0.3 µg kg^{-1} min^{-1}). Anesthesia maintenance was provided with desflurane and remifentanil. Neuromuscular blockers were not used in any of the patients. Anesthetic depth was decided according to jaw laxity and eyelash reflex. Patients' airway was provided with classical LMAs, which were inserted according to the instructions of the manufacturer by an experienced anesthesiologist. LMAs size was determined based on the patients' weight in line with the recommendations of the manufacturer.

LMAs were inflated until intracuff pressure, measured with a hand-held pressure gauge, reached 30-44 mmHg. An additional inflation of 5 mL was allowed if an air leakage was detected in 20 cmH_20 (14.7 mmHg) positive-pressure ventilation [10]. After the end of anesthesia, LMA was removed when adequate spontaneous ventilation was established.

Whether LMAs insertion was successful at the first attempt and duration of LMA insertion (minute) was recorded. If LMAs insertion failed after 2 attempts, a different-size LMA was inserted, and whether it was successful was recorded. Endotracheal intubation was performed if LMA insertion failed after 2 attempts. Ventilation setup was made and positive-pressure ventilation was applied after successful LMA insertion (As to provide tidal volume: 6-8 mL/kg; end tidal CO_2: 35-40 mmHg and positive end expiratory pressure (PEEP): 5-8 cm/H_2O). LMA insertion was evaluated with a scale (very easy, easy, difficult, very difficult, impossible) [11].

Complications during and after LMAs insertion (aspiration and regurgitation, hypoxia; peripheral oxygen saturation < 90% with pulse oximeter; bronchospasm, laryngospasm, airway obstruction, cough, gagging, hiccups, subglottic airway device bloodstain, tongue, lips and teeth traumas) were recorded.

Sore throat and hoarseness of the patients were also investigated and recorded at the postoperative 0^{th}, 2^{nd}, 4^{th}, and 24^{th} hours. Sore throat was assessed with a scale as 0: no sore throat; 1: minimal sore throat (complaints of sore throat only on question); 2: moderate sore throat (accompanying sore throat); and 3: severe sore throat (voice change or hoarseness related to sore throat). Hoarseness was evaluated with a scale as 0: no hoarseness; 1: minimal hoarseness (minimal change in the quality of speech given by the patient when questioned); 2 moderate hoarseness (a disturbing change in the speech quality with the patient's view); and 3: severe hoarseness (great change in the quality of speech that was perceived by the observer) [12,13].

Statistical analysis

Data obtained were analyzed using SPSS 18.00 software (Statistical Package for Social Sciences Inc Chicago, IL). Descriptive statistical methods (number, percentage, mean and standard deviation) were used in the evaluation of qualitative

data, and the Pearson chi-square test, in comparison of qualitative data. Conformity of the data to normal distribution was tested with the Kolmogorov-Smirnov test. In the evaluation of quantitative data showing normal distribution, the independent samples t-test was used. A value of $P<0.05$ was considered statistically significant.

Results

A total of 80 patients were included in the study. The mean age was 46.8 (16.9) years in Group LidoPara, and 48.0 (6.5) years in Group Lido ($P=0.749$). Of the patients in Group LidoPara, 30% (n=12) were female and 70% (n=28) were male, while of the patients in Group Lido these rates were 22.5% (n=9) and 77.5% (n=31), respectively. No statistically significant difference was found between both groups in terms of gender ($P=0.446$) and demographic data (Table 1).

The doses of propofol and remifentanil used in the induction of anesthesia were 147.0 (45.4) mg / 17.0 (9.2) µg in Group Lido and 131.8 (40.4) mg / 19.2 (7.1) µg in Group LidoPara respectively ($P=0.121$, $P=0.229$).

The duration of LMA insertion was 1.7 (0.5) minute in Group LidoPara and 1.5 (0.6) minute in Group Lido. No statistically significant difference was found between the groups. Evaluation and success of LMA insertion are given in Table 2.

Table 1: Comparison of demographic data between groups

	Group LidoPara (n=40) mean (SD)/%	Group Lido (n=40) mean (SD)/%	*P*-value
Age (years)	46.8 (16.9)	48.0 (16.5)	0.749
Gender (Female)	12 (30%)	9 (22.5%)	0.446
Weight (kg)	77.2 (17.3)	75.3(13.6)	0.592
Height (cm)	170.7 (10.3)	171.8(8.3)	0.610
ASA I	13 (32.5%)	15 (37.5%)	0.246
II	25 (62.5%)	19 (47.5%)	
III	2 (5%)	6 (15%)	
Mallampati score I	5 (12.5%)	10 (25%)	0.232
II	30 (75%)	23 (57.5%)	
III	5 (12.5)	7 (17.5%)	
MAP(mmHg)	97.3 (12.6)	93.4 (14.7)	0.218
Heart Rate (beats/min)	80.4 (14.1)	75.6 (15.1)	0.152
SpO_2 (%)	96.1 (2.3)	96.6 (2.3)	0.338

MAP: Mean Arterial Pressure, ASA: American Society of Anesthesia score, SpO_2: Peripheral Oxygen Saturation

Table 2: Evaluation of LMA insertion and comparison of the success of insertion between groups

	Group LidoPara (n=40)/%	Group Lido (n=40)/%	*P*-value
LMA placement success			
First Placement Successful	30 (75%)	33 (82.5%)	0.807
Second Placement Successful	5 (12.5%)	4 (10%)	
Different Size LMA First Placement Successful	2 (5%)	1 (2.5%)	
Endotracheal Intubation	3 (7.5%)	2 (5%)	
Evaluation of LMA placement			
Very Easy	27 (67.5%)	25 (62.5%)	0.865
Easy	8 (20%)	10 (25%)	
Difficult	3 (7.5 %)	4 (10%)	
Very Difficult	0 (0 %)	0(0 %)	
Impossible	2 (5%)	1 (2.5%)	
LMA size			
3	2 (5%)	1 (2.5%)	0.436
4	16 (40%)	22 (55%)	
5	22 (55%)	17 (42.5%)	
AIR VOLUME (ml) (Average 30-44 mmHg pressure)	26.4 (5.3)	24.4 (4.7)	0.091

Complications developed during and after LMA insertion were evaluated, and cough was observed in 1 (2.5%) patient, hiccups in 3 (7.5%) patients and subglottic airway device bloodstain in 2 (5%) patients in Group LidoPara, whereas cough was observed in 1 (2.5%) patient, hiccups in 1 (2.5%) patient and subglottic airway device bloodstain in 1 (2.5%) patient in Group Lido ($P=0.634$).

Minimal hoarseness was found in 1 (2.5%) patient in Group LidoPara and 3 (7.5%) patients in Group Lido at the postoperative 0^{th} hour ($P=0.305$). While no hoarseness was observed in Group LidoPara, minimal hoarseness was found in 3 patients in Group Lido at the postoperative 2^{nd} hour ($P=0.07$). No hoarseness was observed in both groups at the postoperative 4^{th} and 24^{th} hours.

The overall incidence of sore throat in groups LidoPara and Lido were 9 (22.5%), and 13 (32.5%), respectively. No statistically significant difference was found between both groups in terms of resting and swallowing sore throat at the postoperative 0^{th}, 2^{nd}, 4^{th}, and 24^{th} hours (Table 3).

Table 3: Comparison of postoperative resting and swallowing sore throat

	Group LidoPara (n=40)	Group Lido (n=40)	*P*-value
Overall incidence	9 (22.5%)	13(32.5%)	0.317
Sore Throat at Rest			
Postoperative 0 h (none/mild/moderate/severe)	34/2/4/0	32/6/2/0	0.256
Postoperative 2 h (none/mild/moderate/severe)	33/3/4/0	30/8/2/0	0.214
Postoperative 4 h (none/mild/moderate/severe)	34/5/1/0	36/3/1/0	0.757
Postoperative 24 h (none/mild/moderate/severe)	40/0/0/0	39/1/0/0	0.314
Sore Throat at Swallowing			
Postoperative 0 h (none/mild/moderate/severe)	33/6/1/0	34/3/3/1	0.365
Postoperative 2 h (none/mild/moderate/severe)	30/7/3/0	25/14/1/0	0.150
Postoperative 4 h (none/mild/moderate/severe)	30/7/3/0	30/8/2/0	0.875
Postoperative 24 h (none/mild/moderate/severe)	38/2/0/0	39/1/0/0	0.556

Discussion

In the present study, no difference was observed between the combined use of intravenous paracetamol and lidocaine, and lidocaine alone in terms of reducing the overall incidence of POST. Combined paracetamol and lidocaine were found to affect sore throat during postoperative rest and swallowing in a similar way to lidocaine alone.

POST is a complication that might occur after insertion of LMA on patients undergoing general anesthesia and is related to mucosal and mechanical damage due to friction. The pressure between the device and LMA cuff pressure may cause irritation in the pharyngeal mucosa during insertion and administration of anesthesia, which lead to inflammation and trigger several postoperative symptoms, such as sore throat, dysphagia, and dysphonia [1]. Although many attempts have been made to reduce the incidence of POST, its prevention has proven impossible [5].

Multimodal approaches for postoperative pain management have been investigated [9,14], but research on the preventive effects of using two different pharmacological modalities on POST is limited.

Intravenous lidocaine has analgesic, antihyperalgesic and anti-inflammatory properties [15]. The exact mechanism of the prevention of a sore throat by I.V. lidocaine is not clearly known. With the use of lidocaine, trachea will not be stimulated during intubation, which may result in less trauma and inflammation of the trachea. The effect of I.V. lidocaine on POST may be attributed to the lack of stimulation of the laryngeal or tracheal mucosa [16]. The mechanism of Lidocaine when alternating neuronal signal conduction, is blockage of the voltage gated Na+ channel, which is responsible for signal propagation. At a certain level of blockade, the postsynaptic nervous membrane would not be able to be depolarized, and action potential would fail to deliver [17].

The use of lidocaine to prevent postoperative sore throat is a common clinical practice. A meta-analysis by Cochrane Collaboration states that topical and systemic lidocaine treatment generally reduces the risk of POST [5].

Paracetamol has an analgesic effect caused by inhibition of cyclooxygenase. Paracetamol is more effective than placebo in reducing symptoms of acute sore throat [18]. When used for postoperative pain, it is usually administered before the procedure [19,20]. Considering that the maximum analgesic effects of paracetamol is reached 1-2 hours after infusion [20], paracetamol was infused about 30 min before the end of surgery in our study to prevent POST.

Based on the fact that the POST mechanism is an inflammatory process due to mucosal and mechanical damage after LMA placement [1], paracetamol was administered in combination with lidocaine in our study. In a similar study, it was shown that combined infusion of paracetamol and dexamethasone reduced the incidence of POST without serious side effects. The protective effects of combined paracetamol and dexamethasone on POST continued for up to 6 hours postoperatively. It reduced the resting POST incidence at the 1st and 6th postoperative hours by 15% and 17%, respectively [21].

Our study had a lower incidence of POST than other studies [22,23]. In our study, the overall incidence of POST in Group LidoPara was 10% lower than in Group Lido. Although the incidence of POST was lower in the LidoPara Group compared to the Lido Group, this decrease was not statistically significant. The severity of POST was assessed at rest and swallowing. Only mild to moderate sore throat was observed in all patients. There was no significant difference between the two groups during rest and swallowing. In our study, no difference between the groups was attributed to the use of lower doses of paracetamol compared to the literature.

Some studies have reported that tracheal cuff pressure may also affect POST formation. After placement of LMAs, the cuff should be inflated to a target cuff pressure of about 44 mmHg or to the minimum pressure required to form an adequate seal [10,24]. In our study, LMA placement method and LMA cuff pressure were standardized in all patients. A superior aspect of this study was that the abdominal plan block was performed in all patients with the assumption that the POST pain score may vary depending on postoperative analgesics given at the end of the operation.

Limitations

This study has several limitations. First, the effects of paracetamol alone could not be evaluated. Second, comparison with a control group could not be made.

Conclusions

Based on many studies reporting benefits of total and systemic lidocaine therapy in reduction of postoperative sore throat, in the present study comparing the effects of the use of lidocaine alone and in combination with paracetamol, the incidence of POST in resting and swallowing was low with both applications, and both methods produced similar results. Postoperative hoarseness was minimal in both groups.

Further high-quality and randomized controlled studies on the use of topical and systemic lidocaine in reduction of sore throat will be useful. Other drug therapies such as steroids and non-steroidal anti-inflammatory drugs can be more actively studied.

References

1. El-Boghdadly K, Bailey CR, Wiles MD. Postoperative sore throat: A systematic review. Anesthesia. 2016;71:706-17.
2. Dorsch JA, Dorsch SE. Supraglottic Airway devices. In: Dorsch JA, Dorsch SE, editors. Understanding Anaesthesia Equipment. 5th ed. Philadelphia: Lippincott Williams and Wilkins. 2008:461-519.
3. Jaensson M, Gupta A, Nilsson UG. Risk factors for development of postoperative sore throat and hoarseness after endotracheal intubation in women: A secondary analysis. AANA Journal. 2012;80:67-73.
4. Jaensson M, Olowsson LL, Nilsson U. Endotracheal tube size and sore throat following surgery: a randomized-controlled study. Acta Anaesthesiol Scand. 2010;54:147-53.
5. Tanaka Y, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. Cochrane Database Syst Rev. 2015;7:Cd004081.
6. Duggan ST, Scott LJ. Intravenous paracetamol (acetaminophen). Drugs. 2009;69: 101–13.
7. Jebaraj B, Maitra S, Baidya DK, Khanna P. Intravenous paracetamol reduces postoperative opioid consumption after orthopedic surgery: a systematic review of clinical trials. Pain Res Treat. 2013:402510.
8. Olonisakin RP, Amanor-Boadu SD, Akinyemi AO. Morphine sparing effect of intravenous paracetamol for post operative pain management following gynaecological surgery. Afr J Med Med Sci. 2012;41:429–36.
9. Gehling M, Arndt C, Eberhart LH, Koch T, Krüger T, Wulf H. Postoperative analgesia with parecoxib, acetaminophen, and the combination of both: a randomized, double-blind, placebo-controlled trial in patients undergoing thyroid surgery. Br J Anaesth. 2010;104:761–7.
10. Wong DT, Tam AD, Mehta V, Raveendran R, Riad W, Chung FF. New supraglottic airway with built-in pressure indicator decreases postoperative pharyngolaryngeal symptoms: a randomized controlled trial. Can J Anaesth. 2013;60:1197.
11. Hermite JL, Dubout E, Bouvet S, Bracoud LH, Cuvillon P, Coussaye JE et al. Sore throat following three adult supraglottic airway devices: A randomised controlled trial. Eur J Anaesthesiol. 2017;34:417-24.
12. Ebneshahidi A, Mohseni M. Strepsils tablets reduce sore throat and hoarseness after tracheal intubation. Anesth Analg 2010;111:892–4.
13. Aydın GB, Ergil J, Polat R, Sayın M, Akelma FK. Comparison of Siccoral spray, Stomatovis gargle, and Strefen lozenges on postoperative sore throat. J Anesth. 2014;28:494–8
14. Rasmussen ML, Mathiesen O, Dierking G, Christensen BV, Hilsted KL, Larsen TK, et al. Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: a preliminary study. Eur J Anaesthesiol. 2010;27:324–30.
15. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication?. Anesthesiology. 2000;93:858–75.
16. Takekawa K, Yoshimi S, Kinoshita Y. Effects of intravenous lidocaine prior to intubation on postoperative airway symptoms. J Anesth. 2006;20:44–7.
17. Kumar A, Seth A, Prakash S, Deganwa M, Gogia AR. Attenuation of the hemodynamic response to laryngoscopy and tracheal intubation with fentanyl, lignocaine nebulization, and a combination of both:A randomized controlled trial. Anesth Essays Res. 2016;10:661– 6.
18. Thomas M, Del Mar C, Glasziou P. How effective are treatments other than antibiotics for acute sore throat? Br J Gen Pract. 2000;50:817–20
19. Mathiesen O, Rasmussen ML, Dierking G, Lech K, Hilsted KL, Fomsgaard JS, et al.. Pregabalin and dexamethasone in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand. 2009;53:227–35.
20. Ohnesorge H, Bein B, Hanss R, Francksen H, Mayer L, Scholz J, et al. Paracetamol versus metamizol in the treatment of postoperative pain after breast surgery: a randomized, controlled trial. Eur J Anaesthesiol. 2009;26:648–53.
21. Lee J, Park HP, Jeong MH, Kim HC. Combined intraoperative paracetamol and preoperative dexamethasone reduces postoperative sore throat: a prospective randomized study. J Anesth. 2017;31:869-77.
22. Christensen AM, Willemoes-Larsen H, Lundby L, Jakobsen KB. Postoperative throat complaints after tracheal intubation. Br J Anaesth. 1994;73:786–7.
23. Canbay O, Celebi N, Sahin A, Celiker V, Ozgen S, Aypar U. Ketamine gargle for attenuating postoperative sore throat. Br J Anaesth. 2008;100:490–3.
24. Seet E, Yousaf F, Gupta S, Subramanyam R, Wong DT, Chung F. Use of manometry for laryngeal mask airway reduces postoperative pharyngolaryngeal adverse events: a prospective, randomized trial. Anesthesiology 2010;112:652.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1027-1030.
DOI: 10.28982/josam.805122

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

The relationship between body mass index and clinical complications among patients undergoing myomectomy

Myomektomi olan hastalarda vücut kitle indeksi ve klinik komplikasyonlar arasındaki ilişki

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Ethics Committee Approval: The study was conducted after receiving the approval from the Research Ethics Committee of Istanbul Medeniyet Univercity Goztepe Training Hospital (Permission granted /CAAE number: 21.01.2020, Decision no: 2020/0013). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma İstanbul Medeniyet Üniversitesi Göztepe Eğitim Araştıma Hastanesi Etik Kurulu'ndan (Tarih: 21.01.2020 karar no: 2020/0013) gerekli onay alındıktan sonra gerçekleştirildi. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Obesity, a chronic disease which significantly causes disability, is a critical public health concern all over the world. A possible correlation between the complications of uterine leiomyoma and obesity has been recently considered, but no definitive conclusions have been made. The purpose of this study is to investigate the association between body mass index (BMI) and clinical complications among the patients undergoing myomectomy to see whether BMI can affect the clinical outcomes and complications of women with uterine leiomyoma.

Methods: This retrospective cohort study was conducted on the patients undergoing abdominal myomectomy for uterine leiomyoma from September 2016 to December 2019. A total of 287 patients undergoing abdominal myomectomy participated in the study. The patients were divided into two groups based on BMI: BMI <30 kg/m^2 (Group 1) and BMI ≥30 kg/m^2 (Group 2).

Results: The mean ages of the patients in Groups 1 and 2 were 37.08(6.17) years and 37.53 (5.98) years, respectively. Among all, 196 patients had a BMI of <30 kg/m^2 and 91 patients had a BMI of ≥30 kg/m^2. There was no statistically significant difference between the two groups in terms of surgical indication (P=0.970), leiomyoma localization (P=0.793), leiomyoma size (P=0.335), the mean number of fibroids removed (P=0.537), postoperative pathological diagnosis (P=0.189), complications, and the mean duration of hospital stay (P=0.249). There was a statistically significant difference between the two groups in terms of BMI (P<0.001), ALT (P=0.039), and Urea (P=0.018).

Conclusion: BMI did not adversely affect the clinical outcomes of patients undergoing abdominal myomectomy. Obesity is not regarded as a risk factor for poor outcomes.

Keywords: Body mass index, Uterine leiomyoma, Abdominal myomectomy, Obesity

Öz

Amaç: Obezite, tüm dünyada önemli ölçüde engelliliğe ve kritik bir halk sağlığı sorununa neden olan kronik bir hastalıktır. Son zamanlarda uterin leiomyom ve obezite komplikasyonları arasında olası bir ilişki düşünülmüştür, ancak kesin sonuçlara varılmamıştır. Bu çalışmanın amacı, myomektomi olan hastalarda vücut kitle indeksi (VKİ) ve klinik komplikasyonlar arasındaki ilişkiyi araştırmak ve VKİ'nin uterus leiomyomu olan kadınların klinik sonuçlarını ve komplikasyonlarını etkileyip etkilemediğini görmektir.

Yöntemler: Bu retrospektif kohort çalışmaya, Ekim 2016 ve Aralık 2019 arasında uterin leiomyom tanısı alan ve abdominal myomektomi geçiren hastalar alındı. Çalışmaya abdominal miyomektomi uygulanan 287 hasta katıldı. Hastalar VKİ'ye göre iki gruba ayrıldı: VKİ <30 kg/m2 (Grup 1) ve VKİ 30 kg/m2 (Grup 2).

Bulgular: Birinci gruptaki hastaların ortalama yaşı 37,08 (6,17), 2. gruptaki hastaların ortalama yaşı ise 37,53 (5,98) olarak bulundu. VKİ 30 kg/m2 altında olan hasta sayısı 196, VKİ 30 kg/m2 üzerinde olan hasta sayısı ise 91'di. Cerrahi endikasyon (P=0,970), leiomyom lokalizasyonu (P=0,793), leiomyoma boyutu (P=0,335), çıkarılan ortalama myom sayısı (P=0,537), postoperatif patolojik tanı (P=0,189), komplikasyonlar ve ortalama hastanede kalış süresinde (P=0,249) iki grup arasında istatistiksel olarak anlamlı fark yoktu. İki grup arasında VKİ (P<0,001), ALT (P=0,039) ve Üre (P=0,018) açısından istatistiksel olarak anlamlı fark vardı.

Sonuç: VKİ, abdominal myomektomi geçiren hastalarda klinik sonuçları olumsuz bir şekilde etkilemedi. Myomektomi geçiren hastalar arasında obezite, sonuçlar açısından bir risk faktörü olarak değerlendirilmemektedir.

Anahtar kelimeler: Vücut kitle indeksi, Uterin leiomyom, Abdominal myomektomi, Obezite

How to cite/Atıf için: Gürbüz T, Yardımcı OD, Udum S, Günay T. The relationship between body mass index and clinical complications among patients undergoing myomectomy. J Surg Med. 2020;4(11):1027-1030.

Introduction

Uterine leiomyomas, also called myomata or fibroids, are benign pelvic tumors which are common among women [1,2]. The uterine fibroids (UFs) are the monoclonal tumors of the smooth muscle cells of the myometrium, which are composed of large extracellular matrix containing fibronectin, proteoglycan, and collagen [2,3]. The severe symptoms of leiomyomas are anemia and prolonged, irregular menstrual bleeding despite their benign nature. Other disorders such as infertility, recurrent abortion, and preterm labor may occur [4]. The risk factors for UFs are family history, black ethnicity, obesity, and parity [1,3].

Myomectomy is the common surgical method for those who want to have children or retain their uterus. The classic laparotomy incision, laparoscopy, or the robotic approach can be used for myomectomies [5].

Obesity is a chronic disease that causes significant disability and constitutes a critical public health concern all over the world. A correlation between obesity and uterine fibroids has been recently considered, but there are no definitive conclusions [6].

There are various obese patients who undergo surgeries for UFs among studies [7,8]. A study focusing on the outcome and feasibility of laparoscopy showed that 24% of the patients who underwent UF surgery were overweight or obese. It has been reported that BMI may significantly affect the development of fibroids [9]. The risk of fibroids among women weighing 70 kg is three times as much as that among women weighing 50 kg [10].

In this study, we investigated the association between Body mass index (BMI) and clinical complications among patients undergoing myomectomy.

Materials and methods

This retrospective cohort study was conducted on patients who underwent abdominal myomectomy for uterine leiomyoma from September 2016 to December 2019, at Istanbul Medeniyet University Goztepe Training Hospital Gynecology & Obstetrics Clinic. This study was approved by the university /local human research ethics committee and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was carried out with the permission of Research Ethics Committee of Istanbul Medeniyet University Goztepe Training Hospital (Permission granted /CAAE number: 21.01.2020, Decision no: 2020/0013). Patients who had been diagnosed with UFs and operated in our hospital were included in our study. All patients were in the reproductive age (15-49 years). Laparoscopic cases and those who underwent hysterectomy were excluded.

The subjects were divided into two groups based on BMI: BMI <30 kg/m^2 (Group 1) and BMI ≥30 kg/m^2 (Group 2). BMIs were calculated based on the height and weight of the patients during the operation. In addition to the demographic information such as age, gravida, parity, smoking, the complaints (bleeding, pain, infertility, and pelvic pressure), preoperative and postoperative hemogram parameters (Hb: hemoglobin; WBC: white blood cell; PLT: Platelet) and preoperative ALT: alanine transaminase, AST: aspartate transaminase, Urea, Creatinine values, pre-operative endometrial biopsy, fibroid localization (subserous, intramural or submucous), fibroid size, postoperative pathology result (leiomyoma or leiomyosarcoma), hospital stay, complications if any (bleeding, hematoma, ileus, postoperative fever (>38˚), wound infection and bleeding requiring transfusion) were recorded.

When the sample size was calculated with GPower 3.1 (http://www.gpower.hhu.de/) program, the total sample size of two groups compared with the Student's t-test at the effect size of 2%, power of 95% and 0.05 type 1 error, was at least 262 patients.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 26.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistics. The normal distribution of the data was evaluated using the Kolmogorov-Smirnov test. To evaluate the differences between groups for normally and non-normally distributed variables, Independent student t-test and Mann-Whitney U test, respectively, were used. Chi-square test was applied to demonstrate the differences between groups for categorical variables.

Results

A total of 287 patients undergoing abdominal myomectomy participated in this study. The mean ages of Groups 1 and 2 were 37.08 (6.17) years and 37.53 (5.98) years, respectively. One hundred and ninety-six patients had a BMI of <30 kg/m^2 and 91 patients had a BMI of ≥30 kg/m^2.

Table 1 shows the clinical and demographic features of the patients. There was no statistically significant difference in the mean age, parity, smoking, preoperative Hb, postoperative Hb, AST, Platelet, WBC, Creatinine, and Preoperative Endometrium Biopsy between the two groups. Two groups were significantly different in terms of BMI (P<0.001), ALT (P=0.039), and Urea (P=0.018). BMI ≥30kg/m^2 indicated obesity.

Table 1: Clinical and demographic features of the patients

Parameters	Group 1 (BMI <30) (n=196)	Group 2 (BMI ≥ 30) (n=91)	*P*-value
Age	37.08 (6.17)	37.53 (5.98)	0.469**
Parity	1.54 (0.89)	1.67 (1.09)	0.410**
BMI (kg/m$^{2)}$	27.11 (2.20)	31.89 (1.81)	<0.001**
Smoking	8 (4.08%)	5 (5.49%)	0.592***
Preoperative Hb (g/dL)	11.84 (1.47)	12.03 (1.37)	0.301*
Postoperative Hb (g/dL)	10.38 (1.32)	10.44 (1.14)	0.632*
AST (U/L)	17.23 (6.90)	17.43 (5.33)	0.453**
ALT (U/L)	15.87 (9.71)	17.55 (8.77)	0.039**
PLT (x10^3/μL)	230.83 (59.79)	236.01 (59.99)	0.571*
WBC (x10^3/μL)	12.54 (3.60)	12.57 (3.62)	0.994*
Urea (mg/dL)	23.49 (10.10)	24.63 (7.01)	0.018**
Creatinine (mg/dL)	0.68 (0.11)	0.69 (0.06)	0.095**
Preoperative Endometrium Biopsy			
No	60 (30.6%)	34 (37.3%)	0.698***
Proliferative Endometrium	98 (50%)	40 (44%)	
Secretuary Endometrium	14 (7.1%)	8 (8.8%)	
Endometrial Polyp	16 (8.2%)	7 (7.7%)	
Epithelial	8 (4.1%)	2 (2.2%)	

ALT: alanine transaminase, Hb: hemoglobin, WBC: white blood cell, AST: aspartate transaminase, * Student t-test, ** Mann-Whitney U test, *** Chi-square test. Continuous variables are presented as mean (SD) and categorical variables are expressed as n (%).

Table 2 shows the features and complications of leiomyoma. Ninety-one patients (46.4%) in Group 1 and 39 patients (42.9%) in Group 2 had abnormal bleeding which was the most common surgical indication but there was no statistically significant difference between the two groups (P=0.970).

Table 2: Leiomyoma features and complications

Feature	Group 1 (BMI <30) (n=196)	Group 2 (BMI ≥ 30) (n=91)	*P*-value
Surgical indication			0.970**
Ache	35 (17.9%)	17 (18.7%)	
Infertility	31 (15.8%)	17 (18.7%)	
Abnormal bleeding	91 (46.4%)	39 (42.9%)	
Pelvic pressure	25 (12.8%)	12 (13.2%)	
Suspected malignancy	14 (7.1%)	6 (6.5%)	
Leiomyoma localization			0.793**
subserosal	66 (33.7%)	28 (30.8%)	
intramural	97 (49.5%)	45 (49.4%)	
submucosal	33 (16.8%)	18 (19.8%)	
Leiomyoma size (cm)	7.68 (3.82)	8.23 (4.13)	0.335*
Number of fibroids removed	3.08 (4.61)	3.21 (3.8)	0.537*
Postoperative pathological			0.189**
diagnosis	190 (97%)	86 (94.5%)	
Leiomyoma	2 (1%)	-	
Leiomyosarcoma	4 (2%)	5 (5.5%)	
Adenomyosis			
Complications			0.876**
Bleeding requiring	21 (10.7%)	12 (13.2%)	
transfusion	3 (1.5%)	1 (1.1%)	
Intraabdominal hematoma (≥4	6 (3%)	2 (2.2%)	
cm)	5 (2.5%)	3 (3.3%)	
Abdominal wall hematoma	7 (3.6%)	2 (2.2%)	
Postoperative fever (≥38º)	8 (4.1%)	2 (2.2%)	
Ileus	1 (0.5%)	1 (1.1%)	
Wound infection	1 (0.5%)		
Wound separation	1 (0.5%)	-	
Pelvic organ injury		1 (1.1%)	
Bowel damage			
Bladder damage			
Duration of hospital stay	2.35 (0.96	2.27 (1.04	0.249*
(day)			

* Mann-Whitney U test, ** Chi-square test. Continuous variables are presented as mean (SD and categorical variables are expressed as n (%).

Ninety-seven patients (49.5%) in Group 1 and 45 (49.4%) in Group 2 had intramural leiomyomas, which was the most common site, and leiomyoma localizations were similar between the two groups (P=0.793).

The mean size of leiomyoma was 7.68 (3.82) in Group 1 and 8.23 (4.13) in Group 2. The leiomyoma size did not show a statistically significant difference between the two groups (P=0.335). The mean number of fibroids removed was 3.08(4.61) in Group 1 and 3.21(3.8) in Group 2 (P=0.537). One hundred and ninety patients (97%) in Group 1 and 86 patients (94.5%) in Group 2 had leiomyomas, which was the most common postoperative pathological diagnosis (P=0.189). Twenty-one patients (10.7%) in Group 1 and 12 patients (13.2%) in Group 2 needed a blood transfusion (P=0.876). Results also show that the mean duration of hospital stay was 2.35(0.96) in Group 1 and 2.27(1.04) in Group 2 (P=0.249).

Discussion

The aim of this study was to investigate the association between body mass index (BMI) and clinical complications among patients undergoing myomectomy. UFs are common benign gynecological tumors of women at reproductive age. There is not enough information about the etiology of these neoplasms despite the significant issues which they cause for health [11].

Some studies have reported conflicting results about the relationship between BMI and UFs.

A study by Çinar et al. [12] found significant differences between the obese and non-obese groups in duration of hospital stay, gravidity, age, postoperative Hb, the diameter of fibroid (DOF), and complications. In their study, the obese group had higher complications including hemorrhage, postoperative fever, ileus wound, and infection, which is not consistent with our study results.

Wen et al. [13] also found that obese women were significantly exposed to both early and late complications, such as increased hospital stay. Non-serosal types were positive correlated with more complications, and the most common complication during the operation was hemorrhage in obese and non-obese women undergoing abdominal myomectomy. The uterine fibroids were larger in the obese women, who had more wound infection and ileus in the postoperative period, while our study found that the obese and non-obese women showed no significant difference in terms of the leiomyoma size, complications, and bleeding requiring transfusion.

There was a reverse association between BMI and sex hormone-binding globulin (SHBG) levels. A decrease of the SHBG caused an increase in the fraction of biological activity and free estrogen ratio [14,15]. He et al. [16] found lower levels of SHBG in obese individuals.

Burke et al. [17] and Smith et al. [18] found a positive association between central obesity, age, and parity, while our study results found no association between BMI, age and parity.

Some studies found an association between BMI and the risk of post-operative complications. Our study results are not consistent with the results of the studies which found an association between obesity and the risk of bleeding requiring transfusion [19], postoperative complications including infections [20], and the length of hospital stay [21].

Our study results are also not in line with the results of the study by Çoşkun et al. [22] who found a positive correlation between BMI, Alpha–feto protein (AFP) levels and DOF, and a negative correlation between BMI, length of hospital stay and postoperative Hb level, and an association between BMI, bleeding requiring blood transfusion and increased complications after surgery.

Amruta et al. [23] found a direct association between BMI and the risk of fibroids, which does not support our study results.

Our study results support the results of the study by Parazzini [24] who found no positive association between BMI and increased risk of UFs and differs from the study by Lumbiganon who found a positive association between UFs and obesity and the study by Wise et al. [25] who found 21% increase of the risk of UFs development with 10 kg increase of the body weight.

Siedhoff et al. [26] and Lamvu et al. [27] found more clinical usage of less invasive approaches such as laparoscopic myomectomy which can be performed safely for the obese patients.

George et al. [28] reviewed the data of 77 patients who underwent robotic myomectomy and showed no associations between BMI, estimated blood loss, length of hospital stay, or duration of procedure. Nawfal et al. [29] retrospectively reviewed 135 robotic-assisted hysterectomies and found no correlation between BMI and estimated blood loss, the length of

stay, or duration of procedure and no association between BMI and increasing complications.

Sparic et al. [30] reported that obesity was not consistently associated with the risk of leiomyomas. All the above-mentioned studies are consistent with our study results.

Limitations

Like any other studies, the present study has some limitations. The most important limitation of this study is that there was a statistically significant difference between the patients in the two groups in terms of ALT and Urea. This may affect the results of the study, and careful evaluation should be done considering this difference while evaluating the results. Different studies have found conflicting results.

Conclusion

According to the findings of the study, BMI did not adversely affect the clinical outcomes in patients who underwent abdominal myomectomy. Abdominal myomectomy may be a less invasive surgical procedure for both obese and non-obese patients with uterine leiomyoma. Obesity is not regarded as a risk factor for the poor outcomes in patients undergoing myomectomy.

References

1. Stewart EA. Uterine fibroids. Lancet. 2001;357(9252):293-8.
2. Sankaran S, Manyonda IT. Medical management of fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22(4):655-76.
3. Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril. 2007;87(4):725-36.
4. Sunkara SK, Khairy M, El-Toukhy T, Khalaf Y, Coomarasamy A. The effect of intramural fibroids without uterine cavity involvement on the outcome of IVF treatment: a systematic review and meta-analysis. Hum Reprod. 2010;25(2):418-29.
5. Matchar DB, Myers ER, Barber MW, Couchman GM, Datta S, Gray RN, et al. Management of uterine fibroids. Evid Rep Technol Assess (Summ). 2001;(34):1-6.
6. Ilaria S, Marci R. From obesity to uterine fibroids: an intricate network. Curr Med Res Opin. 2018;34(11):1877-79.
7. Shikora SA, Niloff JM, Bistrian BR, Forse RA, Blackburn GL. Relationship between obesity and uterine leiomyomata. Nutrition. 1991;7(4):251-5.
8. Camanni M, Bonino L, Delpiano EM, Migliaretti G, Berchialla P, Deltetto F. Laparoscopy and body mass index: feasibility and outcome in obese patients treated for gynecologic diseases. J Minim Invasive Gynecol. 2010;17(5):576-82.
9. Dandolu V, Singh R, Lidicker J, Harmanli O. BMI and uterine size: is there any relationship?. Int J Gynecol Pathol. 2010;29(6):568-71.
10. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol. 2008;22(4):571-88.
11. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect. 2003;111(8):1037-54.
12. Çinar M, Tokmak A, Güzel AI, Aksoy RT, Özer İ, Yilmaz N, et al. Association of clinical outcomes and complications with obesity in patients who have undergone abdominal myomectomy. J Chin Med Assoc. 2016;79(8):435-9.
13. Wen KC, Horng HC, Wang PH. Hemorrhage: A strong indicator for myomectomy-related complication. J Chin Med Assoc. 2016;79(8):413-4.
14. Dorgan JF, Reichman ME, Judd JT, Brown C, Longcope C, Schatzkin A, et al. The relation of body size to plasma levels of estrogens and androgens in premenopausal women. Cancer Causes Control. 1995;6(1):3-8.
15. Verkasalo PK, Thomas HV, Appleby PN, Davey GK, Key TJ. Circulating levels of sex hormones and their relation to risk factors for breast cancer: a cross-sectional study in 1092 pre- and postmenopausal women (United Kingdom). Cancer Causes Control: CCC. 2001;12(1):47-59.
16. He Y, Zeng Q, Dong S, Qin L, Li G, Wang P. Associations between uterine fibroids and lifestyles including diet, physical activity and stress: a case-control study in China. Asia Pac J Clin Nutr. 2013;22(1):109-17.
17. Burke GL, Jacobs Jr, Sprafka JM, Savage PJ, Sidney S, Wagenknecht LE. Obesity and overweight in young adults: The CARDIA study. Prev Med. 1990 Jul;19(4):476-88.
18. Smith DE, Lewis CE, Caveny JL, Perkins LL, Burke GL, Bild DE. Longitudinal changes in adiposity associated with pregnancy. The CARDIA Study. Coronary Artery Risk Development in Young Adults Study. JAMA. 1994;271(22):1747-51.
19. Harmanli O, Esin S, Knee A, Jones K, Ayaz R, Tunitsky E. Effect of obesity on perioperative outcomes of laparoscopic hysterectomy. J Reprod Med. 2013;58(11-12):497-503.
20. Osler M, Daugbjerg S, Frederiksen BL, Ottesen B. Body mass and risk of complications after hysterectomy on benign indications. Hum Reprod. 2011;26(6):1512-8.
21. Duchesne JC, Schmieg RE Jr, Simmons JD, Islam T, McGinness CL, McSwain NE Jr. Impact of obesity in damage control laparotomy patients. J Trauma. 2009;67(1):108-12;112-4.
22. Çoşkun B, Güzel A, Çoşkun B, Kokanalı D, Şimşir C, Doğanay M . The evaluation of association between body mass index and clinical parameters in women underwent myomectomy. J Health Sci Med / JHSM. 2020;3(1):47-50.
23. Amruta C, Shetty A, Pawaskar N, Desai S. Association between uterine leiomyoma with body mass index and parity in the women of coastal Karnataka, India. Int J Reprod Contracept Obstet Gynecol. 2020;9(2):740-3.
24. Parazzini F, Negri E, La Vecchia C, Chatenoud L, Ricci E, Guarnerio P. Reproductive factors and risk of uterine fibroids. Epidemiology. 1996;7(4):440-2.
25. Wise LA, Palmer JR, Spiegelman D, Harlow BL, Stewart EA, Adams-Campbell LL, et al. Influence of body size and body fat distribution on risk of uterine leiomyomata in U.S. black women. Epidemiology. 2005;16(3):346-54.
26. Siedhoff MT, Carey ET, Findley AD, Riggins LE, Garrett JM, Steege JF. Effect of extreme obesity on outcomes in laparoscopic hysterectomy. J Minim Invasive Gynecol. 2012;19(6):701-7.
27. Lamvu G, Zolnoun D, Boggess J, Steege JF. Obesity: physiologic changes and challenges during laparoscopy. Am J Obstet Gynecol. 2004;191(2):669-74.
28. George A, Eisenstein D, Wegienka G. Analysis of the impact of body mass index on the surgical outcomes after robot-assisted laparoscopic myomectomy. J Minim Invasive Gynecol. 2009;16(6):730-3.
29. Nawfal AK, Orady M, Eisenstein D, Wegienka G. Effect of body mass index on robotic-assisted total laparoscopic hysterectomy. J Minim Invasive Gynecol. 2011;18(3):328-32.
30. Sparic R, Mirkovic L, Malvasi A, Tinelli A. Epidemiology of Uterine Myomas: A Review. Int J Fertil Steril. 2016;9(4):424-35.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1031-1035.
DOI: 10.28982/josam.805389

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

An evaluation of cesarean rate in turkey by the Robson ten group classification system: How to reduce cesarean rates?

Türkiye'de sezaryen oranlarının Robson ten group classification sistemi ile değerlendirilmesi; sezeryan oranları nasıl azaltılır?

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Ethics Committee Approval: Approval was obtained from Institutional Education and Planning Committee of Etlik Zubeyde Hanim Women's Health Education and Research Hospital (10.04.2017/07). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Etlik Zübeyde Hanım Kadın Sağlığı Eğitim ve Araştırma Hastanesi Kurumsal Eğitim ve Planlama Kurulu'ndan onay alındı (10.04.2017/07). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Caesarean section (CS) rates, as is the case in the world, showed a significant increase in Turkey over the last decade. The World Health Organization has approved the Robson10-Group Classification System (TGCS) as a global standard to facilitate the analysis and comparison of CS rates. The present study aimed to analyze the TGCS to CS ratio in Turkey and determine CS reduction strategies.

Methods: The data for this retrospective cohort study were collected from the records of women who gave birth between January 1, 2011 and December 31, 2014 in a tertiary center. All data were obtained from the hospital database and patient files. The patients were grouped using TGCS. The contribution of each group to CS ratios was determined.

Results: Between 2011 and 2014, a total of 25,653 out of 63,476 deliveries were performed by CS. It was determined that the CS rate was 36% in 2011 and increased to 44% in 2014 (P<0.001). According to TGCS, the biggest contribution to this increase belonged to the Class 5 group. This group included 40.7% (2073/5096) of all patients undergoing cesarean section in 2011, 37.3% (2045/5480) in 2012, 27.1% (1859/6857) in 2013, and 36.8% (3025/8220) in 2014. While the rates of patients in Class 1,3 and 10 increased significantly over the years in which the study data were evaluated, rates in Class 2 and 4 decreased (P<0.001).

Conclusion: According to TGCS, strategies to prevent the increase in CS ratios should be developed to reduce Class 1, 3 and 5 patients. In this context, strategies to reduce CS ratios can be established through obstetric practices and the health policies of countries.

Keywords: Primary cesarean, Rising cesarean rates, Robson classification

Öz

Amaç: Sezaryen (CS) oranları tüm dünyada olduğu gibi Türkiye'de son on yılda ciddi bir artış göstermiştir. Dünya Sağlık Örgütü, CS oranlarının analizini ve karşılaştırılmasını kolaylaştırmak için Robson10- Group Sınıflandırma Sistemini (TGCS) küresel bir standart olarak onaylamıştır. Bu çalışmanın amacı Türkiye'de TGCS ile CS oranlarının analiz edilerek CS'yi azaltma stratejilerinin belirlenmesidir.

Yöntemler: Bu çalışma, 1 Ocak 2011 ve 31 Aralık 2014 tarihleri arasında üçüncü basamak bir merkezde doğum yapan kadınların kayıtları toplanarak yapılan retrospektif bir kohort çalışması olarak planlandı. Tüm veriler hastane veri tabanından ve hasta dosyalarından elde edildi. Hastalar TGCS kullanılarak gruplandırıldı. Her grubun CS oranlarına katkısı belirlendi.

Bulgular: 2010-2014 tarihleri arasında 63.476 doğumdan 25.653'ü sezaryen ile gerçekleştirildi. CS oranı yıllar içinde istatistiksel olarak anlamlı artış göstermekteydi (P<0,001). TGCS ye göre bu artışa en büyük katkı Sınıf 5 grubuna aitti. Bu grup, 2011 yılında sezaryen yapılan tüm hastaların %40,7'sini (2073/5096), 2012 yılında %37,3'ünü (2045/5480), 2013 yılında %27,1'ini (1859/6857), 2014 yılında ise %36,8'ini (3025/8220) oluşturmaktaydı. Çalışma verilerinin değerlendirildiği yıllar içinde Sınıf 1, 3 ve 10'daki hasta oranları anlamlı olarak artarken, Sınıf 2 ve 4'teki oranların azalmakta olduğu görüldü (P<0,001).

Sonuç: 2011'de %36 olan CS oranının, 2014'te %44'e yükseldiği saptanmıştır. TGCS ye göre CS oranlarındaki artışı önleme stratejileri Sınıf 1, 3 ve 5 hastalarının azaltılması yönünde geliştirilmelidir. Bu çerçevede CS oranlarını azaltacak stratejiler kadın hastalıkları doğum uzmanlarının uygulamaları ve ülkelerin sağlık politikalarının düzenlenmesiyle oluşturulabilir.

Anahtar kelimeler: Primer sezaryen, Artan sezaryen oranları, Robson sınıflaması

How to cite/Atıf için: Başer E, Kırmızı DA, Özdemirci Ş, Kasapoğlu T, Demirdağ E, Tapısız ÖL, Yalvaç ES, Tekin ÖM. An evaluation of cesarean rate in turkey by the Robson ten group classification system: How to reduce cesarean rates? J Surg Med. 2020;4(11):1031-1035.

Introduction

The first cesarean section (CS) was performed in 1881 by the German gynecologist Ferdinand Adolf Kehrer. It is without question that this procedure, which had almost always ended with a “dead mother and a dead fetus”, is now a life-saving operation that has almost always ended with a “surviving mother and a surviving baby” [1,2]. CS is one of the most common and increasing surgical interventions in the world today. A presentation on October 13, 2018 at Brazil FIGO World Congress, reported that CS rates doubled between 2000 and 2015 as a global fact. This increase was associated with many medical, legal and social factors [3-5]. The ideal cesarean ratio is a topic of discussion for women and healthcare professionals. The World Health Organization (WHO) states that a CS rate of 10-15% can be regarded acceptable. However, many countries cannot catch these rates. CS rates have been reported to be between 24.3 - 32% in North America, 32.3 - 44.3% in Latin America, and 19.6 - 26.9% in Western Europe. In Germany, while cesarean rates were 15.3% in 1991, this rate increased to 31.7% in 2012 [6]. CS applications in absolute CS indications such as contracted pelvis, placenta previa, malpresentations like transverse lie, brow and uterine rupture are life-saving for the fetus and mother. However, in the low-risk group, CS poses a greater risk than vaginal birth, causing an increase in blood transfusions, hysterectomy and maternal mortality [7]. With all these effects and the increase in costs, the increase in CS rates emerges as an important public health problem.

To investigate the mechanisms underlying the global rise in CS rates, it is essential to identify the risks of admission of patients to CS. Accordingly, the Robson Ten Group Classification System (TGCS), which is standard, reliable, consistent, and comparable, is adopted. This system provides optimal maternal and fetal epidemiological information and is considered an effective monitoring tool.

The present study aimed to determine the cesarean rates in Turkey according to the TGCS Robson, evaluate the possible causes of this popular trend in recent years and prevention strategies.

Materials and methods

The data for this retrospective cohort study were collected from the records of women who gave birth between January 1, 2011 and December 31, 2014 at University of Health Sciences Etlik Zubeyde Hanim Women’s Health Education and Research Hospital. All data were obtained from the hospital database and patient files. Approval from the Institutional Local Ethics Committee and Institutional Education and Planning Committee of Etlik Zubeyde Hanim Women’s Health Education and Research Hospital was obtained (10.04.2017/07).

To make the findings of the present study comparable to other studies, the sample group was limited to women whose gestational age was a minimum of 24 weeks or at least a 500-g birth. Relevant information, including previous births (nulliparous or multiparous), number of fetuses (single or multiple), gestational age at the time of delivery, fetal presentation (cephalic, breech, or transverse), and onset of labor and delivery (spontaneous, induced, or planned CS), were directly obtained from the review of the electronic and file medical record system. Also, patients' age, gestational week, fetal birth weights and cesarean indications were determined. All births included in the study were classified according to the modified Robson 10-group clinical criteria approved by the Society of Obstetricians and Gynecologists of Canada (SOGC) [8].

Robson Ten Group Classification System

All women were classified according to the following characteristics based on TGCS (Table 1): (1) parity (nulliparity / multiparity / multiparity with previous caesarean section), (2) the number of fetuses (single / multiple), (3) presentation of the fetus (cephalic / breech / transverse), (4) onset of labor (spontaneous/induced/prelabor caesarean section), (5) gestational age (term or preterm)

Nulliparity was defined as women who gave birth for the first time while multiparity was defined women who previously gave birth once or more. Term pregnancy was defined as those who gave birth at the 37th gestational week or later while preterm pregnancy was defined for those who gave birth before the 37th gestational week. Induction of labor was defined as the use of any medication, amniotomy or cervical balloon in women just before labor. Cesarean delivery rates were calculated by dividing the number of cesarean births by the number of births in the study population.

Table 1: The classification of Robson criteria description of all groups

1. Nulliparous, single cephalic, >37 wks. in spontaneous labor
2. Nulliparous, single cephalic, >37 wks., induced or CS before labor
3. Multiparous (excluding previous CS), single cephalic, >37 weeks in spontaneous labor
4. Multiparous (excluding previous CS), single cephalic, >37 weeks, induced or CS before labor
5. Previous CS, single cephalic, >37 weeks
6. All nulliparous breeches
7. All multiparous breeches (including previous cesarean section)
8. All multiple pregnancies (including previous cesarean section)
9. All abnormal lies or oblique lie (excluding breech presentation) (including previous cesarean section)
10. All singleton, cephalic, ≤36 weeks (including previous cesarean section)

Statistical analysis

The statistical package software SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data. Data was expressed as mean (standard deviation) and in percentages. Continuous variables were investigated using analytical methods (Kolmogorov-Simirnov / Shapiro-Wilk’s test) to determine whether or not they are normally distributed. If the numerical data was non-parametric, the Kruskal Wallis test was conducted, if it was parametric, a One-way ANOVA test was carried out and Bonferroni correction was used for the post-hoc assessment. Relationships between categorical variables were analyzed by the Chi-square test. $P<0.05$ was considered statistically significant.

Results

Over the specified 4-year period, 63,476 births were included in the study. The demographic characteristics of the patients are given in Table 2. The mean age of the patients was 26.9 (5.6) years, the mean weight of the newborns was 3182.3 (594.5) g, and the mean gestational week was 38.4 (2.3) weeks. It was observed that 59.6% of the labors were performed by vaginal delivery and 40.4% occurred by cesarean section. The cesarean rate increased statistically significantly over the years ($P<0.001$). It was determined that the CS rate was 36% in 2011

and increased to 44% in 2014 (Figure 1). There were no statistically significant differences in gender ratios by years (P=0.267). Multiparity rate was significantly higher in other groups in 2014 (P<0.001).

The differences in birth rates between TGCS by years are shown in Table 3 and Figure 2. Accordingly, the rates of cesarean patients in Class 1 and 3 (nulliparous and multiparous women with singleton cephalic full-term pregnancy, with spontaneous labor without previous CS) increased significantly over the years. Class 2 and 4 (nulliparous and multiparous women with singleton cephalic full-term pregnancy who required induction of labor or underwent pre-labour CS) decreased (P<0.001). The largest patient group was in Class 5 (Patients with previous cesarean history, singleton, 37th week of gestation and later, and underwent cesarean section). This group included 40.7% (2073/5096) of all the patients undergoing cesarean section in 2011, 37.3% (2045/5480) in 2012, 27.1% (1859/6857) in 2013, and 36.8% in 2014. (3025/8220). In Class 10 (preterm, singleton, cephalic), CS rates increased significantly over the years (P<0.001). All the cesarean indications are shown in Table 4. The most common indication was fetal distress while the second was cephalopelvic disproportion (CPD). These two indications have been increasing over the years. The third most common cause was macrosomia and it did not differ significantly over the years.

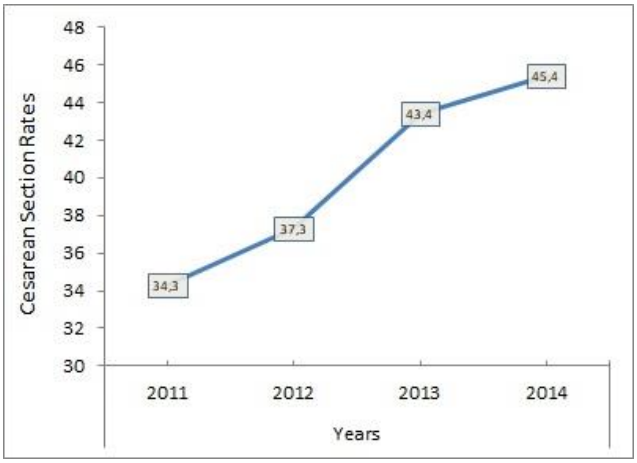

Figure 1: Demonstrating rising increment of overall C/S rates in years between 2011 and 2014

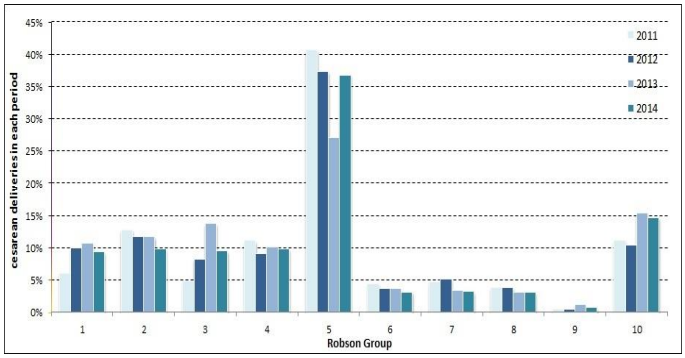

Figure 2: Contribution of each group in the Robson Ten Group Classification System to the overall caesarean section prevalence

Table 2: Demographic characteristics of the patients

	Total n=63476	2011 n=14878	2012 n=14685	2013 n=15803	2014 n=18110	*P*-value
Age (years)	26.9 (5.6)	26.5 (5.6)	26.6 (5.6)	26.9 (5.7)	27.2 (5.7)	<0.001
Birth weight (kg)	3182.3 (594.5)	3180.7 (590.3)	3203.5 (575.9)	3179.9 (614.3)	3163.2 (600.6)	<0.001
Birth week	38.4 (2.3)	38.4 (2.2)	38.4 (2.2)	38.4 (2.4)	38.3 (2.4)	<0.001
Birth type (%)						<0.001
VD	59.6 (37823)	9782 (65.7)	9205 (62.6)	8946 (56.6)	9890 (54.6)	
CS	40.4 (25653)	5096 (34.3)	5480 (37.4)	6857 (43.4)	8220 (45.4)	
Gender (%)						0.267
Male	51.6 (32737)	51.9 (7722)	51.1 (7504)	52.0 (8219)	51.3 (9292)	
Female	48.4 (30739)	48.1 (7156)	48.9 (7181)	48.0 (7584)	48.7 (8818)	
Multi/Nulli-parity (%)						<0.001
Multiparity	59.6 (38436)	62.3 (9272)	63.1 (9256)	58.3 (8743)	56.1 (11165)	
Nulliparity	40.4 (26016)	37.6 (5605)	36.8 (5409)	41.7 (6259)	43.9 (8743)	

Note: Unless otherwise specified, results are presented as mean (standard deviation). VD: vaginal delivery, CS: cesarean section.

Table 3: According to the Robson classification system, the changes in the cesarean rates in the groups according to the years

Year Robson Class	2011 % (n)	2012 % (n)	2013 % (n)	2014 % (n)	*P*-value
1	10 (310)	18.1 (544)	31.6 (730)	28.7 (767)	< 0.001
2	46.5 (651)	46.9 (641)	32.3 (802)	27.1 (805)	< 0.001
3	5.3 (244)	9.5 (453)	28.8 (945)	24.1 (781)	< 0.001
4	37.6 (564)	37.4 (501)	22.2 (697)	23.3 (804)	< 0.001
5	99.4 (2073)	99.7 (2045)	96.8 (1859)	100 (3025)	< 0.001
6	99.1 (224)	99.5 (204)	99.6 (249)	99.6 (260)	0.865
7	96.4 (242)	99.6 (284)	93.9 (231)	99.6 (262)	< 0.001
8	92.8 (194)	93.3 (209)	94.1 (209)	96.2 (253)	0.393
9	100 (25)	100 (29)	100 (79)	100 (57)	0.814
10	38.7 (569)	40.4 (570)	56.4 (1056)	63.3 (1206)	< 0.001
Total	34.3 (5096)	37.3 (5480)	43.4 (6857)	45.4 (8220)	

Data presented as % (n)

Table 4: Distribution of cesarean indication in our institution was different from Robson's criteria between 2011 and 2014

Indications	2011 n (%)	2012 n (%)	2013 n (%)	2014 n (%)	Total n (%)
Fetal distress	1652 (5.5)	1764 (6.0)	1920 (5.7)	2202 (5.8)	7538 (29.1)
CPD	628 (1.7)	908 (3.0)	1162 (3.3)	1515 (3.8)	4213 (16.3)
Non progressive labor& unsuccessful augmentation	458 (1.2)	464 (1.5)	510 (1.2)	948 (1.7)	2380 (9.2)
Macrosomia	588(1.6)	694 (2.3)	1178 (3.4)	1128 (2.5)	3858 (14.9)
Multiple pregnancy	488(1.3)	418 (1.4)	557 (1.3)	613 (1.4)	2076 (8.0)
Primipara aged	83(0.27)	88 (0.29)	64 (0.15)	94 (0.24)	329 (1.3)
In vitro fertilization pregnancies	65(0.10)	58 (0.19)	85 (0.21)	65 (0.15)	273 (1.1)
Owing worse obstetric history	74(0.10)	40 (0.13)	23 (0.05)	17 (0.02)	154 (0.6)
PPROM	554(1.5)	688 (2.3)	778 (2.1)	994 (2.6)	3014 (11.6)
FGR	135 (0.30)	18 (0.06)	33 (0.04)	36 (0.07)	222 (0.9)
Doppler abnormalities	-	-	78 (0.24)	71 (0.17)	149 (0.6)
Preeclampsia	136 (0.49)	160 (0.54)	208 (0.34)	183 (0.38)	687 (2.7)
Systemic disorders	-	-	-	165 (0.26)	165 (0.6)
Maternal anxiety	-	-	25 (0.07)	14 (0.01)	39 (0.2)
Vaginismus & previous vaginal surgical history	81 (0.08)	41 (0.13)	39 (0.10)	75 (0.13)	236 (0.9)
Condyloma	69 (0.12)	23 (0.06)	19 (0.03)	19 (0.03)	130 (0.5)
Placental pathologies	1/150	1/150	1/150	1/150	
Others	85 (0.23)	116 (0.39)	178 (0.46)	81 (0.16)	460 (1.8)
Total	5096	5480	6857	8220	25653

CPD: cephalopelvic disproportion, PPROM: preterm premature rupture of membranes, FGR: fetal growth restriction. Other indications included maternal eyes disorders, lumbosacral disc hernia, congenital hip dislocation, fetal anomalies, vulvar varis and oligohidramniosis

Discussion

The present study shows that there is a significant increase in the rate of CS in Turkey, as in the world. In the 4-year period in the study, the CS rate was 40.4%. It was seen that the biggest contributions to the increase in CS rates were in Robson 1-5 and Robson 10 groups.

According to the Organization for Economic Co-operation and Development (OECD) data in 2011, Turkey is one of the countries with the highest CS rate (47%) with Mexico and China. In Turkey, the cesarean rate was 6.99% in 1993 and increased to 21.2% in 2001, to 37% in 2008 and to 46.7% in 2011 [9]. The repeated or previous CS ratio was 14.1% and constituted the highest proportion of all CS cases in our institution. In the literature, it was seen that the contribution to increasing CS rates was mostly in Robson 5 (Previous CS, single cephalic,> 37 weeks). This result is not surprising since the primary CS rates from America to Ethiopia, France to Canada increased significantly and Robson 5 group increases these rates with the domino effect.

The absence of a decrease in this group was also related to the increase in patients in Groups 1 and 3 and the performance of vaginal birth after cesarean (VBAC) at lower rates than desired. 'Once cesarean, always cesarean' is generally accepted by obstetricians and patients. Previous large-scale studies have shown that complications associated with VBAC are rare [10]. This result did not increase the rate of vaginal deliveries. The lack of a vaginal delivery option for women with previous cesarean delivery had led to an increase in the number of patients who admitted to private hospitals for VBAC. This was thought to be related to the increased complication rates of VBAC [11]. Health policies also have a direct effect on this clinical outcome. In the USA, VBCA rates decreased from 28.3% to 9.2%, and transactions were excluded from the insurance coverage, stating that VBAC may be associated with fetal and maternal complications [12]. As stated by the American Congress of Obstetrician and Gynecologists (ACOG) in 2004, patients who had a cesarean section with a lower segment transverse incision should be monitored during the active labor and a vaginal delivery should be tried if i) the patient can be taken to cesarean section in case of emergency, ii) the patient has a clinically appropriate pelvis, iii) the fetus is less than 4000 grams, iv) no other uterine surgery or rupture anamnesis are present [13]. Robson-1 and Robson 3 groups also had a significant impact on increased CS rates [14-16]. Limiting CS in these groups have been shown as the most effective way to prevent proportional increases in CS.

Examining the Robson 1 group, it was seen that macrosomic fetus, fetal distress and CPD are the most common indications. In our hospital, pregnant women are evaluated with ultrasound before the onset of spontaneous labor or the induction of labor. If fetal macrosomia is suspected (estimated fetal weight ≥4000 grams or fetal abdominal circumference ≥360 mm), the patient is routinely taken to CS. Also, the diagnosis of non-reactive tocoordiographic findings was related to increased cesarean rate in Robson 1 [12]. In the present study, the highest CS indication was fetal distress. Other factors contributing to the increase in this group are socio-economic status, physicians' fear of litigation, and mother's preference for CS. Compared to less developed countries such as Latin countries, primary CS rates in economically developed countries seem to be higher CS [17]. The increase in social status is directly related to the fulfillment of the mother's desire and this is thought to contribute to the increase in CS rates. CS preference of patients can be attributed to reasons such as pregnancy at an advanced age, decreased parity, the increase in pregnancies caused by assisted reproductive techniques, and the fact that patients do not want to feel pain. An important rationale for those who advocate birth with elective cesarean is that this 'non-traumatic delivery' form can prevent intrapartum neurological damage and cerebral palsy (CP). However, data on the effects of delivery on acute and long-term neurological prognosis are limited and the results are contradictory. Despite a five-fold increase in the frequency of cesarean delivery, the fact that the CP prevalence has not changed much is a good example [18, 19]. In a study conducted in Turkey, it was seen that 59% of obstetricians give consent to the optional cesarean section [20]. However, optional cesarean delivery is not carried out in public hospitals. Therefore, the patients who contribute to Group 5 are mostly Group 1 patients who underwent CS in private hospitals [21].

Also, according to the analysis results, the ratio of the Robson 3 group to all CS deliveries increased 2.5-3.5-fold in each year from 2011 to 2014. One of the common reasons for CS in multiparous patients in Turkey is the simultaneous tubal ligation application. CS can also be preferred in advanced age and maternal and neonatal diseases. The Robson 6-7 (all nulliparous breeches and All multiparous breeches, including previous cesarean section) groups did not differ significantly over the years. External cephalic version is not carried out in our clinic. All pregnant women in breech presentation without vaginal cervical dilatation during vaginal examination are delivered with CS. Similarly, in patients in the Robson 8 group (multiple pregnancy), there were no significant changes in the CS rates. ACOG states that if it is the first twin (presenting fetus), breech or transverse labor, CS should be the first choice [22]. Also, many clinicians believe that the best form of delivery is cesarean for pregnancies complicated by two, three or more fetuses [23]. It was seen that Robson 10 (All singleton, cephalic, ≤36 weeks (including previous cesarean section) group increased significantly during the study. This can be associated with the increase in referrals and admissions to our hospital in the complications related to IVF treatments and prematurity.

Robson TGCS is a useful tool that can be applied freely by all healthcare institutions to facilitate the analysis of cesarean delivery rates and it is a guide for strategies according to the increases and decreases in CS rates. The strategies for the reduction of Robson 1-3 are influenced by the presence of country-specific factors. With the Health Transformation Law which was initiated in 2002 in Turkey, CS depending on the mother's request was banned. However, the CS rate was 21% in 2002 and increased to 50% in 2014. Another important detail is the increase in malpractice cases with high compensation up to 35% in parallel with this increase. This may have changed the attitudes, behaviors and practices of the specialists. The studies show that gynecologists and obstetricians act more defensively due to medico-legal fears compared to other branches [24]. This defensive approach has important effects on medical procedures

and the health system. For instance, the use of maneuvers such as the external cephalic version and vacuum-forceps applications appear to be significantly reduced [25-27]. The decrease in these practices may also cause beginner obstetricians to not be able to perform intervened deliveries. Similar problems were discussed in a study conducted in Egypt [27]. Another important point is that legal responsibility is not given to the midwives during the labor process. It was observed that midwives play a more active role in childbirth, as in countries such as Sweden, where low CS rates have been reported to be achieved [28]. Legal liability regulations addressing the midwives in Turkey are not available yet.

Limitations

Strength of the present study was that it examined all the births in the four-year-period in Turkey's second largest maternity hospital. The hospital database was suitable for classification and records were fully reachable. The data were evaluated with accuracy and transparency. In contrast, not evaluating other parameters related to CS such as maternal characteristics, neonatal characteristics and long-term complications of the operation can be considered as the limitations of our study.

Conclusions

With the present study, it was determined that the CS rate was 36% in 2011 and increased to 45% in 2014. TGCS data showed that the key point in reducing CS rates is to decrease Groups 1, 3 and 5. Considering the sociocultural and legal characteristics of Turkey, it was thought that gynecologists and obstetricians play a key role in the reduction of cesarean delivery rates. Implementation of corrective laws on personal rights of physicians, such as malpractice cases and economic concerns can be an effective measure for Turkey and countries with similar problems.

References

1. Todman D. A history of caesarean section: from ancient world to the modern era. Aust N Z J Obstet Gynaecol. 2007;47(5):357-61.
2. Sewell JE. Cesarean section–a brief history. A brochure to accompany an exhibition on the history of cesarean section at the National Library of Medicine. 1993;30.
3. Chong C, Su LL, Biswas A. Changing trends of cesarean section births by the Robson Ten Group Classification in a tertiary teaching hospital. Acta Obst Gyn Scand. 2012;91(12):1422-7.
4. Abdel-Aleem H, Shaaban OM, Hassanin AI, Ibraheem AA. Analysis of cesarean delivery at Assiut University Hospital using the Ten Group Classification System. Int J Gynecol Obstet. 2013;123(2):119-23.
5. Santas G, Santas F. Trends of caesarean section rates in Turkey. J Obstet Gynaecol. 2018;38(5):658-62.
6. Mylonas I, Friese K. Indications for and risks of elective cesarean section. Dtsch Arztebl Int. 2015;112(29-30):489.
7. Clark SL, Belfort MA, Dildy GA, Herbst MA, Meyers JA, Hankins GD. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol. 2008;199(1):36. e1-5.
8. Farine D, Shepherd D. Classification of caesarean sections in Canada: the Modified Robson criteria. J Obstet Gynaecol Can. 2012;34(10):976-9.
9. Hacettepe University Institute of Population Studies. Turkish Population and HealthSurvey, [Online] Available at: http/www.hips.hacettepe.edu.tr/tnsa2008. 2008.
10. Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. N Engl J Med. 2004;351(25):2581-9.
11. Tilden EL, Cheyney M, Guise J-M, Emeis C, Lapidus J, Biel FM, et al. Vaginal birth after cesarean: neonatal outcomes and United States birth setting. Am J Obstet Gynecol. 2017;216(4):403. e1-8.
12. Boyle A, Reddy UM, editors. Epidemiology of cesarean delivery: the scope of the problem. Semin Perinatol. 2012;36(5):308-14.
13. Martel M-J, MacKinnon CJ, Committee CPO, Obstetricians So, Canada Go. Guidelines for vaginal birth after previous Caesarean birth. J Obstet Gynaecol Can. 2005;27(2):164.
14. Nakamura-Pereira M, do Carmo Leal M, Esteves-Pereira AP, Domingues RMSM, Torres JA, Dias MAB, et al. Use of Robson classification to assess cesarean section rate in Brazil: the role of source of payment for childbirth. Reprod Health. 2016;13(3):128.
15. Robson MS. Can we reduce the caesarean section rate? Best Pract Res Clin Obstet Gynaecol. 2001;15(1):179-94.
16. Shaaban M, Sayed Ahmed W, Khadr Z, El-Sayed H. Rising cesarean section rates, a patient's perspective: experience from a high birth rate country. Clin Exp Obstet Gynecol. 2014;41(4):436-9.
17. Tapia V, Betran AP, Gonzales GF. Caesarean section in Peru: Analysis of trends using the Robson classification system. PLoS One. 2016;11(2): e0148138.
18. Grisaru S, Samueloff A. Primary nonmedically indicated cesarean section (" section on request"): evidence based or modern vogue? Clin Perinatol. 2004;31(3):409-30, vii.
19. Signore C, Klebanoff M. Neonatal morbidity and mortality after elective cesarean delivery. Clin Perinatol. 2008;35(2):361-71.
20. Gonen R, Tamir A, Degani S. Obstetricians' opinions regarding patient choice in cesarean delivery. Obstet Gynecol. 2002;99(4):577-80.
21. Eyi EGY, Mollamahmutoglu L. An analysis of the high cesarean section rates in Turkey by Robson classification. J Matern Fetal Neonatal Med. 2019:1-11.
22. Obstetricians ACo, Gynecologists, Obstetricians ACo, Gynecologists. Special problems of multiple gestation. ACOG educational bulletin. 1998;253:323-33.
23. Uzuncakmak C, Guldas A, Aydin S, Var A, Ozcam H. Investigation of cesarean sections at Istanbul Training and Research Hospital Obstetrics and Gynecology Department between 2005 and 2012/SB Istanbul Egitim Arastirma Hastanesi Kadin Hastaliklari ve Dogum Kliniginde 2005-2012 yillari arasinda sezary en ile dogum yapan hastalarin degerlendirilmesi. Istanb Med J. 2013;14(2):112-7.
24. Küçük M. Defensive medicine among obstetricians and gynaecologists in Turkey. J Obstet Gynaecol. 2018;38(2):200-5.
25. Rauf B, Nisa M, Hassan L. External cephalic version for breech presentation at term. J Coll Physicians Surg Pak. 2007;17(9):550-3.
26. Collaris R, Tan P. Oral nifepidine versus subcutaneous terbutaline tocolysis for external cephalic version: a doubleblind randomised trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2009;116(1):74-81.
27. Shaaban MM, Ahmed WS, Khadr Z, El-Sayed HF. Obstetricians' perspective towards cesarean section delivery based on professional level: experience from Egypt. Arch Gynecol Obstet. 2012;286(2):317-23.
28. Josefsson A, Gunnervik C, Sydsjö A, Sydsjö G. A comparison between Swedish midwives and obstetricians & gynecologists opinions on cesarean section. Matern Child Health J. 2011;15(5):555-60.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1036-1040.
DOI: 10.28982/josam.818638

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Right ventricular dysfunction in cirrhosis: A speckle-tracking echocardiography study

Sirozda sağ ventrikül disfonksiyonu: Speckle-tracking ekokardiyografi çalışması

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Ethics Committee Approval: The study protocol was approved by the ethics committee of Gaziosmanpaşa Training and Research Hospital (Approval number: 19.02.2020/41). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Gaziosmanpaşa Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından onaylandı (Onay no: 19.02.2020/41). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: The majority of studies on cardiac dysfunction in patients with cirrhosis are associated with left ventricular (LV) myocardial dysfunction, with fewer studies on right ventricular (RV) function. The aims of this study were to evaluate biventricular function, particularly RV function, in patients with cirrhosis and investigate its relationship with disease severity.

Methods: We included 50 hospitalized and ambulatory patients with cirrhosis and 33 healthy controls. Echocardiographic evaluation was performed with speckle-tracking analysis. Liver disease was graded according to Child-Pugh and Model for End-Stage Liver Disease (MELD) scores.

Results: In our study, the most prevalent etiology of cirrhosis was viral hepatitis (60%), followed by non-alcoholic fatty liver disease (24%). RV-global longitudinal strain (GLS) and LV ejection fraction (EF) values were lower in patients with cirrhosis compared to the control group (both, P=0.001). LVEF was <55% in 19 (38%) patients. Decreases in RV-GLS and LVEF values were more common in patients with ascites (both, P=0.001). However, measurements of RV-GLS and LVEF did not distinguish the degree of severity of liver disease on the basis of Child-Pugh and MELD scores. LV-GLS values between patients with cirrhosis and the control group were similar (P=0.896).

Conclusions: This study showed that RV function was impaired in patients with cirrhosis and more commonly, in patients with ascites. However, values of RV-GLS did not distinguish the degree of severity of liver disease. In addition, the LVEF was low and LV-GLS was normal in patients with cirrhosis.

Keywords: Cirrhotic cardiomyopathy, Right ventricular dysfunction, Echocardiography, Speckle-tracking analysis

Öz

Amaç: Sirozlu hastalarda kardiyak disfonksiyon üzerine yapılan çalışmaların çoğu, sol ventriküler (LV) miyokardiyal disfonksiyon ile ilişkilidir ve sağ ventrikül (RV) fonksiyonu üzerine daha az çalışma vardır. Bu çalışmanın amacı sirozlu hastalarda özellikle RV fonksiyonu olmak üzere, biventriküler fonksiyonu değerlendirmek ve hastalık şiddeti ile ilişkisini araştırmaktır.

Yöntemler: Hastanede yatan ve ayakta tedavi gören 50 siroz hastası ve 33 sağlıklı kontrol çalışmamıza dahil edildi. Ekokardiyografik değerlendirme speckle-tracking analizi ile yapıldı. Karaciğer hastalığı Child-Pugh ve Son Evre Karaciğer Hastalığı Modeli (MELD) puanlarına göre derecelendirildi.

Bulgular: Çalışmamızda sirozun en yaygın etiyolojisi viral hepatit (%60), ardından non-alkolik yağlı karaciğer hastalığı (%24) idi. Sirozlu hastalarda RV-global longitudinal strain (GLS) ve LV ejeksiyon fraksiyonu (EF) değerleri kontrol grubuna göre daha düşüktü (her ikisi de P=0.001). LVEF, 19 (% 38) hastada < %55 idi. Asitli hastalarda RV-GLS ve LVEF değerlerindeki düşüşler daha sıktı (her ikisi de, P=0,001). Bununla birlikte, RV-GLS ve LVEF ölçümleri, Child-Pugh ve MELD skorlarına göre karaciğer hastalığının şiddet derecesini ayırt etmedi. Sirozlu hastalar ile kontrol grubu arasındaki LV-GLS değerleri benzerdi (P=0.896).

Sonuç: Bu çalışma, RV fonksiyonunun sirozlu hastalarda ve daha sık olarak asitli hastalarda bozulduğunu göstermiştir. Bununla birlikte, RV-GLS değerleri, karaciğer hastalığının şiddet derecesini ayırt etmedi. Ayrıca sirozlu hastalarda LVEF düşüktü ve LV-GLS normaldi.

Anahtar kelimeler: Sirotik kardiyomiyopati, Sağ ventrikül disfonksiyonu, Ekokardiyografi, Speckle-tracking analizi

How to cite/Atıf için: Koç DÖ, Şahin T, Öksüz S, Cebe H, Duman AE, Gökden Y, Korkmaz U, Kazaz TG. Right ventricular dysfunction in cirrhosis: A speckle-tracking echocardiography study. J Surg Med. 2020;4(11):1036-1040.

Introduction

The presence of myocardial dysfunction in patients with liver cirrhosis has been defined since the 1960s, and many different cardiac abnormalities associated with liver cirrhosis are grouped under the term cirrhotic cardiomyopathy (CCM) [1]. Components in CCM include impaired cardiac contractility with systolic dysfunction, diastolic dysfunction, a long Q-T interval, and other electromechanical abnormalities [2]. Advanced cirrhosis is associated with a hyperdynamic circulation characterized by high cardiac output and increased cardiac effort, but this may be clinically latent due to a reduced afterload (reduced systemic vascular resistance) and may occur with physical or pharmacological strain [3,4]. In CCM, left ventricular (LV) end-diastolic pressure increases after exercise. However, there is no expected increase in the LV ejection fraction (LVEF) due to an inadequate response in terms of elevation of the cardiac reserve [5].

In cirrhotic patients, most studies have focused on LV function, which is generally examined with tissue Doppler echocardiography [6]. However, cardiac dysfunction is usually underdiagnosed, or diagnosed only when overt cardiac failure has developed in these patients [7]. In cirrhotic patients, right ventricular (RV) dysfunction is associated with prognosis, and a large number of cirrhotic patients exhibit symptoms of RV dysfunction [8]. Therefore, it is extremely important to determine RV as well as LV function in cirrhotic patients [7,9].

Recently, speckle-tracking strain examination has been suggested as a sensitive and proper method for evaluating subclinical systolic dysfunction in several diseases [10]. Speckle-tracking echocardiography delivers objective quantitative measurements of LV and RV (biventricular) segmental and global function without being affected by ventricle size and is useful for evaluating cardiac remodeling [9].

This study compared biventricular function, particularly RV function, between patients with cirrhosis and healthy controls using novel echocardiographic techniques and also investigated whether cardiac abnormalities are associated with the severity and etiology of the disease.

Materials and methods

Fifty consecutive cirrhotic patients who were hospitalized or followed as outpatients and 33 sex- and age-matched healthy subjects were included in this prospective study. The diagnosis of cirrhosis was established by a combination of clinical, biochemical, ultrasonographic, and/or histological findings. Patients with a known history of hypertension, cardiac disease, relevant electrocardiogram abnormalities, malignancy, or active infection were excluded from the study. A detailed medical history, including the etiology and duration of liver disease, was obtained from all subjects. The presence or absence of ascites, esophageal varices, and hepatic encephalopathy was recorded. The presence or absence of ascites was confirmed by ultrasound before enrollment. Patients without ascites were named pre-ascites cirrhotic patients. For laboratory evaluation, liver enzymes, serum bilirubin, albumin level, activated partial thromboplastin time, prothrombin time, the international normalized ratio (INR), and serum creatinine level were measured. Liver function was assessed using Child-Pugh, Model for End-Stage Liver Disease (MELD), and MELD-Sodium (MELD-Na) scores [11,12]. Patients were divided into three prognostic groups according to their Child-Pugh scores (groups A, B, and C). In addition, patients were grouped according to their MELD ($\geq$ 15 and $<$ 15) and MELD-Na ($\geq$ 20 and $<$ 20) scores, as described in a previous study [13].

The study protocol was approved by the ethics committee of our hospital (Approval number: 19.02.2020/41) and conformed to the Declaration of Helsinki. All included patients provided informed consent.

Echocardiography

In this study transthoracic echocardiography was performed by the same cardiologist using the Vivid S60 (GE Vingmed Ultrasound, Horten, Norway) echocardiography system with an M5S (2-4 MHz) probe. The standard apical four- and two-chamber and parasternal axis images were obtained via conventional 2D gray-scale and conventional Doppler echocardiography according to the recent recommendations of the American Society of Echocardiography (ASE) [14]. RV parameters were also examined according to the guidelines of ASE. The modified Simpson's method was used with the 2D echocardiographic technique to measure LVEF [15]. This method also recommended by ASE and it accomplishes by monitoring the LV border in the apical four- and two-chamber images in both end-systole and diastole.

Speckle-tracking echocardiography analyses

Speckle-tracking analysis was performed using the EchoPAC system (GE Healthcare, Chicago, IL, USA). Considering the recommendations of EACVI / ASE / Industry Task Force consensus [16], the endocardial border was manually monitored in the end-systolic frame, starting from one end of the mitral annulus and ending at the other. Apical two-chamber and four-chamber grayscale images were stored digitally for analysis. The strain values of all segments were recorded and averaged to find the LV-GLS and strain ratio. Radial strain curves, epicardial, and endocardial circumferential strain curves were analyzed by the software in the short axis images. For RV GLS, RV strain was analyzed in four segments, three of the right ventricular free wall (basal, middle, and apical segment) and one part of the ventricular septum. We used global strain for RV. LV and RV strain values were analyzed by repeated measurements at two different times by the same cardiologist.

Statistical analysis

The normality of the distributions of the numerical variables were tested with the Shapiro-Wilk test. Student's t-test was used for analyzing statistically significant difference between two normally distributed variables in different groups, and the Mann-Whitney U test was used to compare non-normally distributed variables between the two groups. In comparisons of three or more independent groups, the analysis of variance test was used for normally distributed groups and the Kruskal-Wallis test was used for non-normally distributed groups. Linear regression analysis was performed to investigate the influence of each variable on the measurements. SPSS 22.0 software for Windows (IBM Corp.) was used for the analyses. A *P*-value <0.05 denoted significance.

Results

This study included 50 (62% males) cirrhotic patients and 33 (51.5% males) healthy volunteers. The median age of the patients was 57 years (range: 46–67 years), and that of the control group was 55 years (range: 45.5–66 years). The most prevalent etiology of cirrhosis was viral hepatitis (60%), followed by non-alcoholic fatty liver disease (24%). LVEF, LV global longitudinal strain (LV-GLS), and RV global longitudinal strain (RV-GLS) measurements were similar among patients according to cirrhosis etiology (P>0.05). Patients were classified into groups A (19 patients), B (14 patients), and C (17 patients) according to disease severity on the basis of the Child-Pugh score. MELD scores of 25 (50%) cirrhotic patients were < 15 (Table 1). Cirrhosis was decompensated in 31 (62%) patients, with mean Child-Pugh and MELD scores of 7.50 (3.22) and 15.84 (7.92), respectively, at admission. Of the 50 patients, 18 had no history of ascites. The remaining 32 patients had obvious ascites clinically, which was confirmed on ultrasound. There was a significant relationship between the presence of ascites and RV-GLS and LVEF measurements (both, P=0.001), but not with LV-GLS measurements (P=0.307).

Table 1: Demographic, clinical, and laboratory characteristics of the patients

	Patients (n=50)
Age, mean (SD)	56.96 (13.33)
Male sex, n (%)	31 (62%)
Cirrhosis etiology, n (%)	
Viral	30 (60%)
NAFLD	12 (24%)
Alcohol	4 (8%)
Other	4 (8%)
Child-Pugh class, n (%)	
Group A	19 (38%)
Group B	14 (28%)
Group C	17 (34%)
MELD score, mean (SD)	15.84 (7.92)
MELD-Na score, mean (SD)	16.88 (8.35)
Esophageal varices present, n (%)	
Grade I	16 (32%)
Grade II	12 (24%)
Grade III	17 (34%)
Esophageal variceal bleeding, n (%)	7 (14%)

IQR: interquartile range, NAFLD: non-alcoholic fatty liver disease, MELD: Model for End-Stage Liver Disease, MELD-Na: Sodium Model for End-Stage Liver Disease, SD: standard deviation

RV-GLS measurements in cirrhotic patients were significantly lower than those in the control group (P=0.001). However, no relationship was found between the Child-Pugh (P=0.191), MELD (P=0.331), and MELD-Na (P=0.907) groups and RV-GLS.

LV-GLS measurements were lower in females than in males (P=0.003), but they were similar between the patient and control groups (P=0.896) and among Child-Pugh groups (P=0.516). In addition, LV-GLS measurements did not differ between MELD or MELD-Na groups (P=0.516 and P=0.775, respectively).

LVEF measurements were significantly lower in the patients than in the controls (P=0.001). There was no difference in LVEF measurements based on sex (P=0.085), MELD score (P=0.613), or MELD-Na score (P=0.583). Nineteen patients (38%) had an LVEF < 55%. The majority of patients with LVEF < 55% were classified as Child-Pugh B or C. Of the patients with LVEF < 55%, based on Child-Pugh score, nine (47.4%) were in group C, seven (36.8%) in group B, and three (15.8%) were in group A (P=0.04). There were no significant differences among the groups in terms of mean LVEF values (P=0.188). Also, there was a statistically significant relationship between LVEF and LV-GLS (P=0.001) (Table 2).

There were no significant relationships between LV-GLS, LVEF, and RV-GLS measurements and the presence of esophageal varices, encephalopathy, thrombocytopenia, and increased INR (P<0.05).

Table 2: Relationship between echocardiographic measurements and various parameters

	LV-GLS	RV-GLS	LVEF
Sex			
Males (n=48)	20.12 (2.87) *	18.81 (3.73)	63.13 (12.31)
Females (n=35)	18.52 (1.94)	19.88 (4.05)	62.66 (11.46)
Groups			
Cirrhotic patients (n=50)	19.42 (2.83)	17.05 (3.49) **	55.94 (9.65) **
Control group (n=33)	19.49 (2.33)	22.61 (0.93)	73.52 (5.26)
Child-Pugh class			
Group A (n=19)	19.96 (2.65)	18.03 (3.18)	59.11 (8.60)
Group B (n=14)	18.82 (2.67)	15.79 (3.76)	53.50 (9.66)
Group C (n=17)	19.29 (3.18)	17.01 (3.44)	54.41 (10.33)
MELD score			
< 15 (n=25)	19.03 (2.62)	17.54 (3.44)	56.64 (9.26)
≥ 15 (n=25)	19.53 (3.07)	16.57 (3.54)	55.24 (10.17)
MELD-Na score			
< 20 (n=33)	19.42 (2.71)	17.09 (3.53)	56.48 (9.43)
≥ 20 (n=17)	19.42 (3.12)	16.97 (3.52)	54.88 (10.28)
Ascites			
Pre-ascites (n=18)	19.97 (2.59)	18.18 (3.22)	58.89 (8.56)
Ascites (n=32)	19.11 (2.95)	16.42 (3.52) **	54.28 (9.96) **
Esophageal varices			
Absent or Grade I (n=21)	18.95 (2.73)	18.86 (3.45)	54.62 (9.08)
Grade II or III (n=29)	19.75 (2.89)	17.18 (3.56)	56.89 (10.09)
Cirrhosis etiology			
Hepatitis (n=30)	19.84 (2.81)	16.91 (3.35)	57.50 (9.96)
NAFLD (n=12)	17.92 (2.06)	16.76 (3.82)	51.75 (7.16)
Alcoholic (n=4)	19.25 (3.73)	17.60 (3.62)	54.50 (12.34)
Other (n=4)	20.93 (3.31)	18.45 (4.51)	58.25 (10.90)

All numbers are presented as the mean (SD), LV-GLS: left ventricle global longitudinal strain, RV-GLS: right ventricle global longitudinal strain, LVEF: left ventricle ejection fraction, NAFLD: non-alcoholic fatty liver disease, MELD: Model for End-Stage Liver Disease; MELD-Na: Sodium Model for End-Stage Liver Disease, * P=0.003, males vs. females, ** P=0.001, cirrhotic patients vs. control group, and pre-ascites vs. ascites

Discussion

In this study, we used speckle-tracking strain analysis for cardiac evaluation in patients with cirrhosis of different etiologies. We showed that the RV-GLS and LVEF were decreased in cirrhotic patients. In addition, we found a relationship between RV-GLS and the presence of ascites in cirrhotic patients, with RV-GLS values lower in patients with ascites. However, measurements of RV-GLS did not distinguish the degree of severity of liver disease on the basis of the Child-Pugh and MELD scores. In addition, our study results showed that patients with cirrhosis have normal LV-GLS.

In recent years, studies have focused on the presence of specific cardiac abnormalities in cirrhotic patients [6,17]. Cardiovascular complications in cirrhosis may occur due to humoral, nervous, and hemodynamic changes. The CCM criteria established at the World Gastroenterology Congress in 2005 include echocardiographic parameters for defining subclinical cardiac dysfunction without obvious structural abnormalities [3]. However, the CCM Consortium has recently proposed new criteria based on novel cardiovascular imaging parameters [4]. CCM indicates systolic and diastolic dysfunction and electrophysiological abnormalities [18]. In the 2005 criteria for CCM, LV dysfunction is defined by a low resting LVEF (< 55%) and/or the presence of a blunted contractile response in a myocardial stress test (LVEF stress test >5%). However, due to limited assessment of impaired contractile responses to stress testing in cirrhotic patients, the CCM Consortium recommended evaluation of GLS (normal value –18% to –22%) to detect LV systolic function in patients with cirrhosis with a preserved LVEF (normal value > 50%). In addition, the CCM Consortium

recommendations include minimum criteria for the diagnosis of advanced diastolic dysfunction in cirrhotic patients without known heart disease [4].

The prognostic value of RV function in cardiovascular disease have been shown in several studies [8]. Therefore, it has become increasingly important to quantify RV systolic function. In cirrhotic patients, impaired liver function contributes to increased preload in the right heart. High hepatic venous pressures causing increased preload can deteriorate RV functions. RV function is more difficult to evaluate than LV function. The fine changes in the systolic and the diastolic functions of the heart, which can be seen in cirrhotic patients, may not be detected with the conventional transthoracic echocardiography [19]. Novel echocardiographic techniques can improve the quantitative assessment of RV function. Speckle-tracking strain analysis is a sensitive and reliable method that can accurately evaluate RV and LV function in patients with cirrhosis. This method enables the detection of ventricular dysfunction in three directions—longitudinal, circumferential, and radial, without being affected by ventricle size. Longitudinal deformation is a reliable measure of the extent of myocardial damage, manifests early, and suggests subendocardial disease. Circumferential deformation indicates transmural damage and it manifests relatively late in the disease course [20]. In our study, using speckle-tracking strain analysis, we showed that RV-GLS measurements were significantly lower in patients with cirrhosis than in controls. Our results are similar to those of other studies that found reduced RV strain in patients with cirrhosis [19,21]. In addition, in our study, RV-GLS measurements were lower in patients with ascites than in patients without. Our study showed the importance of evaluating RV function in patients with cirrhosis. However, the RV-GLS measurements were not able to distinguish the degree of severity of liver disease on the basis of Child-Pugh and MELD scores.

We found that LV-GLS values were normal in patients with cirrhosis. In addition, there were no differences in LV-GLS values in patients with cirrhosis according to disease severity and etiology. Sampaio et al. [6] reported lower LV-GLS in patients with cirrhosis compared to the control group, but did not find significant differences in terms of LV-GLS between cirrhotic patient groups according to Child-Pugh scores and etiology. A recent study evaluated LV-GLS in cirrhotic patients and found no differences between patients with and without ascites [22]. Similarly, we could not find a significant difference in LV-GLS measurements between patients with and without ascites in our study.

The EF is the most widely used parameter for representing global LV systolic function. In CCM, the systolic function is usually normal at rest, but the expected increases in LVEF after exercise are absent or insufficient, indicating an inadequate response of the ventricular reserve to an increase in ventricular filling pressure. In our study, we found a lower LVEF in cirrhotic patients compared to control patients. However, the LVEF has been reported to be normal in some studies [23,24], increased in some studies [25,26], and decreased in others [27,28]. A resting EF < 55% has been suggested as a diagnostic criterion for systolic dysfunction in patients with cirrhosis. However, EF is highly dependent on loading conditions, and a higher threshold value may be needed for patients with cirrhosis due to peripheral vasodilation and reduced afterload [29]. The EF is not only an index of contractility but also a subject to both heart rate and valvular function [30]. These reasons probably explain the variable resting EF findings in studies of cirrhotic patients. In addition, the LVEF was lower in patients with ascites in our study. Similarly, in a study by Pozzi et al. [27], the LVEF was reported to be decreased in patients with ascites.

Limitations

The limitations of this study were the small study group and the lack of inclusion of a stress test (physical activity or pharmacological stress) that could better prove subclinical cardiac dysfunction. Also, diastolic dysfunction and dilation of both left and right ventricles require evaluation with additional studies.

Conclusions

This study showed that RV function was impaired in patients with cirrhosis and this was more common in patients with ascites. Patients with cirrhosis exhibited significantly decreased RV function compared with healthy controls. Speckle-tracking strain analysis can better detect subclinical RV dysfunction compared to normal traditional echocardiographic indices. However, the RV-GLS values did not distinguish the degree of severity of liver disease on the basis of Child-Pugh and MELD scores. We also showed that in cirrhotic patients, the LVEF was lower, but LV-GLS was similar between patients and controls. However, more studies are needed to determine the clinical significance of these findings.

References

1. Møller S, Henriksen JH. Cirrhotic cardiomyopathy. J Hepatol. 2010;53(1):179-90. doi: 10.1016/j.jhep.2010.02.023
2. Wong F. Cirrhotic cardiomyopathy. Hepatol Int. 2009;3(1):294-304. doi: 10.1007/s12072-008-9109-7
3. Lee RF, Glenn TK, Lee SS. Cardiac dysfunction in cirrhosis. Best Pract Res Clin Gastroenterol. 2007;21(1):125-40. doi: 10.1016/j.bpg.2006.06.003
4. Izzy M, VanWagner LB, Lin G, Altieri M, Findlay JY, Oh JK, et al. Redefining Cirrhotic Cardiomyopathy for the Modern Era. Hepatology. 2020 Jan;71(1):334-45. doi: 10.1002/hep.30875
5. Wong F, Girgrah N, Graba J, Allidina Y, Liu P, Blendis L. The cardiac response to exercise in cirrhosis.Gut. 2001 Aug;49(2):268-75. doi: 10.1136/gut.49.2.268
6. Sampaio F, Pimenta J, Bettencourt N, Fontes-Carvalho R, Silva AP, Valente J, et al. Systolic and diastolic dysfunction in cirrhosis: a tissue-Doppler and speckle tracking echocardiography study. Liver Int. 2013 Sep;33(8):1158-65. doi: 10.1111/liv.12187
7. Rigolin VH, Robiolio PA, Wilson JS, Harrison JK, Bashore TM. The forgotten chamber: The importance of the right ventricle. Cathet Cardiovasc Diagn. 1995;35(1):18-28. doi: 10.1002/ccd.1810350105
8. Chen Y, Chan AC, Chan SC, Chok SH, Sharr W, Fung J, et al. A detailed evaluation of cardiac function in cirrhotic patients and its alteration with or without liver transplantation.J Cardiol. 2016 Feb;67(2):140-6. doi: 10.1016/j.jjcc.2015.08.001
9. Marmor A, Geltman EM, Biello DR, Sobel BE, Siegel BA, Roberts R. Functional response of the right ventricle to myocardial infarction: dependence of the site of left ventricular infarction. Circulation. 1981;64(5):1005-11. doi: 10.1161/01.cir.64.5.1005
10. Yiu KH, Schouffoer AA, Marsan NA, Ninaber MK, Stolk J, Vlieland TV, et al. Left ventricular dysfunction assessed by speckle-tracking strain analysis in patients with systemic sclerosis: relationship to functional capacity and ventricular arrhythmias. Arthritis Rheum 2011;63:3969–78. doi: 10.1111/ajt.12385
11. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646-9.
12. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464-70. doi: 10.1053/jhep.2001.22172
13. Merli M, Calicchia A, Ruffa A, Pellicori P, Riggio O, Giusto M, et al. Cardiac dysfunction in cirrhosis is not associated with the severity of liver disease. European Journal of Internal Medicine. 2013;24:172–6. doi: 10.1016/j.ejim.2012.08.007
14. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:233-70.
15. Foley TA, Mankad SV, Anavekar NS, Bonnichsen CR, Morris MF, Miller TD, et al. Measuring Left Ventricular Ejection Fraction - Techniques and Potential Pitfalls. European Cardiology. 2012;8(2):108-14. doi:10.15420/ecr.2012.8.2.108
16. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr. 2015 Feb;28(2):183-93. doi: 10.1016/j.echo.2014.11.003
17. Kia L, Shah SJ, Wang E, Sharma D, Selvaraj S, Medina C, et al. Role of pretransplant echocardiographic evaluation in predicting outcomes following liver transplantation. Am J Transplant. 2013 Sep;13(9):2395-401. doi: 10.1111/ajt.12385

18. Møller S, Henriksen JH. Cirrhotic cardiomyopathy: a pathophysiological review of circulatory dysfunction in liver disease. Heart. 2002 Jan;87(1):9-15. doi: 10.1136/heart.87.1.9
19. Zhang Kun, Braun A, von Koeckritz F, Schmuck RB, Teegen EM, Cuspidi C, et al. Right Heart Remodeling in Patients with End-Stage Alcoholic Liver Cirrhosis: Speckle Tracking Point of View. J Clin Med. 2019 Sep;8(9):1285. doi: 10.3390/jcm8091285
20. Bansal M, Sengupta PP. Longitudinal and Circumferential Strain in Patients with Regional LV Dysfunction. Curr Cardiol Rep. 2013 Mar;15(3):339. doi: 10.1007/s11886-012-0339-x
21. Zakia ER, Baha El Deenb NM. Relation of right ventricular dysfunction to the severity of hepatic cirrhosis by different echo modalities using speckle-tracking echocardiography. Al-Azhar Assiut Med J. 2017;15:7–14. doi: 10.4103/1687-1693.213588
22. Nazar A, Guevara M, Sitges M, et al. LEFT ventricular function assessed by echocardiography in cirrhosis: relationship to systemic hemodynamics and renal dysfunction. J Hepatol. 2013;58:51–7.
23. Grose RD, Nolan J, Dillon JF, Errington M, Hannan WJ, Bouchier IA, Hayes PC. Exercise-induced left ventricular dysfunction in alcoholic and non-alcoholic cirrhosis. J Hepatol. 1995 Mar;22(3):326-32. doi: 10.1016/0168-8278(95)80286-x
24. Kelbaek H, Rabøl A, Brynjolf I, Eriksen J, Bonnevie O, Godtfredsen J, et al. Haemodynamic response to exercise in patients with alcoholic liver cirrhosis. Clin Physiol. 1987 Feb;7(1):35-41. doi: 10.1111/j.1475-097x.1987.tb00631.x
25. Laffi G, Barletta G, La Villa G, Del Bene R, Riccardi D, Ticalin P, et al. Altered cardiovascular responsiveness to active tilting in nonalcoholic cirrhosis. Gastroenterology. 1997 Sep;113(3):891-8. doi: 10.1016/s0016-5085(97)70184-7
26. Wong F, Liu P, Lilly L, Bomzon A, Blendis L. Role of cardiac structural and functional abnormalities in the pathogenesis of hyperdynamic circulation and renal sodium retention in cirrhosis. Clinical Science. 1999;97(3):259–67.
27. Pozzi M, Carugo S, Boari G, Pecci V, de Ceglia S, Maggiolini S, et al. Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology. 1997 Nov;26(5):1131-7. doi: 10.1002/hep.510260507
28. Papastergiou V, Skorda L, Lisgos P, Papakonstantinou N, Giakoumakis T, Ntousikos K, et al. Ultrasonographic Prevalence and Factors Predicting Left Ventricular Diastolic Dysfunction in Patients with Liver Cirrhosis: Is There a Correlation between the Grade of Diastolic Dysfunction and the Grade of Liver Disease? The Scientific World Journal. 2012;615057. doi:10.1100/2012/615057
29. Sampaio F, Pimenta J. Left ventricular function assessment in cirrhosis: Current methods and future directions. World J Gastroenterol. Jan 7, 2016;22(1):112-125. doi: 10.3748/wjg.v22.i1.112
30. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012;33:1787-847. doi: 10.1093/eurheartj/ehs104.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1041-1045.
DOI: 10.28982/josam.809898

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Efficacy of caloric vestibular stimulation for the treatment of idiopathic tinnitus

İdiyopatik tinnitus tedavisinde kalorik vestibüler stimülasyonun etkinliği

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Ethics Committee Approval: The study was approved by the Istanbul Medipol University, Ethical Committee (10840098-604.01.01-E.991 5/4/2018). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma İstanbul Medipol Üniversitesi Etik Kurulu tarafından onaylandı (10840098-604.01.01-E.991 04.05.2018). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Caloric vestibular stimulation (CVS) induces the activation of several cortical structures and has been utilized as a neuromodulation technique in the treatment of several disorders. This study purposed to investigate whether CVS would be beneficial in the management of idiopathic tinnitus.

Methods: Patients with unilateral idiopathic tinnitus were enrolled in the study. CVS with cold water (study group) and body temperature (control group) irrigation were applied to the symptomatic ear. All patients underwent a standard audiometric examination and visual analogue scale (VAS), the tinnitus handicap inventory (THI) and the Beck depression inventory (BDI) were administered.

Results: VAS intensity and disturbance values, mean THI and BDI scores did not show any significant changes in the control group. In the study group, a significant improvement in both the tinnitus intensity and disturbance occurred in the first week post-intervention (P<0.001), and a significant decline was observed in median THI and BDI scores as well as the loudness of the tinnitus in the four weeks post-CVS (P<0.001, P<0.001, P=0.004 and P=0.001) respectively).

Conclusion: We can conclude that CVS with cold water leads to a significant decline in the intensity of tinnitus and reduction in the loudness of tinnitus, as well as improving THI and BDI scores.

Keywords: Caloric vestibular stimulation, Cold, Idiopathic tinnitus, Neuromodulation, Tinnitus Handicap Inventory

Öz

Amaç: Kalorik vestibüler stimülasyon (KVS), kortikal yapıların aktivasyonunu indükler ve çeşitli hastalıkların tedavisinde bir nöromodülasyon tekniği olarak kullanılır. Bu çalışma, KVS'nin idiyopatik tinnitus tedavisinde yararlı olup olmayacağını araştırmayı amaçlamıştır.

Yöntemler: Tek taraflı idiyopatik tinnitusu olan hastalar çalışmaya alındı. Semptomatik kulağa soğuk su (çalışma grubu) ve vücut ısısında su (kontrol grubu) olmak üzere KVS irrigasyonu uygulandı. Tüm hastalara standart odyometrik muayene yapıldı ve görsel analog skala (GAS), tinnitus engellilik anketi (TEA) ve Beck depresyon anketi (BDA) uygulandı.

Bulgular: Tinnitus şiddeti ve rahatsız olma GAS değerleri, ortalama TEA ve BDA skorları kontrol grubunda anlamlı bir değişiklik göstermedi. Çalışma grubunda müdahale sonrası ilk haftada hem tinnitus şiddeti hem de rahatsız olma skorlarında anlamlı iyileşme oldu (P<0,001). Çalışma grubunda KVS sonrası dört hafta içinde medyan TEA ve BDA skorlarında ve tinnitus sesinde anlamlı düşüş gözlendi (sırasıyla P<0,001, P<0,001, P=0,004 ve P=0,001).

Sonuç: Soğuk su ile yapılan KVS'nin, tinnitus yoğunluğunda önemli bir düşüşe ve tinnitusun ses şiddetinde azalmaya yol açtığı ve ayrıca TEA ve BDA skorlarını iyileştirdiği sonucuna varabiliriz.

Anahtar kelimeler: Kalorik vestibüler uyarı, Soğuk, İdiyopatik tinnitus, Nöromodülasyon, Tinnitus engellilik anketi

How to cite/Atıf için: Saatçi Ö, Aslıer NGY, Düz ÖA. Efficacy of caloric vestibular stimulation for the treatment of idiopathic tinnitus. J Surg Med. 2020;4(11):1041-1045.

Introduction

Tinnitus is defined as the perception of sound in the absence of an acoustic stimulus. It affects up to 18% of the general population to some extent in industrialized countries, and 0.5% of the patients with tinnitus describe severe disability precluding their ability to lead a normal life [1]. The pathophysiology of tinnitus is heterogeneous and incompletely understood; however, recent evidence indicates that it may result from abnormal neural activity and maladaptive plasticity in response to hearing loss [2]. All levels of the auditory pathways and several non-auditory systems are considered to act in the development and maintenance of tinnitus, with the prepotency of non-auditory systems in determining the level of annoyance of the tinnitus [3]. Several diseases, including age-related hearing loss, Menière's disease, noise-induced hearing loss, acoustic neuroma, depression, chronic otitis media, barotraumas, head injuries, and drug intoxications such as aspirin or quinine toxicity, have been shown to contribute to the development of tinnitus [1].

Various agents including melatonin, lidocaine, antidepressants, anticonvulsants, and anxiolytics have been studied for the medical treatment of tinnitus [4]. The abnormal neuronal activity observed in patients with tinnitus led to the application of neuromodulation methods for its treatment. For this purpose, transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) have been employed in the management of tinnitus. In both single and repeated sessions, tDCS interventions have shown beneficial results in tinnitus symptoms and depression and anxiety comorbid with tinnitus [5]. It has been observed that active rTMS administration of 1-Hz rTMS daily over ten consecutive workdays causes a decrease in tinnitus compared to placebo [6]. However, the treatment of tinnitus is problematic as a scientifically validated medication or cure has not been defined yet.

Caloric vestibular stimulation (CVS), which requires the application of cold or warm water into the external ear canal, has traditionally been a routine diagnostic technique in the neurological assessment of vestibular function. CVS induces activation of a number of cortical structures including the posterior insular and retroinsular cortices, temporoparietal junction, inferior parietal lobule, somatosensory area, parietal operculum, and superior temporal gyrus[7]. CVS was utilized as a neuromodulation technique in the treatment of post-stroke hemineglect, severe chronic pain, hemianesthesia, and bipolar disorder [8].

Implementation of CVS in the suppression of tinnitus was first described by Lamprecht et al. three decades ago [9]. The authors demonstrated that application of warm water (44ºC) into the ear canal was associated with an increase, while the cold-water irrigation (30ºC or 23ºC) caused a decrease in the loudness of the tinnitus. However, another study with 19 patients failed to demonstrate any impact of CVS on the modulation of tinnitus [10]. The conflicting results obtained in previous studies necessitate further research to clarify the role of CVS in the management of tinnitus.

Therefore, in this study, we aimed to investigate whether cold CVS can be beneficial in the management of tinnitus and improve the self-reported disability of the patients associated with tinnitus.

Materials and methods

The study was approved by the Istanbul Medipol University Ethical Committee (10840098-604.01.01-E.991 04/05/2018) and was performed in accordance with the recent version of the Helsinki Declaration. Written informed consent was obtained from all subjects included in the study. The power calculation was based on our pilot study with the first 15 patients. We used paired t-tests to assess the difference between two dependent means for VAS intensity (Pre-treatment: 6.2 (2.3), Post-treatment: 4.6 (1.8), alpha error: 0.05, power: 0.95, effect size: 0.76). Results revealed that at least 20 patients and 20 controls were required for adequate sample size [11].

Patients and Controls

All consecutive patients with the complaint of tinnitus who were admitted to the outpatient clinic of the otorhinolaryngology department of a tertiary center between May 2018 and June 2020 were prospectively enrolled in this study. Detailed medical history was obtained from all participants. All study patients underwent a complete audiological, ontological, and neurological examination to rule out the potentially treatable causes of tinnitus. Blood samples were drawn for complete blood count, serum biochemistry, vitamin B12 levels, thyroid function tests, and erythrocyte sedimentation rate. All patients underwent a standard audiometric examination, pure-tone audiometry, and speech audiometry with a clinical audiometer device in soundproof booths (AC40, Interacoustics, Middelfart, Denmark), and conventional tympanometry (Interacoustics AT235, Denmark). Pitch match frequency and loudness analyses of tinnitus were done for all patients on admission and four weeks after CVS. Advanced examinations such as contrast-enhanced temporal bone or cranial magnetic resonance imaging were requested when required.

A total of 50 patients with idiopathic tinnitus who met the below criteria (mean age 51.3 (8.6) years, minimum 26 – maximum 70 years, 50% male) were enrolled in this study. Thirty patients (15 women and 15 men) who came to our outpatient clinic with the complaint of tinnitus and met the below criteria were identified as the control group (mean age 54.3(8.3) years, minimum 33 – maximum 69 years).

Inclusion criteria:

1. Patients aged between 18 and 75 years.
2. Patients with unilateral tinnitus ongoing for at least six months who had received medical treatment for tinnitus for at least two months and had been refractory to medical treatment, had been free from any kind of medical agents prescribed to relieve the tinnitus for the last three months, and had been diagnosed with non-pulsatile subjective tinnitus.
3. Patients with full capability of communication.

Exclusion criteria:

1. Patients younger than 18 years and older than 76 years.

2. The presence of peripheral or central vestibular disease, cardiovascular disease, previous head trauma, neurological disease, metabolic disease, pregnancy, acute or chronic ear infection, and history of ear surgery.
3. Patients without full capability of communication.

Caloric vestibular stimulation

Study Group

CVS was performed in a 30º head-up position, with the head turned away from the ear being irrigated. Frenzel's goggles were applied to ease the observation of the nystagmus and to avoid fixation. The ear canal of the symptomatic ear was filled with 5-10 ml of cold water (4ºC) [12]. Nystagmus beats occurred approximately 30 seconds after the delivery of cold water and continued for the ensuing 30-45 seconds. In order to avoid post-CVS lightheadedness and nausea, subjects were kept in semi-recumbent position until nystagmus terminated.

Control Group

CVS was performed in 30º head-up position, with the head turned away from the ear being irrigated. Frenzel's goggles were applied to ease the observation of the nystagmus and to avoid fixation. The temperature of the ear canal of the symptomatic ear was measured, then the water was warmed to that degree Celsius, which was in the range of 36.0-36.8ºC. The ear canal was filled with 5-10 ml of water at body temperature as sham procedure. The emergence of nystagmus was inspected for a minute, and once there was no nystagmus, the patient returned to sitting position.

Assessment of tinnitus

A visual analog scale (VAS) was used in the assessment of the tinnitus before CVS (baseline) and repeated one week and one month after the application of CVS. The assessment was carried out in relation to intensity and disturbance. All tinnitus patients were asked to assign a 0 to 10 score to their tinnitus, with the help of a proper ruler (0 points being most favorable and 10 points being least favorable).

Tinnitus Handicap Inventory

The Tinnitus Handicap Inventory (THI) was used to address the disability experienced by the patients due to tinnitus before and four weeks after the application of the CVS. THI is a 25-item questionnaire that probes the functional, emotional, and catastrophic response reactions to tinnitus. Each item of the THI is ranked from 0 to 4 to build up a total score between 0 and 100 points. The THI score of 0–16 means "no or slight handicap", 18–36 indicates "mild", 38–56 indicates "moderate", 58–76 indicates "severe", and a score of 78–100 is classified as "catastrophic handicap" [13].

Beck Depression Inventory

Beck Depression Inventory (BDI) was used in the evaluation of the depressive symptoms before and four weeks after the application of the CVS. BDI is an instrument used for the purpose of diagnosing depression. It consists of 21 items on symptoms and attitudes, with intensities ranging 0-3 [14]. The items refer to sadness, pessimism, sense of failure, lack of satisfaction, guilt, feeling of punishment, self-deprecation, self-accusation, suicidal ideation, crying spells, irritability, social withdrawal, indecisiveness, distortion of body image, inhibition to work, sleep disorder, fatigue, loss of appetite, weight loss, somatic concern, and decreased libido. A BDI score of ≥16 indicates depression, while lower scores address non-depressed individuals.

Statistical analysis

Statistical analyses were carried out using SPSS for Windows, version 21 (SPSS, IBM Corp., Armonk, N.Y., USA). Shapiro–Wilk test was used to check the normality of the variables. Continuous variables are presented as mean (standard deviation (SD)) and categorical variables as frequency (n) and percentage (%). Paired samples t-test and repeated measures ANOVA were employed in comparison of pre- and post-interventional VAS scores and tinnitus frequency and loudness (normally distributed data). The comparison of the pre- and post-interventional THI and BDI scores was performed with the Wilcoxon signed-rank test. Pearson and Spearman correlation analyses were performed to identify the association between the THI score and BDI score before and after CVS. A two-sided *P*-value ≤0.05 was interpreted as statistically significant.

Results

Demographic characteristics and the clinical features of the study and control subjects are presented in Table 1. The symptomatic ear that received CVS treatment was the right ear in 19 (38%) subjects and the left ear in 31 (62%) subjects in the study group, and the right ear of 15 (50%) and left ear of 15 (50%) subjects in the control group. Except for lightheadedness in a few patients, CVS was well tolerated and no complications were recorded during or after the procedure. The distributions of gender, age, and the results of basal audiometric tests and basal self-report questionnaires were not significantly different (*P*>0.05) between the study and control groups.

Table 1: Demographic characteristics and clinical features

Variables	Study Group Mean (SD)	Control Group Mean (SD)	*P*-value
Age,years	51.3 (8.9)	54.3 (8.3)	0.08
Gender			$\chi^{(chi)2}$:0.00;
Male, n	25 (50 %)	15 (50 %)	df:1;
Female, n	25 (50 %)	15 (50 %)	p=1.0
Tinnitus duration, years	4.1 (3.0)	3.1 (2.0)	0.234
R AC threshold	27.5 (9.2) dB	26.6 (13.3) dB	0.661
R BC threshold	21.2 (8.1) dB	21.9 (11.3) dB	0.936
L AC threshold	30.8 (9.2) dB	26.5 (13.5) dB	0.94
L BC threshold	23.3 (6.9) dB	22.5 (11.6) dB	0.526

AC: Air Conduction, BC: Bone Conduction, R: Right, L: Left

The changes in the VAS ratings of the tinnitus from the baseline to four weeks post-CVS are presented in Table 2. VAS intensity and disturbance values did not show any significant changes in the control group. However, significant improvements in both the intensity and disturbance occurred from baseline to the first week post-intervention in the study group (*P*<0.001). VAS intensity and disturbance values had complete improvement one week after treatment in 12 patients. Although intensity and disturbance were still more favorable than the baseline values (*P*<0.001) and different from the controls (*P*<0.001), in the study group, impairment was observed in both intensity and disturbance from the first week post-CVS to the first month post-CVS. Moreover, a significant decline was observed in median THI [48 (14-96) points vs. 40 (8-84) points, *P*<0.001] and BDI scores [13 (2-42) points vs. 8 (1-29) points, *P*<0.001] from baseline to the first month post-CVS in contrast to the controls, who were unchanged (Table 3). The mean BDI score was strongly correlated with the mean THI score before and after CVS in both the study group (r=0.846, *P*<0.001 and

r=0.721, P<0.001, respectively) and controls (r=0.694, P<0.001 and r=0.700, P<0.001, respectively).

Table 2: Change in the VAS score of the intensity and disturbance arising from the tinnitus from baseline to the post-treatment one month in each group and between the groups

	Study Group				Control Group				
	Baseline (mean (SD)	1st week (mean (SD)	1st month (mean (SD)	*P*-value*	Baseline (mean (SD)	1st week (mean (SD)	1st month (mean (SD)	*P*-value*	*P*-value**
VAS (intensity)	6.6 (2.2)[a]	3.1 (1.4)[b]	3.9 (1.9)[c]	<0.001	7.6 (1.7)	7.3 (1.6)	7.4 (1.8)	0.134	<0.001
VAS (disturbance)	6.5 (1.9)[a]	2.9 (1.2)[b]	3.4 (1.7)[c]	<0.001	6.7 (1.9)	6.6 (1.7)	6.6 (1.8)	0.184	<0.001

VAS: visual analogue scale. a,b,c: Same letters in the same row denote the lack of the significant difference between the two variables in the same row. Paired samples t-test, within each group, between the baseline and the first month measurements (p*). Repeated measures ANOVA (group×time×frequency), between the subject effects (p**).

Table 3: The comparison of BDI and THI scores between the pre-and post-CVS interventions in each group

	Study Group			Control Group		
	Pre- CVS	Post- CVS	*P*-value	Pre- CVS	Post- CVS	*P*-value
BDI score Median (min-max)	13 (2-42)	8 (1-29)	<0.001	8.5 (2-32)	9 (2-30)	0.490
THI score Median (min-max)	48 (14-96)	40 (8-84)	<0.001	43 (10-96)	44 (10-96)	0.106

CVS: Caloric Vestibular Stimulation, BDI: Beck Depression Inventory, THI: Tinnitus Handicap Index. *P*= Wilcoxon signed-rank test

Comparisons of pre-and post-CVS tinnitus frequency and loudness for the symptomatic ears within each group and between the groups are presented in Table 4. The loudness of the tinnitus displayed significant reductions in the symptomatic ear of the study patients following the intervention with CVS (P<0.05), whereas no significant change occurred in the frequency of the tinnitus (P>0.05). The change in tinnitus loudness by time was not significantly different from the controls, although there was almost no change observed in those patients.

Table 4: Comparison of pre-and post-CVS levels of tinnitus frequency and loudness for the relevant ear in each group and between groups

	Study Group (Mean (SD)			Control Group (Mean (SD)			
	Pre-CVS	Post-CVS	*P*-value*	Pre-CVS	Post-CVS	*P*-value*	*P*-value**
Tinnitus frequency R	5200 (2067)	4950 (2012)	0.096	5071 (1940)	4929 (1940)	0.336	0.914
Tinnitus frequency L	5356 (2125)	5266 (2099)	0.184	4125 (1360)	4125 (1360)	>0.999	0.047
Tinnitus loudness R	56.5 (13.86)	49.75 (16.89)	0.004	51.1 (13.47)	51.1 (13.75)	>0.999	0.682
Tinnitus loudness L	57.16 (12.15)	54.16 (12.46)	<0.001	57.81 (10.80)	57.19 (11.25)	0.164	0.617

CVS: Caloric Vestibular Stimulation, L:Left, R: Right, SD: Standard Deviation. Paired samples t-test, within each group, between the baseline and the first month measurements (p*). Repeated measures ANOVA (group×time×frequency), between the subject effects (p**).

Discussion

The present study clearly demonstrates that CVS with cold water at 4º C leads to a significant decline in intensity and disturbance of tinnitus as measured with the VAS for the symptomatic ear, compared to the CVS with water at body temperature. The implementation of CVS with water at 4º C also improves THI and BDI scores and decreases the loudness of the tinnitus. To the best of our knowledge, this is the first study that investigates the role of cold CVS in the modulation of idiopathic tinnitus.

The evidence derived from quantitative electroencephalography and neuroimaging studies indicates the involvement of both auditory and non-auditory brain areas in different aspects of tinnitus. The primary and secondary auditory cortices are, therefore, recognized as potential targets for the management of tinnitus [15]. Tinnitus may result from increased neuronal activity within the auditory cortex that develops due to the imbalance between excitatory and inhibitory mechanisms or an adjustment of auditory gain mechanisms [16]. The non-auditory brain areas involved in the pathogenesis of tinnitus include the anterior cingulate cortex, anterior insula, amygdala, orbitofrontal cortex, dorsal lateral prefrontal cortex, posterior cingulate cortex, the precuneus, and the hippocampal and parahippocampal areas [17, 18]. Increased activation of the bilateral superior temporal gyrus, which contains both primary and secondary associations with the auditory areas, have been observed during CVS in previous studies [19]. CVS has been shown to modulate vestibular nerve activity as a consequence of the induction of the endolymphatic flow in the inner ear. CVS might, therefore, affect auditory nerve activity through the participation of the superior temporal gyrus in an auditory–vestibular interaction [12]. The improvement in tinnitus-associated symptoms and audiological measurements accomplished with cold CVS in our study might be associated with the modulation of this multimodal vestibular network by the CVS.

Electrophysiological studies of auditory sensory gating in humans and animal models have demonstrated the involvement of the posterior parahippocampal area in auditory habituation [20,21]. Development of auditory hallucinations following the deactivation of the parahippocampal gyrus in patients with psychotic disorders supports the involvement of the parahippocampal area in auditory procession [22]. Thus, it has been considered that parahippocampal structures are critical in the establishment of auditory memory for tinnitus. In addition, the contralateral parahippocampal area is related to the lateralization of tinnitus [23]. The side of the stimulus is an important component of the cortical activation pattern. Positron emission tomography and functional magnetic resonance imaging studies demonstrated that application of cold CVS leads to contralateral activation in temporoparietal regions, whereas warm CVS leads to the ipsilateral activation of these regions [24]. From the perspective of our findings, we speculate that the hyperactivity of the contralateral parahippocampus in subjects with tinnitus might be rebalanced with the increase in the activity of the ipsilateral parahippocampal area through CVS.

Strong integration between the cortical vestibular system and somatosensory processing has been reported previously [25]. An alteration in the inhibitory effect of the dorsal cochlear nucleus may, therefore, result in tinnitus. Several pieces of research have documented the existence of interconnections from the somatosensory system to the dorsal cochlear nucleus, which may contribute to the development of the somatic tinnitus [26]. The dorsal cochlear nucleus receives input from the somatosensory system, in particular, from the external ear. Thus, the somatosensory inputs arising from the external ear with the application of CVS in our study might have also suppressed the symptoms of tinnitus through the network between the somatosensory system and the dorsal cochlear nucleus. We also consider that CVS application might have suppressed the perception of tinnitus by influencing the autonomic system, auditory system, facial nerve activity, and trigeminal nerve activity.

Among the non-auditory areas of the brain that are related to tinnitus, the limbic system and other forebrain regions

have been the focus of a great number of studies. A bi-directional interconnection exists between the limbic system and the auditory system, and a large variety of brain functions and behaviors have been related to these interconnections [27]. The ventromedial prefrontal cortex and the nucleus accumbens have been documented to be the contributors to the generation and maintenance of tinnitus [28]. The hearing-loss induced hyperactivity in auditory circuits is ordinarily suppressed by the ventromedial prefrontal cortex and the nucleus accumbens; thus, the lack of the proper functioning of these structures may lead to inappropriate neural activity in the thalamus and result in tinnitus. Application of cold water into the external auditory meatus might play a modulatory impact on the interconnections presenting between the limbic and the auditory systems.

The present study demonstrates the positive effects of CVS with cold water on audiologic and self-reported quality measures of idiopathic tinnitus. CVS led to an acute improvement in the self-reported intensity and disturbance of the tinnitus despite the lack of a change in the frequency of the tinnitus. Although an increase in both the intensity and disturbance caused by the tinnitus was reported at the fourth week, it was still encouraging than the baseline scores. This was further supported by the improvement in the THI and BDI scores. Both THI and BDI demonstrate the impact of the tinnitus on the psychological state of the subjects. A possible explanation for the relationship between the depressive symptoms and the tinnitus might be that the 'distress circuit', which includes several limbic structures, contributes to the transition of the tinnitus percept to a distress response [27]. The present study documented the correlation between the BDI score and THI score in both arms. However, whether depression accompanies tinnitus or tinnitus is the cause of the high BDI scores is not clear. In addition, there might be a bidirectional relationship between depression and tinnitus. Further research is required to clearly address the cause-and-effect relationship between tinnitus and depression. In addition to these, although CVS with cold water was effective in tinnitus, CVS application at body temperature did not cause any improvement in tinnitus symptoms. There is no study using water at body temperature as we did in the control group. However, Baguley et al.[10] showed that CVS application with water at 44 ° C had no effect on tinnitus. Our findings in the control group are consistent with the study findings of Baguley et al.

Although the clear explanation of the pathophysiological mechanism of the benefit accomplished with CVS is beyond the scope of this paper, we suggest that modulation of neuronal hyperactivity among the complex interconnections existing between the non-auditory and the auditory structures is the most probable contributor of CVS to the suppression of tinnitus.

Limitations

The most important limitation of our study that needs to be improved is that we failed to demonstrate the functional and structural changes in the particular brain areas with either functional magnetic resonance imaging or electroencephalography during CVS. Thus, we cannot provide a clear topographic explanation to the question 'how does CVS with cold water eliminate or alleviate tinnitus?' More comprehensive studies, including imaging data, are required to accurately address the mechanism of the benefit derived from the CVS.

Conclusion

This study clearly shows that CVS with cold water leads to a significant improvement in symptoms associated with idiopathic tinnitus compared to CVS with water at body temperature. It can be speculated that the benefit derived from CVS is related to its modulatory effects on the cortical, thalamic, and limbic areas, and the neuronal network between the dorsal cochlear nucleus and the somatosensory system. More research is needed to identify the precise neuronal pathways affected by CVS and to observe its long-term effects.

References

1. Savage J, Waddell A. Tinnitus. BMJ Clin Evid. 2014;0506. PMID: 25328113
2. Knipper M, Van Dijk P, Nunes I, Ruttiger L, Zimmermann U. Advances in the neurobiology of hearing disorders: recent developments regarding the basis of tinnitus and hyperacusis. Progress in neurobiology. 2013;111:17-33.
3. Riga M, Komis A, Maragoudakis P, Korres G, Ferekidis E, Danielides V. Objective assessment of subjective tinnitus through contralateral suppression of otoacoustic emissions by white noise: effects of frequency, gender, tinnitus bilaterality and age. Acta Otorhinolaryngologica Italica. 2018;38:131.
4. Langguth B, Elgoyhen AB, Cederroth CR. Therapeutic Approaches to the Treatment of Tinnitus. Annu Rev Pharmacol Toxicol. 2019;59:291-313.
5. Yuan T, Yadollahpour A, Salgado-Ramírez J, Robles-Camarillo D, Ortega-Palacios R. Transcranial direct current stimulation for the treatment of tinnitus: a review of clinical trials and mechanisms of action. BMC Neurosci. 2018;19:66.
6. Folmer RL, Theodoroff SM, Casiana L, Shi Y, Griest S, Vachhani J. Repetitive Transcranial Magnetic Stimulation Treatment for Chronic Tinnitus: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2015;141:716-22.
7. Bottini G, Sterzi R, Paulesu E, Vallar G, Cappa SF, Erminio F, et al. Identification of the central vestibular projections in man: a positron emission tomography activation study. Experimental brain research. 1994;99:164-9.
8. Miller SM, Ngo TT. Studies of caloric vestibular stimulation: implications for the cognitive neurosciences, the clinical neurosciences and neurophilosophy. Acta neuropsychiatrica. 2007;19:183-203.
9. Lamprecht J, Morgenstern C. [Bilateral caloric long-term irrigation as a method for the differentiation of tonal tinnitus]. Laryngologie, Rhinologie, Otologie. 1985;64:17-20.
10. Baguley DM, Knight R, Bradshaw L. Does caloric vestibular stimulation modulate tinnitus? Neurosci Lett. 2011;492:52-4.
11. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. Behavior research methods. 2009;41:1149-60.
12. Suzuki M, Kitano H, Ito R, Kitanishi T, Yazawa Y, Ogawa T, et al. Cortical and subcortical vestibular response to caloric stimulation detected by functional magnetic resonance imaging. Brain Res Cogn Brain Res. 2001;12:441-9.
13. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. Archives of otolaryngology--head & neck surgery. 1996;122:143-8.
14. Huang C, Chen JH. Meta-Analysis of the Factor Structures of the Beck Depression Inventory-II. Assessment. 2015;22:459-72.
15. De Ridder D, De Mulder G, Verstraeten E, Van der Kelen K, Sunaert S, Smits M, et al. Primary and secondary auditory cortex stimulation for intractable tinnitus. ORL; journal for oto-rhino-laryngology and its related specialties. 2006;68:48-54; discussion -5.
16. Norena AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neuroscience & Biobehavioral Reviews. 2011;35:1089-109.
17. Vanneste S, De Ridder D. The auditory and non-auditory brain areas involved in tinnitus. An emergent property of multiple parallel overlapping subnetworks. Frontiers in systems neuroscience. 2012;6:31.
18. Simonetti P, Oiticica J. Tinnitus Neural Mechanisms and Structural Changes in the Brain: The Contribution of Neuroimaging Research. International archives of otorhinolaryngology. 2015;19:259-65.
19. Marcelli V, Esposito F, Aragri A, Furia T, Riccardi P, Tosetti M, et al. Spatio-temporal pattern of vestibular information processing after brief caloric stimulation. European journal of radiology. 2009;70:312-6.
20. Bickford PC, Luntz-Leybman V, Freedman R. Auditory sensory gating in the rat hippocampus: modulation by brainstem activity. Brain research. 1993;607:33-8.
21. Boutros NN, Arfken C, Galderisi S, Warrick J, Pratt G, Iacono W. The status of spectral EEG abnormality as a diagnostic test for schizophrenia. Schizophrenia research. 2008;99:225-37.
22. Diederen KM, Neggers SF, Daalman K, Blom JD, Goekoop R, Kahn RS, et al. Deactivation of the parahippocampal gyrus preceding auditory hallucinations in schizophrenia. The American journal of psychiatry. 2010;167:427-35.
23. Vanneste S, Van de Heyning P, De Ridder D. Contralateral parahippocampal gamma-band activity determines noise-like tinnitus laterality: a region of interest analysis. Neuroscience. 2011;199:481-90.
24. Bense S, Bartenstein P, Lutz S, Stephan T, Schwaiger M, Brandt T, et al. Three determinants of vestibular hemispheric dominance during caloric stimulation: a positron emission tomography study. Annals of the New York Academy of Sciences. 2003;1004:440-5.
25. Ferre ER, Day BL, Bottini G, Haggard P. How the vestibular system interacts with somatosensory perception: a sham-controlled study with galvanic vestibular stimulation. Neurosci Lett. 2013;550:35-40.
26. Eggermont JJ. Tinnitus: neurobiological substrates. Drug discovery today. 2005;10:1283-90.
27. Galazyuk AV, Wenstrup JJ, Hamid MA. Tinnitus and underlying brain mechanisms. Current opinion in otolaryngology & head and neck surgery. 2012;20:409-15.
28. Leaver AM, Renier L, Chevillet MA, Morgan S, Kim HJ, Rauschecker JP. Dysregulation of limbic and auditory networks in tinnitus. Neuron. 2011;69:33-43.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1046-1051.
DOI: 10.28982/josam.793759

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Spatiotemporal relationship analysis of the 2019-nCoV patients hospitalized in Istanbul: A retrospective database analysis

İstanbul'da hastanelere başvuran 2019-nCov hastalarının yer-zaman ilişkisinin incelemesi: Geçmişe dönük bir veri tabanı incelemesi

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Ethics Committee Approval: Umraniye Research and Training Hospital Clinical Research Ethics Committee, 4/28/2020, B.10.1.TKH.4.34.H.GP.0.01-133 All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Ümraniye Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu, 28.04.2020, B.10.1.TKH.4.34.H.GP.0.01-133. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: The COVID-19 epidemic has reached every country in the world. Control strategies require effective tracing and isolation activities. Electronic mapping techniques are used in the visualization of spreading characteristics of COVID-19. The Geospatial Information System became an exceedingly popular open web tool to inform professionals and the public. These systems allow public health authorities to monitor the spreading characteristics and plan effective control strategies. The objective of this study was to identify the spatiotemporal mutual relationship of COVID19 patients living in two of the biggest districts of Istanbul (Kadikoy and Uskudar) who were admitted to the hospital.

Methods: A total of 672 adult patients who were diagnosed with possible or confirmed COVID19 infection were included in the analysis. COVID19 diagnosis was confirmed either with positive RT-PCR test or radiographic chest imaging plus the presence of symptoms of the infection. Pearson correlation analysis and Moran's correlation analysis were applied to the data set. Small pieces of regions [100,000 x 100,000] were set for the districts, and each event origin was fitted into the proper region using cartesian coordinate information. Getis-Ord hot spot analysis was performed to pinpoint the infections with higher concentration over time.

Results: Pearson's correlation revealed no significant results, while Moran's analysis showed a significant correlation between distance and admission date [I: 0.64]. We identified at least 10 relevant hot spots in 3 districts.

Conclusion: Determining the spatiotemporal relationship among cases of a central hospital may inform local authorities about dissemination patterns and help improve control measures against epidemics.

Keywords: Spatiotemporal Relationship Analysis, 2019-nCoV, Counties

Öz

Amaç: COVID-19 virüsünü salgını dünyanın neredeyse her yerine yayılmış durumdadır. Kontrol yöntemleri ise etkili takip ve izolasyon yöntemleri gerektirmektedir. Elektronik haritalama teknikleri COVID-19 virüsünün yayılma özelliklerini görselleştirmede kullanılmaktadır. Konum Bazlı Bilgi Sistemi yetkilileri ve halkı bilgilendirmek için çoğunlukla tercih edilmektedir. Bu sistemler halk sağlığı yetkililerine hastalığın yayılma özelliklerini göstererek, daha etkili kontrol planlaması yapılmasını sağlamaktadır. Bu çalışmanın amacı İstanbul'un en büyük iki ilçelerinden ikisinde (Kadıköy ve Üsküdar) yaşayan ve COVID-19 nedeniyle hastaneye kabul edilen hastaların yer-zaman ilişkilerinin belirlenmesidir.

Yöntemler: COVID-19 enfeksiyonu tanısı onaylanmış/olası 672 yetişkin hasta bu çalışmaya dahil edilmiştir. COVID-19 teshisleri; ya pozitif sonuçlanan RT-PCT testleri ile ya da hastalığın belirtilerini görülüyorsa radyolojik göğüs tetkikleri ile doğrulanmıştır. Veriler Pearson korelasyon analizi ve Moran's korelasyon analizi ile değerlendirilmiştir İlçeler için küçük bölge parçaları [100.000 x 100.000] ayarlandı ve her olgunun kaynağı kartezyen yer belirleme kullanılarak kurulan küçük bölge parçalarına oturtuldu. Zaman içerisinde yoğunluğun artması ile enfeksiyonu tam olarak belirlemek için Getis-Ord sıcak nokta analizi kullanılmıştır.

Bulgular: Mesafe ve hastaneye kabul edilme süresi arasında Pearson korelasyonuna göre ilişki bulunmazken, Moran korelasyonun da anlamlı bir ilişki bulmuştur [I:0.64]. 3 bölgede en az 10 sıcak nokta tespit edilmiştir.

Sonuç: İndeks hastane vakaları arasındaki yer-zaman ilişkisinin belirlenmesi, yerel yetkililere hastalığın yayılma örüntüsü hakkında bilgi verebilir ve salgınlara karşı kontrol önlemleri geliştirilmesine yardımcı olabilir.

Anahtar kelimeler: Yer-zamansal ilişki incelemesi, 2019-nCoV, İlçeler

How to cite/Atıf için: Şaylan B, Özkan D. Spatiotemporal relationship analysis of the 2019-nCoV patients hospitalized in Istanbul: A retrospective database analysis. J Surg Med. 2020;4(11):1046-1051.

Introduction

Since the beginning of 2020, the world was overshadowed by the rapidly spreading novel severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] named COVID-19. The World Health Organization reported 3679499 confirmed cases of COVID-19, including 254199 deaths globally, as of 6:32pm CEST, 7 May 2020 [1]. On the 11th of March, the first coronavirus infection case was reported in Turkey and there are 135569 confirmed cases and 3689 deaths reported as of the 8th of May, most of which were detected in the city of Istanbul [1].

During the COVID19 epidemic, choosing the best intervention strategy is critical to effectively control the spreading of disease, especially when uncertainties regarding the disease are present. Control measures can be categorized under two main strategies: Suppression or mitigation. Both strategies require effective tracing and isolation activities. Time of contact with suspected or confirmed cases and location are two important variables to better understand infectivity characteristics of the virus and dependency of virus dissemination on human behavior. Although health professionals started using conventional mapping techniques to visualize the relationship between place and health many centuries ago [2], new technological tools capturing spatiotemporal data were used in China to early identify spreading characteristics and plan effective use of resources [3]. Similar mapping techniques are being used in the visualization of spreading characteristics of other viral diseases for decades. Country-level maps are produced to show the distribution of viral diseases over time [4]. Throughout these mapping methods, it was possible to estimate the movement of the pandemics and future patterns of spread. Geospatial and time analysis is a valuable tool in determining the spatial spread and quantifying determinants of contamination. In countries where health and sociodemographic data collection systems are developed, such information has been widely used by governments to identify the spatiotemporal movement of chronic infections [5,6]. This analysis method has been also used to identify hot spots for the infection source in geographies where preventive measures must be planned considering both individual and geographic-area variation [7]. Location and time are two important environmental determinants of health status because they include risk factors of contagious diseases. Integrating and analyzing location-based real-world information and generating predictive modelling using novel information technologies during the pandemic can help health care providers and planners to identify those risk factors and new methods for prevention [8]. Recently, Geospatial Information System dashboards have developed open web tool applications by WHO and other scientific institutions to inform professionals and the public. Furthermore, the dedicated mobile phone-based application was used to collect personal data from public authorities and inform users about their risks in a highly detailed spatial scale [9].

All published studies and dashboards use country or regional data sources for geospatial analysis. However, most of the logistic and health sources planning must be conducted at the district level, as well. Under the social distancing and strict travel restriction circumstances, narrower scaled modelling of spatiotemporal maps may be more useful and realistic to understand dissemination and control it. The Turkish government has implemented severe social distancing measures and travel restrictions immediately after the detection of the first COVID19 case in the country [10]. All COVID19 patient-related real-time data, including actual residential information are collected from hospitals and stored in a central database [Public Health Management System] for surveillance and home-based treatment purposes. It allows public health authorities to monitor all events at thousands of public health facilities simultaneously and centrally.

In this study, we aimed to identify the spatiotemporal mutual relationship of COVID19 diagnosed patients living in two of the biggest districts of Istanbul [Kadikoy and Uskudar] who were admitted to our hospital by using residential address-based information systems and patients' clinical data.

Materials and methods

Patient data collection and diagnosis

All patients over 18 years of age admitted to 2. Abdulhamid Han Research and Training Hospital [N 41°00'05.4", E 29°01'11.2"] who were diagnosed with possible or confirmed COVID19 infection between 1st of March – 9th of April 2020 are included in the analysis. COVID19 diagnosis was confirmed either with a positive RT-PCR test developed by the Turkish Ministry of Health central GDPH Microbiology Reference Laboratory or radiographic chest imaging plus symptom array of the infection [Fever, acute respiratory symptoms, travel, contact with a COVID19 patient]. All clinical, laboratory and demographic data were retrieved from the hospital local database and Public Health Management System. Geolocation information for each patient is obtained using patients' residential addresses. Before starting geospatial analysis, the data set is modified to remove incomplete or ineligible data from the data set. All analysis mentioned below are applied to cleansed data set to prevent the results from being affected by inconsistencies in the data set. A total of 672 patients with valid address data and admission dates were included in our analysis. Descriptive analysis of the cases was completed using IBM SPSS Statistics Version 20.0. The study area, Istanbul City, is located between Black Sea and Marmara Sea, [in 41° 0' 54.4932" N latitude and 28° 58' 46.3080" E longitude], with a total area of about 5461km2, with 15,52 million habitants and with metro density of 2987/km^2. Kadikoy and Uskudar districts have total area of about 25.2km^2 and 46.41km^2, respectively, and populations of 482.713 and 531.825, respectively. The Medical Ethics Committee at Umraniye Research and Training Hospital approved the study on the 28th of April 2020. As all patients give consent for data collection and retrospective research at the hospital level, it needed no consent from the participants.

Geospatial analysis and mapping of COVID19 infections

To calculate spatial weight for each event, exact latitude and longitude information was attained using address information in the application form. For every address line in the admission form, a request to get coordinate information is sent to Google Geolocation API via Python script, and exact coordinates

are returned. This process was completed using Python 3.7 distribution. A distance matrix containing spherical distance from each patient to all other patients is created. To use application date as a measurement for infection propagation, application date data is converted to scaler values as an offset from the first case $[o_0]$. Interpatient distances and admission dates are the selected to be used in geospatial analysis. The distance information obtained from the distance matrix with 672 columns and 672 rows is the first input to be used in every analysis mentioned below.

Inter-distances between patients were calculated by their geo-coordinates. Geospatial analysis is divided into three parts, starting from determining the dependency of the whole data set to analyzing each patient, respectively.

In the first part, a correlation analysis is applied to data set to reveal the relationship between patients. In this phase, the Pearson correlation coefficient, a widely used correlation coefficient indicating a linear association between independent variables [11], is used to measure linear dependency between infection and location of patients. However, geospatial variables are rarely eligible for linear dependency analysis. Therefore, a correlation coefficient designed to measure geospatial dependency, Moran's I, is used in the second part of the analysis [12]. Geospatial correlation was applied to reveal whether admission dates were correlated with distances between all patients.

After the geospatial correlation for the whole data set is obtained, the origin point of every infection is analyzed in the third part. This part of the analysis aims to find out whether cases center upon any area by using Getis-Ord's hot spot analysis [13]. In this phase, each patient is analyzed in conjunction with every other patient regarding the distance between patients and the admission date. In a highly infectious disease, regions with high concentration of infection are required to be explored and isolated. Thus, finding and isolating these spots play a crucial role in getting ahead of disease spread.

Design study

This study aims to find a mutual relationship between different cases with the positive COVID-19 test results. Address information for each case and application that the institution is selected as input variables to establish a correlation between cases. The study is designed as three phases: Data preparation, correlation analysis and hot spot analysis.

Phase I – Data preparation

Patient data is reduced to 672 separate cases with two features, address information of the patient and application date. In order to calculate a spatial weight for each event, exact latitude and longitude information should be obtained. For every address line in the admission form, a request to get coordinate information is sent to Google Geolocation API via Python script, and exact coordinates are returned.

Inter-distances were calculated using their geo-coordinates. Spherical distances with given latitude and longitude can be calculated with the formula suggested by José de Mendoza y Ríos [14], which was later called the "Haversine Distance."

$$d = 2 \times r \times arcsin\left(\sqrt{sin^2\left(\frac{\Delta_\varphi}{2}\right) \times \cos\varphi_1 \times \cos\varphi_2 \times sin^2\left(\frac{\Delta_\lambda}{2}\right)}\right) \quad [1]$$

$$\Delta_\varphi = \varphi_2 - \varphi_1 \quad [2]$$

$$\Delta_\lambda = \lambda_2 - \lambda_1 \quad [3]$$

d: Spherical distance

r: Radius of the sphere*

***:** $r_{Earth} \approx 6{,}371$

The distance matrix is created with the distance between the residential address of each patient to all other patients' residential addresses. The distance information taken from the distance matrix with 672 columns and 672 rows is the first input to be used in every analysis mentioned below.

The second input is selected as admission date, considering the aim of this study to find out the relationship between infection date and geographic proximity. However, the admission date is not eligible to use in calculations with distance due to the format of the date data. Thus, to use admission date as a measurement for infection propagation, admission date data was converted to scaler values as an offset from the first case $[o_0]$.

Phase II – Correlation analysis

In the second phase, Pearson correlation analysis was applied to the data set. There are two data sets created for Pearson correlation analysis, including raw and modified data. Raw data consist of two columns to compare:

$o_{0_{ij}}$: marginal o_0 from event i to event j

d_{ij} : distance from home of event i to home of event j

The second data set was created to fit spatial data better to Pearson's. Frequency analysis is completed on data to fit each event into a related category on the scale of measurement [15]. The analysis yielded 300 different categories covering all the data of both $o_{0_{ij}}$ and d_{ij}.

Pearson's analysis with the original data set has resulted in correlation coefficient **0** which indicates no correlation at all. Along with that, Pearson's analysis with grouped data set resulted in an r-value of $5.9 \times \mathrm{E} - 13$ which is again too small, almost indicating zero correlation.

Following Pearson correlation analysis, Moran's correlation analysis is applied next. In Moran's analysis, each data is positioned in a pre-defined discrete geographical region. Since the cartesian coordinates system is continuous, small pieces of regions [100,000 x 100,000] are set on the Anatolian side of Istanbul, and each event origin is fitted into the proper region using cartesian coordinate information.

Further, adjacency of events should be defined, and an adjacency matrix should be formed. Adjacency between cells can be defined by using either Moore neighborhoods [Queen's case] or Von Neumann neighborhoods [Rook's case] [16]. Queen's case is selected for this study and an adjacency matrix is formed. Adjacency matrix became a basis for the weight matrix $[w_{ij}]$ by assigning the highest spatial weight to the closest two origins and similarly assigning lowest weight to most distant two origin. Using $o_{0_{ij}}$ and w_{ij}, Moran's I is calculated.

$$I = \frac{1}{S^2} \times \frac{\sum_i \sum_j w_{ij} \times \left(o_{0_i} - \overline{o_0}\right) \times \left(o_{0_j} - \overline{o_0}\right)}{W} \quad (1)$$

$$W = \sum_{i=1}^{N} \sum_{j=1}^{N} w_{ij} \quad [2]$$

$$S^2 = \frac{\sum_{i=1}^{N} \left(o_{0_i} - \overline{o_0}\right)^2}{N} \quad [3]$$

Moran's I has a value from -1 to +1 where;

- -1 refers to perfect dispersion [negative correlation]
- 0 refers to perfect randomness [no spatial correlation]
- +1 refers to perfect clustering [positive correlation]

Moran's analysis is applied to the patient data set and resulted in an I value of **0.64**, which indicates a positive correlation.

Phase III – Hot spot analysis

A hot spot refers to a place of more than usual interest, activity, or popularity comparing to other areas. In epidemiology, hot spot indicates a region with high concentration of a disease [17]. Hot spot analysis techniques are derived from dispersion studies aiming to understand the distribution of points in space [18]. The aim of hot spot analysis in any spatial relationship study is to pinpoint the event with a higher concentration of defined measurement among the distribution of all events. Hot spot analysis lets discover location related clusters while making detecting anomalies easier [19].

Getis and Ord offered a hot spot metric, G^* to identify spatial patterns and find the events with a higher concentration of measurement metrics. Getis-Ord's methodology evaluates each data point respecting distances between other data points and proximity of admission dates.

$$G^* = \frac{\sum_j^n w_{ij} x_j - \bar{X} \times \sum_j^n w_{ij}}{S \times \sqrt{\frac{\left[\left(n \times \sum_j^n w_{ij}{}^2\right) - \left(\sum_j^n w_{ij}\right)^2\right]}{n-1}}} \quad [1]$$

$$\bar{X} = \frac{\sum_j^n x_j}{n} \quad [2]$$

$$S = \sqrt{\frac{\sum_j^n x_j{}^2}{n} - \left(\bar{\bar{X}}\right)^2} \quad [3]$$

The Getis-Ord. analysis is applied to all 672 origin points in the data set. Distance between the location of the selected patient and the location of the next patient is used as w_{ij} in the formula. As for x_j, offset value of admission [$o_{0_{ij}}$] is used. After evaluation of all 672 locations using distance and admission information, a total number of 10 events emerged as the hot spots.

Results

The mean age of patients was 51.54 (SD:16.42) years, and 53.9% of patients were male. Among all, 27.5% of patients were treated as an outpatient, 5.2% died, 50.4% were discharged and 16.8% were still hospitalized during the study period. Majority of cases were in Uskudar (30.95%), Kadikoy (10.26%), Umraniye (15.47%), Atasehir (7.29%) districts. A detailed distribution map can be seen in figure 1. Peak date of admissions (57 patients, 8.5%) was on the 9th of April, and most patients were admitted to the hospital between the 1st and 15th of April (Figure 2).

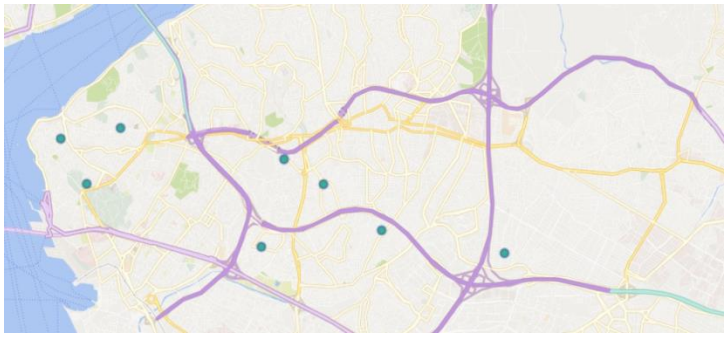

Figure 1: 10 hot spots emerged following hot spot analysis

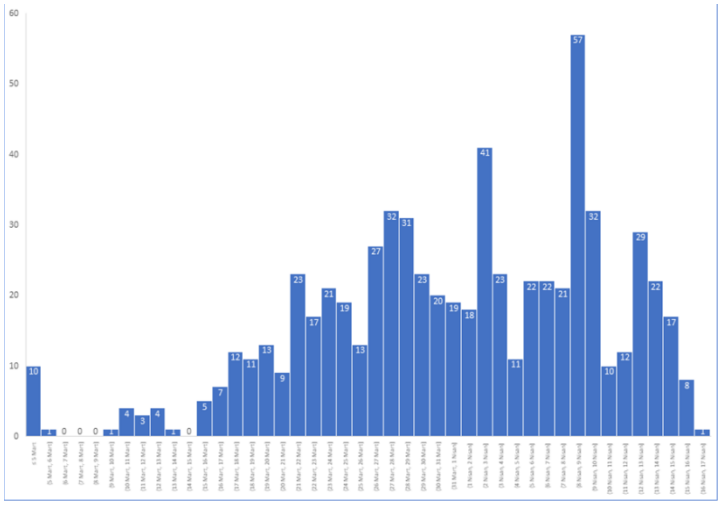

Figure 2: Number of admission per day

Admission dates and distances between patients are given as input with two different approaches, traditional approach, and categorical distance approach [Figure 3]. The traditional approach returned the Pearson's correlation coefficient $r = 0$ which indicates no linear dependency at all. Similarly, the categorical distance approach returned an exceedingly small r value; $5.9 \times E - 13$.

Moran's I, a correlation coefficient specifically designed to measure location-based relationship, is used in the second step of the analysis. Moran's analysis returned a correlation coefficient of 0.64 which significantly implies a correlation between distance and admission date.

In hot spot analysis, while Getis-Ord's G^* increases, hot spots in the data set emerges. Our data set of 672 patients revealed at least 10 relevant hot spots [5 in Kadikoy, 4 in Uskudar and 1 in Atasehir districts], information of which can be found in Figure 3 below.

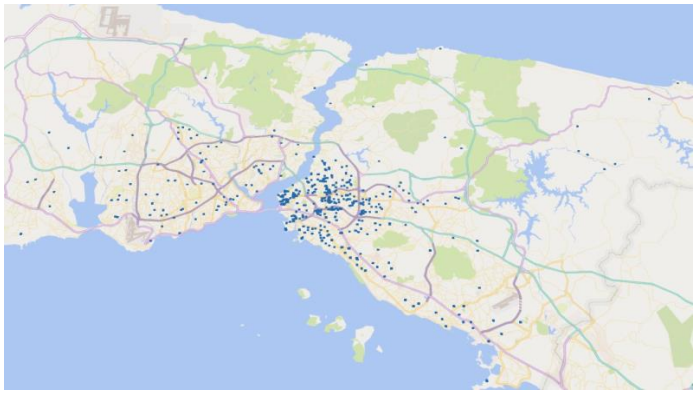

Figure 3: Case density map of the sample group

Discussion

The purpose of this study was to identify the spatiotemporal mutual relationship of COVID19 diagnosed patients living in two counties of Istanbul and we found that there is a significant correlation between distance and admission date. In addition, we found at least 10 relevant hot spots (5 spots in Kadikoy and 5 spots in surrounding districts) that should be considered as the most important location-time points for the dissemination of the disease in our sample. Consecutive and interrelated admissions of those individuals to our central hospital shows that there is a modellable dissemination pattern of the virus within a small but densely populated geography. Detected hot spots require more attention for the initial dissemination and control of the source of disease.

Our hospital was the earliest designated hospital for COVID19 treatment only after the breakout of the pandemic in the North-East part of Istanbul. The number of diagnosed patients over time in this hospital reflects and confirms the similarity with the acute course of the pandemic in the city. To date, COVID19-related geospatial and spatiotemporal analysis are limited and in contrast with previous studies, we investigated spatiotemporal analysis of the infection in a limited geography. Hence the results may be more useful to elucidate early dissemination and control from local management perspective together with country-wise preventive measures. Particularly when general shutdowns and curfews were heavily criticized [20], surveillance measures could be implemented in limited geography based on this local analysis to abate economic and social impacts.

The data used in our analysis have several limitations. First, the data was extracted from a single hospital. As not all patients from these districts were admitted to our hospital, the patient pool could not reflect all dissemination pattern although most of the initial cases were accumulated in our hospital, which was assigned as a COVID19 reference center. Second, population-based testing was not used to identify asymptomatic cases, therefore, spreading of infections through asymptomatic cases could not be included in our correlation analysis. Third, as for geospatial correlation, patient data set covers patients getting treated at the institution coming from different districts of Istanbul. This fact prevents analysis to see the whole picture in two districts included in the analysis. However, 0.64 I value with this missing picture indicates that, if the same analysis can be applied to whole patients' data of these districts, a very strong spatial correlation is to be obtained. Fourth, the effect of cases' daily mobility before admission to the hospital could not be included in the correlation analysis. Finally, hot spot analyses require considerably big data sets to set a profound base to identify location-based dependencies. Considering the data set used in Getis-Ord analysis is relatively small and concentrated on a few districts in Istanbul, it would be expected not to get any meaningful hot spot location at all. However, even with this particular small data set, Getis-Ord's G^* is yielding decent results that imply bigger data sets related to infectious diseases fit the analysis particularly well. Linear correlation yielded that, Pearson's r is not a good indicator of geolocation-based correlation. Even though converting data to a more discrete pattern helps, the correlation coefficient was still too insignificant.

A recently published study showed a distribution pattern of COVID19 in a large-scale spatial [total area of about 185,900 km2] but limited temporal analysis (15 days) in Hubei Province, China [21]. Six types of temporal patterns were defined based on increasing and significant abrupt changes at the county level. However, the spatial data are collected at the city/county level and it is not based on the residential address. They also explained abrupt temporal and spatial changes based on the increases in daily testing capacity and on implementation of mobility control measures from Wuhan. Despite a large number of cases, it only provided temporal changes according to confirmed data from districts, and spatial resolution was limited at the district level. Our study spatial data is based on point location and time. Similarly, we identified a spatial cluster that can be useful for timely control of population flows to prevent a larger outbreak of disease.

Hubei Province study included cases confirmed with nucleic acid only. Hitherto, low sensitivity nucleic acid tests, poor consistency between the positive rate of initial nucleic acid tests, and clinical findings were heavily criticized in China [22]. Our study included both RT-PCR testing positive and CT confirmed cases.

Limitations

There will be future study proposals, but limitations to this study are irrelevant for now.

Conclusion

The results of our study suggest that there is a strong spatiotemporal relationship among the cases of an index hospital, accepting patients from a limited geographic and densely populated area. The early identification of the dissemination pattern and hot spots throughout a similar analysis during the second wave of the pandemic may lead to a more effective control with a less negative impact on economic and social life. This analysis could be further improved using additional data sources and more precise clinical information for the calculations. Expansion of data source set from one hospital to all health care units in the city [increase in the number of patients] and using first symptom appearance date instead of hospital admission date will further improve the precision of the results and could lead more generalizable conclusions.

References

1. WHO Coronavirus Disease (COVID-19) Dashboard. https://covid19.who.int/ Access 07.05.2020.
2. Koch T. 1831: The map that launched the idea of global health. Int J Epidemiol. 2014; 43:1014-20.
3. Zhou C, Su F, Pei T, Zhang A, Du Y, Luo B, et al. Covid-19: challenges to GIS with big data. Geography and Sustainability. 2020 Mar;1:77-87.

4. Bull SE, Briddon RW, Sserubombwe WS, Ngugi K, Markham PG, Stanley J. Genetic diversity and phylogeography of cassava mosaic viruses in Kenya. J Gen Virol. 2006 Oct; 87:3053-3065.
5. Kauhl B, Heil J, Hoebe CJ, Schweikart J, Krafft T, Dukers-Muijrers NH. The spatial distribution of hepatitis C virus infections and associated determinants -an application of a geographically weighted poisson regression for evidence-based screening interventions in hotspots. Plos One. 2005 Sep;10(9).
6. Wang L, Xing J, Chen F, Yan R, Ge L, Qin Q, et al. Spatial analysis on hepatitis C virus infection in mainland China: from 2005 to 2011. Plos One. 2014;9(10).
7. Daw MA, Buktir Ali LA, Daw AM, Sifennasr NEM, Dau AA, Agnan MM, et al. The geographic variation and spatiotemporal distribution of hepatitis C virus infection in Libya: 2007-2016. BMC Infect Dis. 2018 Nov;18(594).
8. Venna SR, Tavanaei A, Gottumukkala RN, Raghavan VV, Maida AS, Nichols S. A novel data-driven model for real-time influenza forecasting. IEEE Access. 2019;7:7691-701.
9. Kamel Boulos MN, Geraghty EM. Geographical tracking and mapping of coronavirus disease COVID-19/severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] epidemic and associated events around the world: how 21st century GIS technologies are supporting the global fight against outbreaks and epidemics. Int J Health Geogr. 2020 Mar;19(8).
10. Guner R, Hasanoglu I, Aktas F. COVID-19: Prevention and control measures in community. Turk J Med Sci. 2020 Apr; 50(3):571-577.
11. Kass RE, Caffo BS, Davidian M, Meng XL, Yu B, Reid N. Ten simple rules for effective statistical practice. Plos Comput Biol. 2016;12(6).
12. Moran PAP. Notes on continuous stochastic phenomena. Biometrika. 1950;37:17-23.
13. Getis A, Ord JK. The analysis of spatial sssociation by use of distance statistics. Geographical Analysis. 1992;24:189-206.
14. Florian C. A history of mathematical notations. New York: Cosimo Inc.; 1929.
15. Gravetter FJ, Wallnau LB. Statistics for the behavioral sciences. Belmont: Wadsworth – Thomson Learning; 2000.
16. Lloyd C. Spatial data analysis: an introduction for GIS users. Oxford: Oxford university press; 2010.
17. McGraw-Hill Concise Dictionary of Modern Medicine. https://medical-dictionary.thefreedictionary.com/hot+spot. Access 07.08.2020.
18. Chakravorty S. Identifying crime clusters: the spatial principles. Middle States Geographer. 2018;28:53-8.
19. Sánchez Martín JM, Rengifo Gallego JI, Blas Morato R. Hot spot analysis versus cluster and outlier analysis: An enquiry into the grouping of rural accommodation in extremadura (Spain). Int J Geo-Inf. 2019;8(176).
20. Protests over responses to the COVID-19 pandemic. https://en.wikipedia.org/w/index.php?title=Protests_over_responses_to_the_COVID-19_pandemic&oldid=958106480. Access 23.05.2020.
21. Yang W, Deng M, Li C, Huang J. Spatio-temporal patterns of the 2019-nCoV epidemic at the county level in Hubei province, China. Int J Environ Res Public Health. 2020;17(7):2563.
22. Zhifeng J, Feng A, Li T. Consistency analysis of COVID-19 nucleic acid tests and the changes of lung CT. J Clin Virol. 2020 Jun;127.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1052-1056.
DOI: 10.28982/josam.805189

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Association between suicide idea and anxiety sensitivity in obsessive-compulsive disorder: A controlled study

Obsesif-kompülsif bozukluk hastalarında anksiyete duyarlılığı ve intihar düşüncesi arasındaki ilişki: Kontrollü çalışma

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Ethics Committee Approval: The study protocol was approved by the Sakarya University Ethics Committee approval with approval date 26/06/2020 and approval number approval: 26/06/2020-376. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma, 26/06/2020 onay tarihi ve 26/06/2020-376 onay numarası ile Sakarya Üniversitesi Etik Kurulu onayı tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Obsessive-compulsive disorder (OCD) is associated with suicide risk, but controversy remains about the frequency and burden of suicidality in OCD. This study aimed to identify the relationship between anxiety sensitivity and suicidal idea in patients with OCD.

Methods: This controlled study included 36 OCD patients and 36 healthy controls. All individuals were evaluated with Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Anxiety Sensitivity Index-3 (ASI-3) and Suicide Probability Scale (SPS). Demographic data were obtained from each patient.

Results: Seventy-two individuals with a mean age of 31.89 (9.69) years were included in this study. No significant differences were found between the groups with regards to individual and family histories of suicide attempt and the presence of other chronic diseases ($P>0.05$ for each). The patients had significantly higher BDI, BAI and ASI-3 scores than the controls ($P>0.05$ for each). There were significant correlations between BDI, BAI, ASI-3 and SPS desperation, suicide ideation scores, hostility scores and total scores ($P<0.05$ for each).

Conclusion: The present study revealed that depression and anxiety status are important for suicide risk in OCD patients. Therefore, it is recommended to always evaluate the risk of suicide in these patients.

Keywords: Obsessive-compulsive disorder, Anxiety, Depression, Suicidality

Öz

Amaç: Obsesif kompulsif bozukluk (OKB) intihar riski ile ilişkilidir, ancak OKB'de intihar sıklığı ve yükü konusunda hala bir tartışma vardır. Bu çalışmanın amacı obsesif-kompülsif bozukluk (OKB) hastalarındaki anksiyete duyarlılığı ile intihar düşüncesi arasındaki ilişkiyi saptamaktır.

Yöntemler: Bu kontrollü çalışma 36 OKB hastası ve 36 sağlıklı kontrolü içermekteydi. Tüm olgular Beck Depresyon Skalası (BDS), Beck Anksiyete Skalası (BAS), Yale-Brown Obsesyon Kompülsiyon Ölçeği (YBOKÖ), Anksiyete-Sensivite İndeksi-3 (ASI-3) ve İntihar Olasılığı Ölçeği (İOÖ) ile değerlendirildi. Demografik veriler her hastadan kayıt edildi.

Bulgular: Yetmiş iki olgu çalışmaya dahil edildi. Ortalama yaş 31,89 (9,69) idi. Gruplar arasında intihar girişim hikâyesi, ailede intihar girişim hikâyesi ve herhangi bir kronik hastalık varlığı açısından fark yoktu. BDS, BAÖ ve ASI-3 skorları hasta grubunda kontrol grubuna göre anlamlı olarak daha yüksekti ($P>0,05$). BDS, BAÖ, ASI-3 ve İOÖ umutsuzluk, intihar düşüncesi, düşmanlık ve total skorları arasında anlamlı korelasyonlar saptandı ($P>0,05$).

Sonuç: Bu çalışma depresyon ve anksiyete durumunun OKB hastalarında intihar riski için önemli olduğunu saptamıştır. Bu nedenle OKB tanısı alan hastaların intihar düşüncesi açısından her zaman değerlendirilmesi önerilir.

Anahtar kelimeler: Obsesif-kompülsif bozukluk, Anksiyete, Depresyon, İntihar

How to cite/Atıf için: Ay R, Kılınçel O. Association between suicide idea and anxiety sensitivity in obsessive-compulsive disorder: A controlled study. J Surg Med. 2020;4(11):1052-1056.

Introduction

Obsessive-compulsive disorder (OCD), which affects about 2% of general population [1], is associated with suicide risk. Previously, this risk was considered low because these patients were thought to successfully suppress aggressive impulses [2] but recent reviews and meta-analyses showed that risk of suicide in OCD is higher than estimated [3]. Suicide idea without attempt is determined as an important predictor for suicide attempts [4,5]. If risk factors for ongoing suicide idea are examined carefully, clinicians can protect OCD patients against future suicide attempts. Controversy remains about the frequency and burden of suicidality in OCD. A meta-analysis by Khan et al. showed that mortality rate due to suicide in OCD patients with distinct anxiety disorders was 0.08% [3]. In the meta-analysis of Angelakis et al. [6], although the methodological qualities of the included studies were low, there was a significant association between OCD and suicidality with two different subtypes (suicide attempts and suicidal ideation). On the other hand, in 2019, Albert and colleagues reviewed 31 studies about suicide risk and OCD and revealed that suicidality appears a relevant condition in patients with OCD [7].

Anxiety sensitivity is an important individual difference factor that has been linked to suicidal idea [8]. Also, comorbid anxiety symptoms severity can be a suicide risk predictor in patients with OCD [9]. Therefore, clinicians should be aware of the anxiety severity in OCD patients in terms of suicide risk.

Finally, there is conflicting evidence about the relationship between suicidal behavior and OCD. This study aimed to identify and explore the clinical and demographic factors associated with suicidal idea in OCD patients.

Materials and methods

Study design

The study protocol of this controlled trial was approved by the Sakarya University Ethics Committee on 26/06/2020 with the number 26/06/2020-376. All participants were informed of the study and signed written informed consents before interventions. The study included 36 patients who visited the Psychiatry Outpatient Clinic of Sakarya Yenikent State Hospital between 29 June 2020 and 31 August 2020.

Participants and sample size calculation

The present study was conducted on 36 patients diagnosed with OCD (patient group) based on DSM-5 criteria, and 36 healthy individuals (control group). All patients in the study gave informed consent. The only inclusion criterion was being aged between 18 and 65 years. Exclusion criteria included having any other neurological conditions which may affect cognitive functions. With an α error of 0.05 and a power of 80%, the sample size was calculated as at least 18 patients per group.

Measurements

Beck Depression Inventory (BDI), Anxiety Sensitivity Index-3 (ASI-3), Suicide Probability Scale (SCS), Beck Anxiety Inventory (BAI), and Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) were used to evaluate all individuals. Demographic information was obtained from each patient. OCD was diagnosed with the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I) [10] by a trained psychiatrist, which was also useful in excluding any other psychiatric disorders among the study groups. The Turkish version of the scale was used [11].

Beck Depression Inventory (BDI)

BDI is a 21-item survey evaluating items related to the depression symptoms i.e., irritability, hopelessness, feelings of guilt or being punished, cognitive problems, physical symptoms such as fatigue, lack of sexual desire, and weight loss. A score ≥17 indicates having depression [12]. The validation study of the Turkish BBS was performed by Hisli et al [13].

Beck Anxiety Inventory (BAI)

BAI is 21-item self-report questionnaire originally developed to differentiate clinical anxiety from normal anxiety [14]. The validation study of the Turkish BAI was performed by Ulusoy et al. [15].

Anxiety Sensitivity Index-3 (ASI-3)

ASI-3 includes 18 items which assess anxiety-related physical, cognitive, or social concerns. Items are rated on a 5-point Likert scale from very little (0) to very much (4), with subscale scores ranging from 0 to 24 and total scores ranging from 0 to 72 [16]. The validation study of the Turkish ASI-3 was performed [17].

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

Y-BOCS is a scale that measures how severe the obsessive-compulsive symptoms are. Scores range between 0 (no symptoms) and 4 (severe symptoms), and a total score is obtained by summing 10 items and can range between 0 and 40 [18]. Ranges of severity include subclinical (0 to 7 points), mild (8 to 15 points), moderate (16–23 points), severe (24 to 31 points) and extreme (32 to 40 points). The validation study of the Turkish Y-BCOS was performed [19].

Suicide Probability Scale (SCS)

This is a 36-item screening scale designed to help assess suicide risk in adolescents and adults [20]. The validation study of the Turkish SCS was performed by Atlı et al. [21].

Statistical analysis

SPSS v21 (SPSS Inc., Chicago, IL, USA) was used to perform all analyses. Shapiro-Wilk test was performed for checking the normality. Data are presented as median (minimum - maximum) or mean (SD) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. Normally distributed variables were assessed using the independent samples t-test, and non-normally distributed variables, with the Mann Whitney U test. Chi-square tests or Fisher's exact tests were performed to analyze categorical variables. Pearson and Spearman correlation coefficients were calculated to evaluate relationships between continuous variables. Multiple linear regression analysis (stepwise selection method) was used to determine significant factors of the Suicide Probability Scale scores. Two-tailed *P*-values of below 0.05 were considered statistically significant.

Results

Seventy-two individuals (36 patients and 36 controls) with a mean age of 31.89 (9.69) years [mean (SD); range 19-58] were included in this study. There were 30 (83.33%) females in the patient group and 25 (69.44%) females in the control group. No significant differences were found between groups in terms of age (P=0.255), gender (P=0.267), marital status (P=0.480),

smoking status (P=0.512) and alcohol abuse (P=0.114) (Table 1). The controls had significantly higher education status than the patients (P=0.044). There were 19 (52.78%) unemployed individuals in the patient group while only one (2.78%) unemployed individual in the control group (P<0.001) (Table 1).

In the patient group, 9 (25.00%) individuals were diagnosed with obsessive-compulsive disorder less than a year ago while 12 (33.33%) individuals had this disorder since one to five years and 15 (41.67%) individuals were diagnosed more than five years ago. Fourteen (38.89%) patients were using antidepressants and 5 (13.89%) were using a combination of antidepressants and antipsychotics. Y-BCOS scores were 14.11 (4.94) for obsessive scores, 13.72 (5.35) for compulsive scores and 27.83 (9.94) for total scores (Table 1).

Among the control and patient groups, one (2.78%) and three (8.33%) individuals, respectively, had a history of suicide attempts. In addition, two (5.56%) individuals had a family history of suicide attempt and one (2.78%) had another chronic disease among the patient group while there were no individuals with family histories of suicide attempts or other chronic diseases among the control group. No significant differences found were between the groups in terms of suicide attempt history (P=0.614), suicide attempt history in the family (P=0.493) and presence of another chronic disease (P=1.000) (Table 1).

The patients had significantly higher Beck Depression Inventory (BDI), Anxiety Sensitivity Index-3 (ASI-3) and Beck Anxiety Inventory (BAI) scores than the controls (P<0.001, P<0.001) and P=0.001, respectively). In addition, Suicide Probability Scale (SPS) desperation, negative self-evaluation and total scores were significantly higher in the patients (P<0.001). No significant differences were found between groups in terms of suicide ideation and hostility scores (P=0.725 and P=0.198 respectively) (Table 1).

There were significant correlations between BDI and SPS desperation scores (r=0.716, P<0.001), SPS suicide ideation scores (r=0.431, P<0.001), SPS hostility scores (r=0.597, P<0.001), SPS total scores (r=0.773, P<0.001), BAI and SPS desperation scores (r=0.559, P<0.001), SPS suicide ideation scores (r=0.330, P=0.005), SPS hostility scores (r=0.496, P<0.001) and SPS total scores (r=0.557, P<0.001), ASI-3 and SPS desperation scores (r=0.603, P<0.001), SPS suicide ideation scores (r=0.444, P<0.001), SPS hostility scores (r=0.590, P<0.001) and SPS total scores (r=0.653, P<0.001). There were no significant correlations between SPS scores, age, and Yale–Brown Obsessive Compulsive Scale scores (P>0.05) (Table 2).

Multiple linear regression analysis determined that the patient group had higher SPS total scores than the control group (P=0.031) (Figure 1) and individuals with higher Beck Depression Inventory scores had higher SPS total scores (P<0.001) (Figure 2, Table 3). Other variables included in the model, namely, age (P=0.756), gender (P=0.258), education status (P=0.557), marital status (P=0.073), employment status (P=0.341), smoking status (P=0.087), alcohol abuse (P=0.895), suicide attempt history (P=0.751), BAI scores (P=0.831) and ASI-3 scores (P=0.301) were insignificant.

Table 1: Summary of individuals characteristics and inventory/scale scores

	Groups		
	Patients Group (n=36) (%)	Control Group (n=36) (%)	*P*-value
Age (range)	27 (19 – 58)	32 (19 – 51)	0.255
Gender			
Female	30 (83.33%)	25 (69.44%)	0.267
Male	6 (16.67%)	11 (30.56%)	
Education status			
Primary school	8 (22.22%)	2 (5.56%)	0.044*
High school	15 (41.67%)	12 (33.33%)	
Higher education	13 (36.11%)	22 (61.11%)	
Marital status			
Single	20 (55.56%)	16 (44.44%)	0.480
Married	16 (44.44%)	20 (55.56%)	
Employment status			
Unemployed	19 (52.78%)	1 (2.78%)	<0.001*
Student	8 (22.22%)	7 (19.44%)	
Employed	9 (25.00%)	28 (77.78%)	
Smoking	4 (11.11%)	7 (19.44%)	0.512
Alcohol abuse	3 (8.33%)	9 (25.00%)	0.114
Duration of disease			
0 - 1 year	9 (25.00%)	-	N/A
1 - 5 years	12 (33.33%)	-	
> 5 years	15 (41.67%)	-	
Suicide attempt	3 (8.33%)	1 (2.78%)	0.614
Suicide attempt in family	2 (5.56%)	0 (0.00%)	0.493
Chronic disease	1 (2.78%)	0 (0.00%)	1.000
Drug usage			
Absent	17 (47.22%)	-	N/A
Antidepressant	14 (38.89%)	-	
Antidepressant + Antipsychotic	5 (13.89%)	-	
Beck Depression Inventory	20.75 (12.85)	10.89 (7.93)	<0.001*
Beck Anxiety Inventory	17 (0 - 47)	6 (0 - 19)	<0.001*
Anxiety Sensitivity Index-3	27.5 (2 - 56)	16 (3 - 56)	0.001*
Yale–Brown Obsessive Compulsive Scale			
Obsessive	14.11 (4.94)	-	N/A
Compulsive	13.72 (5.35)	-	N/A
Total	27.83 (9.94)	-	N/A
Suicide Probability Scale			
Desperation	26.5 (17 - 44)	21 (12 - 33)	<0.001*
Suicide ideation	12 (8 - 25)	12 (8 - 21)	0.725
Negative self-evaluation	23.5 (14 - 32)	17 (9 - 33)	<0.001*
Hostility	14 (8 - 23)	12.5 (7 - 24)	0.198
Total	78.72 (13.16)	64.28 (14.88)	<0.001*

*P>0.05, Data are given as mean (SD) or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables

Table 2: Correlations between Suicide Probability Scale scores and age, other inventory/scale scores

		Suicide Probability Scale				
		Desperation	Suicide ideation	Negative self-evaluation	Hostility	Total
Age	r	0.028	-0.058	0.021	-0.145	-0.002
	p	0.816	0.627	0.860	0.225	0.988
Beck Depression Inventory	r	0.716*	0.431*	0.214	0.597*	0.773*
	p	<0.001	<0.001	0.072	<0.001	<0.001
Beck Anxiety Inventory	r	0.559*	0.330*	0.114	0.496*	0.557*
	p	<0.001	0.005	0.340	<0.001	<0.001
Anxiety Sensitivity Index-3	r	0.603*	0.444*	0.129	0.590*	0.653*
	p	<0.001	<0.001	0.281	<0.001	<0.001
Yale–Brown Obsessive Compulsive Scale						
Obsessive	r	-0.060	0.147	-0.099	0.200	0.107
	p	0.729	0.392	0.565	0.243	0.535
Compulsive	r	-0.004	0.156	-0.180	0.210	0.068
	p	0.980	0.364	0.293	0.219	0.694
Total	r	-0.056	0.128	-0.146	0.212	0.090
	p	0.746	0.458	0.395	0.214	0.603

* Correlation is significant at the 0.05 level (2-tailed)

Table 3: Significant factors of the Suicide Probability Scale scores, multiple linear regression analysis

	Unstandardized β	Standardized β	*P*-value	95.0% CI for β	
(Constant)	55.340		<0.001	50.788	59.891
Beck Depression Inventory	0.821	0.611	<0.001	0.574	1.068
Patients	6.350	0.203	0.031	0.612	12.088

Dependent Variable: Suicide Probability Scale scores; R2=0.520; F=37.405; P<0.001, CI: Confidence interval

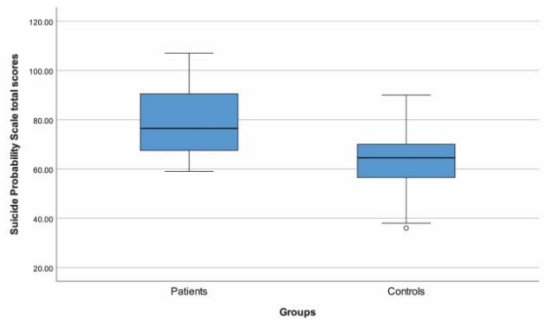

Figure 1: Box-plots of the Suicide Probability Scale total scores with regard to groups

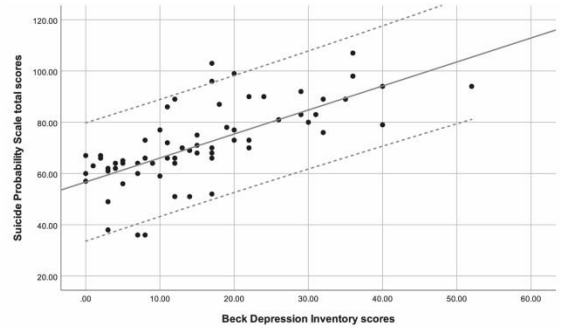

Figure 2: Scatter-dot plot between Suicide Probability Scale and Beck Depression Inventory scores

Discussion

Few studies have evaluated suicidal risk and anxiety sensitivity in patients diagnosed with OCD [22]. Most OCD patients do not have any suicidal ideation or suicide attempts in their lives. Therefore, it is important to identify the predictors for suicidal ideation and attempts of suicide in OCD, to screen subjects at greater risk. This study aimed to explore the features of suicidality in OCD patients and examine the relationship between suicide idea and OCD.

Concerning sociodemographic factors, Albert et al. found that male gender, old age, and poor socioeconomic status were associated with suicide risk [23]. On the other hand, in another study evaluating the suicide risk in OCD patients, the authors found no statistically significant differences between patients having or not having suicide ideas with regards to age [24]. We also did not find any significant differences between age and SPS scores.

Lifetime anxiety disorder is a highly relevant factor in lifelong suicidal idea and suicide attempts after controlling for sociodemographic characteristics and comorbid diseases [25]. In Balcı et al.'s study [24], there were significant correlations between the grade of SI and anxiety severity. Consistent with this study, we found significant correlations between BAI and SPS desperation, suicide ideation scores, hostility scores and total scores. In addition, BAI scores were significantly higher in the OCD group. We evaluated ASI-3 and SPS scores and found significant correlations between ASI-3 and SPS desperation, suicide ideation scores, hostility scores and total scores. There was an association between anxiety sensitivity and suicide idea in study population without OCD. Based on this association, it can be concluded that individuals with OCD can reduce suicide risk by decreasing anxiety sensitivity [7]. In a randomized clinical trial, one session of anxiety sensitivity cognitive concerns intervention was found to provide a significantly higher reduction of anxiety sensitivity and change suicidality at one-month follow-up [26]. Therefore, physicians should be aware of anxiety concerns for reducing the suicide risk in OCD patients.

It is well known that comorbid depression is a major contributor to suicidality [7, 24, 27]. Diacunu et al. [28] evaluated 311 subjects with OCD and divided them into the groups without depression or personality disorders or with pure depression. They revealed that risk for nonfatal suicidal behavior may be increased by the obsessive-compulsive disorder independent of depressive disorders. In a study by Torres et al., comorbid major depressive disease increased the suicide attempt risk 28.75-fold [29]. Consistent with these studies, we found that individuals with higher Beck Depression Inventory scores had higher SPS total scores and there were significant correlations between BDI and SPS desperation, suicide ideation scores, hostility scores and total scores.

There were studies evaluating the relationship between Y-BCOS scores and suicidality. A study by Kamath et al. found that T-BCOS obsession scores were higher in OCD patients with suicide idea and suicide attempts and severity of OCD did not seem a significant risk factor [30]. In another study by Balcı et al. [24] the authors found that although the Y-BOCS scores did not significantly differ between OCD patients with suicide idea and suicide attempts, the severity of OC symptoms was correlated with the level of suicide idea. Unlike these studies, our study did not find any correlations between Y-BCOS scores and SPS scores. This may be due to the small number of patients with suicide attempts in our sample.

Limitations

There are some limitations in this study. First, the power of the analyses performed was reduced because of the small sample size. Second, number of suicidal attempts was only 4 and, logistic regression analysis could not be performed to determine significant risk factors of the suicide attempt. Third, this study did not evaluate some variables associated with suicidal idea such as genetic factors and childhood trauma and did not compare the duration of disease due to small sample size. The open-label characteristic of the study is a factor that can increase researcher bias [31]. On the other hand, unlike most other studies in the literature, this study had a healthy control group for eliminating the factors for suicidality in OCD.

Conclusion

Suicidal behavior is a complicated process because of several demographic and clinical factors. Several contributing factors should be determined by the physicians to detect the suicide risk early. The present study revealed that depression and anxiety status are important for suicide risk in OCD patients. Symptom severity of OCD is related with both ideation of suicide and suicide attempts; therefore, it is recommended to always evaluate the suicidal risk in patients with OCD in terms of ideation of suicide. Further research on larger sample sizes and evaluating subgroups of OCD are needed.

References

1. Nagy NE, El-Serafi DM, Elrassas HH, Abdeen MS, Mohamed DA. Impulsivity, hostility and suicidality in patients diagnosed with obsessive compulsive disorder. Int J Psychiatry Clin Pract. 2020;24(3):284-92.
2. Coryell W. Obsessive-compulsive disorder and primary unipolar depression. Comparisons of background, family history, course, and mortality. J Nerv Ment Dis. 1981;169(4):220-4.
3. Khan A, Leventhal RM, Khan S, Brown WA. Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord. 2002;68(2-3):183-90.
4. Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. J Consult Clin Psychol. 1974;42(6):861-5.
5. Joiner TE Jr, Steer RA, Brown G, Beck AT, Pettit JW, Rudd MD. Worst-point suicidal plans: a dimension of suicidality predictive of past suicide attempts and eventual death by suicide. Behav Res Ther. 2003;41(12):1469-80.
6. Angelakis I, Gooding P, Tarrier N, Panagioti M. Suicidality in obsessive compulsive disorder (OCD): a systematic review and meta-analysis. Clin Psychol Rev. 2015;39:1-15.
7. Albert U, De Ronchi D, Maina G, Pompili M. Suicide Risk in Obsessive-Compulsive Disorder and Exploration of Risk Factors: A Systematic Review. Curr Neuropharmacol. 2019;17(8):681-96.
8. Stanley IH, Boffa JW, Rogers ML, et al. Anxiety sensitivity and suicidal ideation/suicide risk: A meta-analysis. J Consult Clin Psychol. 2018;86(11):946-60.
9. Fawcett J, Scheftner WA, Fogg L, Clark DC, Young MA, Hedeker D, et al. Time-related predictors of suicide in major affective disorder. Am J Psychiatry. 1990;147(9):1189-94.
10. First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), clinician version, user's guide, Washington, DC: American Psychiatric Association; 1997.
11. Kundakçi T, Sar V, Kiziltan E, Yargiç IL, Tutkun H. Reliability and validity of the Turkish version of the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D): a preliminary study. J Trauma Dissociation. 2014;15(1):24-34.

12.Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;4:561-71.
13.Hisli N. Reliability and validity of Beck Depression Inventory among university students. Turk Psikoloji Dergisi 1989;7(23):3-13.
14.Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety: psychometric properties. J Consult Clin Psychol. 1988;56:893–7.
15.Ulusoy M, Şahin N, Erkmen H. Turkish version of Beck Anxiety inventory: Psychometric Properties. J Cogn Psychother 1998;12(2):163-72.
16.Taylor S, Zvolensky MJ, Cox BJ, Deacon B, Heimberg RG, Ledley DR, et al. Robust dimensions of anxiety sensitivity: development and initial validation of the Anxiety Sensitivity Index-3. Psychol Assess. 2007;19:176-88.
17.Mantar A, Yemez B, Alkın T. Anksiyete Duyarliliği Indeksi-3'ün Türkçe Formunun Geçerlik ve Güvenilirlik Calışması [The validity and reliability of the Turkish version of the anxiety sensitivity index-3]. Turk Psikiyatri Derg. 2010;21(3):225-34.
18.Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischmann RL, Hill CL, Heninger GR, Charney DS. The Yale-Brown Obsessive Compulsive Scale. I. Development, use, and reliability. Arch Gen Psychiatry. 1989 Nov;46(11):1006-11.
19.Karamustafalıoğlu OK, Ucışık AM, Ulusoy M, Erkmen H. Yale-Brown Obsesyon-Kompülsiyon Derecelendirme Ölçeğinin Geçerlilik ve Güvenilirlik Çalışması. 29. Ulusal Psikiyatri Kongresi Program ve Bildiri Özetleri Kitabı, Bursa Savaş Ofset;1993. p. 86.
20.Cull J, Gill W. Suicide probability scale. Los Angeles, CA: WPS, 1982.
21.Atlı Z, Eskin M, Dereboy C. The Validity and the Reliability of Suicide Probability Scale (SPS) in Clinical Sample. J Clin Psy. 2009;12(3):111-124.
22.Khosravani V, Sharifi Bastan F, Samimi Ardestani M, Jamaati Ardakani R. Early maladaptive schemas and suicidal risk in an Iranian sample of patients with obsessive-compulsive disorder. Psychiatry Res. 2017;255:441-8.
23.Albert U, Speciani M, De Ronchi D, Atti AR, Maina G, Bélteczky Z, et al. Factors associated with increased suicide risk in obsessive-compulsive disorder. J Psychopathol. 2018;24:154–63.
24.Balci V, Sevincok L. Suicidal ideation in patients with obsessive-compulsive disorder. Psychiatry Res. 2010;175(1-2):104-8.
25.Bolton JM, Cox BJ, Afifi TO, Enns MW, Bienvenu OJ, Sareen J. Anxiety Disorders and Risk for Suicide Attempts: Findings from the Baltimore Epidemiologic Catchment Area Follow-up Study. Depression and Anxiety. 2008;25:477–81.
26.Raines AM, Short NA, Allan NP, Oglesby ME, Schmidt NB. Examination of a brief anxiety sensitivity cognitive concerns intervention on suicidality among individuals with obsessive-compulsive symptoms. Contemp Clin Trials. 2015;45:191-5.
27.Maina G, Albert U, Rigardetto S, Tiezzi M.N, Bogetto F. Suicidio e disturbo ossessivo-compulsivo. Giornale Italiano di Psicopatologia. 2006;12:31–7.
28.Diaconu G, Turecki G. Obsessive-compulsive personality disorder and suicidal behavior: evidence for a positive association in a sample of depressed patients. J Clin Psychiatry. 2009;70(11):1551-6.
29.Torres AR, Ramos-Cerqueira AT, Ferrão YA, Fontenelle LF, do Rosário MC, Miguel EC. Suicidality in obsessive-compulsive disorder: prevalence and relation to symptom dimensions and comorbid conditions. J Clin Psychiatry. 2011;72(1):17-26.
30.Kamath P, Reddy YC, Kandavel T. Suicidal behavior in obsessive-compulsive disorder. J Clin Psychiatry. 2007;68:1741–50.
31.Kılınçel O, Kılınçel Ş, Gündüz C, Cangür Ş, Akkaya C. Klozapinin Hızlı Döngülü Bipolar Afektif Bozuklukta Duygudurum Düzenleyicisi Olarak Rolü. Turk Psikiyatri Dergisi 2019;30(4):268-71.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1057-1062.
DOI: 10.28982/josam.811241

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Analysis of apoptosis of kidney tissue by the tunel method and histomorphological changes in rabbit kidney model due to unilateral supravesical obstruction

Tavşan böbrek modelinde tek taraflı supravezikal tıkanıklığa bağlı böbrek dokusunda oluşan apoptozisin tunel yöntemiyle analizi ve histomorfolojik değişiklikler

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Ethics Committee Approval: All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: There is a need for effective, cheap, and fast method to detect apoptosis. In some studies, we see that newer, more difficult, expensive, or less effective methods are used. We wanted to show that the TUNEL method has serious advantages and can still be used alone. In this study, it was aimed to investigate whether there is a significant difference in the number of apoptotic cells in partial obstruction (PO) and complete obstruction (CO) by using terminal deoxytransferase-mediated bio-dUTP nick and labeling (TUNEL) method in renal tissue. We also evaluated histopathological changes after renal obstruction.

Methods: In this study, 29 rabbits were used. Supravesical obstruction was created in 24 rabbits. Five rabbits were used as the control group. Twelve kidneys were examined after creating unilateral partial obstruction and 12, after the creation of unilateral complete obstruction. Histomorphological changes in kidney tissues in routine Haemetoxylene-Eosine (HE) preparations and apoptosis in preparations obtained by TUNEL method were examined.

Results: Apoptotic cells were observed especially in the tubules by the TUNEL method. The average number of apoptotic cells in CO and PO groups were 190.66 and 40.58, respectively. In the CO group, the number of apoptotic cells was significantly higher than that in the PO group ($P<0.001$). Interstitial fibrosis, chronic inflammatory infiltration, tubular destruction (vacuolar changes, cystic and atrophic tubules) were observed in both groups. These changes were more limited, and mild, in the PO group, and severe and widespread in the CO group.

Conclusion: TUNEL method is one of the highly effective methods in detecting apoptosis. It was observed that apoptosis and pathological changes developing in the kidney tissue after complete obstruction were more severe and widespread.

Keywords: Renal obstruction, Apoptosis, TUNEL method

Öz

Amaç: Literatürde, bazı çalışmalarda, daha yeni, ama pratikte değerlendirme güçlükleri olan, pahalı veya etkinliği az yöntemlerin kullanıldığını görüyoruz. Terminal deoxytransferase-mediated bio-dUTP nick and labeling (TUNEL) yönteminin ciddi avantajları olduğunu ve halen tek başına kullanılabileceğini göstermek istedik. Bu nedenle, deneysel olarak tavşan üreterinde kısmi ve tam obstrüksüyon oluşturulmasından sonra böbrek dokusunda gelişen apopitozisin şiddetinin, TUNEL yöntemi kullanılarak belirlenmesi, gruplar arasında anlamlı bir fark olup olmadığı ve yanısıra oluşan histopatolojik değişiklikleri değerlendirme amaçlandı.

Yöntemler: Mesane üstü seviyesinde üreter geçişinin kısmi ve tam olarak engellenmesi yoluyla-12 tam obstrüksiyon, 12 kısmi obstrüksiyon grubu-, 5 taneside kontrol grubu olmak üzere- toplam 29 adet tavşan böbreği kullanıldı. Böbrek dokusunda gelişen histomorfolojik değişiklikler Hematoksilen-Eozin (HE) preperatlarda, apoptozis ise TUNEL yöntemiyle hazırlanan preperatlarda mikroskopik olarak incelendi. Obstrüksiyon sonrası oluşan apopitozisin tam ve kısmi obstrüksiyon grupları arasında istatistiksel olarak anlamlı farklılığı olup olmadığı araştırıldı.

Bulgular: Apopitotik hücreler, TUNEL yöntemiyle net olarak gösterildi. Apopitozisin, özellikle tübül epitelinde yoğunlaştığı görüldü. Tam obstrüksiyon grubunda, ortalama apopitotik hücre sayısı 190,66 ve kısmi obstriksüyon grubunda ise 40,58 idi. Tam obstrüksiyon grubunda apopitotik hücre sayısı kısmi obstrüksiyon grubuna göre anlamlı derecede yüksekti ($P<0,001$). 2 grupta da interstisyel fibrozis, kronik iltihabi infiltrasyon, tübüler yıkım (vakuoler değişiklikler, kistik ve atrofik tübüller) gözlendi. Bu değişiklikler kısmi tıkanma grubunda daha sınırlı, hafif, tam tıkanma grubunda şiddetli ve yaygın idi.

Sonuç: TUNEL yönteminin apopitozisi belirlemede etkinliği yüksek yöntemlerden biri olduğu gösterildi. Tam tıkanma sonrası böbrek dokusunda gelişen apopitozisin ve patolojik değişikliklerin çok daha şiddetli ve yaygın olduğu görüldü.

Anahtar kelimeler: Renal obstrüksiyon, Apopitozis, TUNEL yöntemi

How to cite/Atıf için: Uçak R, Topcu ŞO, Sarı İ. Analysis of apoptosis of kidney tissue by the tunel method and histomorphological changes in rabbit kidney model due to unilateral supravesical obstruction. J Surg Med. 2020;4(11):1057-1062.

Introduction

Apoptosis was first described in 1972 by Austrian pathologist John Kerr [1]. It is an active system associated with many genes and has a definition similar to leaf dump in Greek due to combination of the words apo (= separate) and ptosis (= falling). Understanding the mechanisms involved in apoptosis in mammalian cells was triggered by the investigation of programmed cell death during the development of nematode Caenorhabditis elegans [2]. Apoptosis is a cell death pathway in which cells activate enzymes that breakdown their nuclear DNA and nuclear / cytoplasmic proteins. The resulting cellular debris breaks away from the main structure and apoptosis, which means "falling of leaves," occurs. It may develop during physiological events such as organogenesis and tissue growth or may be induced by pathological stimuli. Therefore, the mechanisms leading to apoptosis have attracted attention and been extensively studied. For this purpose, studies investigated what role it plays in the mechanisms of human diseases through experimental studies in many animal models [3].

Renal obstruction due to the deterioration of tissue nutrition is one of the important problems. The role of apoptosis in this process has been investigated in many studies. In addition, in various experimental studies, the differences in apoptotic cell density after partial and / or complete obstruction of the kidney and the mechanisms of apoptosis have been investigated or reviewed [4-11]. The mechanisms and causes of apoptosis development are important, so it is necessary to determine the apoptosis developing in the tissue clearly and healthily. There are many methods with high sensitivity and can be applied to determine apoptosis. The TUNEL method is one of the most commonly used methods in determining apoptosis. It is a system that detects DNA fractures by enzymatic reaction. The reaction with the TUNEL method is highly descriptive and only the nuclei of the apoptosis are stained. The method is based on the specific binding of Tdt to the 3-OH ends of the DNA following synthesis of the polyoxynucleotide polymer and enables the detection of DNA fractures within the cell. With this method, the presence of apoptotic cells can easily be detected in sections obtained from paraffin blocks where the sampled tissues are embedded. It is an important advantage that preparations can be evaluated with light microscopy [12-20].

In this study, we aimed to investigate whether there is a significant difference in the number of apoptotic cells in partial and complete renal obstruction by the TUNEL method. We also evaluated histopathological changes after renal obstruction. In addition, the TUNEL method is used in studies investigating whether apoptosis occurs and whether it is involved in the mechanisms responsible for the development of different lesions. In addition, the TUNEL technique is used in studies where active substance use and treatment effectiveness are evaluated. Therefore, it was aimed to evaluate the effectiveness and usability of TUNEL method in terms of contribution to the literature.

Materials and methods

A total of 29 animals (New Zealand adult rabbits with an average weight of 1500-2000 grams) were included in the study. They were fed standard diet [18% protein, 3% fat, 20% fiber foods and 10% carbohydrates, 0.009 mg / kg vitamin complex (A-B-C-E)]. Animals were divided into three groups: Unilateral complete obstruction group (12 rabbits), unilateral partial obstruction group (12 rabbits), control group (5 rabbits). Sodium pentobarbital (0.04mg / kg) was injected into the peritoneum. After cleaning and dressing under sterile conditions, the skin was shaved from the midline abdomen. The layers were passed through a 13-15 cm long, midline abdominal incision. The bleeding was quickly controlled with 4/0 vicryl. Full obstruction left ureteropelvic obstruction was performed by suturing the ureter with 5/0 silk 4-5 cm distal to the renal pelvis. Partial obstruction was created by passing through the ureter tunnel and approaching the edges close to each other by creating a 15 mm tunnel to the psoas muscle. After bleeding control, the layers were closed in the anatomical plane. Following intraperitoneal administration of the same dose of anesthetic agent to the control group, the longitudinal abdominal incision was closed with 4/0 vicryl. One month later they were sacrified with a high-dose anesthetic agent. Left and right kidneys were excised according to technique by providing sterile conditions. The left and right kidneys of 12 rabbits in two groups and the left kidney of 5 animals in the control group were fixed with a 10% buffered formaldehyde solution. After the samples of kidney tissue including cortex and medulla were obtained, tissue follow-up was performed. Following this procedure, 5 micron thick sections were taken from the tissues embedded in paraffin blocks and two preparations were used from each case. Histopathological changes in HE preparations after obstruction were examined. The other one was stained by TUNEL method to show apoptotic cells using Oncor's Apoptag Peroxidase kit-cathologist no: S7100- USA (Equilibration Buffer, Reaction Buffer, TdT Enzyme, Stop/Wash Buffer, Anti-Digoxigenin-Peroxidase). In TUNEL method preparations, especially after apoptosis of renal tubular epithelial cells, dense chromatin localized to the nucleus was stained as light-dark brown. Apoptotic cell number / 1000 cells were determined at high magnification (x400) by light microscope. Pathological evaluation was done blindly by two different pathologists. Apoptotic cell count was recorded in 12 cases in both groups.

Statistical analysis

SPSS 15.0 package program was used for statistical analysis of the data. Categorical measurements were compared in numbers and percentages, continuous measurements were averaged, deviations were compared between groups, the distribution was checked, and Mann Whitney U test was used in binary variables. In all tests, $p<0.05$ was considered statistically significant.

Results

Histopathological findings in complete obstruction group

Ischemic changes in obstructed kidneys were evaluated in HE sections. Hydronephrotic changes were observed macroscopically. Most tissues had interstitial fibrosis and mononuclear inflammatory cell infiltration. Calcification and steatosis were observed in one case. Dilatation and vacuolar degeneration were detected in tubules. Cystic atrophy was

observed in some tubules. Thickening of the vessel walls and erythrocyte accumulation in some vessel lumens were observed. In addition, inflammatory infiltration, which concentrates around the vessels and disrupts the endothelium in some places, was noticed (Figure 1, 2).

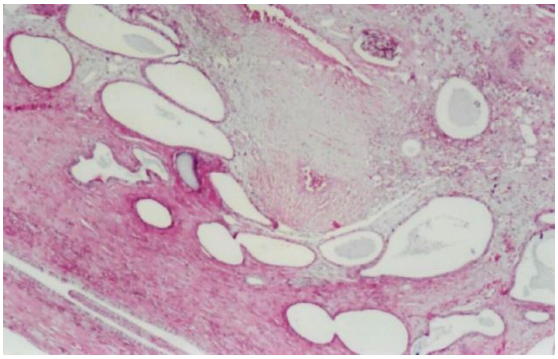

Figure 1: Cystic / atrophic tubules and severe fibrosis in renal tissue after complete obstruction, HE x40

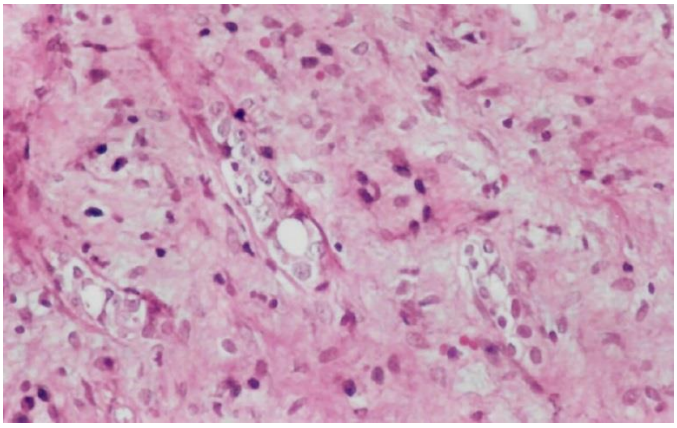

Figure 2: Atrophic renal tissue with a small number of tubules with severe fibrosis after complete obstruction and vacuolar degeneration in the epithelium, HE x100

Histopathological findings in partial obstruction group

In some cases, interstitial fibrosis and mononuclear inflammatory cell infiltration were observed. In some cases, inflammatory cell infiltration was intense in the perivascular region. Some vessels had erythrocyte accumulation in the lumen. In one case, there was bleeding and necrosis in the parenchyma. Some of the tubules were distorted and mild nuclear degeneration and vacuolization were observed in epithelial cells (Figure 3).

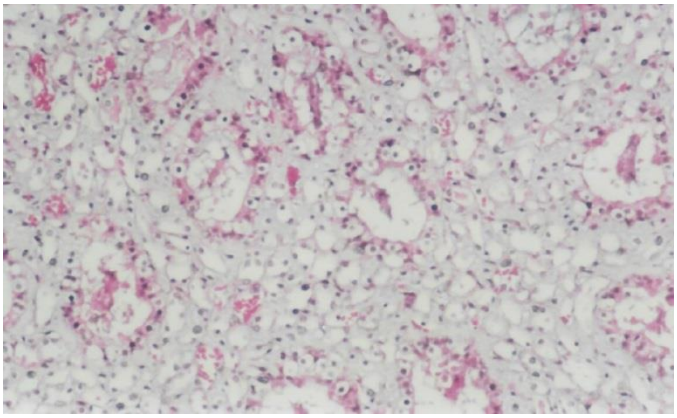

Figure 3: Congestion in the renal tissue after partial obstruction, dense vacuolar degeneration in the tubular epithelium, HE x40

Fibrosis and tubular involvement were more severe in completely obstructed kidneys.

It was emphasized that there was no significant pathological finding in the control kidney sections.

Findings in TUNEL method

The lowest number of apoptotic cells in the CO group was 3/1000, the highest was 441/1000 (Table 1) (Figure 4). These values were 2/1000 and 170/1000 (Table 2), respectively, in the PO group (Figure 5, 6). The average number of apoptotic cells in the CO and PO groups were 190.66 (160.62) and 40.58 (58.63), respectively. The number of apoptotic cells in the kidneys in the CO group was significantly higher than those in the PO group (P<0.001). Apoptotic cells were rarely seen in the control group.

Table 1: Number of apoptotic cells determined in rabbit kidneys in CO group

Complete obstruction (CO) group	Apoptotic cell count (n/1000)
1	3
2	3
3	3
4	51
5	66
6	210
7	219
8	242
9	335
10	350
11	365
12	441

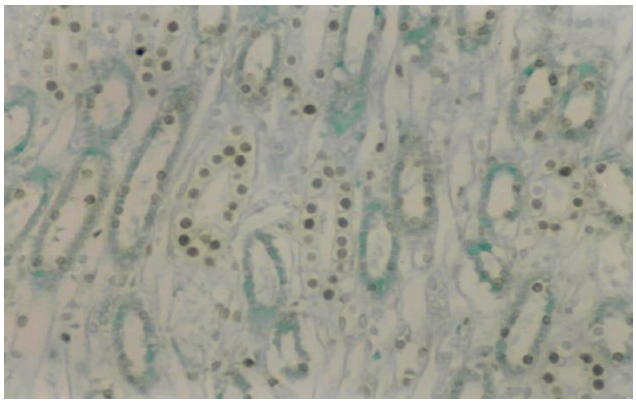

Figure 4: Light-dark brown nuclear staining, showing the presence of frequent apoptosis in tubules after complete obstruction, TUNEL, x100

Table 2: Number of apoptotic cells determined in rabbit kidneys in the PO group

Partial obstruction (PO) group	Apoptotic cell count (n/1000)
1	2
2	2
3	4
4	5
5	6
6	7
7	7
8	18
9	47
10	78
11	141
12	170

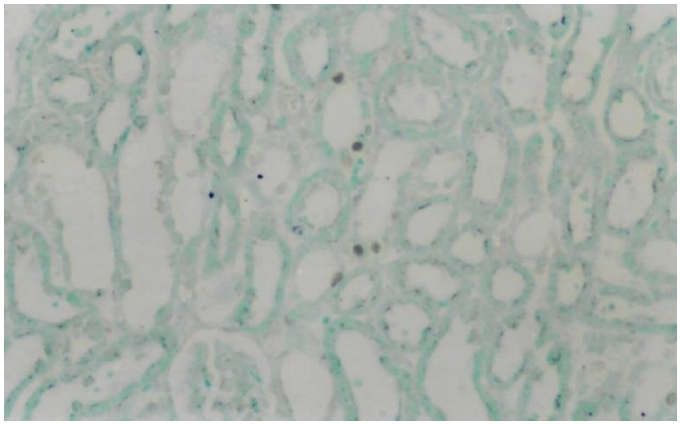

Figure 5: Presence of rare apoptosis in tubules after partial obstruction, light-dark brown nuclear staining, TUNEL, x100

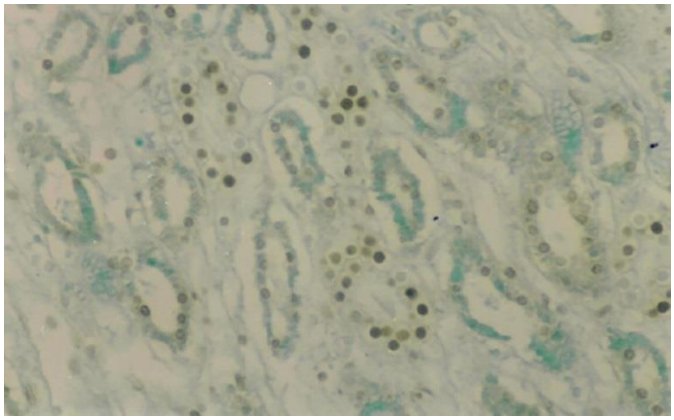

Figure 6: Presence of frequent apoptosis in tubules after partial obstruction, light-dark brown nuclear staining, TUNEL, x100

Typically, apoptotic cells in kidney tissue were observed in the proximal and distal tubules in the deep part of the cortex and in the medulla layer, and in the lining epithelial cells in the collection ducts. Apoptosis is rarely seen in the vascular walls and interstitium. In TUNEL method preparations, apoptotic cells were identified as light-dark brown stained areas localized to the nucleus, which were clearly separated from the cytoplasm, especially in tubules, on a green background.

Discussion

Obstructive uropathy due to unilateral ureteral obstruction (UUO) has characteristic functional and structural changes. UUO is characterized by tubular cell damage, interstitial inflammation and fibrosis due to hydrostatic pressure caused by obstruction. Therefore, molecular mechanisms of apoptosis have been investigated as a model of events that occur during irreversible acute kidney injury and human chronic kidney disease [4]. In the first few days after ureteral obstruction, a decrease in GFR, a decrease in kidney blood flow, interstitial edema and leukocyte infiltration are observed. Hydronephrosis and tissue loss develop over time, pronounced tubular atrophy, interstitial fibrosis and interstitial inflammation ocur [4-8]. In experimental models evaluating tubulointerstitial pathologies developing after obstruction, tubular epithelial cell damage and interstitial inflammation are observed in the acute phase. If this tubular injury cannot be regenerated, necrosis or apoptosis and subsequent scar tissue may occur. The most important morphological changes in this process are atrophy, focal necrosis, epithelial regeneration, apoptosis, inflammation, interstitial fibrosis, and thrombosis development [21,22]. Apoptosis is stimulated in the tissue exposed to oxygen metabolites after acute renal ischemia. In conclusion, tubules and blood vessels are the main targets for injury due to renal ischemia and are usually observed in the most severe external medulla [5,7,22]. Although the most serious involvement in our cases was in the medulla layer, the cortical layer was affected and the concentration of apoptotic cells in the tubules was remarkable. In our study, apoptosis, interstitial fibrosis, chronic inflammation, and tubular atrophy were observed in all kidneys, especially in the CO group, due to obstruction. In some cases, focal necrosis and thrombosis were seen. The most severe destruction occurs in the outer medulla layer and especially in the tubules due to the characteristics of normal circulation.

Tubular epithelial cells are responsible for high transport activity. This function is supported by mitochondrial function, oxygen depletion affects the mitochondrial function severely. Intensive studies of the mechanism of tubular destruction have highlighted 3 mechanisms of epithelial cell loss: Necrosis, loss of cell integrity, and apoptosis. Ischemia affecting cell functioning is the basis of the formation of these 3 mechanisms. The common finding of ischemia is tubular basement membrane rupture. Nephron involvement probably comes later. Afterwards, local inflammatory response occurs in the environment. Because of these data, studies on inhibition of tubular cell apoptosis have begun and it has been shown that kidney damage can be stopped [23].

In investigations for the control of apoptosis, stimulation and prevention mechanisms were investigated. It is known that three different precursor types of signaling pathways are involved in the induction of apoptosis. Mitochondria / cytochrome-C mediated apoptosis is induced by death activators binding to cell surface receptors, and endoplasmic reticulum mediated apoptosis. In general, molecules such as calcium, ceramide, bcl-2 family, p53, caspases, proteins such as cytochrome c and mitochondria play a role in the regulation of apoptosis. Naturally, the balance mechanisms between cell proliferation and apoptosis are regulated and managed at the molecular level through mediators. Some of these have been understood in experimental models [7,9-11,24]. Apoptotic pathways active in the glomerular and tubular epithelium include survival factor deprivation, death receptor activation, mitochondrial damage, endoplasmic reticulum stress, lysosomal destabilization, and caspase cascade activation. These pathways are interrelated but show stimulus-specific differences [25]. Various cytokines and growth factors, particularly TNF-alpha [26], osteopontin [27], TGF-1, angiotensin, nuclear factor-κB (NF-κB), are involved in the development of occlusion-induced renal fibrosis and apoptotic cell death [28]. In addition, Omi / HtrA2 has been shown to be associated with apoptotic signaling pathways in tubular epithelial cells affected by unilateral ureteral obstruction [29]. Over time, the mechanisms of apopitosis-related proteins were understood and new ones were discovered. The main proteins associated with apoptosis in the kidney tissue formed in UUO include Angiotensin 2, Caspases, Fas-L, ICAM-I, IL-6, TGF-beta, VCAM-I, MCP-I, TNF-alpha, and the proapoptotic-proinflammatory mechanism. Nitric oxide, Heat shock protein-70 and COX-2 have antiapoptotic effects. Also, mediators (TGF-beta, SMA, Vimentin, PDGF, Integrin (β1), PAI-1, TIMP-1, CTGF) are known to cause fibrosis and exacerbate the process leading to loss of function in the obstructed kidney [30]. Apoptotic cell death is usually a response to the cell's microenvironment, and this response requires the activation of molecules that bring death to the cell or the inactivation of prosurvival molecules that prolong the life of the cell. Both are currently potential therapeutic targets [25]. Many active ingredients are tried for achieving these goals. Among them, calcium channel blockers that have previously been shown to be effective [31], fluuorofenidone which inhibits collagen-1 overexpression leading to renal fibrosis, indirectly antiapoptotic effect [32], angiotensin-2 receptor antagonists fimasartan [33], erythropoietin receptor, bcl -2, erythropoietin, which has antiapoptotic effects by suppressing bcl-x1 mRNA release [34], rhein, which is thought to suppress the bax and bcl2 proteins

associated with apoptosis [35], colchicine, which is suggested to be antiapoptotic by suppressing caspase-3 and fibronectin [36], bcl-2, molecules such as troxerutin [37], which is effective on many proteins such as bax, TNF-alpha, and Ulinastatin [38], which is used in the treatment of acute pancreatitis and whose antiapoptotic effect has been tested in the cell damage that occurs in the brain, has been shown to reduce the pathological degeneration in the tissue by affecting the mechanisms that cause apoptosis in the UUO kidney.

Apoptosis is an established mechanism not only to control cell number and tissue size, but also to remove infected, damaged or stressed cells from the organism. Therefore, the ability to detect and manage apoptosis is essential in the control and treatment of diseases [13]. Determination of apoptosis was originally based on morphological criteria. Later, DNA breaks were identified by finding that which caspases were activated. Currently used methods are based on morphological, immunohistochemical, immunological, biochemical, and molecular biology [13,17-20]. These include light microscopy, special / fluorescent dyes, immunohistochemistry, electron microscopy, PCR, TUNEL, DNA agarose gel electrophoresis, Flow cytometry, In situ3 - end labeling method (ISEL), Western blotting and caspase colorimetric assay, Nuclease assay [20]. The most common methods are Spectroscopy, Electron Microscopy, Electrophoresis, immunohistochemistry (staining with Annexin V, Caspase 3, p53, M30), TUNEL and Flow cytometry [13].

Morphological evaluation in light microscopy, although easy and cheap, is subjective and is not preferred because of low reproducibility. Evaluation in electron microscopy is a highly accurate method, but it is time consuming, expensive and a small area of tissue can be examined. Determination of apoptosis by electrophoresis is advantageous in terms of being easy, precise, and quantitative. However, living, apoptotic or necrotic cell differentiation may not occur due to the damage it can cause to the cell membrane. Flow cytometry evaluates live and fixed cells individually, easily, quickly and accurately. It is sensitive to the amount of apoptosis. It is time consuming due to multi-step and enzymatic precursor processes. Immunohistochemistry can be preferred as it is easy and inexpensive. The biggest problem is that the methods used require separating, washing and transferring the cells. These procedures can damage cell membranes and alter the cell population distribution of viable, apoptotic and / or necrotic cells [13,17-20].

TUNEL is based on the direct marking of the 3 hydroxyl ends of DNA breaks and therefore the measurement can be defined directly at the molecular level. DNA breaks occur very early in apoptosis, so the method also detects apoptotic cells that are not yet recognized based on changes in morphology. Therefore, it gives the opportunity to determine the first reactions of apoptosis. In addition to DNA breaks, DNA content can also be measured. However, the disadvantage is that the sensitivity and specificity of this technique depend on the concentration of fixative and terminal transferase enzyme used [17]. Today, there are many experimental studies using the UUO model, especially for treatment. While evaluating apoptosis in these, the combination with TUNEL and newer techniques (especially western blotting, flow cytometry and immunohistochemical examinations) are preferred. In these studies, the apoptosis indices obtained in the TUNEL method complement each other with the results of other new techniques and provide information on the efficacy of the molecules investigated for treatment [35,39,40]. In addition, TUNEL method is used alone and effectively in many experimental study models other than the UUO model. In our study, the clarity of the data supports this [41,42].

The strengths of the study are the large number of subjects, the use of control subjects, the use of the surgical technique by the experienced urologist, no technical problems in the application of the TUNEL method, and the blind evaluation of the results by two different pathologists.

Limitations

The lack of comparative analysis of the results we obtained using the TUNEL method with another current and effective method limits the value of the study.

Although we think that the TUNEL method can be used alone in experimental studies investigating the therapeutic efficacy of active ingredients in this field, it may be preferable to use combination with new techniques that confirm the robustness of the results.

In our study, apoptotic cells were clearly demonstrated by the TUNEL method. Technical artifact was minimal and excluded from evaluation. As expected, the number of apoptotic cells in CO was much higher than that in PO. There was a statistically significant difference in the number of apoptotic cells between the two groups. In complete obstruction, the severity of apoptosis and associated pathological changes, fibrosis and atrophy were more intense than partial obstruction.

Conclusions

Apoptosis is a phenomenon that has been handled in many aspects, is still up-to-date, and is used mostly to direct therapeutic research. It continues to be examined especially on the basis of the UUO model in terms of its formation mechanisms and methods of determination. With the passage of time, although there are many new apoptosis assessment methods, the TUNEL method continues to be used alone or in combination with other current methods, due to its applicability and reproducibility, as well as not being too time consuming and expensive.

References

1. Kerr JF, Wylie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. Br J Cancer. 1972;26:239-57. PMID:4561027. doi: 10.1038/bjc.1972.33.
2. Horvitz HR. Genetic control of programmed cell death in the nematode Caenorhabditis elegans. Cancer Res. 1999;59:1701–6. PMID: 10197583.
3. Kumar V, Abbas AK, Aster JC. Cell injury, cell death, and adaptations. Robbins Basic Pathology, 10.th ed. 2018. Chapter 2, 31-56. Elsevier, Philadelphia, Pennsylvania.
4. Ucero AC, Gonçalves S, Benito-Martin A, Santamaría B, Ramos AM, Berzal S, et al. Obstructive renal injury: from fluid mechanics to molecular cell biology. Open Access J Urol. 2010;2:41–55. PMID: 24198613 doi: 10.2147/rru.s6597
5. Shanley FF. The pathology of Chronic Renal İschemia. Seminars in Nephrology. 1996;16(1);21-32.
6. Ucero AC, Benito-Martin A, Izquierdo MC, Sanchez-Niño MD, Sanz AB, Ramos AM, et al. Unilateral ureteral obstruction: beyond obstruction. International Urology and Nephrology. 2014;46(4):765–77. doi: 10.1007/s11255-013-0520-1.
7. Truonga L, Petrusevska G, Yang G, Gurpınar T, Shappeli S, Lechago J et all. Cell apoptosis and proliferation in experimental chronic obstructive uropathy. Kidney İnt. 1996;50;200-7. doi: 10.1038/ki.1996.303 PMID: 8807589.
8. Truonga L, Gabera L, Eknoyand G. Obstructive Uropathy. Experimental Models for Renal Diseases: Pathogenesis and Diagnosis. Contrib Nephrol. 2011;169:311–26. doi: 10.1159/000314578.
9. Yeh CH, Chiang HS, Lai TY, Chien CT. Unilateral Ureteral Obstruction Evokes Renal Tubular Apoptosis via the Enhanced Oxidative Stress and Endoplasmic Reticulum Stress in the Rat Neurourology and Urodynamics. 2011;30:472–9. doi: 10.1002/nau.20855
10. Chevalier RL. Prognostic factors and biomarkers of congenital obstructive nephropathy. Pediatric Nephrology. 2016;31(9):1411–20. PMID:26667236.doi: 10.1007/s00467-015-3291-3
11. Xu Y, Ruan S, Wu X, Chen H, Zheng K, Fu B. Autophagy and apoptosis in tubular cells following unilateral ureteral obstruction are associated with mitochondrial oxidative stress. International journal of molecular medicine. 2013;(31):628-36. doi: 10.3892/ijmm.2013.1232.

12. Hughes J, Gobe G. Identification and quantification of apoptosis in the kidney using morphology, biochemical and molecular markers. Nephrology. 2007;12(5):452-8. doi: 10.1111/j.1440-1797.2007.00854.x.
13. Martinez MM, Randall DR, Pappas D. Detection of apoptosis: A review of conventional and novel techniques (Critical Review). Anal Methods. 2010;2:996-1004. doi: 10.1039/c0ay00247j
14. Loo DT. In Situ Detection of Apoptosis by the TUNEL Assay: An Overview of Techniques. Methods in Molecular Biology. 2011;682:3-13. doi 10.1007/978-1-60327-409-8_1.
15. Lebon C, Rodriguez GV, El Zaoui I, Jaadane I, Behar-Cohen F, Torriglia A. On the use of an appropriate TUNEL assay to identify apoptotic cells, Analytical Biochemistry. 2015; doi: doi: 10.1016/j.ab.2015.04.007.
16. Crowley LC, Marfell BJ, Waterhouse NJ. Detection of DNA Fragmentation in Apoptotic Cells by TUNEL. Cold Spring Harb Protoc. 2016;(10)3 doi: 10.1101/pdb.prot 087221.
17. Archana M; Bastian, Yogesh TL, Kumaraswamy KL. Various methods available for detection of apoptotic cells--a review. Indian J Cancer. 2013 Jul-Sep;50(3):274-83. doi: 10.4103/0019-509X.118720. PMID: 24061471.
18. Bozza WP, Twomey JD, Kim S-R, Zhang B. Detection of Apoptosis: From Bench Side to Clinical Practice.Apoptosis Methods in Toxicology. Methods in Pharmacology and Toxicology, Muganda PM. (ed.), 2016, Chapter 2, Pages 13-29, Springer Science+Business Media New York. doi: 10.1007/978-1-4939-3588-8_2.
19. Banfalvi G. Methods to detect apoptotic cell death. Apoptosis. 2017;22(2):306-23. doi: 10.1007/s10495-016-1333-3.
20. Nambiar KS, Hegde V. Apoptosis detection modalities: A brief review. International Dental & Medical Journal of Advanced Research. 2016;2:1–5. doi: 10.15713/ins.idmjar.53.
21. Eddy A. Experimental insight into the tubulointertitial disease accompanying primary glomerular lesions. J Am Soc Nephrol. 1994;5(6):12373-87.
22. Chevalier RL. The proximal tubule is the primary target of injury and progression of kidney disease: role of the glomerulotubular junction. Am J Physiol Renal Physiol. 2016;311(1):145–61. doi: 10.1152 / ajprenal.00164.2016.
23. Docherty NG, O'Sullivan OE , Büyük DA, Fitzpatrick JM, Watson RW. Evidence that inhibition of tubular cell apoptosis protects against renal damage and development of fibrosis following ureteric obstruction. Am J Physiol Renal Physiol. 2006;290:4–13. doi: 10.1152 / ajprenal. 00045.2005.
24. Nagalakshmi VK, Li M, Shah S, Gigliotti JC, Klibanov AL, Epstein FH, et al. Changes in cell fate determine the regenerative and functional capacity of the developing kidney before and after release of obstruction. Clinical Science. 2018;132(23):2519-45; doi: 10.1042 /CS2018062.
25. Sanz AB, Santamaría B, Ruiz-Ortega M, Egido J, Ortiz A. Mechanisms of renal apoptosis in health and disease. J Am Soc Nephrol. 2008;19(9):1634-42. doi: 10.1681/ASN.2007121336.
26. Adachi T, Sugiyama N, Yagita H, Yokoyama T. Renal atrophy after ischemia–reperfusion injury depends on massive tubular apoptosis induced by TNFα in the later phase. Medical Molecular Morphology. 2014;47(4):213–23. PMID:24407718 doi: 10.1007/s00795-013-0067-3.
27. Ophascharoensuk V, Giachelli CM, Gordon K, Hughes J, Pichler R, Brown P, et al. Obstructive uropathy in the mouse: Role of osteopontin in interstitial fibrosis and apoptosis. Kidney International. 1999;56(2):571-80. doi: 10.1046/j.1523-1755.1999.00580.x.
28. Misseri R, Meldrum KK. Mediators of Fibrosis and Apoptosis in Obstructive Uropathies. Curr Urol Rep. 2005;6:140–5. doi: 10.1007/s11934-005-0083-5.
29. Kim J, Kim DS, Park MJ, Cho H-J, Zervos AS, Bonventre JV, et al. Omi/HtrA2 protease is associated with tubular cell apoptosis and fibrosis induced by unilateral ureteral obstruction. Am J Physiol Renal Physiol. 2010;298:1332–40. doi: 10.1152/ajprenal.00737.2009.
30. Jackson L, Woodward M, Coward RJ. The molecular biology of pelvi-ureteric junction obstruction. Pediatr Nephrol. 2018;33(4):553-71. doi: 10.1007/s00467-017-3629-0.
31. Topcu SO, Celik S, Erturhan S, Erbagci A, Yagci F, Ucak R. Verapamil prevents the apoptotic and hemodynamic changes in response to unilateral ureteral obstruction. Int J Urol. 2008;15(4):350-5. doi: 10.1111/j.1442-2042.2008.01992.x.
32. Yang H, Zhang W, Xie T, Wang X, Ning W. Fluorofenidone inhibits apoptosis of renal tubular epithelial cells in rats with renal interstitial fibrosis. Braz J Med Biol Res. 2019;52(11):e8772. doi: 10.1590/1414-431X20198772.
33. Cho JH, Choi SY, Ryu HM, et al. Fimasartan attenuates renal ischemia-reperfusion injury by modulating inflammation-related apoptosis. Korean J Physiol Pharmacol. 2018;22(6):661-70. doi: 10.4196/kjpp.2018.22.6.661.
34. Park E, Cox M, Scotland K, Buttyan R, Lange D. Erythropoietin promotes functional recovery via anti-apoptotic mechanisms in mouse unilateral ureteral obstruction. Cell Stress Chaperones. 2020;25(2):245-51. doi: 10.1007/s12192-020-01067-3
35. Chen Y, Mu L, Xing L, Li S and Fu S. Rhein alleviates renal interstitial fibrosis by inhibiting tubular cell apoptosis in rats. Biol Res. 2019;52:50. doi: 10.1186/s40659-019-0257-0.
36. Kim S, Jung ES, Lee J, Heo NJ, Na KY, Han JS. Effects of colchicine on renal fibrosis and apoptosis in obstructed kidneys. The Korean Journal of Internal Medicine. 2018;33:568-76. doi: 10.3904/kjim.2016.131.
37. Kaeidi A, Taghipour Z, Allahtavakoli M, Fatemi I, Hakimizadeh E, Hassanshahi J. Ameliorating effect of troxerutin in unilateral ureteral obstruction induced renal oxidative stress, inflammation, and apoptosis in male rats. Naunyn Schmiedebergs Arch Pharmacol. 2020;393(5):879-88. doi: 10.1007/s00210-019-01801-4.
38. Zhang QF. Ulinastatin inhibits renal tubular epithelial apoptosis and interstitial fibrosis in rats with unilateral ureteral obstruction. Mol Med Rep. 2017;16(6):8916-22. doi: 10.3892/mmr.2017.7692.
39. Yuan J, Shen Y, Yang X, Xie Y, Lin X, Zeng W, et al. Thymosin β4 alleviates renal fibrosis and tubular cell apoptosis through TGF-β pathway inhibition in UUO rat models. BMC Nephrol. 2017;18:314. doi.org/10.1186/s12882-017-0708-1.
40. Hosseinian S, Bideskan AE, Shafei MN, Sadeghnia HR, Soukhtanloo M, Shahraki S, et al. Nigella sativa extract is a potent therapeutic agent for renal inflammation, apoptosis, and oxidative stress in a rat model of unilateral ureteral obstruction. Phytother Res. 2018;32(11):2290-8. doi: 10.1002/ptr.6169.
41. Kartal H, Büyük B. Effects of alpha-lipoic acid on skeletal muscle ischemia-reperfusion injury in mice. J Surg Med. 2020;4(7):567-72. doi: 10.28982/josam.764953.
42. Büyük B, Karakoç E. Effects of thiopental in cold ıschemia in liver transplation: An experimental study. J Surg Med. 2019;3(2):143-8. doi: 10.28982/josam.460075.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1063-1067.
DOI: 10.28982/josam.806401

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Presentation and management of pediatric elbow septic arthritis: Case series

Pediatrik dirsek septik artritinin sunumu ve tedavisi: Olgu serisi

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Ethics Committee Approval: This study was approved by Istanbul Health Sciences University, Kanuni Sultan Süleyman Training and Research Hospital ethics committee; decision no: 2020.08.190; date: 9/3/2020). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma İstanbul Sağlık Bilimleri Üniversitesi, Kanuni Sultan Süleyman Eğitim ve Araştırma Hastanesi etik kurulu (karar no: 2020.08.190; tarih: 03.09.2020) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Septic arthritis is an emergency orthopedic situation, and septic arthritis of the elbow is rarely seen. The aim of this study was to evaluate the clinical and radiological determinants of septic arthritis of the elbow and review the mid-term clinical results.

Methods: A case-series study was conducted on patients who visited a tertiary pediatric hospital between January 2015-January 2017, were diagnosed with septic arthritis of the elbow, and treated with drainage and debridement. All evaluations included obtaining a thorough history, physical examination, and radiological and laboratory workup. In the laboratory tests, full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood culture were examined. Mayo scores of the elbows were evaluated in the last follow-up visit.

Results: Five patients (5 elbows) including 3 males and 2 females with a mean age of 79 months (2-161 months) were included in this case-series. All patients presented with pain, signs of local inflammation (swelling, redness, increased heat) and fever (>38.5°). All patients had leukocytosis (leukocyte count>11,000), along with elevated CRP and ESR levels. Their mean CRP value during hospitalization was 110.2 (range: 17.5-285) and the mean ESR level was 46 (range: 24-85). The patients were followed up for a mean of 47 months (range: 31-58 months). At the final follow-up examination, the mean Mayo Elbow Performance Score of all the patients was 82.3 (range: 79-85), which was considered a good outcome.

Conclusion: Septic arthritis should always be kept in mind in patients presenting to the Emergency Department with severe elbow function restriction together with fever, redness, swelling and no significant trauma history. To obtain successful clinical results, early debridement, irrigation, antibiotics use are important.

Keywords: Septic arthritis, Elbow, Septic joint, Pediatric orthopedics

Öz

Amaç: Septik artrit acil bir ortopedik durumdur. Dirseğin septik artriti diğer eklemlere göre daha nadir görülmektedir. Bu çalışmanın amacı, dirsek septik artritinin klinik ve radyolojik belirleyicilerini değerlendirmek ve orta dönem klinik sonuçlarını gözden geçirmektir.

Yöntemler: Ocak 2015-Ocak 2017 tarihleri arasında üçüncü basamak bir çocuk hastanesine başvuran ve septik artrit tanısı alan ve ardından drenaj ve debridman ile tedavi edilen hastalardan vaka serisi çalışması yapıldı. Tüm değerlendirmeler; hasta geçmişi, fiziksel muayene ve radyolojik ve laboratuvar incelemelerini içeriyordu. Laboratuvar testlerinde tam kan sayımı, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP) ve kan kültürü incelendi. Ayrıca hastaların son takiplerinde dirsek Mayo skorları da incelendi.

Bulgular: Değerlendirme; yaş ortalaması 79 ay (2-161 ay) olan 3 erkek ve 2 kadın olmak üzere 5 hasta (5 dirsek) üzerinde yapıldı. Tüm hastalar ağrı, lokal inflamasyon belirtileri (şişlik, kızarıklık, ateş artışı) ve ateş (>38.5 °) ile başvurdu. Laboratuvar tetkiklerinde lökosit sayısı >11.000 olarak tanımlanan tüm hastalarda lökositoz tespit edildi ve tüm hastaların CRP ve ESR değerleri yüksekti. Hastanede yatış sırasında ortalama CRP düzeyi 110,2 (17,5-285) ve ortalama ESR düzeyi 46 (24-85) idi. Hastalar ortalama 47 ay (31-58 ay) takip edildi. Son takip muayenesinde, tüm hastaların Mayo Dirsek Performans Skoru ortalama 82.3 (79-85) idi ve iyi bir sonuç olarak değerlendirildi.

Sonuç: Acil servise şiddetli dirsek fonksiyon kısıtlaması ile başvuran ateş, kızarıklık ve şişlik ile başvuran ve önemli travma öyküsü olmayan hastalarda septik artrit her zaman akılda tutulmalıdır. Başarılı klinik sonuçlar elde etmek için erken debridman, irigasyon ve antibiyotik kullanımı önemlidir.

Anahtar kelimeler: Septik artrit, Dirsek, Septik eklem, Pediatrik ortopedi

How to cite/Atıf için: Kılıç B, Agar A. Presentation and management of pediatric elbow septic arthritis: Case series. J Surg Med. 2020;4(11):1063-1067.

Introduction

Septic arthritis is an emergency orthopedic condition. Diagnosis is an especially fundamental problem in children who cannot communicate their symptoms [1]. In developed countries, the incidence of pediatric acute bacterial septic arthritis is estimated to be 4-10/100 [2]. Intra-articular infection may result from hematogenous spread, contracting a local infection or inoculation directly into the joint. These infections can potentially lead to complications such as arthritis, osteomyelitis, misalignment, and limb length discrepancy. Previous studies have shown that up to 29% of pediatric patients who underwent had septic arthritis or osteomyelitis could be left with sequelae such as osteonecrosis, limb length discrepancy, and pathological fractures, all of which could lead to lifelong disability and functional limitations [3-5].

Septic arthritis may affect any joint in childhood, but the hips and knees are the most frequently involved, constituting 70% of pediatric septic arthritis cases [6]. When a painful knee or hip joint is encountered, septic arthritis should always be kept in mind in the initial diagnosis. Although septic arthritis of the elbow is rarely seen, there are a few publications in literature, mostly case reports. As it is seen so infrequently, diagnosis is more difficult, and if this diagnosis is not considered, incorrect treatment may be administered, causing permanent sequelae in the joint and surrounding bones.

There is no single test for the diagnosis of septic arthritis, so a clinical estimation algorithm based on a combination of factors makes diagnosis easier. One of these algorithms includes four important diagnostic variables related to septic arthritis of the hip, as defined by Kocher et al [7]. The presence of each one of these independent multivariable predictors has a cumulative effect, and when all four variables are identified, there is a 99.6% likelihood of septic arthritis in the hip of the child. As it is not possible to apply such a clinical estimation algorithm for septic arthritis of the elbow, the diagnosis and treatment of septic arthritis of the elbow is difficult.

The aim of this study was to evaluate the clinical and radiological determinants of septic arthritis of the elbow and review mid-term clinical results.

Materials and methods

A retrospective study was conducted in patients who presented at a tertiary level pediatric hospital between January 2015 and January 2017, were diagnosed with septic arthritis of the elbow, and treated with drainage and debridement. Approval for the study was granted by the Local Ethics Committee (Istanbul Health Sciences University, Kanuni Sultan Süleyman Training and Research Hospital ethics committee; decision no: 2020.08.190; date: 9/3/2020). Throughout the defined study period, a total of 5 patients who underwent elbow arthrotomy, irrigation and debridement, were identified.

All evaluations included a full history, physical examination, and radiological and laboratory examinations. In the laboratory tests, full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and blood culture were examined. To discount fracture or other bone lesions, plain radiographs were taken of the elbow. If septic arthritis was suspected, arthrosynthesis was applied under ultrasonography (USG) guidance. Then, intra-articular collection and spread were evaluated more clearly in all the patients by obtaining magnetic resonance images (MRI) under emergency conditions to reveal the presence of osteomyelitis, which was not determined in any of the patients.

The synovial fluid analysis included white blood cell count and distribution, gram staining and culture assays. Patients determined to have septic arthritis of the elbow underwent emergency surgical drainage and received empirical intravenous antibiotics.

The data obtained from the medical records included age, gender, affected side, history of trauma to the elbow, history of chronic disease, clinical findings (body temperature, sensitivity, effusion), laboratory test results, and arthrosynthesis results. Fever was defined as an oral temperature of ≥38.5°. A definitive diagnosis of septic arthritis was made when there was bacterial reproduction in synovial fluid culture and white blood cell count in synovial fluid was ≥50,000 cells/m^3. In all the patients, the interventions were performed under general anesthesia. Entry was made with a lateral incision to the elbow joint, arthrotomy was performed, then the joint was debrided and irrigated. A drain was used in all the patients for fluid drainage. All the drains were removed on postoperative day 1. An above-the-elbow plaster cast was applied and used for 10 days postoperatively. On the 10^{th} day, the cast and the sutures were removed, and passive and active elbow range of movement exercises were started. Until the culture results were received, along with consultation with a pediatric infectious diseases specialist, cefotaxime and cloxacillin were started as empirical antibiotics in the postoperative period. When the culture results were received, the antibiotic treatment was switched to drugs specific to the agent. The patients were followed up postoperatively in the orthopedic ward, where intravenous antibiotic therapy and laboratory parameters were evaluated at 3-day intervals. When patients' clinical statuses improved and a response to treatment was observed in laboratory parameters, they were discharged with oral antibiotic treatment. Antibiotics were administered to all patients intravenously for 3 weeks (during hospitalization) and per oral route for 3 weeks. Laboratory and clinical follow-up were performed at 1-week intervals for 6 weeks.

Results

A total of five patients (5 elbows) including 3 males and 2 females with a mean age of 79 months (2-161 months) were evaluated. The right elbow was involved in 3 patients and the left elbow, in 2 patients. Case examples are presented in Figures 1a-1c and 2a-2c.

On presentation, none of the patients had a history of trauma or any known chronic diseases. All patients presented with pain, signs of local inflammation (swelling, redness, increased heat) and fever (>38.5°). In the laboratory tests, leukocytosis was determined in all the patients (WBC>11,000), and CRP and ESR values of all patients were elevated. The mean CRP level during hospitalization was 110.2 (range, 17.5-285) and the mean ESR level was 46 (range, 24-85) (Table 1).

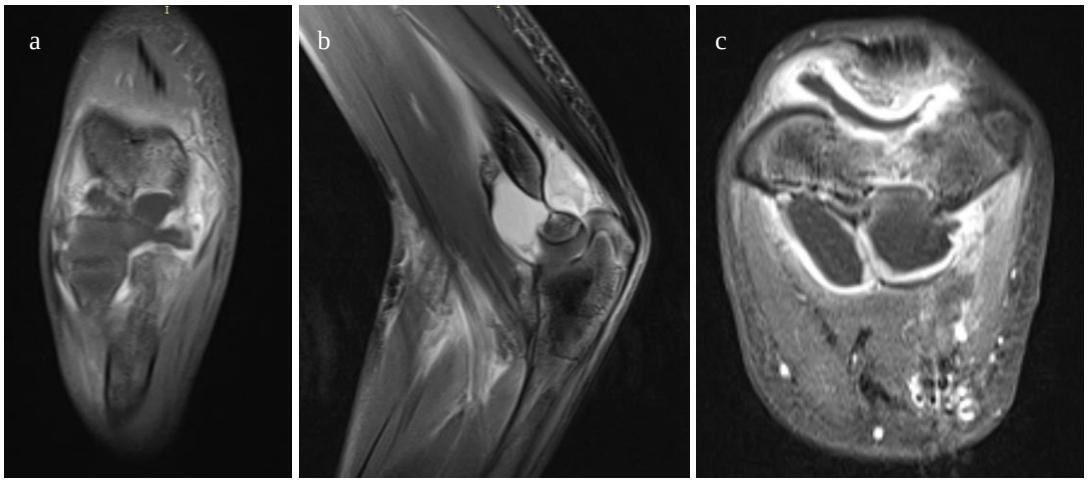

Figure 1: Preoperative MR image of the right elbow of a 13-year-old male patient (Patient 4) (a: coronal MR image, b: Sagittal MR image, c: axial MR image)

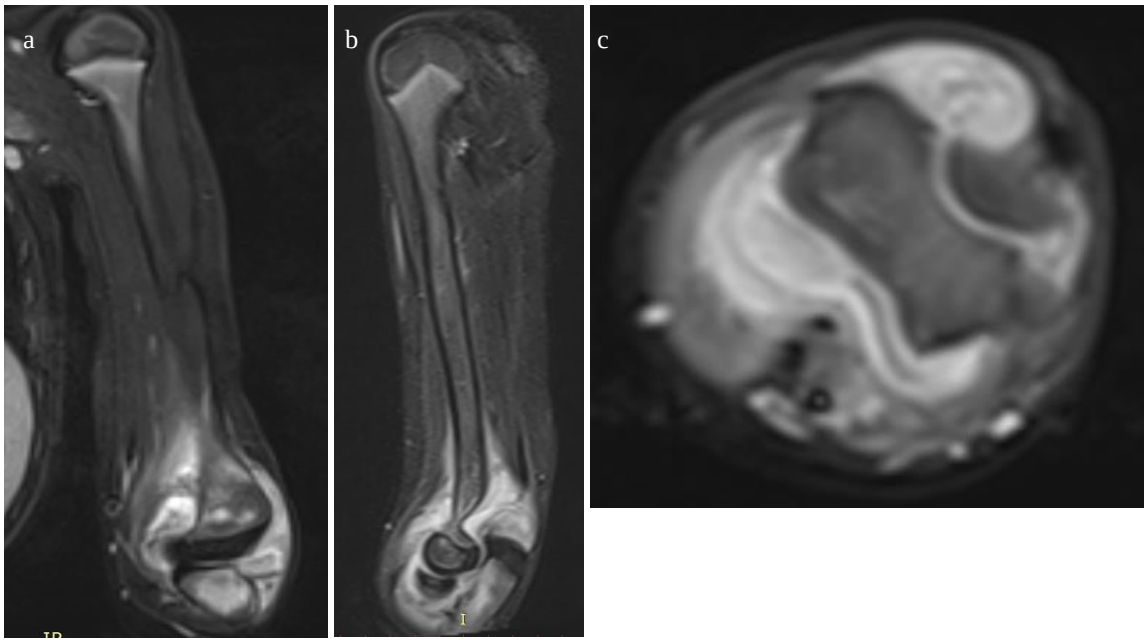

Figure 2: Preoperative MR image of the left elbow of a 7-year-old male patient (patient 5) (a: coronal MR image, b: sagittal MR image, c: axial MR image)

The mean time from onset of patient complaints to surgery was 1.4 days (range, 0-2 days) (Table 1). The culture results showed production of MSSA in 4 patients, and streptococcus pyogenes in 1 patient. The mean length of stay in hospital was 22.4 days (range, 21-24 days), and the mean duration of antibiotic treatment was 42 days (Table 1). Empirical antibiotic treatment was administered to all the patients until the intraoperative culture results were obtained, which was followed by antibiotics specific to the bacteria identified in the cultures. The antibiotics were administered based on consultations with a pediatric infectious diseases specialist. Oxacillin and gentamicin were administered to 4 (75%) patients and oxacillin and ceftriaxone, to one (25%).

The patients were followed up for a mean of 47 months (range, 31-58 months). At the final follow-up examination, the mean Mayo Elbow Performance Score [8] of all patients was 82.3 (range, 79-85), which was considered a good outcome (Table 1). No continuation of pathology was determined in the clinical and laboratory results at the final follow-up examinations. No complications were seen in any of the patients.

Table 1: Laboratory and clinical findings of patients

	ESR (mm/saat)	CRP (mg/L)	WBC ($10^3/\mu L$)	Mayo	Length of hospitalization (day)	Duration of antibiotic use (day)	Time from application to operation (days)
Patient 1	24	17.46	25.93	79	20	40	0
Patient 2	42	141.21	15.27	EX	15	23	4
Patient 3	85	285	16.97	83	21	42	0
Patient 4	48	71.32	14.32	82	22	44	3
Patient 5	31	35.98	13.86	85	24	41	0

Discussion

The main findings of this study were that septic arthritis of the elbow is uncommon, but pediatric orthopedic surgeons should use laboratory and radiological evaluations when there is clinical suspicion and should make every effort to perform debridement and irrigation to the joint as soon as possible to avoid destructive complications.

It has been reported in literature that an elbow, misdiagnosed as nursemaid's elbow or that which cannot be fully treated may be septic arthritis [9]. This is the most common diagnostic error for this disease. The differential diagnosis should be made clinically or from the presence of effusion shown on ultrasonography. Effusion is not seen in nursemaid's elbow. In 1% of nursemaid's elbow cases, there may be underlying osteomyelitis or septic arthritis [9]. To determine whether the patient is immunosuppressive and learn if there is a history of

infection which may have caused hematogenous spread, anamnesis is extremely important.

In the early stage of the disease, radiological changes may be observed on direct radiographs, and it is important to know that at a mean of 2-3 weeks after disease onset, periosteal reaction and radiological changes occur in the subacute period. Therefore, ultrasound is extremely useful to strengthen the diagnosis in the acute period. In some cases, it is difficult to determine minimal collection in the elbow with examination. In these cases, ultrasound shows intra-articular collection and inflammation, and in non-acute cases it allows the possibility of evaluation of the periosteum. However, computed tomography (CT), and magnetic resonance imaging (MRI) are more useful than direct radiographs in the determination of soft tissue and bone tissue infection, although there are problems such as the amount of radiation exposure in CT and the expense of MRI, and the need for anesthesia because of the age of the patient. In our practice, direct radiographs are obtained routinely for every patient seen in the Emergency Department, and in cases with suspected septic arthritis, following intra-articular effusion determined on USG first, MRI was obtained under emergency conditions to reveal any pathology in adjacent bones.

ESR and CRP showed changes in all the cases in this series. These data were consistent with the data reported in previous studies [10,11]. The CRP value is reported as a specific parameter for septic arthritis of the elbow, but WBC may be normal in some patients [12]. CRP value is also an important parameter for disease follow-up. In the current study, attention was paid to the CRP value during follow-up and at the end of treatment.

In the current study, the etiological agent was identified in the synovial fluid culture of all (100%) 5 patients, and other studies have similarly reported that the bacteria responsible could be identified in 82%-95% of cases [13,14]. In the literature, gram positive cocci were reported as the micro-organism responsible in up to 92% of cases of pediatric septic arthritis [15]. When the cultures of the patients were examined in the current study, a reproduction of MSSA was observed in 4 patients and Strep. Pyogenes, in one patient. Despite the reproduction in culture in all study patients, it has been stated in literature that culture results may be negative in up to 20% of septic arthritis cases [16]. That culture production was determined in all the cases in this series is thought to be due to the patients not having received antibiotics before the diagnosis, therefore, there was no antibiotic suppression, and all the arthrosyntheses were performed under USG guidance. In cases where no micro-organism is produced in the culture, diagnosis of septic arthritis can be made using the criteria described by Newman [17]. At least one of the following criteria must be met: Positive synovial fluid culture, negative synovial fluid culture with positive blood culture, negative culture associated with previous antibiotic use, purulent synovial fluid in the shoulder or elbow joint drainage.

Osteomyelitis is seen frequently in children with septic arthritis, with reported rates of 17%-33% [18,19]. Especially in patients where diagnosis is missed and intervention is late, the likelihood of osteomyelitis development is higher [20]. In the 5 patients treated in this study, osteomyelitis was not determined in any patient, which was thought to be associated with the early interventions performed.

Although the subject of how long antibiotherapy should be continued in septic arthritis patients remains a matter of debate, there are studies recommending continuation for 6 weeks and others recommending that treatment is terminated with the follow-up of laboratory parameters [21]. In the current study, antibiotherapy was continued throughout hospitalization of the patients, who were then discharged with oral antibiotics when the clinical and laboratory findings improved.

Early diagnosis and treatment can prevent the destructive results that can occur in septic arthritis, such as elbow instability, joint stiffness, and extremity shortness [7,22,23]. No complication development in any of the patients in this series can be attributed to the early diagnosis and treatment. At the final follow-up examination, the mean Mayo score was 82.3, and functional results were worse in comparison with the data in the literature [7]. This may be since in previous studies that have reported functional results, only arthrosynthesis followed by antibiotic therapy was administered, whereas in the current study, open surgical intervention of the joint was performed with debridement.

Limitations of the current study include the sparse number of cases, the absence of a control group in which different treatment methods were used, and long-term follow-up.

Conclusion

Septic arthritis should always be kept in mind in patients presenting at the Emergency Department with severe elbow function restriction together with fever, redness and swelling and no significant trauma history. However, no findings may be observed on direct radiographs in the early stage, therefore, when there is clinical suspicion, puncture must be applied under USG guidance. MRI is extremely useful in the determination of adjacent bone pathologies. To obtain successful clinical results, early debridement, irrigation, and the use of antibiotics are important.

References

1. Rutz E. Septic arthritis of the hip joint in children is an emergency. Afr J Paediatr Surg. 2012 Jan-Apr;9(1):1-2. doi: 10.4103/0189-6725.93292. PMID: 22382095.
2. Arnold JC, Bradley JS. Osteoarticular Infections in Children. Infect Dis Clin North Am. 2015 Sep;29(3):557-74. doi: 10.1016/j.idc.2015.05.012. PMID: 26311358.
3. Baghdadi T, Saberi S, Sobhani Eraghi A, Arabzadeh A, Mardookhpour S. Late sequelae of hip septic arthritis in children. Acta Med Iran. 2012;50(7):463-7. PMID: 22930377.
4. Forlin E, Milani C. Sequelae of septic arthritis of the hip in children: a new classification and a review of 41 hips. J Pediatr Orthop. 2008 Jul-Aug;28(5):524-8. doi: 10.1097/BPO.0b013e31817bb079. PMID: 18580366.
5. Sukswai P, Kovitvanitcha D, Thumkunanon V, Chotpitayasunondh T, Sangtawesin V, Jeerathanyasakun Y. Acute hematogenous osteomyelitis and septic arthritis in children: clinical characteristics and outcomes study. J Med Assoc Thai. 2011 Aug;94 Suppl 3:S209-16. PMID: 22043778.
6. Ahmed H, Dix-Peek S, Martin N, Hoffman EB. Septic arthritis in children: a 20-year study. In: Orthopaedic Proceedings. The British Editorial Society of Bone & Joint Surgery, 2005. p. 279-279.
7. Kocher MS, Mandiga R, Zurakowski D, Barnewolt C, Kasser JR. Validation of a clinical prediction rule for the differentiation between septic arthritis and transient synovitis of the hip in children. J Bone Joint Surg Am. 2004 Aug;86(8):1629-35. doi: 10.2106/00004623-200408000-00005. PMID: 15292409.
8. Morrey BF, An KN, Chao EYS. Functional evaluation of the elbow. In: Morrey BF, editor. The elbow and its disorders. 2nd edition. Philadelphia: WB Saunders; 1993. pp. 86–89.
9. Desbiolles A, Carls F, Dube S, Hirsig J. Pronation douloureuse--Ein diagnostischer Reinfall bei eitriger Arthritis und Osteomyelitis des Ellbogens im Kleinkindesalter [Painful pronation--a diagnostic pitfall in septic arthritis and osteomyelitis of the elbow in infancy]. Z Kinderchir. 1987 Jun;42(3):187-9. German. doi: 10.1055/s-2008-1075582. PMID: 3617945.
10. Leslie BM, Harris JM 3rd, Driscoll D. Septic arthritis of the shoulder in adults. J Bone Joint Surg Am. 1989 Dec;71(10):1516-22. PMID: 2592392.
11. Mehta P, Schnall SB, Zalavras CG. Septic arthritis of the shoulder, elbow, and wrist. Clin Orthop Relat Res. 2006 Oct;451:42-5. doi: 10.1097/01.blo.0000229322.30169.29. PMID: 16906071.
12. Nduaguba AM, Flynn JM, Sankar WN. Septic Arthritis of the Elbow in Children: Clinical Presentation and Microbiological Profile. J Pediatr Orthop. 2016 Jan;36(1):75-9. doi: 10.1097/BPO.0000000000000390. PMID: 25575360.
13. Kennedy N, Chambers ST, Nolan I, Gallagher K, Werno A, Browne M, et al. Native Joint Septic Arthritis: Epidemiology, Clinical Features, and Microbiological Causes in a New Zealand Population.

J Rheumatol. 2015 Dec;42(12):2392-7. doi: 10.3899/jrheum.150434. Epub 2015 Nov 1. PMID: 26523022.

14. Weston VC, Jones AC, Bradbury N, Fawthrop F, Doherty M. Clinical features and outcome of septic arthritis in a single UK Health District 1982-1991. Ann Rheum Dis. 1999 Apr;58(4):214-9. doi: 10.1136/ard.58.4.214. PMID: 10364899; PMCID: PMC1752863.
15. Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA, et al; Active Bacterial Core Surveillance Program of the Emerging Infections Program Network. Methicillin-resistant Staphylococcus aureus disease in three communities. N Engl J Med. 2005 Apr 7;352(14):1436-44. doi: 10.1056/NEJMoa043252. Erratum in: N Engl J Med. 2005 Jun 2;352(22):2362. PMID: 15814879.
16. Bowakim J, Marti R, Curto A. Elbow septic arthritis in children: clinical presentation and management. J Pediatr Orthop B. 2010 May;19(3):281-4. doi: 10.1097/BPB.0b013e3283387d2d. PMID: 20300010.
17. Frank G, Mahoney HM, Eppes SC. Musculoskeletal infections in children. Pediatr Clin North Am. 2005 Aug;52(4):1083-106, ix. doi: 10.1016/j.pcl.2005.04.003. PMID: 16009258.
18. McCarthy JJ, Dormans JP, Kozin SH, Pizzutillo PD. Musculoskeletal infections in children: basic treatment principles and recent advancements. Instr Course Lect. 2005;54:515-28. PMID: 15948476.
19. Montgomery CO, Siegel E, Blasier RD, Suva LJ. Concurrent septic arthritis and osteomyelitis in children. J Pediatr Orthop. 2013 Jun;33(4):464-7. doi: 10.1097/BPO.0b013e318278484f. PMID: 23653039.
20. Lavy CB, Thyoka M. For how long should antibiotics be given in acute paediatric septic arthritis? A prospective audit of 96 cases. Trop Doct. 2007 Oct;37(4):195-7. doi: 10.1258/004947507782332775. PMID: 17988472.
21. Helito CP, Noffs GG, Pecora JR, Gobbi RG, Tirico LE, Lima AL, et al. Epidemiology of septic arthritis of the knee at Hospital das Clínicas, Universidade de São Paulo. Braz J Infect Dis. 2014 Jan-Feb;18(1):28-33. doi: 10.1016/j.bjid.2013.04.010. Epub 2013 Sep 9. PMID: 24029436.
22. Fabry G, Meire E. Septic arthritis of the hip in children: poor results after late and inadequate treatment. J Pediatr Orthop. 1983 Sep;3(4):461-6. doi: 10.1097/01241398-198309000-00008. PMID: 6630490.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1068-1072.
DOI: 10.28982/josam.821632

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Effectiveness and reliability of percutaneous microwave ablation therapy in early stage renal cell cancer: Intermediate term results

Erken evre renal hücreli kanserde perkütan mikrodalga ablasyon tedavisinin etkinliği ve güvenirliği: Ara dönem sonuçları

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Ethics Committee Approval: This study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (Number: 71522473/050.01.04/547). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma Sakarya Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylandı (Sayı: 71522473/050.01.04/547). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Percutaneous tumor ablation is the most important alternative to surgery in early stage renal cell cancers (RCC). Although many studies are conducted with radiofrequency ablation and cryoablation therapy in RCC, the data regarding microwave ablation (MWA) is more limited. In this study, we aimed to evaluate the efficacy of percutaneous MWA in the treatment of RCC, its safety in terms of residual renal function and other complications, and its clinical results.

Methods: In T1b patients, the suitability for MWA was evaluated with a urologist based on characteristics such as size, and location of the mass (intestinal proximity, proximity to the main renal vascular structures and renal pelvis). Fourteen T1a, five T1b and one T2 RCC patients treated with MWA were included in this retrospective study. MWA was preferred when partial nephrectomy was highly risky or contraindicated due to medical comorbidities or the patients refused to undergo surgical treatment. The patients were ablated with uncooled MWA device with 30W energy under sedation or general anesthesia under ultrasound guidance for an average of 13 minutes. Multiple antennas were used for masses larger than 4 cm. Hydrodissection with saline was performed in cases where there was a non-target organ adjacent to the lesion. Lesion size, location of the lesion, ablation time, complications, Charlson comorbidity index, Hb, and creatinine values were recorded. Patients were followed by CT.

Results: The mean age of the patients was 68.9 years, and the median lesion size was 2.8 cm. While the tumor was exophytic in 12 patients, it was intraparenchymal or endophytic in 8 patients. The average Charlson comorbidity index score of the patients was 6.9. Technical success was achieved in all patients. Average ablation time was 13 minutes. Minor complications occurred in 3 patients. The median follow-up period of the patients was 13.5 months. In Kaplan Meier analysis, progression-free survival was 12 months. During follow up, distant organ metastasis was not observed in any of the patients, recurrence was observed in 2, and no patients died.

Conclusion: MWA can be applied in early stage RCCs with very high technical success. The results of our study show that MWA is effective and highly reliable in RCCs. It can be safely applied, especially in patients who are not suitable for surgery and in residual RCCs.

Keywords: Microwave ablation, RCC, RCC ablation, RCC MWA, Interventional radiology

Öz

Amaç: Bu çalışmada perkütan mikrodalga ablasyonun (MWA) renal hücreli kanser (RCC) tedavisinde etkinliğini, rezidüel renal fonksiyon açısından ve diğer yan etkiler açısından güvenirliğini ve klinik sonuçlarını değerlendirmeyi amaçladık.

Yöntemler: Bu retrospektif çalışmaya MWA ile tedavi edilen 14 T1a, 5 T1b ve 1 T2 RCC hastası dahil edildi. Hastalara soğutmasız sistem MWA cihazı ile 30W enerji ile sedasyon veya genel anestezi altında, ultrason eşliğinde ortalama 13 dakika boyunca ablasyon uygulanmıştır. 4 cm üzerindeki kitlelerde birden çok anten kullanıldı. Lezyon komşuluğunda hedef dışı organ bulunduğu durumlarda salin ile hidrodiseksiyon yapıldı. Lezyon boyutu, lezyonun yerleşimi, ablasyon süresi, komplikasyonlar, Charlson komorbidite indeksi, Hb ve kreatinin değerleri kaydedildi. Hastalar işlem sonrası 1. Gün, 1. Ay, 3.-6.-12.18. ve 24. aylarda CT ile takip edilmiştir.

Bulgular: Hastaların yaş ortalaması 68,9 (9,8) idi. Ortanca lezyon boyutu 2,8 cm (range, 1,9-7,1 cm) idi. 12 hastada (%60) tümör egzofitik iken 8 hastada (%40) intraparankimal veya endofitikti. Hastaların ortalama Charlson comorbidity index skoru 6,9 (1,8) idi. Tüm hastalarda teknik başarı sağlandı. Ortalama ablation süresi 13 dakikaydı (9-15 mins). 3 hastada (%15) minör komplikasyon gelişti. Hastaların ortanca takip süresi 13,5 ay idi (range 6-24 ay). Kaplan Meier analizinde progresyonsuz sağ kalım 12 ay olarak bulundu. Hiçbir hastada takip sırasında uzak organ metastazı izlenmedi. 2 hastada takip sırasında nüks gözlendi. Kanser-spesifik survival oranı %100 idi.

Sonuç: MWA erken evre RCC'lerde oldukça yüksek teknik başarı ile uygulanabilir. Çalışmamızın sonuçları RCC'lerde MW ablasyonun etkili ve oldukça güvenilir olduğunu göstermektedir. Özellikle cerrahiye uygun olmayan hastalarda ve rezidü RCC'lerde güvenle uygulanabilir.

Anahtar kelimeler: Mikrodalga ablasyon, RCC, RCC ablasyonu, RCC MWA, Girişimsel radyoloji

How to cite/Atıf için: Ateş ÖF. Effectiveness and reliability of percutaneous microwave ablation therapy in early stage renal cell cancer: Intermediate term results. J Surg Med. 2020;4(11):1068-1072.

Introduction

Renal cell carcinoma (RCC) accounts for 2.2-3% of all cancers worldwide [1]. The incidence of RCC, especially the number of small masses, has increased in recent years [2]. According to The European Association of Urology RCC guidelines, the gold standard treatment method for T1a RCC is partial nephrectomy (PN) [3].

Percutaneous tumor ablation is the most important alternative to surgery in early stage RCCs in patients with comorbid diseases or otherwise unsuitable for surgery [4, 5]. Although resection and surgical margin control are higher in PN, it has been shown that ablation methods affect the renal functions less and provide similar survival rates in early stage RCC [6].

The most common thermal ablation methods are radiofrequency ablation (RFA) and cryoablation. Microwave ablation (MWA) applications have also increased in recent years [7, 8]. There are studies showing that there is no significant difference between cryoablation, RFA and MWA methods in terms of therapeutic function, effects on renal function and complications in RCC [9]. Although many studies are conducted with RFA and cryoablation therapy in RCC in the literature, there is more limited data regarding MWA.

In this study, we aimed to evaluate the efficacy of percutaneous MWA in the treatment of RCC, its safety in terms of residual renal function and other complications, and its clinical results.

Materials and methods

This retrospective cohort study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (Number: 71522473/050.01.04/547). Informed consent was obtained before the percutaneous ablation treatment, after the purpose of the procedure and possible complications were discussed with the patient.

Patient selection

Twenty-one consecutive patients who underwent percutaneous microwave ablation for RCC treatment between January 2019 and July 2020, and a total of 25 procedures were included in our study. One patient was excluded from the study because the pathological result was oncocytoma. Twenty patients were T1N0M0 (14 T1a, 6 T1b), and suitable for PN or ablation. One patient had T2N0M0 RCC, and ablation decision was made due to tumor size, comorbidities, and the atrophic kidney of the patient. The patients were referred by urologists experienced in urological oncology in both open and laparoscopic surgery, and MWA was preferred because of age, comorbidities, single kidney, dysfunction in the other kidney (atrophy etc.), shorter hospital stay and the patient's refusal to undergo surgical treatment. In T1b patients, the suitability for MWA was evaluated together with the urologist due to characteristics such as size, location of the mass (intestinal proximity, proximity to the main renal vascular structures and renal pelvis) or when PN is highly risky or contraindicated due to medical comorbidities. Patients with contraindications in terms of thermal ablation (uncorrectable coagulopathy, refusal to accept the procedure), renal vein embolism and those with distant organ or lymph node metastases were excluded from the treatment.

Microwave ablation procedure

While the patient was in the lateral decubitus position with the relevant kidney on the upper side, the area to be punctured was determined with ultrasound and properly disinfected with 10% povidone iodine. After a sterile pouch was put on the 2-5 Mhz ultrasound probe (Affiniti, Philips Healthcare, Bothell, Washington), local anesthesia was administered with 1% lidocaine, and an approximately 5 mm smooth incision was made on the skin with a No.11 scalpel. Core biopsy was performed with an 18G, fully automatic needle under ultrasound guidance, and the MWA antenna was placed in the appropriate position within the lesion. The procedure was performed with the patient under conscious sedation (by increasing the dose of sedation when the patient felt pain), and general anesthesia was administered in 3 patients, considering the patient's compliance and preference.

For MWA, a 2.45 Mhz 17G uncooled system that allows treatment with multiple antennas at the same time (TATO, Biomedical, Italy) was used. If the lesion size exceeded 4 cm (T1b), two antennas were used at the same time. Approximately 2 cm distance was left between these two antennas depending on the size of the lesion. A 7.1 cm sized RCC was treated by placing 3 antennas at the same time so that the distance between the antennas was approximately 2.5 cm.

Ultrasound-guided hydrodissection was performed with a 21G needle when there was an intestinal loop, colon, or liver neighboring the lesion at 1 cm or closer to the targeted ablation area. Saline was used for hydrodissection, and saline injection (50-250 cc) was given until there was a minimum of 1 cm between the non-target organ and the tumor.

To reach the targeted ablation zone, 30W energy was applied for an average of 13 minutes (9-15 minutes depending on the target ablation zone size). During ablation, the extension of the ablation area with ultrasound was continuously followed by the gas echogenicity generated during ablation. Ablation continued until we were sure that the ablation zone covered the tumor with a minimum margin of 5 mm. After the ablation was completed, the antenna was removed by ablating the antenna tract.

Follow-up

After the patients were controlled by ultrasonography immediately after the procedure, they were followed up clinically. Hb, Htc, urea and creatinine values were evaluated before the procedure, at the 6^{th} hour and 24 hours after the procedure. Multiphasic contrast-enhanced (precontrast, arterial venous and late phase) CT (64-row multidetector CT scanner, LightSpeed VCT; GE Healthcare, Milwaukee, WI, USA) was obtained 24 hours after the procedure to control effective ablation. Patients were followed up with control CT imaging at the 1^{st}, 3^{rd}, 6^{th}, 12^{th}, 18^{th} and 24^{th} months. Complementary ablation procedure was applied to the patient after one week in case of insufficient ablation. If there was an area of enhancement in the mass in the CT performed at the 24^{th} hour after the procedure, it was considered an insufficient ablation. Although there was no enhancement area in the first CT after the procedure, if there was nodular or heterogeneous enhancement in the mass in the subsequent follow-up CT, it was considered recurrence.

Patients' age, gender, tumor size, tumor location (exophytic, partially exophytic, intraparenchymal), pre- and post-procedure Hb, Htc, creatinine values, number of repetitive procedures and complications were evaluated. The tumor was considered exophytic if there was significant bulging in the kidney contours, intraparenchymal in the case of no bulging in the kidney contour but extension towards the sinus and endophytic if it was adjacent to the collecting system (Figures 1-2). Ablation time, number of antennas used, hospital stay were recorded. Charlson comorbidity index was calculated [10]. Complications that did not require treatment or hospitalization were defined as minor complications. Complications that required additional treatment or prolonged hospital stay were major complications.

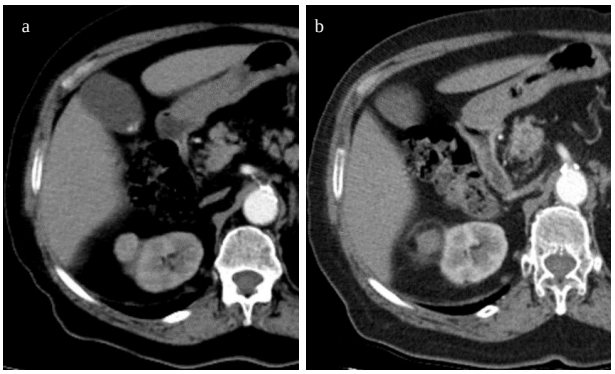

Figure 1: a. Preoperative CT image shows exophytic contrast enhanced mass on right kidney b. Postoperative 18. months CT image shows no contrast enhancement on the mass

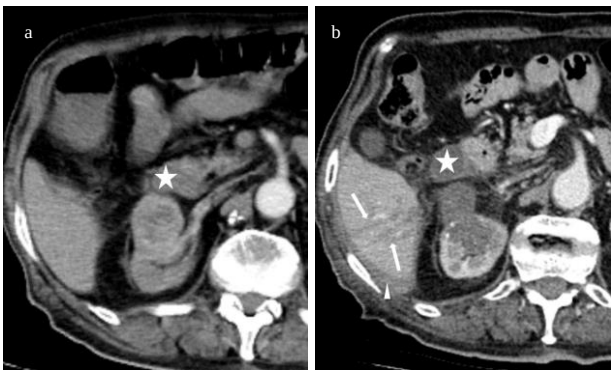

Figure 2: a. Preoperative contrast-enhanced axial CT image shows exophytic contrast enhanced mass on right kidney. The intestinal loop is located almost adjacent to the mass (star). b. Postoperative 24 hour contrast-enhanced CT shows no enhancement in the mass. Fluid density in the perihepatic area due to hydrodissection (arrowhead). Intestinal wall damage is not observed. Hypodense lines are observed in the liver due to transhepatic placement of the antennas and tract ablation at the end of the procedure (arrows).

Statistical analysis

MedCalc (ver. 12, Ostend, Belgium) was used for statistical analysis. Descriptive statistics were presented as median (minimum-maximum) and mean (standard deviation). Categorical variables were expressed as frequencies and percentages. Correlation analysis was performed with the Pearson correlation coefficient. Progression-free survival was evaluated by the Kaplan-Meier method. Progression-free survival was defined as the time between ablation and the last CT.

Results

Fifteen (75%) of 20 patients were male and 5 (25%) were female. The mean age of the patients was 68.9 (9.8) years. Median lesion size was 2.8 cm (1.9-7.1 cm). Pathological diagnosis was clear cell carcinoma in 10 patients (50%), chromophobe cell carcinoma in 3 patients (15%) and papillary cell carcinoma in 5 patients (25%). While the tumor was exophytic in 12 patients (60%), it was intraparenchymal or endophytic in 8 patients (40%). The average Charlson comorbidity index score of the patients was 6.9 (1.8). Patient and pathology characteristics are summarized in Table 1.

Table 1: Patient, tumor and procedure characteristics

Characteristics	Value
Median Age (years)	68.9 (49-81)
Gender, n (%)	
Male	15 (75)
Female	5 (25)
Median Charlson Comorbidity Index	6.9 (4-10)
RCC Stage, n (%)	
T1a	14 (70)
T1b	5 (25)
T2a	1 (5)
Tumor Localization, n (%)	
Exophytic	12 (60)
Partially Exophytic	7 (35)
Intraparenchymal	1 (5)
Histologic subtype, n (%)	
Clear Cell	10 (50)
Papillary	5 (25)
Chromophobe	3 (15)
Carcinoma NOS	2 (10)
Median ablation time (min)	13 (9-15)
Median Duration of Hospitalization (days)	1
Multiple Ablation Sessions (%)	4 (20)

In 10 patients, surgical treatment was not appropriate due to severe comorbidities, while ablation treatment was not considered appropriate in 4 patients due to borderline kidney functions, in 2 patients due to having a single kidney or because the other kidney was atrophic, and in 4 patients because the patient refused surgical treatment.

Average ablation time was 13 minutes (9-15 mins). All patients were discharged the day after the procedure and followed up on an outpatient basis. Two sessions were applied to 4 patients (20%), and one session was applied to 16 patients (80%). Hydrodissection was performed with an average of 120 cc saline (50-250 cc) in 10 of 24 procedures.

Minor complications occurred in 3 patients (15%). A moderate increase in liver function tests was observed in the patient who was treated transhepatically and with 2 antennas. Since it was asymptomatic, the patient was followed up on an outpatient basis. In the 1st week, values returned to normal. Minimal hemorrhage was observed in the post-procedure ultrasound image in 1 patient. The hemorrhage did not increase, Hb values of the patient were stable and the patient, who did not require transfusion during follow-up, was discharged the day after the procedure. Urinoma was detected in 1 patient at the 1st month follow-up after the procedure. The urinoma of the patient, who was asymptomatic, regressed at the 3rd month follow-up and no additional treatment was needed. No significant decrease in Hb or increase in creatinine values were observed in any of the patients.

Patients were followed for at least 6 months and the median follow-up period of the patients was 13.5 months (range 6-24 months). In Kaplan Meier analysis, progression-free survival was 12 months. Distant organ metastasis was not observed in any of the patients during follow-up. Recurrence was observed in 2 patients during follow-up. Recurrence in one patient occurred at the 6th month after the first procedure and the other, at the 12th month. Since the patients were not suitable for surgery due to their comorbidities, MW ablation was performed again in these patients and recurrence was treated. There were no recurrences at the 9th and 12th months following the second procedures in the patients who developed recurrences at the 6th

and 12th months following the first procedures (Figure 3). No patients died during follow-up. Median progression-free survival was 12 months in Kaplan-Meier analysis (Figure 4).

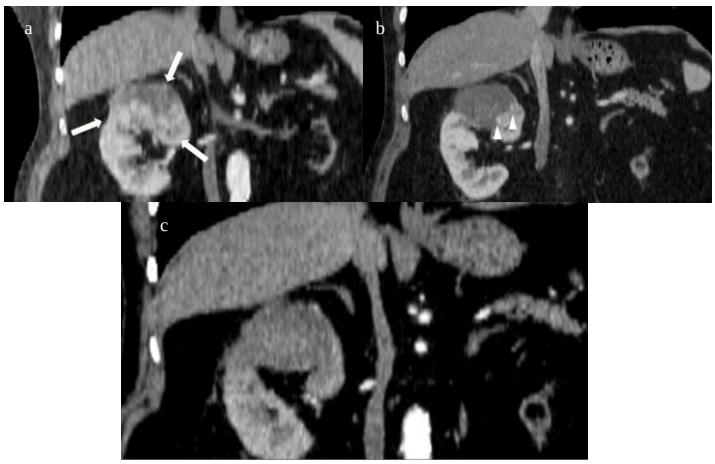

Figure 3: a. Preoperative coronal CT image shows endophytic contrast enhanced mass (Arrows), RCC b.Postoperative 12. Month postcontrast coronal CT image shows nodular enhancement compatible with relapse (arrowheads). c. No enhancement is observed in the CT taken after the treatment of the recurrent lesion

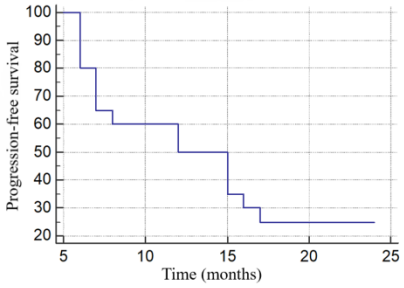

Figure 4: Kaplan-Meier analysis

Discussion

The most important result of our study is that technically successful MW ablation was achieved in all patients. Although 5 of our patients were T1b and 1 was T2a, and multiple sessions were performed in 4 patients (3 T1b, 1 T2a), the ablation procedure was successfully completed in all patients. In 2 patients, the reason for the recurrent procedure was recurrence (no increase in size, but enhancement in follow-up CT), and none of the patients progressed in the tumor stage. There was no cancer-related mortality or morbidity. Although the Charlson Comorbidity Index of the patients who were treated was quite high, no major complications were observed in any patient. Although 3 of the patients had minor complications, all of the patients could be discharged after 1 day of observation.

Tumor size was over 4 cm in all patients who required repeat ablation. All T1a tumors were successfully treated in a single session, and no residual tumors or recurrence was observed in these patients. One of the patients had a single functioning kidney, and the largest length of the tumor in this patient was 7.1 cm. However, no increase was observed in the creatinine values of the patient after the ablation procedure. The treatment of the patient was carried out in 2 sessions as adequate ablation could not be achieved in the first session. The patient was in the 7th month of follow-up and no recurrence was observed. Although ablation therapy is a treatment option especially in T1a RCCs, as in our patient, ablation treatment can be tried with the decision of the oncologic council in patients who have a single kidney and are not suitable for surgical treatment (partial or total nephrectomy) due to their comorbidities and after discussing the risks with the patient. Especially in large tumors, MW will be more useful as it provides a faster and wider ablation compared to RF ablation [9,11].

Unlike RF ablation, since MW ablation provides heating of water molecules with microwave stimulation, independent of the thermal conductivity of the tissue, carbonization does not occur and it is possible to reach a larger ablation area [12]. In addition, effective ablation is more difficult to achieve with RF, since the "heat sink effect" will be more intense during RF ablation, especially in large tumors, in a highly perfused kidney, which contains many arterial structures [13,14]. Some centers even apply arterial embolization before RF ablation to reduce the heat sink effect and enhance effectiveness [15]. However, in MW ablation, this effect is minimal since heat is transmitted directly to the target tissue rather than through the tissue [16].

While ablation is easier in T1a tumors due to their size, the ablation procedure is more complex in larger tumors. We preferred to use more than one antenna at the same time in these patients. This meant that there were at least two different electromagnetic energy sources at the same time, which meant that more energy could be delivered at once, however, it was possible to reach even more ablation fields due to electromagnetic synergy in the boundary zones [17,18].

It is known that during microwave ablation therapy, a less controlled ablation area is provided compared to RF due to rapid ablation [19]. However, the MW antenna we used provided a more controlled ablation with low energy (30W) in a long time (approximately 13 minutes). This is a very facilitating factor, especially in avoiding off-target ablation of adjacent organs or anatomical structures. In addition, ultrasound-guided hydrodissection was applied between the tumor and the non-target organ in the presence of non-target organs such as the bowel loop, colon loop, vascular structure, and liver in the vicinity of the targeted ablation area to prevent off-target ablation and possible complications. Hydrodissection is a very safe procedure [20,21], and our patients did not develop complications due to hydrodissection or off-target ablation.

Due to the development and increasing use of imaging methods, the frequency of detecting small-sized RCC is increasing [2,22]. In these patients, the first treatment option for guidelines is surgery, especially partial nephrectomy rather than nephrectomy due to better kidney function and lower risk of complications. However, ablation is an alternative treatment option to surgical treatment in elderly patients with comorbidities and are considered unfit in terms of surgery, patients with multiple tumors, with a single kidney, and those at risk of completely losing kidney function to surgery [4]. Even in studies with solitary kidney patients, ablative therapies have been shown to be fairly safe for kidney function [15,23]. It has been demonstrated that ablation therapy has similar efficacy in T1a lesions compared with partial nephrectomy, although less complication rates have been observed [24–26].

Studies have reported effective treatment success ranging from 91% to 97% and tumor progression varying between 0% and 23% for tumors below 4 cm with RF [27-29]. High recurrence or progression has been reported in some studies

with MW [30]. However, as in our study, technical success with MW is similar to RF in many studies [7,9]. In addition, studies with MW show that much larger masses are treated with ablation [31].

Some studies have reported no tumor progression with MW, even if the tumor size is over 4 cm [31]. However, in ablation treatments, it has been shown that as the tumor size increases, the incidence of recurrence increases and disease-free survival decreases [32,33]. In our study, recurrence was observed in 2 patients, and 2 patients with recurrence were RCC stage T1b.

Limitations

Our study has some important limitations. The first is that the study is retrospective and the number of patients is relatively small. Especially the number of T1b and T2 patients is not sufficient for such a study. Studies with more patients and centers are needed to demonstrate the efficiency and reliability of MW in large tumors. In addition, the follow-up period was not long in our study, a longer follow-up period is required to show long-term results.

Conclusion

The results of our study show that MW ablation is effective and highly reliable in early stage RCCs. It can be safely applied, especially in patients who are not suitable for surgery and in residual RCCs. However, multicenter randomized controlled studies with larger populations and longer follow-up periods designed in comparison with other treatment methods are required.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.
2. Wong MC, Goggins WB, Yip BH, Fung FD, Leung C, Fang Y, et al. Incidence and mortality of kidney cancer: temporal patterns and global trends in 39 countries. Scientific reports. 2017;7(1):1-10.
3. Ljungberg B, Bensalah K, Bex A, Canfield S, Dabestani S, Hofmann F, et al. EAU guidelines on renal cell carcinoma. European Association of Urology. 2018;1.
4. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, et al. European association of urology guidelines on renal cell carcinoma: the 2019 update. European urology. 2019;75(5):799-810.
5. Motzer RJ, Jonasch E, Agarwal N, Bhayani S, Bro WP, Chang SS, et al. Kidney cancer, version 2.2017, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network. 2017;15(6):804-34.
6. Uhlig J, Strauss A, Rücker G, Hosseini ASA, Lotz J, Trojan L, et al. Partial nephrectomy versus ablative techniques for small renal masses: a systematic review and network meta-analysis. European radiology. 2019;29(3):1293-307.
7. Filippiadis D, Mauri G, Marra P, Charalampopoulos G, Gennaro N, De Cobelli F. Percutaneous ablation techniques for renal cell carcinoma: current status and future trends. International Journal of Hyperthermia. 2019;36(2):21-30.
8. Lin Y, Liang P, Yu X-L, Yu J, Cheng Z-g, Han Z-Y, et al. Percutaneous microwave ablation of renal cell carcinoma is safe in patients with renal dysfunction. International Journal of Hyperthermia. 2017;33(4):440-5.
9. Zhou W, Herwald SE, McCarthy C, Uppot RN, Arellano RS. Radiofrequency ablation, cryoablation, and microwave ablation for T1a renal cell carcinoma: a comparative evaluation of therapeutic and renal function outcomes. Journal of Vascular and Interventional Radiology. 2019;30(7):1035-42.
10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of Clinical Epidemiology. 1987;40(5):373-83.
11. Laeseke PF, Lee Jr FT, Sampson LA, van der Weide DW, Brace CL. Microwave ablation versus radiofrequency ablation in the kidney: high-power triaxial antennas create larger ablation zones than similarly sized internally cooled electrodes. Journal of Vascular and Interventional Radiology. 2009;20(9):1224-9.
12. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics. 2005;25(suppl_1):S69-S83.
13. Zhou W, Arellano RS. Thermal ablation of T1c renal cell carcinoma: a comparative assessment of technical performance, procedural outcome, and safety of microwave ablation, radiofrequency ablation, and cryoablation. Journal of Vascular and Interventional Radiology. 2018;29(7):943-51.
14. Wright AS, Sampson LA, Warner TF, Mahvi DM, Lee J, Fred T. Radiofrequency versus microwave ablation in a hepatic porcine model. Radiology. 2005;236(1):132-9.
15. Hoffmann R-T, Jakobs TF, Kubisch CH, Trumm C, Weber C, Siebels M, et al. Renal cell carcinoma in patients with a solitary kidney after nephrectomy treated with radiofrequency ablation: mid term results. European journal of radiology. 2010;73(3):652-6.
16. Maaref Y, Pakravan H, Jafarpur K. Numerical Analysis of the Heat Sink Effect of Blood Vessels on Hepatic Radiofrequency and Microwave Ablation. Modares Mechanical Engineering. 2019;19(7):1711-20.
17. Brace CL, Laeseke PF, Sampson LA, Frey TM, van der Weide DW, Lee Jr FT. Microwave ablation with multiple simultaneously powered small-gauge triaxial antennas: results from an in vivo swine liver model. Radiology. 2007;244(1):151-6.
18. Liang P, Dong B, Yu X, Yu D, Wang Y, Feng L, et al. Prognostic factors for survival in patients with hepatocellular carcinoma after percutaneous microwave ablation. Radiology. 2005;235(1):299-307.
19. Glassberg MB, Ghosh S, Clymer JW, Qadeer RA, Ferko NC, Sadeghirad B, et al. Microwave ablation compared with radiofrequency ablation for treatment of hepatocellular carcinoma and liver metastases: a systematic review and meta-analysis. OncoTargets and therapy. 2019;12:6407.
20. Lee SJ, Choyke LT, Locklin JK, Wood BJ. Use of hydrodissection to prevent nerve and muscular damage during radiofrequency ablation of kidney tumors. Journal of vascular and interventional radiology. 2006;17(12):1967-9.
21. Cheng Z, Yu X, Han Z, Liu F, Yu J, Liang P. Ultrasound-guided hydrodissection for assisting percutaneous microwave ablation of renal cell carcinomas adjacent to intestinal tracts: a preliminary clinical study. International Journal of Hyperthermia. 2018;34(3):315-20.
22. Hollingsworth JM, Miller DC, Daignault S, Hollenbeck BK. Rising incidence of small renal masses: a need to reassess treatment effect. Journal of the National Cancer Institute. 2006;98(18):1331-4.
23. Wah TM, Irving HC, Gregory W, Cartledge J, Joyce AD, Selby PJ. Radiofrequency ablation (RFA) of renal cell carcinoma (RCC): experience in 200 tumours. BJU international. 2014;113(3):416-28.
24. Talenfeld AD, Gennarelli RL, Elkin EB, Atoria CL, Durack JC, Huang WC, et al. Percutaneous ablation versus partial and radical nephrectomy for T1a renal cancer: a population-based analysis. Annals of internal medicine. 2018;169(2):69-77.
25. Guan W, Bai J, Liu J, Wang S, Zhuang Q, Ye Z, et al. Microwave ablation versus partial nephrectomy for small renal tumors: Intermediate-term results. Journal of surgical oncology. 2012;106(3):316-21.
26. Shangqian W, Chao Q, Zhihang P, Qiang C, Pu L, Pengfei S, et al. Radiofrequency ablation versus partial nephrectomy for the treatment of clinical stage 1 renal masses: a systematic review and meta-analysis. LWW; 2014.
27. Tracy CR, Raman JD, Donnally C, Trimmer CK, Cadeddu JA. Durable oncologic outcomes after radiofrequency ablation: experience from treating 243 small renal masses over 7.5 years. Cancer. 2010;116(13):3135-42.
28. Lyrdal D, Andersson M, Hellström M, Sternal J, Lundstam S. Ultrasound-guided percutaneous radiofrequency ablation of small renal tumors: clinical results and radiological evolution during follow-up. Acta Radiologica. 2010;51(7):808-18.
29. Zagoria RJ, Pettus JA, Rogers M, Werle DM, Childs D, Leyendecker JR. Long-term outcomes after percutaneous radiofrequency ablation for renal cell carcinoma. Urology. 2011;77(6):1393-7.
30. Castle SM, Salas N, Leveillee RJ. Initial experience using microwave ablation therapy for renal tumor treatment: 18-month follow-up. Urology. 2011;77(4):792-7.
31. Wells SA, Wheeler KM, Mithqal A, Patel MS, Brace CL, Schenkman NS. Percutaneous microwave ablation of T1a and T1b renal cell carcinoma: short-term efficacy and complications with emphasis on tumor complexity and single session treatment. Abdominal Radiology. 2016;41(6):1203-11.
32. Johnson BA, Sorokin I, Cadeddu JA. Ten-year outcomes of renal tumor radio frequency ablation. The Journal of urology. 2019;201(2):251-8.
33. Chang X, Zhang F, Liu T, Ji C, Zhao X, Yang R, et al. Radio frequency ablation versus partial nephrectomy for clinical T1b renal cell carcinoma: long-term clinical and oncologic outcomes. The Journal of urology. 2015;193(2):430-5.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1073-1076.
DOI: 10.28982/josam.816374

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

Prognostic factors for survival among gastric cancer patients receiving neoadjuvant chemotherapy: A cross sectional study from Turkey

Neoadjuvan kemoterapi alan mide kanseri hastalarında surviye etkili prognostik faktörler: Türkiye'den kesitsel bir çalışma

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Ethics Committee Approval: The study protocol was approved by Kartal Koşuyolu High Specialty Training and Research Hospital Ethics Committee with the number 2020/9/363. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma protokolü Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi Etik Kurulu tarafından 2020/9/363 numarası ile onaylandı. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Gastric cancer is usually diagnosed once it has reached the advanced stage and is one of the leading causes of cancer-related deaths. We investigated the prognostic factors for survival among gastric cancer patients undergoing neoadjuvant chemotherapy to prolong overall survival.

Methods: A retrospective review was made of patients who underwent surgery for gastric cancer between November 2006 and September 2019. Clinicopathological characteristics were assessed in 46 patients receiving neoadjuvant chemotherapy and 194 patients not receiving neoadjuvant therapy. A Cox regression analysis was used to assess the prognostic factors for survival among the patients receiving neoadjuvant chemotherapy.

Results: The patients receiving neoadjuvant chemotherapy accounted for 19.2% of the total. The tumors in these patients were located primarily in the upper and middle portions (73.9%), to a statistically significant degree (P=0.001). There was no statistical difference in survival between the two groups, although a high number of positive lymph nodes was identified among the patients receiving neoadjuvant chemotherapy as the most significant prognostic factor for survival (P<0.01).

Conclusion: After neoadjuvant chemotherapy, multiple positive lymph nodes are the most important prognostic factor for survival; postoperative chemotherapy protocol can be changed or other methods can be applied together with chemotherapy.

Keywords: Gastric cancer, Neoadjuvant therapy, Prognostic factors, Overall survival

Öz

Amaç: Mide kanseri ileri evrede karşımıza çıkar ve kansere bağlı ölümler arasında en üst sıralarda yer almaktadır. Overall sürviyi uzatmak için neoadjuvan kemoterapi alan mide kanseri hastalarında surviye etkili prognostik faktörleri araştırmayı amaçladık.

Yöntemler: Kasım 2006 - Eylül 2019 tarihleri arasında mide kanseri nedeniyle ameliyat edilen hastalar retrospektif olarak incelendi. Neoadjuvan kemoterapi alan 46 hasta ile neoadjuvan kemoterapi almayan 194 hasta klinikopatolojik özelliklerine değerlendirildi. Neoadjuvan kemoterapi alan hastaların surviye etki eden prognostik faktörleri Cox regresyon analizi ile değerlendirildi.

Bulgular: Neoadjuvan kemoterapi alan hastalar tüm hastaların %19.2'sini oluşturmaktaydı. Bu hastaların tümör yerleşim yeri genellikle üst ve orta yerleşimliydi (%73,9) ve istatistiksel bir farklılık mevcuttu (P=0,001). İki grup arasında sürvi bakımından istatistiksel bir farklılık yoktu. Ancak neoadjuvan kemoterapi alan hastaların pozitif lenf nodu sayısının fazla olması surviye etkili en önemli prognostik faktör olarak bulundu (P<0,01).

Sonuç: Neoadjuvan kemoterapi sonrası pozitif lenf nodu sayısının yüksek olması sürvi bakımından en önemli prognostik faktör olup, cerrahi sonrası kemoterapi protokolü değiştirilebilinir veya kemoterapi ile beraber başka yöntemler uygulanabilinir.

Anahtar kelimeler: Mide kanseri, Neoadjuvan kemoterapi, Prognostik faktörler, Genel sürvi

How to cite/Atıf için: Uzun O, Gülmez S, Senger AS, Öz A, Özduman MÖ, Ofluoğlu CB, Polat E, Duman M. Prognostic factors for survival among gastric cancer patients receiving neoadjuvant chemotherapy: A cross sectional study from Turkey. J Surg Med. 2020;4(11):1073-1076.

Introduction

Gastric cancer is the sixth most common type of cancer around the world, and is among the leading causes of cancer-related death [1]. More than 50% of all gastric cancer cases are diagnosed in the early stage in Asian countries like Japan and South Korea, whereas it is usually diagnosed only after reaching an advanced stage in Western countries, including the United States [2]. Stage at admission is the most important determinant of prognosis for gastric cancer [3]. Depending on the tumor, node and metastasis (TNM) system, the 5-year survival of early stage patients is above 90%, compared to a mean survival of 25% in stage III or stage IV patients, 60% of whom develop local recurrence or distant metastases [3]. The treatment approach to locally advanced gastric cancer varies from region to region around the world. The standard treatment for gastric cancer is perioperative chemotherapy or postoperative adjuvant chemotherapy in Western countries, including the United States, while in Asian countries, adjuvant chemotherapy after D2 gastrectomy is the standard treatment approach [4]. There have been several studies claiming that perioperative chemotherapy in gastric cancer results in decreased tumor diameter, leading to regression in tumor stage, increase in radical resection rates, no rise in postoperative complication rates and improvement in survival [5-7]. That said, there are also ongoing studies aimed at determining which perioperative regime should be applied, and for how long, as the prognostic factors for survival are still not exactly known in patients receiving neoadjuvant chemotherapy [7].

In the present study, we investigate the prognostic factors for survival among patients receiving neoadjuvant chemotherapy due to gastric cancer.

Materials and methods

This retrospective review included 320 patients operated due to gastric cancer in the Health Sciences University Kartal Koşuyolu High Specialty Educational and Research Hospital between November 2006 and September 2019. Patient details were accessed from clinical records and pathology reports. The assessment date for the survival analysis was accepted as August 31, 2020. D2 lymph node dissections were performed in line with the approach recommended by the Japanese Research Society for the Study of Gastric Cancer (JRSSG) [8], and the Tumor, Node, Metastasis (TNM) classification system of the American Joint of Committee on Cancer (AJCC), (8^{th} Edition, 2018) for staging within the study [9]. Of all, 15 patients with positive peritoneal cytology, 10 patients with liver metastasis during surgery, six patients with positive distal or proximal surgical margins, 15 patients who died within the first 90 days, and 28 patients with a depth of wall invasion into the mucosa or submucosa (T1) were excluded from the study. Consequently, the study was completed with 240 patients. Among diffuse-type patients, four were Borrmann classification type III (ulcero-infiltrative). Surgery-related complications were considered as those occurring within the first 30 days following surgery.

Statistical analysis

The normality of the numerical variables was analyzed with a Kolmogorov-Smirnov test, which revealed a non-normal distribution based on $P<0.05$, therefore, median (IQR) values were used. Categorical variables were expressed as numbers and percentages. The patients were divided into two groups based on whether they underwent adjuvant therapy. Chi-square test, a Fisher's exact test and a Mann-Whitney U test were used to determine any statistical differences between the groups within the categorical variables. The survival of the two groups was analyzed with a Kaplan-Meier test, while a log-rank test was used to identify any difference. The prognostic factors among the patients undergoing neoadjuvant chemotherapy were examined with univariate and multivariate analyses using a stepwise Cox regression analysis approach. Statistical analyses were conducted using the SPSS 26 soft version, and a *P*-value of <0.05 was considered statistically significant.

Results

Of the 240 patients included in the study, 19.2% (46 patients) were operated after undergoing neoadjuvant chemotherapy. The patients were divided into two groups, based on whether they received preoperative chemotherapy. The clinicopathological characteristics of the patients were compared between the two groups, and no statistical difference was found in terms of gender, age, tumor diameter, Lauren classification, total number of lymph nodes removed, metastatic lymph node status and stage, presence of vascular invasion, presence of perineural invasion, complication status or length of hospital stay. In contrast, a statistical difference was noted in tumor localization and type of surgery ($P=0.001$) (Table 1).

Table 1: Comparison of clinicopathological characteristics of patients by receipt of neoadjuvant therapy

		Neoadjuvant therapy				
		No		Yes		
		n	%	n	%	*P*-value
Gender	Male	133	68.6%	37	80.4%	0.111
	Female	61	31.4%	9	19.6%	
Location	Upper	41	21.1%	20	43.5%	0.001*
	Middle	48	24.7%	14	30.4%	
	Distal	105	54.1%	12	26.1%	
Type of Surgery	Subtotal	104	53.6%	12	26.1%	0.001*
	Total	90	46.4%	34	73.9%	
Lauren Classification	Intestinal type	59	30.4%	13	28.9%	0.841
	Diffuse type	135	69.6%	32	71.1%	
Depth of invasion	T1	0	0.0%	2	4.3%	0.040**
	T2	25	12.9%	4	8.7%	
	T3	90	46.4%	25	54.3%	
	T4	79	40.7%	15	32.6%	
N stage	N0	60	30.9%	10	21.7%	0.666
	N1	38	19.6%	8	17.4%	
	N2	32	16.5%	10	21.7%	
	N3a	39	20.1%	12	26.1%	
	N3b	25	12.9%	6	13.0%	
Stage	Stage I	15	7.7%	4	8.7%	0.659
	Stage II	73	37.6%	14	30.4%	
	Stage III	106	54.6%	28	60.9%	
Vascular invasion	Negative	71	36.6%	11	23.9%	0.103
	Positive	123	63.4%	35	76.1%	
Perineural invasion	Negative	53	27.3%	17	37.0%	0.196
	Positive	141	72.7%	29	63.0%	
Complications	No	144	74.2%	28	60.9%	0.071
	Yes	50	25.8%	18	39.1%	
		Median	IQR	Median	IQR	
Age		63	53–69	61	52–65	0.071
Tumor size (cm)		5.0	3.5–7.0	4.8	3.0–7.0	0.607
Total number of lymph nodes		24	17–32	26	19–35	0.289
Length of hospital stay (days)		9	8–14	10	8–18	0.253

*Chi-square $P<0.05$, **Likelihood ratio $P<0.05$

The tumor was proximally located in 43.5% and 21.1% of the patients receiving and not receiving neoadjuvant therapy, respectively. Accordingly, 73.9% of the patients receiving neoadjuvant therapy underwent a total gastrectomy, compared with 46.4% of those not receiving neoadjuvant therapy. There

was also a statistical difference in the depth of wall invasion by the tumor between the two groups (P=0.040). Although early stage (T1) patients were excluded from the study, the stage of tumor invasion depth was found to be T1 in two patients receiving neoadjuvant therapy.

There was no statistical difference in survival between the two groups (P=0.571) (Figure 1), with the mean survival of patients receiving neoadjuvant therapy being 56.305(7.545) months, compared to 71.695 (4.878) among those who did not receive neoadjuvant therapy (Table 2).

Table 2: Comparison of overall survival with the Kaplan-Meier method by neoadjuvant chemotherapy status

	Mean(SD)(months)	95% CI	*P*-value
No	71.695(4.878)	62.134-81.256	0.571
Yes	56.305(7.545)	41.516-71.094	
Overall	71.346(4.541)	62.446-80.245	

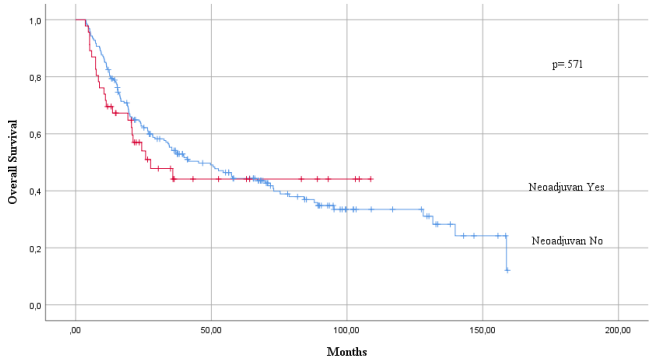

Figure 1: Comparison of survival of patients according to neoadjuvant chemotherapy status.

The prognostic factors for survival among patients receiving neoadjuvant therapy were examined via univariate and multivariate analyses using a stepwise Cox regression analysis. The univariate and multivariate analyses revealed no prognostic significance of gender, age, tumor localization, Lauren classifications, tumor diameter, depth of wall invasion, total number of lymph nodes removed, the presence of vascular invasion or perineural invasion. The N stage, on the other hand, was found to have significant prognostic value in both the univariate and multivariate analyses (P<0.001, P=0.001, respectively) (Table 3). An increased number of positive lymph nodes was a poor prognostic factor for survival among patients receiving neoadjuvant therapy.

Table 3: Univariate and multivariate analyses of prognostic factors for survival among patients receiving neoadjuvant therapy

	Univariate analysis		Multivariate analysis	
	OR (95.0% CI)	*P*-value	OR (95.0% CI)	*P*-value
Gender	0.879 (0.299-2.586)	0.814	2.930 (0.486-17.662)	0.241
Age	1.016 (0.966-1.068)	0.541	1.045 (0.959-1.138)	0.315
Location				
Upper		0.822		0.137
Middle	0.817 (0.296-2.250)	0.695	0.202 (0.035-1.181)	0.076
Lower	1.157 (0.439-3.045)	0.768	1.169 (0.185-7.373)	0.868
Borrmann Classification				
Type I		0.905		0.828
Type II	1.306 (0.380-4.487)	0.672	1.134 (0.142-9.044)	0.905
Type III	1.260 (0.298-3.985)	0.694	0.708 (0.145-3.451)	0.669
Lauren classification	3.225 (0.959-10.912)	0.058	0.615 (0.081-4.643)	0.637
Tumor size	1.082 (0.951-1.231)	0.230	1.305 (0.981-1.736)	0.068
Depth of invasion		0.900		0.988
N Stage				
N0		<0.001**		0.001*
N1	3.683 (0.672-20.180)	0.133	13.560 (1.049-175.315)	0.046
N2	2.073 (0.379-11.336)	0.400	1.380 (0.127-14.964)	0.791
N3a	3.770 (0.782-18.191)	0.098	4.068 (0.402-41.201)	0.235
N3b	39.254 (6.465-238.344)	<0.001	153.897 (8.396-282.031)	0.001
Total number of lymph nodes	0.982 (0.945-1.021)	0.362	0.963 (0.916-1.013)	0.149
Vascular invasion	4.019 (0.940-17.178)	0.061	2.245 (0.148-34.179)	0.560
Perineural invasion	2.186 (0.810-5.899)	0.122	2.039 (0.432-9.624)	0.368

OR: odds ratio, CI: confidence interval, *P<0.05, **P<0.001

Discussion

In Western countries, neoadjuvant chemotherapy is administered as a standard treatment approach in resectable gastric cancer patients with a tumor depth of wall invasion beyond the muscularis propria (T2 and higher) and/or with significant perigastric lymph node involvement [5,6]. In Japan, in contrast, the standard treatment approach to locally advanced gastric cancer is neoadjuvant therapy with S-1 chemotherapy after gastrectomy with D2 lymph node dissection, although there are ongoing studies into the neoadjuvant therapy approach [4]. The aim in neoadjuvant chemotherapy in locally advanced gastric cancer is to diminish the tumor size, and thereby increasing the radical resection rate, and to benefit from its positive effects on survival without increasing postoperative complication rates. Despite the specified benefits, neoadjuvant chemotherapy may rarely lead resectable gastric cancer patients to become unresectable during or after treatment [11]. As such, studies into the optimal treatment approach are ongoing [7].

In the present study, we compared the clinicopathological characteristics of patients receiving and not receiving neoadjuvant therapy, and identified differences in tumor depth of wall invasion, tumor localization and type of surgery between the two groups. The tumors of the patients receiving neoadjuvant therapy had generally a proximal localization, which concurs with the findings of a French study in which the majority of patients were reported to have proximally located gastric tumors, and differences were noted only in R0 resection between the two groups [12].

Several meta-analyses have reported significant improvements in disease-free survival and overall survival in those receiving neoadjuvant chemotherapy, along with no increase in complications or postoperative mortality [3,13,14]. These studies suggest that prolonged survival can be attributed to the neoadjuvant chemotherapy, although no other prognostic factors for survival were noted among patients receiving neoadjuvant therapy. The meta-analysis by Liao et al. [15] reported that neoadjuvant chemotherapy did not increase postoperative morbidity and mortality, and had no effect on overall survival. Likewise, the study by Hashemzadeh et al. [11] reported neoadjuvant chemotherapy to increased resectability in locally advanced gastric cancer, but suggested that more randomized controlled trials were required to establish its effect on survival. In the CRITICS trial, postoperative radiotherapy was administered after perioperative chemotherapy with the same chemotherapy protocol, however no effect on overall survival was seen in those with gastric cancer [16]. No preoperative or postoperative radiotherapy was administered to any of the patients in the present study, and no difference in survival could be identified between the two groups. In the examination of the prognostic factors for survival in the neoadjuvant chemotherapy group, both the univariate and multivariate analyses identified greater postoperative lymph node involvement as the most significant prognostic factor.

Our study is limited by its retrospective and singe-center design, and the low number of patients receiving neoadjuvant therapy.

Conclusion

Gastric cancer is usually identified only once it has reached an advanced stage in countries without a gastric cancer-screening program, and various treatment methods are applied to decrease cancer-related mortality. Neoadjuvant chemotherapy is a treatment method that is used to prolong the disease-specific survival by increasing R0 resectability. In the present study, the most significant prognostic factor for survival was the number of positive lymph nodes among patients receiving neoadjuvant chemotherapy. In the event of postoperative multiple positive lymph nodes being identified in this patient group, postoperative chemotherapy protocol can be changed or other methods can be applied together with chemotherapy. More prospective randomized controlled studies are required in this regard.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019;144:1941–53. doi: 10.1002/ijc.31937.
2. Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric Cancer: Descriptive Epidemiology, Risk Factors, Screening, and Prevention. Cancer Epidemiol Biomarkers Prev. 2014;23:700–13. doi: 10.1158/1055-9965.EPI-13-1057.
3. Miao Z-F, Liu X-Y, Wang Z-N, Zhao T-T, Xu Y-Y, Song Y-X, et al. Effect of neoadjuvant chemotherapy in patients with gastric cancer: a PRISMA-compliant systematic review and meta-analysis. BMC Cancer. 2018 Jan 31;18(1):118. doi: 10.1186/s12885-018-4027-0.
4. Tokunaga M, Sato Y, Nakagawa M, Aburatani T, Matsuyama T, Nakajima Y, et al. Perioperative chemotherapy for locally advanced gastric cancer in Japan: current and future perspectives. Surg Today. 1234;50:30–7. doi: 10.1007/s00595-019-01896-5.
5. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006 Jul 6;355(1):11-20. doi: 10.1056/NEJMoa055531.
6. Tian SB, Yu JC, Kang WM, Ma ZQ, Ye X, Yan C, et al. Effect of Neoadjuvant Chemotherapy Treatment on Prognosis of Patients with Advanced Gastric Cancer: a Retrospective Study. Chinese Med Sci J. 2015;30:84–9. doi: 10.1016/S1001-9294(15)30017-1.
7. Sun Y, Yang L, Wang C, Zhao D, Cai J, Li W, et al. Prognostic factors associated with locally advanced gastric cancer patients treated with neoadjuvant chemotherapy followed by surgical resection. Oncotarget. 2017 Sep 6;8(43):75186-75194. doi: 10.18632/oncotarget.20660.
8. Kodera Y, Sano T. Japanese gastric cancer treatment guidelines 2014 (ver. 4) Japanese Gastric Cancer Association 1. Gastric Cancer. 2017 Jan;20(1):1-19. doi: 10.1007/s10120-016-0622-4.
9. Marano L, D'Ignazio A, Cammillini F, Angotti R, Messina M, Marrelli D, et al. Comparison between 7th and 8th edition of AJCC TNM staging system for gastric cancer: Old problems and new perspectives. Transl Gastroenterol Hepatol. 2019;4:2–5. doi: 10.21037/tgh.2019.03.09.
10. Al-Batran S-E, Homann N, Pauligk C, Illerhaus G, Martens UM, Stoehlmacher J, et al. Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer The AIO-FLOT3 Trial Supplemental content. JAMA Oncol. 2017;3:1237–44. doi: 10.1001/jamaoncol.2017.0515.
11. Hashemzadeh S, Pourzand A, Somi MH, Zarrintan S, Javad-Rashid R, Esfahani A. The effects of neoadjuvant chemotherapy on resectability of locally-advanced gastric adenocarcinoma: A clinical trial. Int J Surg. 2014;12:1061–9. doi: 10.1016/j.ijsu.2014.08.349.
12. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: An FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29:1715–21. doi: 10.1200/JCO.2010.33.0597.
13. Xu A-M, Huang L, Liu W, Gao S, Han W-X, Wei Z-J. Neoadjuvant Chemotherapy Followed by Surgery versus Surgery Alone for Gastric Carcinoma: Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One. 2014 Jan 30;9(1):e86941. doi: 10.1371/journal.pone.0086941.
14. Coccolini F, Nardi M, Montori G, Ceresoli M, Celotti A, Cascinu S, et al. Neoadjuvant chemotherapy in advanced gastric and esophago-gastric cancer. Meta-analysis of randomized trials. Int J Surg. 2018;51:120–7. doi: 10.1016/j.ijsu.2018.01.008.
15. Liao Y, Yang ZL, Peng JS, Xiang J, Wang JP. Neoadjuvant chemotherapy for gastric cancer: A meta-analysis of randomized, controlled trials. J Gastroenterol Hepatol. 2013;28:777–82. doi: 10.1111/jgh.12152.
16. Cats A, Jansen EPM, van Grieken NCT, Sikorska K, Lind P, Nordsmark M, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19:616–28. doi: 10.1016/S1470-2045(18)30132-3.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1077-1081.
DOI: 10.28982/josam.811687

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

A novel approach in the diagnosis and follow-up of sarcoidosis

Sarkoidozun tanı ve takibinde yeni bir yaklaşım

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Ethics Committee Approval: Ethical approval was obtained from T.C Afyonkarahisar Health Sciences University Clinical Research Ethics Committee, dated 6/5/2020, number 2020/6. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Etik onay, T.C Afyonkarahisar Sağlık Bilimleri Üniversitesi Klinik Araştırmalar Etik Kurulundan 05.06.2020 tarih, 2020/6 nolu numara ile alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: Sarcoidosis is characterized by the presence of non-caseous granulomas that can involve all organs, especially the lungs and mediastinal lymph nodes. No biomarker investigated in recent years appears to be specific for sarcoidosis. We aimed to investigate and evaluate the relationship between neutrophil-lymphocyte ratios (NLR), platelet-lymphocyte ratios (PLR), monocyte-lymphocyte ratios (MLR), eosinophil-lymphocyte ratios (ELR), and blood count parameters in sarcoidosis patients.

Methods: A total of 150 individuals comprising 97 sarcoidosis patients, and 53 controls, were included in the study. The data were recorded retrospectively. Chest X-ray findings were analyzed with regards to age, gender, body mass index, modified medical research concept (MMRC) dyspnea scale and respiratory function parameters. Blood count, NLR, PLR, MLR, eosinophil/basophil ratio (EBR) were evaluated in patients with sarcoidosis.

Results: Hemoglobin (g/dl) and lymphocyte count (103 /UL) values were significantly lower in sarcoidosis patients, while red blood cell distribution width standard deviation (RDW SD) (fl), neutrophil count (103 /UL), monocyte count (103 /UL), basophil count (103 /UL), NLR, PLR, MLR values were significantly higher compared to the control group. However, platelet (103 /UL), MPV and EBR values were similar.

Conclusion: Our study showed that MLR value, which was not previously used in sarcoidosis patients, is an important biomarker in the diagnosis of sarcoidosis, just as NLR.

Keywords: Sarcoidosis, Lymphadenopathy, Monocyte, Lymphocyte, Lung

Öz

Amaç: Sarkoidoz, akciğerler ve mediastinal lenf nodları başta olmak üzere tüm organları tutabilen non-kazeifiye granülomların varlığı ile karakterize bir hastalıktır. Yıllardır yapılan araştırmalarda sarkoidoz için spesifik bir biyobelirteç gösterilememiştir. Çalışmamızda, sarkoidoz hastalarında nötrofil-lenfosit oranları (NLO), trombosit-lenfosit oranları (PLR), monosit-lenfosit oranları (MLR), eozinofil-lenfosit oranları (ELR), kan sayım parametreleri arasındaki ilişkiyi araştırmayı ve çıkan sonuçları değerlendirmeyi amaçladık.

Yöntem: Çalışmaya 97 sarkoidoz hastası, 53 kontrol olmak üzere toplam 150 kişi dahil edildi. Veriler geriye dönük olarak kaydedildi. Göğüs röntgeni bulguları yaş, cinsiyet, vücut kitle indeksi, modifiye tıbbi araştırma kavramı (Mmrc) dispne ölçeği ve solunum fonksiyon parametreleri dikkate alınarak analiz edildi. Sarkoidozlu hastalarda kan sayımı, NLR, PLR, MLR, eozinofil / bazofil oranı (EBR) değerlendirildi.

Bulgular: Sarkoidoz hastaları ile kontrol grubunun laboratuvar değerleri karşılaştırıldığında, sarkoidoz hastalarında hemoglobin (g/dl) değeri ve lenfosit sayısı (103 /UL) değerleri, kontrol grubuna göre anlamlı olarak düşük bulundu. Aksine, kırmızı kan hücresi dağılım genişliği standart sapması (RDW SD) (fl), nötrofil sayısı (103 /UL), monosit sayısı (103 /UL), bazofil sayısı (103 /UL), NLR, PLR, MLR değeri sarkoidoz hastalarınında kontrol grubuna göre anlamlı derecede yüksek bulundu. Trombosit (103 /UL), MPV ve EBR değerleri karşılaştırıldığında ise anlamlı bir fark gözlenmedi.

Sonuç: Bu çalışma bize, sarkoidoz hastalarında daha önce kullanılmayan MLR değerinin NLR değeri gibi sarkoidoz tanısında kullanılabilecek önemli bir biyobelirteç olabileceğini göstermiştir.

Anahtar kelimeler: Sarkoidoz, Lenfadenopati, Monosit, Lenfosit, Akciğer

Introduction

Sarcoidosis is a systemic disease of unknown etiology characterized by the presence of non-caseating granulomas which may involve all organs, especially the lungs and mediastinal lymph nodes. Having varying symptoms, the fact that many patients may be asymptomatic, and having clinical and radiological findings that might be confused with infection and malignancies lead to difficulties in diagnosis [1]. Diagnosis is made by considering clinical, radiological, laboratory findings, and the presence of non-caseating granulomatous inflammation, after excluding other probable pathologies [2]. Granuloma in sarcoidosis is characterized by multinucleated giant cells formed by monocyte-derived epithelioid histiocytes and CD41 T lymphocytes. A small number of cells in or near the granuloma are CD81 T lymphocytes, fibroblasts, regulatory T cells, and B lymphocytes [3]. Sarcoidosis is frequently diagnosed with suspicion arising from chest x-ray findings during routine examination [4]. Symptoms can range from cough, shortness of breath, chest pain, low-grade fever, fatigue, weight loss, and night sweating to Lofgren's Syndrome accompanied by bilateral hilar lymphadenopathy and erythema nodosum [5].

Pulmonary sarcoidosis can be examined in five radiological stages as follows: Stage 0: Chest x-ray is normal, Stage 1: Presence of only hilar and mediastinal lymphadenopathy, Stage 2: Presence of Lymphadenopathy (LAP) and pulmonary infiltration, Stage 3: Presence of pulmonary infiltration alone, Stage 4: Presence of pulmonary fibrosis. This staging gives us information about the prognosis of the disease [6]. Pulmonary involvement is not observed in stage 0 and stage 1 while spontaneous remission is observed in most cases. Therefore, treatment is planned only in symptomatic cases with organ involvement. Steroids are used in basic therapy. Immunosuppressive therapy and Anti-Tumor Necrosis Factor (TNF) agents might also be used in patients with severe clinical conditions [7].

In recent years, many studies have been conducted on serological biomarkers, pulmonary and breathing biomarkers, and bronchoalveolar lavage biomarkers for use in the diagnosis. However, they were found to have limited benefits and not applicable to sarcoidosis [8].

Studies conducted in recent years state that neutrophil/lymphocyte ratio (NLR), which shows changes in neutrophils and lymphocytes, might be a reliable biomarker for hematological parameters [8].

Platelet/lymphocyte ratio (PLR) was investigated in sarcoidosis patients, and a significant relationship was detected between the diagnosis of sarcoidosis and lung parenchymal involvement [9].

NLR and PLR activities are affected by many chronic diseases and inflammatory conditions, such as cardiovascular diseases and malignancies. An increase in these parameters suggests poor prognosis while a decrease suggests a good prognosis [10]. It has been shown that low NLR and PLR values in patients with lung cancer indicate increased response to chemotherapy and might be associated with a good prognosis [11].

In this study, we aimed to investigate and evaluate the relationship between neutrophil-lymphocyte ratios (NLR), platelet-lymphocyte ratios (PLR), monocyte-lymphocyte ratios (MLR), eosinophil-lymphocyte ratios (ELR), and blood count parameters in sarcoidosis patients.

Materials and methods

A total of 150 individuals, 97 sarcoidosis patients and 53 healthy individuals, were included in this study. The data of sarcoidosis patients and the control group were retrospectively evaluated in terms of age, gender, body mass index (BMI), presence of chronic disease, smoking, modified medical research council dyspnea scale (MMRC), and pulmonary function parameters. The classification of sarcoidosis patients was made as follows: Stage 0: Chest x-ray is normal, Stage 1: Presence of only hilar and mediastinal lymphadenopathy, Stage 2: Presence of Lymphadenopathy (LAP) and pulmonary infiltration, Stage 3: Presence of pulmonary infiltration alone, Stage 4: Presence of pulmonary fibrosis. Pulmonary involvement is not observed in stages 0 and 1, which were named the “early-stage group” while those with lung parenchymal involvement constitute Stages 3 and 4, “the advanced stage group”. Blood count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), and eosinophil/basophil ratio (EBR) values of the sarcoidosis patients in various stages were compared with other participants of the study. The “Receiver Operator Characteristics Curve” (ROC) analysis method was used to determine which of these parameters were more specific and sensitive for this disease.

Complete blood counts were measured by spectrophotometry/impedance. Venous blood samples were drawn into ethylenediaminetetraacetic acid tubes and sent to the laboratory. Hemoglobin (g/dl), hematocrit (%), red blood cell distribution width standard deviation (RDW SD), platelet count (10^3 /UL), mean platelet volume (MPV), neutrophil count (10^3 /UL), lymphocyte count (10^3 /UL), monocyte count (10^3 /UL), basophil count (10^3 /UL), eosinophil count (10^3 /UL), NLR, PLR, MLR, and ELR results were noted.

Pulmonary function tests (PFTs) were performed by 3 experienced technicians in the pulmonary function test laboratory. The following conditions were met by the participants: Not taking antihistamines for at least 3-4 days, not having received cromolyn and short-acting bronchodilator therapy for at least 8 hours, not having received long-acting bronchodilator and long-acting theophylline and nedocromil therapy for at least 48 hours and not taking leukotriene receptor antagonists (LTRAs) for at least 24 hours. They were asked not to consume any tea, coffee, fizzy drinks, or chocolate on the day of the test. Participants were rested for 5 minutes before the test.

Statistical analysis

SPSS v20 program was used in statistical analysis. Data were shown as mean (standard deviation), number of individuals, and percentage. The compliance of quantitative data to normal distribution was assessed with Kolmogorov-Smirnov, and Shapiro - Wilk tests, and graphical evaluations. Student's t-test was used to compare the two groups of normally distributed quantitative data, and the Mann-Whitney U test was utilized to compare the two non-normally distributed data groups. Pearson's

chi-square test and Fisher's exact test were used for the comparison of qualitative data. Relationships between variables were analyzed using Spearman correlation analysis. ROC (Receiver Operator Characteristics Curve) analysis was used to measure the sensitivity and specificity continuous variables.

Results

A total of 150 individuals, 97 sarcoidosis patients and 53 healthy individuals (control group) were included in this study. Among sarcoidosis patients, 55 (56.7%) were female and 42 (43.3%) were male. In the control group, 34 (64.2%) were female and 19 (35.8%) were male. The mean ages of the sarcoidosis patients and the control group were 59.64 (19.07) years and 34.20 (5.93) years, respectively. Body mass index (BMI) (kg /cm^2) was 25.21 (18.21-39.84) among sarcoidosis patients and 24.09 (19.82-35.19) in the control group. The modified medical research council dyspnea scale (MMRC) scores were 2 (0-3) and 1 (0-1) among the sarcoidosis patients and the control group, respectively (Table 1). Fifty-three (54.6%) sarcoidosis patients were classified as Stage 1, 36 (37.1%), as Stage 2, 6 (6.2%), as Stage 3 and 2 (2.1%), as Stage 4.

Table 1: Demographic features of patients in the study

	Sarcoidosis (N=97)	Control (N=53)	Total (N=150)	*P*-value
Gender				
Female N	55 (56.7%)	34 (64.2%)	89 (100%)	
Male N	42 (43.3%)	19 (35.8%)	61 (100%)	
Age	59.64 (19.07)	34.20 (5.93)	48.03 (18. 07)	<0.001
Height (cm)	169 (153-187)	174 (160-180)	168 (150-187)	0.364
Weight (kg)	78 (48-102)	75 (58-98)	75 (48-102)	0.143
BMI (kg/cm^2)	25.21 (18.21-39.84)	24.09 (19.82-35.19)	25.43 (17.82-39.84)	0.028
MMRC	2 (0-3)	1 (0-1)	1 (0-3)	<0.001
Smoking status (years)	22 (3-56)	15 (8-30)	22 (3-56)	0.170
Smoking (persons)	32 (33%)	14 (26.4%)		
Comorbid disease	26 (26.8%)	0		
Sarcoidosis stage				
Stage 1	53 (54.6%)	-	53 (54.6%)	
Stage 2	36 (37.1%)	-	36 (37.1%)	
Stage 3	6 (6.2%)	-	6 (6.2%)	
Stage 4	2 (2.1%)	-	2 (2.1%)	

BMI: Body mass index, MMRC: Modified Medical Research Council Dyspnea Scale

A total of 9 (25%) patients from stage 2, 4 (75%) patients from stage 3, and 1 (50%) patient from stage 4 had the history of steroid treatment while 1 patient from stage 4 was still on steroid therapy.

Eye involvement of sarcoidosis was detected in 3 patients. All patients with eye involvement were Stage 2. Lymph node involvement was observed in all 53 Stage 1 patients, all 36 Stage 2 patients, and in 1 (50%) Stage 4 patient. None of the patients in Stage 3 had lymph node involvement. None of the patients had liver or neurological involvement. A total of 9 (17%) patients in stage 1, 16 (44.4%) patients in stage 2, and 1 (50%) patient in stage 4 had chronic diseases such as hypertension, diabetes mellitus, and cardiovascular diseases. None of the stage 3 sarcoidosis patients had any chronic diseases.

Patients without lung involvement had early-stage (53 patients) while patients with lung parenchymal involvement were considered to have advanced-stage (44 patients) sarcoidosis. Among pulmonary function parameters such as % FEV1, % FVC, and % FEV1 / FVC, FVC (LT) and FEV1 / FVC values of sarcoidosis patients were decreased significantly compared to the control group (Table 2).

There was a significant decrease in the pulmonary parameters of advanced-stage sarcoidosis patients when compared with early-stage sarcoidosis patients (Table 3).

Hemoglobin (g/dl) values and lymphocyte count (103 /UL) were significantly lower in sarcoidosis patients, while red blood cell distribution width standard deviation (RDW SD) (fl), neutrophil count (103 /UL), monocyte count (103 /UL), basophil count (103 /UL), NLR, PLR, MLR values were significantly higher compared to the control group. However, platelet (103 /UL), MPV and EBR values were similar (Table 4).

Table 2: Comparison of PFT values in sarcoidosis patients and control group

Respiratory Function Test Values	Sarcoidosis (N=97)	Control (N=53)	Total (N=150)	*P*-value
FEV1 (LT)	3.13(1.07)	3.42(0.80)	3.23(0.99)	0.091
FVC (LT)	3.71(1.21)	4.13(0.99)	3.86(1.15)	0.032
FEV1/FVC	79.53(9.06)	83.45(7.85)	80.92(8.83)	0.009

FEV1: Forced expiratory volume in the 1st second, FVC: Forced vital capacity

Table 3: Comparison of PFT values in early and advanced sarcoidosis patients

Respiratory Function Test Values	Sarcoidosis Early Stage (N=53)	Sarcoidosis Advanced Stage (N=44)	*P*-value
FEV1 (LT)	3.50(0.91)	2.69(1.10)	<0.001
FVC (LT)	4.03(1.06)	3,33(1.29)	0.004
FEV1/FVC	81.46(8.31)	77.21(9.46)	0.021

FEV1: Forced expiratory volume in the 1st second, FVC: Forced vital capacity

Table 4: Mean laboratory values of the study and control groups

Laboratory Values	Sarcoidosis (N=97)	Control (N=53)	Total (N=150)	*P*-value
Hemoglobin (g/dL)	13.40(1.92)	14.07(2.05)	13.64(1.98)	0.047
Hematocrit (%)	71.85(5.08)	43.08(5.35)	42.29(5.19)	0.167
Red Cell Distribution Width (RDW SD)	43.90(35.10-71.60)	40.80 (36.90-47.70)	42.50 (35.10-71.60)	<0.001
Platelet (10^3/UL)	260 (73-496)	258 (150-487)	259 (73-496)	0.995
Mean Platelet Volume (MPV)	10.00(1.16)	10.27(1.04)	10.10(1.12)	0.170
Neutrophil (10^3/UL)	21 (1-51)	13 (1-41)	5.09 (2.01-23.62)	<0.001
Lymphocytes (10^3/UL)	1.88 (0.26-8.44)	2.18 (1.38-4.14)	2.06 (0.26-8.44)	0.017
Monocyte (10^3/UL)	0.60 (0.14-2.10)	0.48 (0.23-0.94)	0.57 (0.14-2.10)	0.003
Basophil (10^3/UL)	0.05 (0.01-0.43)	0.03 (0.01-0.12)	0.04 (0.01-0.43)	0.019
Eosinophil (10^3/UL)	0.14 (0.01-1.86)	0.12 (0.01-0.53)	0.13 (0.01-1.86)	0.138
Neutrophil Lymphocyte Ratio (NLR)	2.79 (0.85-42.19)	1.77 (0.67-4.79)	2.31 (0.67-42.19)	<0.001
Platelet/Lymphocyte Ratio (PLR)	127.95 (24.88-1350.00)	117.75 (55.84-278.15)	121.10 (24.88-1350)	0.03
Monocyte/Lymphocyte Ratio (MLR)	0.31 (0.07-1.26)	0.23 (0.11-0.43)	0.27 (0.07-1.26)	<0.001
Eosinophil/Basophil Ratio (EBR)	4.25 (0.10-93.00)	3.85 (0.33-21.00)	4 (0.10-93)	0.750

There was a significant increase in lymphocyte (10^3 /UL) values and a significant decrease in the PLR of patients in the advanced stage. No significant differences were detected in other values (Table 5).

Table 5: Comparison of laboratory data of early and advanced sarcoidosis patients

Laboratory Values	Sarcoidosis Early Stage (N=53)	Sarcoidosis Advanced Stage (N=44)	*P*-value
Hemoglobin (g/dL)	13.13(2.00)	13.72(1.78)	0.137
Hematocrit (%)	41.33(5.28)	42.48(4.80)	0.269
Red Cell Distribution Width (RDW SD)	44.30 (35.10-68.90)	43.50 (36.40-71.60)	0.210
Platelet (10^3/UL)	264 (73-437)	248 (166-496)	0.401
Mean Platelet Volume (MPV)	10.12(1.29)	9.86(1.05)	0.262
Neutrophil (10^3/UL)	24 (1-51)	18 (1-41)	0.261
Lymphocytes (10^3/UL)	1.73 (0.26-8.44)	2.10 (0.59-5.00)	0.036
Monocyte (10^3/UL)	0.60 (0.14-1.18)	0.60 (0.23-2.10)	0.312
Basophil (10^3/UL)	0.04 (0.01-22)	0.01 (0.01-0.43)	0.120
Eosinophil (10^3/UL)	0.14 (0.01-1.86)	0.21 (0.01-0.70)	0.459
Neutrophil / Lymphocyte Ratio (NLR)	2.88 (1.15-42.90)	2.39 (0.85-12.49)	0.062
Platelet / Lymphocyte Ratio (PLR)	149.77 (24.88-1350.00)	119.78 (50.82-502.27)	0.020
Monocyte / Lymphocyte Ratio (MLR)	0.33 (0.12-1.26)	0.31 (0.07-1.06)	0.674
Eosinophil / Basophil Ratio (EBR)	4.00 (0.01-93.00)	4.33 (0.10-15.00)	0.994

When ROC analysis was performed in terms of NLR, the confidence interval was 0.748 (0.669-0.826) and the cut-off value was 2.148. Its sensitivity and specificity were 70.1% and 69.8%, respectively (Figure 1). These values were statistically significant (P<0.01).

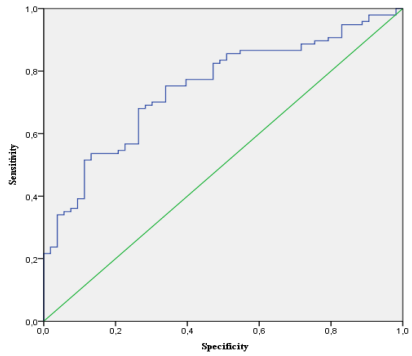

Figure 1: NLR Receiver Operator Characteristics Curve (ROC) Chart

According to ROC analysis results, the confidence interval, cut-off value, sensitivity, and specificity of MLR were 0.733 (0.655-0.812), 0.257, 68.1%, and 68.8%, respectively (P<0.01) (Figure 2).

According to ROC analysis, the confidence interval, cut-off value, sensitivity and specificity of PLR were 0.607 (0.514-0.701), 120.548, 54.6%, and 54.7%, respectively (P=0.03) (Figure 3).

ROC analysis of EBR revealed that the confidence interval, cut-off value, sensitivity and specificity were 0.475 (0.379-0.572), 3.928, 53.6%, and 50.9%, respectively, none of which were significant (P=0.619) (Figure 4).

The sensitivity and specificity of the NLR and PLR values were remarkably close to each other and statistically significant.

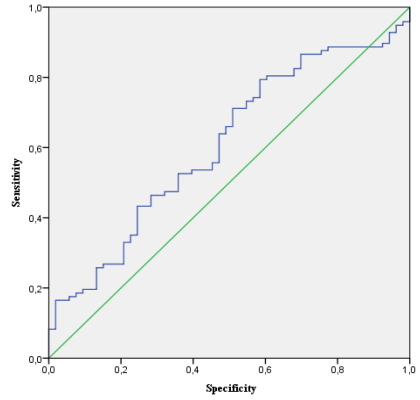

Figure 2: MLR Receiver Operator Characteristics Curve (ROC) Chart

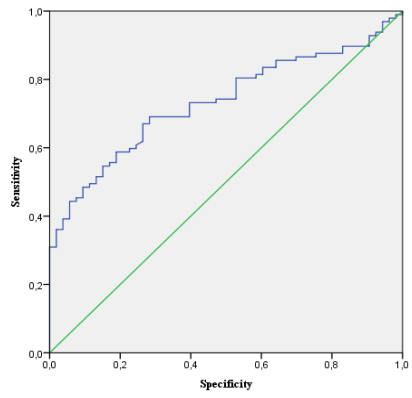

Figure 3: PLR Receiver Operator Characteristics Curve (ROC) Chart

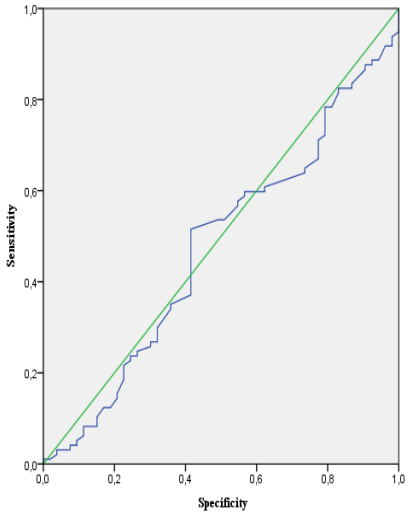

Figure 4: EBR Receiver Operator Characteristics Curve (ROC) Chart

This study has proven that MLR can be used instead of NLR in the diagnosis and follow-up for sarcoidosis patients. PLR values were also statistically significant; however, their sensitivity and specificity were lower than those of NLR and MLR. EBR values were not statistically significant and they were not helpful in the diagnosis of sarcoidosis (Figure 5).

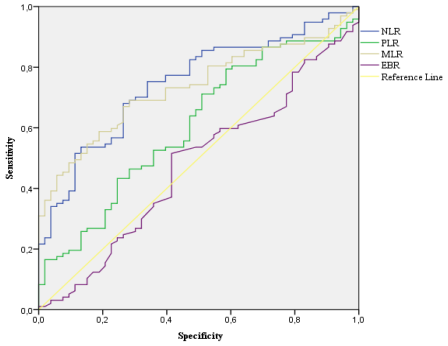

Figure 5: Comparison of ROC Charts

Discussion

The lung is affected in more than 90% of sarcoidosis patients [12]. A biomarker that is specific to sarcoidosis has not been identified yet. However, in clinical studies, hematological changes such as leukopenia, leukocytosis, anemia, eosinophilia, lymphopenia, thrombocytopenia were observed [13].

Angiotensin-converting enzyme (ACE) is produced from the epithelioid cells of granulomas in sarcoidosis, and the increase in ACE levels may be significant in terms of the diagnosis of sarcoidosis [14]. However, an increase in the ACE level is also observed in Gaucher disease, tuberculosis, hyperthyroidism, and fungal infections [15]. Therefore, this test is not sensitive enough for the diagnosis of sarcoidosis.

Dirican et al. [9] suggested that MPV values were higher in sarcoidosis patients compared to the control group and there was no significant difference in the MPV values of the stages of sarcoidosis.

Gupta et al. [13] detected lymphopenia in 26.66% of sarcoidosis patients and stated that the most common hematological abnormality was lymphopenia.

The reason lymphopenia is thought to be the accumulation of CD4+ T lymphocytes around the granulomas and their antiproliferative effect on effector T lymphocytes [16].

MPV values of sarcoidosis patients and controls did not significantly differ in our study. Similarly, there was no significant difference in MPV values of early and advanced-stage sarcoidosis patients.

The RDW-SD, hemoglobin, neutrophil, lymphocyte, monocyte, and basophil levels of sarcoidosis patients significantly differed from those of the controls.

Although published clinical studies show that NLR can be an objective measurement for hematological parameters, it is affected by malignancies, cardiovascular diseases, and many inflammatory conditions, which raises doubts about its prognostic value [8].

In our study, there was a significant difference between sarcoidosis patients and the control group in terms of NLR value. There was no statistically significant difference between early and advanced stage sarcoidosis patients.

Mirsaeidi et al. [9] reported that the cut-off value was around 3.5 while sensitivity and specificity were 50.0% and 78.0%, respectively. It was concluded in same study that NLR and PLR values of sarcoidosis patients with parenchymal involvement were significantly higher, and cut off values were 2.4 and 158, respectively.

In our study, NLR and PLR values were statistically significant in sarcoidosis patients, like the studies in the literature. We determined that the cut off value for NLR was 2.148, and sensitivity and specificity were 70.1% and 69.8%, respectively, while for PLR, the same parameters were 120.548, 54.6%, and 54.7%, respectively.

In our study, we detected that MLR values of sarcoidosis patients significantly differed from those of controls, however, MLR values of early and advanced stage sarcoidosis patients were similar.

The confidence interval, sensitivity, and specificity of NLR values and MLR values were remarkably close to each other and significant in sarcoidosis patients.

In previous studies, MLR values were not investigated in sarcoidosis patients. Our study is the first to evaluate this parameter in this patient group.

Limitations

The rarity of sarcoidosis limited the number of patients included in the study.

Conclusions

This study showed that confidence intervals, sensitivity, and specificity of MLR was close to those of NLR among sarcoidosis patients. Therefore, we think that MLR can be used instead of NLR in the diagnosis and follow-up of this disease. In addition, EBR did not prove to be a reliable prognostic marker in pulmonary sarcoidosis.

References

1. Soto-Gomez N, Peters JI, Nambiar AM. Diagnosis and Management of Sarcoidosis. Am Fam Physician. 2016;93(10):840-8.
2. Hunninghake GW, Costabel U, Ando M, Baughtman R, Cordier JF, du Bois R, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. Sarcoidosis, Vasc Diffus lung Dis Off J WASOG. 1999;16(2):149-73.
3. Baughman RP, Culver DA, Judson MA. A concise review of pulmonary sarcoidosis. Am J Respir Crit Care Med. 2011;183(5):573-81. doi: 10.1164/rccm.201006-0865CI
4. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the E. Am J Respir Crit Care Med. 1999;160(2):736-55. doi: 10.1164/ajrccm.160.2.ats4-99
5. Jain R, Yadav D, Puranik N, Guleria R, Jin J-O. Sarcoidosis: Causes, Diagnosis, Clinical Features, and Treatments. J Clin Med. 2020;9(4). doi: 10.3390/jcm9041081
6. Sulica R, Teirstein AS, Kakarla S, Nemani N, Behnegar A, Padilla ML. Distinctive clinical, radiographic, and functional characteristics of patients with sarcoidosis-related pulmonary hypertension. Chest. 2005;128(3):1483-9. doi: 10.1378/chest.128.3.1483
7. Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. Sarcoidosis, Vasc Diffus lung Dis Off J WASOG. 2008;25(2):76-89.
8. Ocal N, Dogan D, Ocal R, Tozkoparan E, Deniz O, Ucar E et al. Effects of radiological extent on neutrophil/lymphocyte ratio in pulmonary sarcoidosis. Eur Rev Med Pharmacol Sci. 2016;20(4):709-14.
9. Yalnız E, Karadeniz G, Üçsular FD, Erbay Polat G, Şahin GV. Predictive value of platelet-to-lymphocyte ratio in patients with sarcoidosis. Biomark Med. 2019;13(3):197-204. doi: 10.2217/bmm-2018-0252
10. Akboga MK, Canpolat U, Yuksel M, Yayla C, Yılmaz S, Turak O et al. Platelet to lymphocyte ratio as a novel indicator of inflammation is correlated with the severity of metabolic syndrome: A single center large-scale study. Platelets. 2016;27(2):178-83. doi: 10.3109/09537104.2015.1064518
11. Liu D, Jin J, Zhang L, Li L, Song J, Li W. The Neutrophil to Lymphocyte Ratio May Predict Benefit from Chemotherapy in Lung Cancer. Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol. 2018;46(4):1595-605. doi: 10.1159/000489207
12. Baughman RP, Teirstein AS, Judson MA, Rossman MD, Yeanger JRH, Brenıtz EA et al. Clinical characteristics of patients in a case control study of sarcoidosis. Am J Respir Crit Care Med. 2001;164(10 Pt 1):1885-9. doi: 10.1164/ajrccm.164.10.2104046
13. Gupta D, Rao VM, Aggarwal AN, Garewal G, Jindal SK. Haematological abnormalities in patients of sarcoidosis. Indian J Chest Dis Allied Sci. 2002;44(4):233-6.
14. Silverstein E, Pertschuk LP, Friedland J. Immunofluorescent localization of angiotensin converting enzyme in epithelioid and giant cells of sarcoidosis granulomas. Proc Natl Acad Sci U S A. 1979;76(12):6646-8. doi: 10.1073/pnas.76.12.6646
15. Lieberman J, Nosal A, Schlessner A, Sastre-Foken A. Serum angiotensin-converting enzyme for diagnosis and therapeutic evaluation of sarcoidosis. Am Rev Respir Dis. 1979;120(2):329-35. doi: 10.1164/arrd.1979.120.2.329
16. Loke WSJ, Herbert C, Thomas PS. Sarcoidosis: Immunopathogenesis and Immunological Markers. Int J chronic Dis. 2013;2013:928601. doi: 10.1155/2013/928601.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1082-1085.
DOI: 10.28982/josam.811354

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN=2602-2079

The effects and reliability of the hydroxychloroquine-azithromycin combination on the cardiac conduction system in patients with coronavirus disease 2019

Koronavirüs 2019 hastalığı olan hastalarda hidroksiklorokin-azitromisin kombinasyonunun kalp iletim sistemi üzerindeki etkileri ve güvenilirliği

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Ethics Committee Approval: The ethics committee of Bursa Uludag University Hospital approved this retrospective study and waived the need of informed consent (29/4/2020,2020-7/21). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bursa Uludağ Üniversitesi Hastanesi etik kurulu bu retrospektif çalışmayı onayladı ve bilgilendirilmiş onam gerekliliğinden feragat etti (29/4/2020,2020-7/21). İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

Aim: The COVID-19 virus influenced the world since late 2019 and affected millions of people. Although there is no unambiguous evidence in the treatment of COVID-19, the combination of hydroxychloroquine and azithromycin entered the protocols globally to reduce virus replication and take advantage of its immunomodulatory effects. It has been stated that both drugs extend QTc. However, the frequency of QTc prolongation in combinational drug use, and its effect on the primary endpoint, as well as the predictive values of QTc prolongation are not clear.

Methods: A total of 135 patients who received hydroxychloroquine, azithromycin, and oseltamivir for suspected / definitive COVID-19 with viral pneumonia were examined in this single-center, retrospective study,

Results: The mean age was 55.6 (19.1) years, and 61 (45%) patients were female. According to the initial ECG values, the QTc1 value was 422.44 (35.72) ms, while the QTc2 value was 446.91 (36.71) ms (P<0.001). The ECG evaluation after medication use indicated that the number of patients with a QTc value >500 ms was 6 (4.4%). The number of patients with prolongation in QTc values >60 ms was 7 (5.1%). The frequency of prolongation in QTc was 26% in intensive care unit patients, and 2% in low-risk patients in the inpatient unit. An elevation in troponin values >14 ng/L and a low GFR are predictors for QTc prolongation. None of these patients developed malignant arrhythmia or sudden cardiac death.

Conclusion: Hydroxychloroquine and azithromycin combinations used in COVID-19 patients cause a prolongation in the QTc. The incidence of prolongation in QTc varies according to the comorbid characteristics and clinical status of the patients. Before starting hydroxychloroquine and azithromycin, the risk factors and clinical status of the patients should be well evaluated.

Keywords: COVID-19, Long QT, Arrhythmia

Öz

Amaç: COVID-19 virüsü 2019'un sonlarından bu yana tüm dünyayı ve milyonlarca insanı etkiledi. COVID-19 tedavisinde net bir kanıt olmamasına rağmen, hidroksiklorokin ve azitromisinin kombinasyonu, virüs replikasyonunu azaltmak ve immünomodülatör etkilerinden yararlanmak için dünya çapında protokollere girmiştir. Her iki ilacın ayrı ayrı kullanımlarında QTc'yi uzattığı belirtilmiştir. Bununla birlikte, kombinasyonel ilaç kullanımında QTc uzamasının sıklığı ve bunun birincil sonlanım noktası üzerindeki etkisi ve ayrıca QTc uzamasının prediktif değerleri net değildir.

Yöntemler: Çalışma tek merkezli, retrospektif bir çalışma olarak tasarlandı. Viral pnömonili şüpheli / kesin COVID-19 nedeniyle hidroksiklorokin, azitromisin ve oseltamivir alan 135 hasta incelendi.

Bulgular: Ortalama yaş 55,6 (19,1) yıldı ve 61 (%45) hasta kadındı. İlk EKG değerlerine göre QTc1 değeri 422,44 (35,72) ms, QTc2 değeri 446,91 (36,71) ms (P<0,001) bulundu. İlaç kullanımı sonrası EKG değerlendirmesi, QTc değeri >500 ms olan hasta sayısının 6 (%4,4) olduğunu gösterdi. QTc değerlerinde >60 ms uzaması olan hasta sayısı 7 (%5,1) idi. QTc'de uzama sıklığı yoğun bakım hastalarında %26 iken, yataklı servis birimindeki düşük riskli hastalarda sıklık %2 idi. Troponin değerlerinde >14 ng/L yükselme ve düşük GFR, QTc uzaması için belirleyicilerdir. Bu hastaların hiçbirinde malign bir aritmi veya ani kalp durması gelişmedi.

Sonuç: COVID-19 hastalarında kullanılan hidroksiklorokin ve azitromisin kombinasyonları QTc'de uzamaya neden olur. QTc'de uzama insidansı, hastaların komorbid özelliklerine ve klinik durumuna göre değişir. Hidroksiklorokin ve azitromisine başlamadan önce, hastaların risk faktörleri ve klinik durumu iyi değerlendirilmelidir.

Anahtar kelimeler: COVID-19, Uzun QT, Aritmi

How to cite/Atıf için: Uğuz B, Zengin İ, Topal D, Öztaş S, Tiryakioğlu SK, Yılmaztepe MA. The effects and reliability of the hydroxychloroquine-azithromycin combination on the cardiac conduction system in patients with coronavirus disease 2019. J Surg Med. 2020;4(11):1082-1085.

Introduction

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization in March 2020 [1], infecting 3,136,505 people worldwide and causing death in 221,436 as of April 28, 2020 [2]. The first confirmed case in Turkey was officially announced on March 11, 2020. As of April 28, 114,653 cases and 2992 deaths occurred in Turkey from COVID-19 [3].

Though not yet a proven treatment for COVID-19, hydroxychloroquine (an analog of chloroquine) has been used in treatment protocols; researchers predict that it reduces viral proliferation and improves patient survival rates [4]. Both analogs have long been used in prophylactic pharmacotherapy for malaria, and hydroxychloroquine is also used as an antirheumatic. Both suppress the activities of pH-dependent proteases by increasing vesicular pH, thereby reducing cytokine (e.g., Tumor necrosis factor-α and Interleukin-6) production [5]. Also, in *in vitro* studies, both analogs show effectiveness against angiotensin- converting-enzyme 2 (ACE2) receptors, which is how the culprit virus (severe acute respiratory syndrome coronavirus 2) enters target cells [6]. Therefore, both analogs are anticipated to reduce the ACE2-mediated process and might also provide beneficial immunomodulatory effects during the post-viral cytotoxic storm often observed with COVID-19. As a result, these drugs have been included in treatment protocols in many countries [4].

Azithromycin, on the other hand, is an antibacterial that belongs to the macrolide group. It has immunomodulatory and anti-inflammatory properties beyond its antibiotic properties [7-9]. A study conducted in Korea showed that the risk of lengthening the QTc interval was increased when patients started treatment with azithromycin, particularly when aged between 60 to 79 years [10].

Throughout the pandemic, our center has followed the protocols of the Republic of Turkey Ministry of Health regardless of the clinical situation. The protocol specifies a loading dose of 2x400 mg hydroxychloroquine and 1x500 mg azithromycin followed by 5 daily doses of 2x200 mg hydroxychloroquine and 1x250 mg azithromycin for maintenance. Oseltamivir, dosed at 75 mg twice daily, is added when signs of viral pneumonia require hospitalization [11]. Although some data show that both azithromycin and hydroxychloroquine prolong the QTc interval when used separately, the prevalence of this and its effects on the primary endpoint in COVID-19 are unclear when combined. It is known that combining multiple proarrhythmic drugs leads to a prolonged QTc interval but that the drug-induced risk of torsades de pointes is highly variable. Therefore, use of this drug combination is predictive of an increased QTc interval, but the prevalence of this effect is unknown. Patients with multiple comorbidities or those being treated with multiple drugs that can prolong the QTc interval are at greater risk for COVID-19 and drug-induced QTc interval lengthening. It is important, when evaluating a patient from this group, to consider that the virus can cause primary myocardial damage.

The purpose of this study was to analyze the effects on the QTc interval of HCQ-AZ when used to treat probable or confirmed COVID-19 in patients showing signs of viral pneumonia. An additional aim was to determine its effect on mortality.

Materials and methods

This study was designed as a single-center retrospective analysis of patients hospitalized in our center between 11 March 2020 and 28 April 2020 with diagnosed viral pneumonia and probable or confirmed COVID-19 treated with HCQ-AZ.

Exclusion criteria included initial QTc interval exceeding 500 milliseconds (ms), presence of acute coronary syndrome, known allergies or contraindications to the treatment drugs, and known hereditary long QT syndrome. Also excluded were patients for whom our measures of interest could not be determined from the recorded ECGs.

Patients are admitted to our intensive care unit for any one of the following: Respiratory rate of at least 30/min, dyspnea and laborious breathing accompanied by SpO_2 not reaching 90% or 70 mm Hg in room air, oxygen requirement of at least 5 L/min with a nasal cannula, lactate level exceeding 2 mmol/L, hypotension (systolic blood pressure not reaching 90 mm Hg or dropping at least 40 mm Hg from the usual, or a mean arterial pressure not reaching 65 mm Hg), signs of skin hypoperfusion, signs of organ dysfunction such as confusion, abnormal kidney or liver tests, thrombocytopenia, elevated troponin levels and arrhythmia. Intensive care was provided according to the requirements stated in the health ministry directive [11]. Those who met one or more of these criteria were considered 'critically ill.' Patients who are hemodynamically stable and do not need advanced respiratory and organ support anymore were admitted "non-critically ill" and transferred to the ward.

For all patients, ECG is recorded daily. A baseline corrected QT interval (QTc1) and the maximum corrected QT interval after treatment (QTc2) were evaluated by at least two independent cardiologists, calculated using the Bazett formula (from DII/V5 derivations). Patients were classified based on the Tisdale Scale, developed by Tisdale et al. [12] in 2013. Those scoring less than 7 were considered to have low risk, and those scoring more than 11 were considered to have high risk.

Statistical analysis

Demographic data, QT intervals and QTc intervals were examined. Measured values were described using mean (standard deviation [SD]), and SPSS 22.0 was used to perform statistical comparisons. The normality of the distributions of the groups was compared using the Kolmogorov-Smirnov test, and categorical variables were analyzed using the chi-square test. A *t* test was used to compare electrocardiographic parameters between two groups. When $P<0.05$, significance was recognized.

Results

In total, 195 patients were identified, but 60 were excluded, leaving 135 enrolled participants. Mean age was 55.6 (19.1) years (range, 19-86 years), and 61 (45%) were women. Comorbidities included hypertension (47 patients, 34.8%), Type 2 diabetes mellitus (31 patients, 23.0%), stable coronary disease (25 patients, 18%) and congestive heart failure (7 patients, 5%; Table 1).

Tisdale scores were determined, and at the time, 43 patients (32%) were critically ill. Across all patients in the intensive care unit, the Tisdale score averaged 10.2, and 19 patients (44.1%) were considered to have high risk (Tisdale score ≥11) (Table 1). Invasive mechanical ventilation was required for 18 patients (41%). Vasoactive drugs were administered to 9 patients (20%), and other treatments lengthening the QT interval were administered to 11 patients (25.5%). Diuretic treatments were administered to 13 patients (30%). Of those admitted to non-critical patients (92 patients), the average of Tisdale score was 6.5, drugs that could prolong the QTc interval were administered to 25, and diuretics were administered to 16 (Table 2).

Table 1: Patients' demographics

Demographic variable	Number of patients (n=135)	Percentage (%)
Age (y)	55.6(19.1)	19-86
Sex (female/male)	61/74	45/55
Hypertension	47	34.8
Type 2 DM	31	23
Coronary heart disease	25	18
Congestive heart failure	7	5
Chronic kidney failure	7	5
Abnormal liver function	20	14
Tisdale score <7	100	66.6
7 ≤ Tisdale score ≤ 10	16	11
Tisdale score ≥ 11	19	14
Admitted to intensive care unit	43	33
Admitted to inpatient care services	92	68

Table 2: Characteristics of critically and non-critically ill patients

	Critically ill patients (n=43)	Non-critically ill patients (n=92)	*P*-value
QTc ≥ 500 ms	5 (11.6 %)	1 (1.0%)	<0.001
ΔQTc > 60 ms	6(13.9 %)	1 (1.0%)	<0.01
Need to mechanical ventilation	18	0	<0.001
Tisdale score ≥11	19 (44%)	0 (0%)	<0.001
Need to vasopressure support	9 (20%)	0	<0.001
Using QTc-prolonging drugs	11 (25%)	20 (21%)	>0.05
Diuretics usage	13 (30%)	9(10%)	<0.05
Serum potassium <3.5 mEq at QTc peak	4(9.3%)	7 (7.6%)	>0.05
Age ≥68	25(58 %)	15(16%)	<0.05
Female	14 (33%)	35 (38%)	>0.05
Baseline QTc≥460 ms	15 (35%)	7(8%)	<0.05
Comorbid disorders	13 (30%)	5 (5%)	<0.05

QTc1: baseline QTc interval, QTc2: maximum corrected, QTc: interval after treatment, ΔQT: change in corrected QT interval

Mean (SD) QTc1 was 422.44 (35.72) milliseconds (ms) and mean QTc2 was 446.91(36.71) milliseconds (ms) (P<0.001). According to baseline values, the number of patients with QTc <460 ms was 113 (83.7 %), while the number of patients with QTc ≥460 ms was 22(16.3 %). After HCQ-AZ use, ECGs showed that QTc exceeded 500 ms for 6 patients (4.4%) and was lengthened by more than 60 ms for 7 patients (5.1 %). Of those with QTc exceeding 500 ms, 5 were monitored in the intensive care unit and 1 in the inpatient unit. Of those with QTc interval lengthening by more than 60 ms, 6 (13.9 %) were monitored in the intensive care unit and 1(1.0%) in the inpatient unit. QTc prolongation was observed in 26% of the patients admitted to intensive care unit, whereas QT interval was prolonged in only 2% of the patients in non-critical group of patients. Pathological QTc prolongation rate was 9.6 % among all patients. The initial QTc values of the patients admitted to the intensive care were longer than those of non-critical ill patients (455.5 (32.7) vs. 404.0 (23.6), P<0.001).

Pathological QTc interval lengthening occurred in 11 of 22 patients (50.0 %) with QTc intervals exceeding 460 ms. On the other hand, this occurred in 2 of the 113 patients (1.7%) not in this group. The difference is significant (P<0.05).

Of the 43 people thought to be critically ill and admitted to the intensive care unit, 11 had pathological QTc prolongation. Tisdale scores of all critical patients were 10.2, while Tisdale scores of patients with prolonged QTc intervals were 9.7 on average. The Tisdale score of 2 non-critical patients was 7 on average. Diuretic drug use, comorbid disorders, and baseline QTc ≥460 msn were significantly higher in intensive care patients. There was no significant difference in electrolyte values of both groups.

Even though mean (SD) QTc intervals did not initially differ between patients with troponin levels exceeding 14 ng/L [428.4 (36.7) ms] compared to all others [426.3 (31.5) ms, P<0.05], the difference was significant after treatment [448.4 (48.0) ms vs. 421.2 (35.9) ms; P=0.001], showing QTc interval lengthening. Similarly, no difference was seen between patients with low Glomerular Filtration Rates (GFR) compared to those with normal GFRs [431.0 (39.4) vs. 418.0 (30.8) ms; $P<0.05$], but after drug therapy was initiated, the increase was remarkable between those with GFRs not reaching 60 mL/min [445.4 (46.1) ms] vs. all others [421.2 (33.5) ms; P=0.006]. Differences based on liver enzyme levels did not differ before or after drug therapy [426.9 (37.9) vs. 419.8 (35.4) ms; P>0.05 before drug therapy and 448.1 (52.2) vs. 427.7 (40.8) ms; P>0.05 after]. Troponin levels exceeding 14 ng/L and GFRs less than 60 mL/min predict pathological prolongation of the QTc interval, and liver dysfunction does not (Table 3).

Table 3: Factors associated with pathological QTc interval lengthening

	Troponin > 14 ng/L n = 45	Troponin < 14 ng/L n = 90	*P*-value
QTc1(ms)	428.4(36.7)	426.3(31.5)	>0.05
QTc2(ms)	448.4 (48.0)	429.2 (35.9)	0.001
	GFR < 60 mL/min n = 33	GFR > 60 mL/min n= 102	
QTc1(ms)	431.0 (39.4)	418.0 (30.8)	>0.05
QTc2 (ms)	445.4 (46.1)	421.2 (33.5)	0.006
	AST, ALT↑; n = 47	AST, ALT↓; n = 88	
QTc1 (ms)	426.9 (37.9)	419.8 (35.4)	>0.05
QTc2 (ms)	448.1 (52.2)	427.7 (40.8)	>0.05

QTc1: baseline QTc interval, QTc2: maximum corrected QTc interval after treatment, GFR: glomerular filtration rate, ALT: alanine transaminase, AST: aspartate transaminase, AST, ALT↑, twice the normal value, NS: not significant

Pathological QTc interval lengthening and malignant arrhythmias were not detected in any patients who died at the primary endpoint. These patients were lost based on respiratory failure. Lengthening of the QTc interval does not predict death. Lengthening was progressive, increasing to a peak on the second or third days.

Discussion

Both HCQ and AZ are drugs that can prolong QT interval, and concomitant usage increases the risk. Case reports document that hydroxychloroquine and chloroquine can prolong the QTc interval, particularly with long-term use [7], yet the World Health Organization has not issued a warning about this effect even though these drugs are commonly used as long-term antirheumatics [8].

Unlike the protocols applied in other countries, oseltamivir was part of the treatment plan in our patient population. By itself, oseltamivir at any dose was shown to provide no distinct change in the electrocardiograms (ECGs) of more than 300 volunteers; it did not affect the PR, QRS or QT intervals and did not cause pathological lengthening of QTc intervals (instead, it might have shortened the interval) [13]. That study went on to evaluate the effect of a combined hydroxychloroquine / azithromycin (HCQ-AZ) treatment.

In the present study, the incidence of QTc prolongation was 9.6%. Approximately 85% of the patients with pathological QTc prolongation were those hospitalized and monitored in the intensive care unit. QTc prolongation was observed in 26% of the patients admitted to intensive care unit, whereas QT interval was prolonged in only 2% of the patients in non-critical group of patients. In intensive care patients, QT prolongation depends on several factors including diuretic usage, comorbidities such as renal failure and baseline Qtc >460msn. Furthermore, these patients were older, had more comorbidities and septic complications and were using multiple drugs. These findings demonstrated that the occurrence of QTc interval lengthening due to the use of HCQ-AZ depends on the underlying clinical condition of the patient. When multiple drug therapies and multiple comorbidities intervene and when the patient is admitted to receive critical intensive care, the risk for QT interval prolongation is high. On the other hand, HCQ-AZ is safely used in patients who are clinically stable.

The frequency of lengthened QTc intervals was greater among those monitored in the intensive care unit compared to those given inpatient care, suggesting that this group of patients should be evaluated using a unique algorithm. Frequency of follow-up can be reduced when a patient has good clinical status, a normal troponin level, a normal GFR and a basal ECG showing a QTc interval that is less than 460 milliseconds. In intensive care patients, torsades de pointes did not occur, given that prolongation of the QTc interval is common, and monitoring should be vigilant. Remarkably, the Tisdale scores for those with prolonged QTc intervals were lower than those for patients in the intensive care unit. In this group of patients, troponin levels and GFRs should be considered along with the Tisdale score to increase reliability.

Our striking finding was that QTc interval lengthening is associated with low GFRs and elevated troponin levels. In patients with moderate renal impairment (GFR not reaching 60 ml/min), lengthening of the QTc interval might be associated with hydroxychloroquine removal from the kidney. In this study, patients with acute myocardial infarction were excluded based on an assumption that they could significantly affect mean values for the QTc interval. However, we found that some participants had elevated troponin levels. This was found to be type 2 myocardial damage or myocarditis. One limitation of this study is that these two are indistinguishable. However, in practice, a more careful evaluation of the QTc interval would be useful for patients with high troponin levels and for those who began drug therapy after being assessed in the clinic.

In patients admitted to our intensive care unit, when the QTc interval is measured consecutively (daily), peak values are seen, on average, 2 to 3 days after admission. Because pathological QTc interval prolongation occurs in 2-3 days, the second ECG should be performed after 48 hours, and a patient with pathological prolongation must be followed closely.

There were a several limitations to the study. First, the sample size is relatively small. Although patients presenting with acute coronary syndrome were excluded from the study, myocarditis that might be associated with COVID-19 during their hospitalization and the effects of this condition on QTc were not clearly defined. Since the control group was not included in this retrospective study, the isolated contribution of COVID-19 infection to QTc prolongation could not be clearly determined.

Conclusion

In the patient population infected with COVID-19, the pathological QTc prolongation rate was 9.6%. In subgroup analyses, QTc interval lengthening was associated with high troponin levels and low GFRs. The risk of developing pathological QTc was significantly increased in patients with initial QTc ≥460 ms. Prolongation of QTc occurs on average at 2-3 days. Multiple factors cause QT prolongation in patients who are hospitalized and admitted to the intensive care unit. In addition to standard risk assessments, troponin levels and GFRs should be considered when evaluating patients with COVID-19.

References

1. WHO-Director-General's opening remarks at the media briefing on COVID-19-11 March 2020.[https://www.who.int/dg/speeches/detail/who-director-general-s-opening –remarks –at-the-media-briefing-on-covid-19-11-march-2020]
2. World Health Organization. [https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports]
3. Republic of Turkey Ministery of Health Official Website .[https://covid19bilgi.saglik.gov.tr/tr]
4. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019- nCoV) in vitro. Cell Res 2020 Feb 4 [Epub ahead of print]. doi: 10.1038/s41422-020-0282-0.
5. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases. The Lancet infectious diseases. 2003;3(11):722-7. doi: 10.1016/S1473-3099(03)00806-5
6. Vincent MJ, Bergeron E, Benjannet S, Bobbie R Erickson, Pierre E Rollin, Thomas G Ksiazek, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virology Journal. 2005;2(1):1-10. doi: 10.1186/1743-422X-2-69
7. Chen C-Y, Wang F-L, Lin C-C. Chronic Hydroxychloroquine Use Associated with QT Prolongation and Refractory Ventricular Arrhythmia.Clinical Toxicology. 2006;44(2): doi: 10.1080/15563650500514558
8. Chugh SS, Reinier K, Singh T, Uy-Evanado A, Socoteanu C, Peters D, et al. Clinical perspectıve. Circulation. 2009;119(5):663-70. doi: 10.1161/CIRCULATIONAHA.108.797035
9. .Gautret P, Lagier JC, Parola P, Hoang VT, Medded L, Morgan Maılhe et al. Hydroxycloroquine and azithromycin as a treatment of COVID-19:preliminary results of an open-label non-randomized clinical trial. medRxiv 2020.03.16.20037135. doi:. 10.1101/2020.03.16.20037135
10. Choi Y, LimH-S, Chung D. Choi J, Yoon D. Risk evaluation of azithromycin-induced QT prolongtion in real world practise. BioMed Research İnternational. 2018;ID1574806. doi: 10.1155/2018/1574806
11. Republic of Turkey Ministery of Health COVID-19(SarS –CoV-2) guide 25.03.2020 https://www.tahud.org.tr/file/4f42cbfd-bbd9-4bf4-91b0-29698f53f198/COVID-19_Rehberi.pdf
12. Tisdale JE, Jaynes HA, Kingery JR, Mourad NA, Trujillo TN, Overholser BR, et al. Development and validation of a risk score to predict Qt interval prolongtion in hospitalized patients. Circ Cardiovasc Qual Outcomes. 2013;6(4):479-87. doi: 10.116/cırcoutcomes.113.000152.
13. Dutkowski R, Smithb JR, Davies BE. Safety and pharmacokinetics of oseltamivir at standard and high dosages. International Journal of Antimicrobial Agents. 2010;35:461–7. doi: 10.1016/j.ijantimicag.2009.12.023

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1086-1088.
DOI: 10.28982/josam.803776

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Saphenous vein graft aneurysm after coronary artery bypass graft surgery: A case report

Koroner bypass cerrahisi sonrası gelişen safen ven anevrizması: Olgu sunumu

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Abstract
Aneurysm of the saphenous vein, which is the most used graft in coronary bypass surgery, is a rare complication. While saphenous vein dilatation forming in the early or late stages after bypass surgery can be symptomatic, it can also be diagnosed incidentally. Aneurysms forming in the late stages are atherosclerotic while those forming in the initial stages are mostly connected to venous damage. In the present case, a saphenous aneurysm with atherosclerotic causes was detected in a patient 20 years after coronary bypass surgery. The patient was admitted with chest pain, syncope, and dizziness complaints. Examination revealed a saphenous vein aneurysm measuring 28x30 mm. The patient underwent surgery, and the aneurysm was resected.
Keywords: Saphenous vein, Aneurysm, Coronary artery bypass

Öz
Koroner bypass cerrahisinde en sık kullanılan greft olan safen veninin anevrizmaları nadir rastlanan bir komplikasyondur. Erken veya geç dönemde oluşan safen ven dilatasyonları semptomatik olabildikleri gibi bazen tesadüfen de teşhis edilebilir. Geç dönemde oluşan anevrizmalar genellikle aterosklerotik nedenli iken erken dönemde oluşan anevrizmalar sıklıkla ven hasarına bağlı olmaktadır. Bu olguda koroner bypass cerrahisi yapılan hastada 20 yıl sonra aterosklerotik nedenli safen ven anevrizması saptandı. Göğüs ağrısı, baygınlık, baş dönmesi şikayeti ile başvuran hastanın yapılan tetkiklerinde 28x30 mm boyutlarında safen ven anevrizması tespit edildi. Hasta operasyona alındı ve anevrizma rezeksiyonu yapıldı.
Anahtar kelimeler: Safen ven, Anevrizma, Koroner arter bypass

Introduction

The saphenous vein is the most used autogenous graft in coronary bypass and peripheral artery surgeries. If this graft, usually carrying the blood of the venous system, is arterialized, and exposed to higher pressure, it may lead to saphenous vein dilatation and rarely, aneurysm [1-9]. Aneurysm of a saphenous vein graft was first reported by Carrasquilla in patients whose carotid arteries were fixed with veins [2]. Saphenous vein aneurysm developing after coronary bypass was first reported by Riahi in 1975 [3,6,9,10].

We herein report an aneurysm that developed in the saphenous vein 20 years after coronary bypass surgery.

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Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/19/2020
Yayın Tarihi: 19.11.2020

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How to cite / Atıf için: Reyhanoğlu H, Özcan K, Edem E. Saphenous vein graft aneurysm after coronary artery bypass graft surgery: A case report. J Surg Med. 2020;4(11):1086-1088.

Case presentation

A 68-year-old patient who had undergone coronary bypass surgery 20 years ago presented with complaints of chest pain, syncope, and dizziness. An X-ray showed a paracardiac mass, pushing the right hemithorax. A thoracic computed tomography performed after confirmation of the diagnosis showed an aneurysm, defined as a 'saccular aneurysmal vascular structure,' adjoining the right atrium (Figure 1).

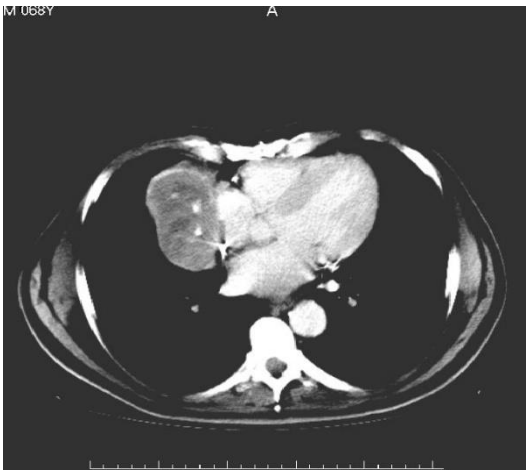

Figure 1: A computed tomography image of the thorax showing the saccular aneurysmal vascular structure

Coronary angiography revealed a saphenous aneurysm measuring 28 × 30 mm in the right saphenous graft (aorta–right coronary artery) (Figure 2).

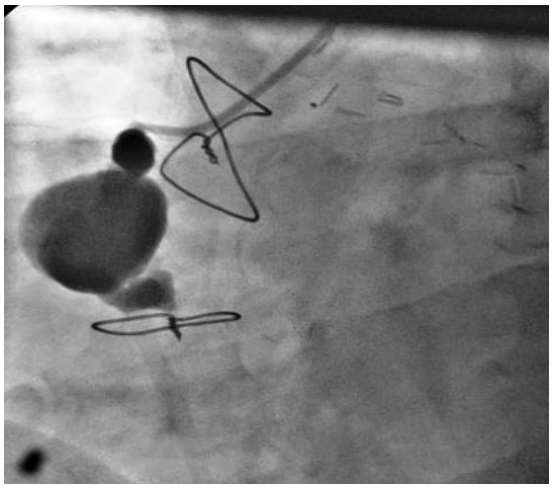

Figure 2: A coronary angiographic image of the saphenous aneurysm.

A right anterolateral thoracotomy was performed. An aneurysm measuring 28 × 30 mm in size was observed adjoining the right atrium and exerting pressure. The sac was incised to show thrombotic and calcified contents (Figure 3). After resecting the aneurysm wall, the right saphenous vein was tied proximally. The distal part of the right coronary artery was explored for bypass; however, there was too much fibrosis and the lumen was not appropriate for grafting. The operation was performed on a beating heart, and cardiopulmonary bypass was not performed. The patient was discharged on the 6th postoperative day uneventfully.

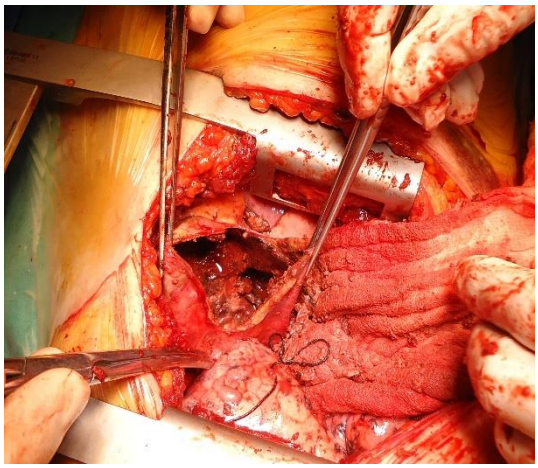

Figure 3: A surgical specimen of the aneurysm sac

Discussion

Saphenous vein aneurysm developing after coronary bypass surgery is a rarely seen complication [1-3,5-7,9]. Aneurysms developing between 11 days and 21 years and varying in diameter from 1 to 13 cm have been reported [6,10]. In their study on 168 saphenous vein aneurysms, Ramirez et al. [9] reported that 4.2% of the cases were diagnosed within 1 year, 6.1% of the cases within 1–5 years, 21.2%, within 5–10 years, and 68.5%, after 10 years. According to the sizes and localizations of saphenous vein aneurysms, physicians may encounter cardiac symptoms or mediastinal mass pressure [1,9]. Nevertheless, one third of the cases are diagnosed incidentally [9]. These patients may have chest pain related to myocardial ischemia, cardiac failure findings due to compression arrhythmia, hemoptysis, bleeding, hemothorax after sudden rupture, and superior vena cava syndrome [6,7,9-11].

Although the mechanisms underlying aneurysm development are not exactly known, graft necrosis, hypertension, vein damage during graft preparation, atherosclerosis developing on the graft, and weakness in the vein wall are suggested reasons [1,5-7]. Aneurysm is more frequent in right coronary artery grafts and less frequent in left anterior descending and circumflex artery grafts [9]. One of the hypotheses suggested for the more frequent occurrence of aneurysm in the right coronary artery graft is that the saphenous vein is more commonly used in this coronary artery [9]. Another suggested hypothesis is the preference for wider parts of the saphenous vein as there is no diameter disproportion in the right coronary artery.

Aneurysms are classified as early or late stage according to their time of development [9]. Early stage (<12 months) aneurysms are caused by vein damage or weakness of the wall, whereas late-stage aneurysms are caused by atherosclerosis [1,3-7,9,10,12]. Early-stage aneurysms are related to the structure of a pseudoaneurysm, usually saccular, and commonly develop in the first couple months after surgery [6,8-10]. These aneurysms are caused by weakness of the saphenous vein wall, damage during vein removal, or defects in the anastomosis line [7-10,12]. Venous valves extending up to the media layer on the vein wall are weaker, and the smooth muscle layer in this area is longitudinal, not circular. This causes the development of a weak area that may lead to an aneurysm [1,6]. Late-stage aneurysms mostly show the true aneurysm structure [7,8,10,12]. True

aneurysms are fusiform; they are caused by atherosclerosis and contain 3 vascular layers, e.g., vascular aneurysms [7-10,12]. Inside the sac of this type of aneurysm, commonly developed over 8–10 years, thrombosis secondary to atherosclerosis develops and causes graft occlusion [1,6,9]. The aneurysm in the present case was this type of aneurysm with atherosclerotic characteristics.

Saphenous aneurysms can be diagnosed using echocardiography, direct X-ray lung radiography, computed tomography, magnetic resonance scanning, and coronary angiography [1,6,7,10-12]. Computed tomography and magnetic resonance scanning are especially important for determining the pressure exerted on neighboring areas and differential diagnosis [6,8]. Coronary angiography is important to decide whether additional revascularization other than aneurysm resection is necessary [8,12].

In surgical treatment, ligation, aneurysm resection and if necessary, coronary revascularization are performed [6,8,10,11]. Other treatment choices include percutaneous coil embolization and embolization with covered stents [6,7,9-12]. The first percutaneous attempt in this category was reported by Kim et al. in 1983 [13]. Percutaneous embolization may be preferred to prevent the risks of re-sternotomy, especially in patients for whom additional revascularization will not be performed, or in patients with a high surgical risk [6,7,9]. In the present case, we did not try percutaneous closure because of the large size of the aneurysm sac and the possibility of revascularization to the right coronary artery.

Conclusions

In patients with mediastinal or paracardiac mass after coronary bypass surgery, saphenous aneurysm should not be overlooked during diagnosis. These cases may be associated with cardiac symptoms; occasionally, they can be asymptomatic and diagnosed incidentally. In these patients, the planned surgical treatment will prevent risks, such as sudden rupture, coronary embolism, and cardiac failure.

References

1. Yavuz S, Celkan A, Turk T, Ozdemir İA. Aneurysm of an aortocoronary saphenous vein bypass graft. Turkish Journal of Thoracic and Cardiovascular Surgery. 1999;7:336-8.
2. Carrasquilla C, Weaver AW. Aneurysm of a saphenous vein graft to the common carotid artery. Vasc Surg. 1972;6:66-8.
3. Riahi M, Vasu CM, Tomatis LA, Schlosser RJ, Zimmerman G. Aneurysm of saphenous vein bypass graft to coronary artery. J Thorac Cardiovasc Surg. 1975;70:358-9.
4. Neitzel GF, Barboriak JJ, Pintar K, Qureshi I. Atherosclerosis in aortocoronary bypass grafts. Morphologic study and risk factor analysis 6 to 12 years after surgery. Arteriosclerosis. 1986;6:594-600.
5. Van de Wal RMA, Van Verkum JW, Le cocq d'armandville MC, Plokker HWT, Morshuis WJ. Giant aneurysm of an aortocoronary venous bypass graft compressing the right ventricle. Neth Heart J. 2007;15:252-4.
6. Abbasi M, Soltani G, Shomali A, Javan H. A large saphenous vein graft aneurysm one year after coronary artery bypass graft surgery presenting as a left lung mass. Interactive Cardio Vascular and Thoracic Surgery. 2009;8:691–3.
7. Pulling TM, Uyesugi WY. Aneurysm of an autologous aorta to right coronary artery reverse saphenous vein graft presenting as a mediastinal mass: a case report. Cases Journal. 2008;1;340.
8. Kalimi R, Palazzo RS, Graver LM. Giant aneurysm of saphenous vein graft to coronary artery compressing the right atrium. Ann Thorac Surg. 1999;68;1433-7.
9. Ramirez FD, Hibbert B, Simard T, Pourdjabbar A, Wilson KR, et al. Natural history and management of aortocoronary saphenous vein graft aneurysms: a systematic review of published cases. Circulation 2012;126:2248-56
10. Breton LH, Pavin D, Langanay T, Roland Y, Leclercq C, Beliard JM, et al. Aneurysms and pseudoaneurysms of saphenous vein coronary artery bypass grafts. Heart 1998;79:505-8.
11. Boczar KE, Hibbert B, Simard T, Hibbert R, Chan V, O'Brien ER. Giant saphenous vein graft aneurysm presenting as ST-elevation myocardial infarction. Circ J. 2014;78:769-71.
12. Nölke L, McGovern E, Wood EA. Saphenous vein graft aneurysms; the true, false and ugly! Interact Cardiovasc Thorac Surg. 2004;3:631-3.
13. Kim D, Guthaner DF, Wexler L. Transcatheter embolization of a leaking pseudoaneurysm of saphenous vein aortocoronary bypass graft. Cathet Cardiovasc Diagn. 1983;9:591-4.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1089-1091.
DOI: 10.28982/josam.731192

Case report
Olgu sunumu

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A rare cause of cholestasis: Congenital right diaphragmatic hernia

Kolestazın nadir bir nedeni: Konjenital sağ diafragma hernisi

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Informed Consent: The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastanın ebeveynlerinden yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract

An 82-day-old infant, investigated for sudden onset jaundice and acholic feces, was referred to our department, as no gallbladder was observed by abdominal ultrasonography. Her chest x-ray revealed an elevated right diaphragm, and the breath sounds were diminished on the right. Suspicious arteriovenous malformation in the fifth segment of the right lobe accompanied by a rotation anomaly of liver was reported. Tomography scans showed right diaphragmatic hernia where the left lobe of liver and gallbladder herniated to the thoracic space. In this case with right Bochdalek hernia, the bile ducts had kinked in the thoracic cavity, causing obstructive jaundice. If the kinking continues despite relocation of organs into the abdominal cavity, cholecystectomy-hepaticojejunostomy is an effective and reliable surgical method. Myriad pathologies may cause cholestasis, and surgical reasons should be investigated and diagnosed without delay to improve prognosis. For closure of the diaphragmatic defect, primary repair should be the preferred method. With this case, we wanted to emphasize a highly different presentation of Bochdalek hernia and remind that diaphragmatic hernia should be kept in mind in patients presenting with cholestasis and acholic stools.

Keywords: Obstructive jaundice, Acholic feces, Cholestasis, Diaphragmatic Hernia

Öz

82 günlük kız hasta ani gelişen sarılık, akolik dışkılama olması nedeniyle yapılan Abdominal Ultrasonografisinde safra kesesinin görülmemesi üzerine kliniğimize yönlendirildi. Akciğer grafisinde sağ diyafram elevasyonu mevcut idi. Hastanın muayenesinde aynı tarafta solunum sesleri azalmış olarak alınıyor idi. Çekilen Tomografisinde sağ diyafragmatik herni mevcut ve karaciğer ile safra kesesi toraks boşluğuna herniye idi. Olgumuzda sağ Bochdalek hernisi mevcut idi ve safrayollarının torasik kavitede sıkışmasına bağlı obstrüktif sarılık gelişmiş idi. Operasyon sırasında alınan karaciğer biyopsisinde fibroz bulguları oluşmaya başlamış idi. Operasyona alınan hastanın abdominal organları yerine alınarak, kolesistektomi ve hepatikojejunostomi operasyonu yapıldı. Erken tanı ve tedavi ile hastanın takibinde yapılan karaciğer biyopsisinde karaciğerde gelişen bulguların düzelmeye başladığı görüldü. Kolestaz, çok çeşitli etyolojik nedenlere bağlı olabilmekle birlikte cerrahi nedenlerin ivedilikle tanı ve tedavisinin yapılması prognoz açısıdan önem arz etmektedir. Bu olgu ile Bochdalek hernisinin çok farklı bir prezantasyon şeklini sunmak istedik. Kolestaz ile gelen akolik dışkısı mevcut olan hastaların ayırıcı tanısında diafragma hernisi de akılda tutulmalıdır.

Anahtar kelimeler: Obstrüktif sarılık, Akolik gaita, Kolestaz, Diyafragmatik hernia

Introduction

Congenital diaphragmatic hernia occurs in about one in every 2000-5000 live births [1]. Bochdalek hernias are left-sided in 78-84% of cases, right-sided in 14-20% and even more rarely bilateral [2,3]. Although congenital right diaphragmatic hernia (CRDH) is known as a condition that may cause obstructive jaundice, it is quite rare fortunately [4]. These hernias typically occur before or shortly after birth and only % 5- 25 develop after 2 months of age [5]. An 82-day-old female infant was diagnosed with CRDH when examined due to obstructive jaundice. With this case, we wanted to emphasize a highly different presentation of Bochdalek hernia and remind that diaphragmatic hernia should be kept in mind in patients presenting with sudden onset jaundice, cholestasis and acholic stools.

How to cite / Atıf için: Taşkın DG, Emre Ş, Özmen E, Kepil N, Adaletli İ, Kutlu T, Çokuğraş FÇ, Erkan T, Şenyüz OF. A rare cause of cholestasis: Congenital right diaphragmatic hernia. J Surg Med. 2020;4(11):1089-1091.

Case presentation

Our 82-days-old term female patient who had no abnormalities in her prenatal follow-up was investigated in another institution for sudden onset jaundice and acholic feces developed within the last week. The patient was referred to our department, as no gallbladder was observed in the abdominal ultrasonography. She had no history of perinatal trauma or distress and she was icteric on physical examination. The liver was 3/2.5 cm palpable subcostally. Her cardiovascular system examination was normal. Laboratory test results were as follows: AST: 91 IU/L (2.2x upper limit of normal (ULN)), ALT: 69 IU/L (1.7x ULN), GGT: 1044 IU/L (41.7x ULN), LDH: 302 IU/L (normal), ALP: 589 IU/L (3.8x ULN), total bilirubin: 8.9 mg/dL (7.4x ULN), direct bilirubin: 8.07 mg/dl (40x ULN). Her chest x-ray revealed an elevated right diaphragm (Figure 1).

After the x-ray findings we found that the breath sounds were diminished on the right side on auscultation. In abdominal ultrasonography (USG), no gallbladder was observed and a suspicious arteriovenous malformation appearance in the fifth segment of right lobe accompanied by a rotation anomaly of liver was reported. Thoracic and abdominal computed tomography (CT) scans revealed a right diaphragmatic hernia. CT scans showed that the left lobe of liver and gallbladder were herniated into the thoracic space (Figure 2).

Venous stasis in the left lobe of liver was noted and it was concluded that the image imitating an arteriovenous malformation was the gallbladder shifted to the paravertebral area and that extrahepatic biliary ducts may be kinked. Magnetic resonance (MR) cholangiographic assessment was planned to confirm the biliary pathology. MR cholangiography showed that the left lobe of liver was in the thorax and that intrahepatic biliary tracts were dilated due to kinked external biliary ducts (Figure 3).

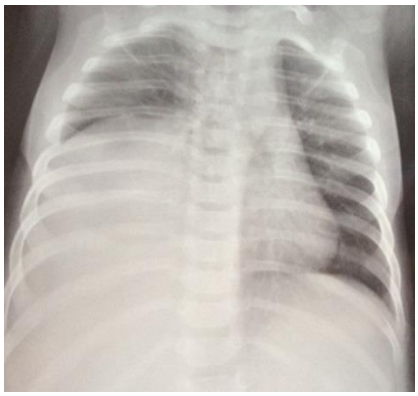

Figure 1: Posteroanterior Chest X-ray; Right diaphragm eventration

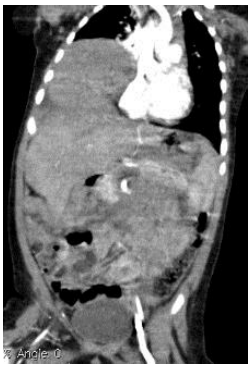

Figure 2: CT scan with intravenous contrast agent showing the placement of CRDH, liver and bile ducts in thoracic cavity

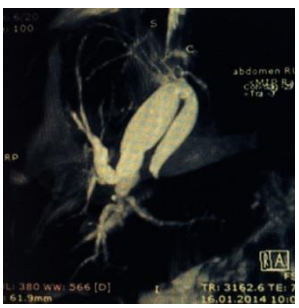

Figure 3: MR cholangiography showing intrahepatic biliary tract dilatation because of kinked up extrahepatic bile ducts

In surgical exploration performed when she was 100 days old, a right sided Bochdalek hernia was found. An ileal segment, right lobe of liver and gallbladder were noted in thoracic cavity. The right lobe had a shapeless structure as it had developed in thoracic cavity. The gallbladder was enlarged with thickened walls. Extrahepatic biliary ducts were kinked up on themselves and hepatic channel along with bile ducts were dilated, 1.1 cm in diameter. Perfusion and hemodynamics were stable as the liver and gallbladder were relocated into the abdominal cavity.

Cholecystectomy, hepaticojejunostomy, 1 cm distal to the right and left hepatic channels, and end-to-side jejunojejunostomy were performed. The congenital defect on diaphragm was repaired. Histopathologic evaluation of liver biopsy taken during surgery revealed severe bile stasis, parenchymal degeneration, mild inflammatory activity, and marked fibrosis (Figures 4, 5).

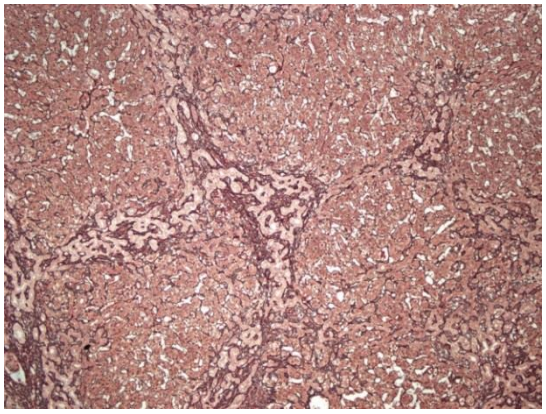

Figure 4: A reticulin stain reveals the parenchyma framework of the lobule in the formerly biopsy (x40)

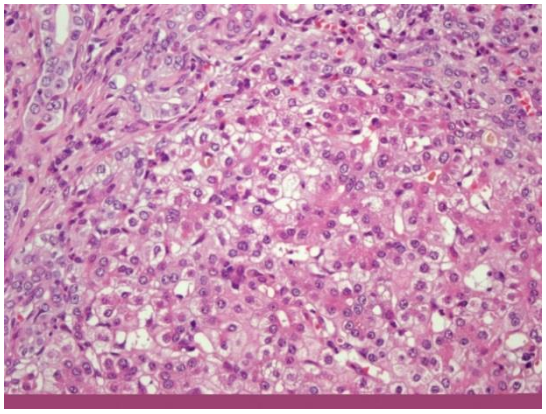

Figure 5: In the same biopsy material, mild inflammation, and mild bile duct proliferation were observed in the parenchyma. Hematoxylin and eosin. x100

She passed a cholic stool on the 4th postoperative (PO) day, oral nutrition was initiated on 5th PO day and laboratory values at discharge on the 8th PO day were as follows: AST: 44IU/L, ALT: 11 IU/L, GGT: 27I U/L, ALP: 103 IU/L, total bilirubin: 1.4 mg/dL, direct bilirubin: 1.02 mg/dL. Laboratory test results of the first visit to our outpatient clinic were within normal ranges. Liver biopsy was performed at the 8th month after the operation due to evidence of severe fibrosis in the first liver biopsy. The last biopsy revealed no cirrhosis and significant reduction of fibrosis from severe to mild in comparison with the first one (Figures 6, 7). The patient is still followed uneventfully by our outpatient clinic. Written consents were obtained from the patient's caregivers for this case presentation.

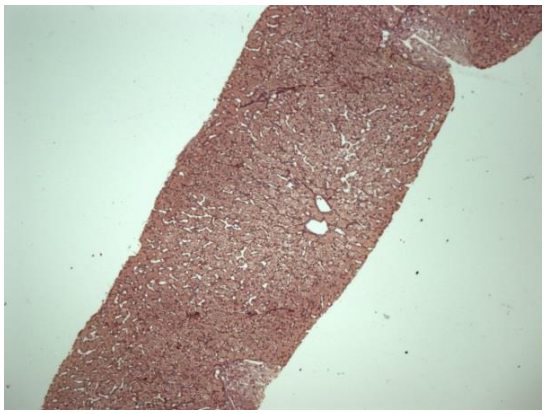

Figure 6: New biopsy material showed no fibrosis. Reticulin stain. x40

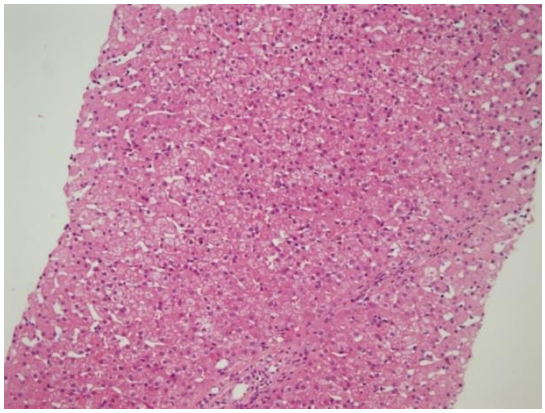

Figure 7: Parenchymal and portal tracts are regular in the new biopsy sample. Hematoxylin and eosin (x100)

Discussion

While most congenital diaphragmatic hernias manifest through dyspnea in the first 24 hours, 10-20% of cases are diagnosed at a future date [6,7]. BH in adults is mostly asymptomatic, hence, it is usually discovered incidentally [8]. Between 40-90% of cases are diagnosed prenatally by MR imaging and USG [9, 10]. In cases with postnatal dyspnea, it is diagnosed easily by physical examination and chest x-ray. In cases without dyspnea, on the other hand, diagnosis comes later due to concomitant pathologies and recurrent lung infections. In jaundiced patients, the reasons of cholestasis, whether it be medical or surgical, should be investigated without delay.

Diagnosis of CRDH is more difficult than that of congenital left diaphragmatic hernia. Chest x-ray is often inadequate in this group, and patients are diagnosed by thoracic CT scan [11]. Correspondingly, chest x-ray and USG were inadequate for diagnosis in our case and USG yielded a false diagnosis of arteriovenous malformation.

Three main problems may be encountered during the surgical treatment of CRDH. First, venous stasis and hemodynamic impairment in liver and portal areas may occur because of kinked hepatic veins when the liver is placed in the abdominal cavity. Second, the hepatic veins may be injured during the repair of diaphragm, and third, inadequate intraabdominal volume for the liver and other organs after the repositioning may cause difficulties in abdominal wall closure. In our case, none of the above occurred and the diaphragm was successfully repaired. The abdomen was closed surgically without any complications.

When the literature is reviewed, right sided Bochdalek hernias causing obstructive jaundice in neonates and infants are quite rare. In two reported cases, jaundice developed due to stasis in herniated and kinked extrahepatic bile ducts. As no problem was experienced in bile passage after the relocation of organs, no interventions were performed on the bile duct and gallbladder.

On the contrary, bile ducts and gallbladder were highly dilated and thickened in our case. Despite the transfer of organs into the abdominal cavity, folding of extrahepatic bile duct on itself continued to take place and thus, cholecystectomy, hepaticojejunostomy and an end-to-side jejunojejunostomy were performed. Cholic stool were observed on the 4th postoperative day and her total bilirubin levels decreased down to 2 mg/dl on the 8th PO day.

Conclusions

CRDH cases without dyspnea may present with digestive system-related and hepatobiliary findings in later phases. Chest X-rays are a useful diagnostic tool in addition to thorax CT, especially in unclear cases [12]. CT with intravenous contrast agent is a reliable and effective modality for diagnosis. In right Bochdalek hernia cases presenting with obstructive jaundice, kinking of bile ducts should be resolved, immediate diagnosis should be made and fibrosis or cirrhosis due to hepatic bile stasis should thereby be prevented. If the kinking of extrahepatic bile ducts continues despite transfer of organs into the abdominal cavity, cholecystectomy-hepaticojejunostomy is an effective and reliable surgical method. For the closure of diaphragmatic opening, primary repair should be preferred as first-line approach. Reconstruction with patch is chosen only in case of increased abdominal compartment syndrome risk or for cases when a primary repair is technically not feasible.

References

1. Jain V, Agarwala S, and Bhatnagar V. Recent advances in the management of congenital diaphragmatic hernia. Indian Journal of Pediatrics. 2010;77(6):673–8.
2. Migliazza L, Bellan C, Alberti D, Auriemma A, Burgio G, Locatelli G, et al. Retrospective study of 111 cases of congenital diaphragmatic hernia treated with early high-frequency oscillatory ventilation and presurgical stabilization. J Pediatr Surg. 2007;42:1526–32.
3. Kinoshita F, Ishiyama M, Honda S, Matsuzako M, Oikado K, Kinoshita T, et al. Late-presenting posterior transdiaphragmatic (Bochdalek) hernia in adults: prevalence and MDCT characteristics. Journal of Thoracic Imaging. 2009;24(1):17–22.
4. Jones HG, Kadhim A, Nutt M. Congenital diaphragmatic hernia: an unusual cause of obstructive jaundice. Ann R Coll Surg Engl. 2012;94:8-9.
5. Sandstrom CK, Stern EJ. "Diaphragmatic hernias: a spectrum of radiographic appearances," Current Problems in Diagnostic Radiology 2011;40(3):95–115.
6. Becmeur F, Jamali RR, Moog R, Keller L, Christmann D, Donato L, et al. Thoracoscopic treatment for delayed presentation of congenital diaphragmatic hernia in the infant: A report of three cases. Surg Endosc. 2001;15:1163-6.
7. Bagłaj M. Late-presenting congenital diaphragmatic hernia in children: a clinical spectrum. Pediatr Surg Int. 2004;20:658-69.
8. Coco D, Leanza S. An Atypical Presentation of a Strangulated Bochdalek Hernia in a 60-Year-Old Man. Macedonian Journal of Medical Sciences. 2019;7(11):1818-20.
9. Lewis DA, Reickert C, Bowerman R, Hirschl RB. Prenatal ultrasonography frequently fails to diagnose congenital diaphragmatic hernia. J Pediatr Surg. 1997;32:352-6.
10. Garne E, Haeusler M, Barisic I, Gjergja R, Stoll C, Clementi M. Congenital diaphragmatic hernia: Evaluation of prenatal diagnosis in 20 European regions. Ultrasound Obstet Gynecol. 2002;19:329-33.
11. Zeina AR, Weiner D, Reindorp N, Kassem E, Klein-Kremer A. Late presentation of congenital right diaphragmatic hernia: clinical and radiological features. Pediatr Int. 2011;53:790-1.
12. Sutedja B and Muliani Y. Laparoscopic repair of a Bochdalek hernia in an adult woman . Asian J Endosc Surg. 2015;8:354-6.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1092-1094.
DOI: 10.28982/josam.741940

Journal of Surgery and Medicine
e-ISSN: 2602-2079

A case of acute renal failure requiring emergency hemodialysis due to hypothermia-associated rhabdomyolysis

Hipotermi ilişkili rabdomiyoliz nedeniyle acil hemodiyaliz ihtiyacı gelişen akut böbrek yetmezliği olgusu

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Abstract

Hypothermia is described as a decrease in body temperature below 35 °C. Although the body reacts neuroendocrinally, behaviourally, and cardiovascularly against sudden changes in temperature, uncontrolled hypothermia can lead to severe complications such as rhabdomyolysis, acute renal failure, coma, coagulopathy, malignant cardiac arrhythmia, and cardiac collapse. Herein, we aimed to emphasize hypothermia, its serious complications such as rhabdomyolysis and related acute kidney injury in a 60-year-old male patient exposed to environmental cold.

Keywords: Emergency, Hemodialysis, Hypothermia, Rhabdomyolysis, Renal failure

Öz

Hipotermi vücut iç sıcaklığının 35 °C'nin altına düşmesi olarak tanımlanmaktadır. Çevredeki ani ısı değişimlerine karşı vücut nöroendokrinal, davranışsal ve kardiovasküler olarak tepki göstermekle birlikte kontrol altına alınamayan hipotermi rabdomiyoliz, akut böbrek yetmezliği, koma, koagülopati, malign kardiyak aritmi, kardiyak kollaps vb. ciddi komplikasyonlara neden olabilmektedir. Bu olgu sunumu ile soğuğa maruz kalan altmış yaşındaki erkek hastada gelişen hipotermi ve hipoterminin potansiyel komplikasyonlarına vurgu yapılmak istenmiştir.

Anahtar kelimeler: Acil, Hemodiyaliz, Hipotermi, Rabdomiyoliz, Böbrek yetmezliği

Introduction

Hypothermia occurs when the internal body temperature drops below 35 degrees [1-3]. According to the standard classification, hypothermia is classified as mild, moderate, and severe according to body core temperature being between 32-35 °C, 28-32 °C and <28 °C, respectively [4,5]. Although the body reacts neuroendocrinally, behaviorally, and cardiovascularly against sudden changes in temperature, uncontrolled hypothermia can lead to severe complications such as rhabdomyolysis, acute renal failure, coma, coagulopathy, malignant cardiac arrhythmia, and cardiac collapse. To date, several cases of acute renal failure requiring emergency hemodialysis after hypothermia due to rhabdomyolysis have been reported in the literature. In this respect, our case is remarkable.

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Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Previous presentation: The study was presented as an oral presentation at the 15th Turkish Emergency Medicine Congress, November 21-24, 2019, Regnum Carya Convention Center, Antalya, Turkey

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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How to cite / Atıf için: Vural A, Ekiz M, Günaydın M. A case of acute renal failure requiring emergency hemodialysis due to hypothermia-associated rhabdomyolysis. J Surg Med. 2020;4(11):1092-1094.

Case presentation

A 60-year-old male patient with a history of chronic renal failure and a psychiatric problem (psychotic disorder without treatment) was transported to our emergency department by the 112 emergency team. We determined that the patient lived alone. After a fire, the patient, who had no protective clothing on him, was found semi-unconscious by the locals about 6 hours later. On the day of the incident, the weather in Giresun, a coastal province in Turkey that borders the Black Sea, was very cloudy, the coastal areas were rainy, the heights of the inner parts were snowy, and the highest temperature was 8 °C. The patient's general condition was poor when he was admitted to the emergency department. Glasgow coma scale value (GCS) of the patient was 14 (E4M6V4). The vital signs were as follows: Blood pressure: 110/70 mm-Hg, Heart Rate: 41 beats per minute (bpm), respiratory rate: 16 /minute, fever: 33.2 °C and finger blood glucose: 150 mg/dl. On neurological examination, he was confused, and his in-depth tendon reflex examination was hypoactive. In other systemic examinations, respiratory sounds were mildly coarse, heart sounds were (S1 + S2 +) rhythmic and bradycardic, and abdominal examination was normal. The patient had dry and hard skin, stiffness in body muscles, and severe sensitivity to touch after prolonged exposure to cold. No tremor was detected. There was mild cyanosis, bruising, and severe pain in bilateral foot and toes, more prominent in the first and second fingers of the right foot.

In the pre-hospital period, the body temperature was not measured, and the patient was given passive external heating with the help of heat bags and blankets by 112. During hospitalization, the patient was provided active external heating with a forced-air warming system through the blanket and minimally invasive heating with intravenous fluid support heated to 40-42 °C and bladder lavage. The patient's body core temperature increased to 36.2 °C within 30 minutes after heating supports.

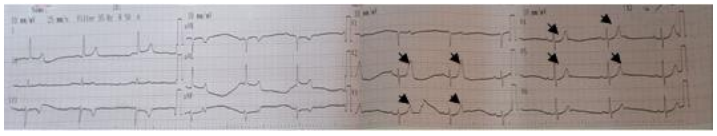

Figure 1: The patient's ECG at admission time to the emergency department, Electrocardiography (ECG) revealed sinus bradycardia (41 bpm) and peaked T waves (black arrows) more prominent in anterior leads (V2 - V5)

Electrocardiography (ECG) revealed sinus bradycardia (41 bpm), and peaked T waves more prominent in chest leads (Figure 1). There was no pathology in the chest radiograph. In the laboratory findings, the blood urea level was higher than 455 mg/dl, creatinine was 7.61 mg/dl, creatine kinase (CK) level was higher than 2149 U/L and potassium level was 8.23 mmol/L. These findings were in favor of acute renal failure (ARF) and rhabdomyolysis. In the blood gas analysis, Ph, PCO_2, HCO_3, were in favor of severe metabolic acidosis with an increased anion gap. The patient's laboratory findings are summarized in Table 1 A, B. The patient had acute renal failure associated with rhabdomyolysis, which is based on chronic renal failure. Therefore, emergency hemodialysis support was given in two sessions (3 hours at the first session and 2 hours at the second session). After one week of follow-up, the patient was discharged without sequelae. Informed consent for treatment was assumed through the doctrine of implied consent, and also verbal consent was obtained from the patient for the study.

Table 1: Laboratory findings of the patient admitted to the emergency department

A) Patient's hemogram and biochemistry results		Reference range
WBC (/L)	26.42 x 10^9	4.3-10.3 X 10^9
Platelet (/L)	188 x 10^9	150-400 x10^9
HCT (%)	47.7	41-53
AST (U/L)	24	<40
ALT (U/L)	6	<40
PT (s)	15.8	10-14
aPTT (s)	34.7	23-35
D-Dimer (ng/ml)	3337	<500
LDH (U/L)	281	135-225
CK (U/L)	>2149	39-308
urea(mg/dL)	>455	15-42
Creatinine(mg/dL)	7.61	0.7-1.2
Amylase(U/L)	116	28-100
Calcium(mg/dL)	9.9	8.5- 10.2
Sodium(mEq/L)	138	135-145
Potassium(mEq/L)	8.23	3.5-5.5
Glucose (mg/dL)	150	70-110
B) Other laboratory findings		Reference range
Venous Blood Gas		
Ph	7.129	7.35-7.45
PCO2 (mm-Hg)	38.7	35-45
PO2 (mm-Hg)	32.9	80-100 (arterial blood gas)
HCO3act (mmol/L)	12.6	22-26
HCO3std(mmol/L)	12.1	22-26
AnGap (mEq/L)	29.6	8-16
Lactate(mmol/L)	4.97	<2
Blood ethanol level (mg/dL)	<0.1	Negative
Urine	Dark, concentric	

AnGap: Anion Gap, WBC: White blood cell, HCT: hematocrit, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, PT: Prothrombin time Aptt: Activated partial thromboplastin time, LDH: Lactate dehydrogenase, CK: Creatine kinase

Discussion

In our case, the temperature of the patient was measured as 33.2 °C. According to the classical description, the degree of hypothermia of the patient was Stage 1 (mild). However, we believe that the hypothermia of the patient was Stage 2 (moderate) based on the patient's severe clinical findings and since the emergency team immediately began to warm the patient. Hypothermia-related deaths are associated with some risk factors including advanced age (>65 years), male gender, falls, cold environment, insufficient protective clothing, a history of drug use that changes consciousness, and cardiovascular diseases [5,6]. In parallel, there were the risk factors mentioned above related to hypothermia in our patients.

There are many causes of rhabdomyolysis leading to acute renal failure but drug abuse, alcohol intoxication, and compression injuries are the most common causes of rhabdomyolysis [7]. In rare cases, hypothermia may cause rhabdomyolysis due to excessive tremor, prolonged vasoconstriction, and profound hypoxia [8]. Rhabdomyolysis also developed in our patient as a result of prolonged tremor and immobilization after exposure to cold.

There are a few cases of hypothermia-related rhabdomyolysis in the literature [9,10]. Similar to our case, Chase et al. [8] reported that a 29-year-old male patient who developed rhabdomyolysis after accidental hypothermia was discharged with only heating techniques. In our case, however, the patient was provided active external heating with a forced-air warming system through the blanket, minimally invasive heating with intravenous fluid support heated to 40-42 °C and bladder lavage. Moreover, emergency hemodialysis was performed.

Conclusion

Hypothermia is a life-threatening condition. Early recognition and rapid treatment of this clinical condition are vital to prevent complications. Also, rhabdomyolysis and acute renal failure should be considered as potential complications in patients presenting with hypothermia.

References

1. Hanania NA, Zimmerman JL. Accidental hypothermia. Crit Care Clin. 1999 Apr;15(2):235-49. doi: 10.1016/s0749-0704(05)70052-x. PMID: 10331126.
2. van der Ploeg GJ, Goslings JC, Walpoth BH, Bierens JJ. Accidental hypothermia: rewarming treatments, complications and outcomes from one university medical centre. Resuscitation. 2010 Nov;81(11):1550-5. doi: 10.1016/j.resuscitation.2010.05.023. Epub 2010 Aug 11. PMID: 20702016.
3. Brown DJ, Brugger H, Boyd J, Paal P. Accidental hypothermia. N Engl J Med. 2012 Nov 15;367(20):1930-8. doi: 10.1056/NEJMra1114208. Erratum in: N Engl J Med. 2013 Jan 24;368(4):394. PMID: 23150960.
4. Danzl DF, Pozos RS. Accidental hypothermia. N Engl J Med. 1994 Dec 29;331(26):1756-60. doi: 10.1056/NEJM199412293312607. PMID: 7984198.
5. Biem J, Koehncke N, Classen D, Dosman J. Out of the cold: management of hypothermia and frostbite. CMAJ. 2003 Feb 4;168(3):305-11. PMID: 12566336; PMCID: PMC140473.
6. Baumgartner EA, Belson M, Rubin C, Patel M. Hypothermia and other cold-related morbidity emergency department visits: United States, 1995-2004. Wilderness Environ Med. 2008 Winter;19(4):233-7. doi: 10.1580/07-WEME-OR-104.1. PMID: 19099327.
7. Bonnor R, Siddiqui M, Ahuja TS. Rhabdomyolysis associated with near-drowning. The American Journal of the Medical Sciences. 1999 Sep;318(3):201-2. DOI: 10.1097/00000441-199909000-00018.
8. Chase CD, Smith RA. Hypothermia-induced Rhabdomyolysis: A Case Report. J Emerg Med. 2015 Dec;49(6):e177-8. doi: 10.1016/j.jemermed.2015.07.015. Epub 2015 Sep 26. PMID: 26416131.
9. Dearing N, Norgard NB. Rhabdomyolysis in a patient receiving high-dose simvastatin after the induction of therapeutic hypothermia. Ann Pharmacother. 2010 Dec;44(12):1994-7. doi: 10.1345/aph.1P352. Epub 2010 Nov 2. PMID: 21045169.
10. Hung CF, Huang TY, Lin PY. Hypothermia and rhabdomyolysis following olanzapine injection in an adolescent with schizophreniform disorder. Gen Hosp Psychiatry. 2009 Jul-Aug;31(4):376-8. doi: 10.1016/j.genhosppsych.2008.09.009. Epub 2008 Oct 18. PMID: 19555799.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1095-1097.
DOI: 10.28982/josam.747219

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Trial of hirudotherapy in labial necrosis: A case report

Labial nekrozda hirudoterapi denemesi: Olgu sunumu

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Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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Abstract
Treatment of a patient who developed post-operative labial necrosis was aimed with hirudotherapy. A Bartholin cyst was excised but because of the size of the cyst, labial asymmetry occurred, therefore, labial reconstruction was performed on the left labium majus. On post-operative Day 2, the labia became ischemic and necrosis began to develop. We applied hirudotherapy, but no difference was observed after the 5th day. Part of necrotic labium spontaneously split from the healthy tissue underneath. Leech therapy has been used for a long time; however, it was approved by FDA in 2004 and it is a very rarely used treatment method in gynecology. There are no guidelines on duration of leech application, and we wanted our case to set an example. In our case, we eventually had to excise the necrotic labium, which may be due to delay or the insufficient length of leech therapy.
Keywords: Hirudotherapy, Necrosis, Labiaplasty, Postoperative care, Leech therapy

Öz
Bartolin kist eksizyonu sonrası labial nekroz gelişen bir hastanın hirudoterapi ile tedavisi amaçlandı. Büyük kist boyutundan dolayı labial asimetri mevcuttu, bu nedenle sol labium majusta labial rekonstrüksiyon yapıldı. Ameliyat sonrası 2. günde iskemi ve nekroz gelişen hastaya hirudoterapi uygulandı, ancak 4. ve 5. günden sonra bir fark izlenmedi ve nekrotik labiumun bir kısmı alttaki sağlıklı dokudan kendiliğinden ayrıldı. Sülük tedavisi uzun süredir kullanılmaktadır, ancak 2004 yılında FDA tarafından onaylanmıştır ve jinekolojide çok nadir kullanılan bir tedavi yöntemidir. Sülük uygulamasının süresine ilişkin bir kılavuz yoktur, bu nedenle olgumuzun bir örnek oluşturması istenmiştir. Bizim vakamızda, nihayetinde nekrotik labiumu eksize etmek zorunda kalınmıştır, ancak bu sülük tedavisinin gecikmesine bağlı olabilir veya tedavi süresi yeterince uzun olmayabilir.
Anahtar kelimeler: Hirudoterapi, Nekroz, Labioplasti, Postoperatif bakım, Sülük terapisi

Introduction

Hirudotherapy, which is use of leeches as a complementary treatment, has been applied in medicine since the ancient times. Medical records show its use in Egyptian, Chinese, Anglo Saxon, Arabic and Greek medicine [1,2]. Although it has been abandoned with the rising of modern medical technology and practice, hirudotherapy gained attention again recently.

Hirudo medicinalis is a hermaphroditic aquatic blood-sucking worm measuring 3 to 5 cm and weighing 1 to 2 grams when fasting [3]. A leech can ingest from 5 to 20 mL of blood from 15 minutes to 2 hours, and spontaneously detach itself from the tissue. After detachment, the site where the leech has bitten continues to bleed. The leech's saliva harbors several substances, anticoagulants like hirudin, calin, inhibitors of kallikrein, hyaluronidase, histamine-like vasodilators, collagenase, and analgesic compounds [4,5]. It has also been shown that leeches secrete broad-spectrum antibacterial peptides [6].

Indications of hirudotherapy vary. It is used in varicose veins to draw blood from deeper tissues, in chronic skin diseases, transplanted or reimplanted tissues, thrombotic disorders, and in rheumatologic diseases to reduce pain and inflammation[6,7].

Though plastic surgeons and complementary medicine experts use medical leeches widely, it is not common in gynecology. We herein present a case of labial necrosis after Bartholin cyst excision, managed with hirudotherapy.

How to cite / Atıf için: Doğan O, Çoban U, Ayhan I, Kasapoğlu A, Çalışkan E. Trial of hirudotherapy in labial necrosis: A case report. J Surg Med. 2020;4(11):1095-1097.

Case presentation

A 36-year-old woman presented in the gynecology outpatient clinic with swelling of vulva. She had no personal or family history of any chronic disease. She had not been using any medication. Gynecologic examination revealed that the patient had a 7 cm wide Bartholin cyst on left labium majus. Right labia appeared normal. Speculum examination and transvaginal ultrasound was not performed because the patient was a virgin.

After informing patient about the condition, we decided to perform Bartholin cyst excision. Operation was uneventful, without hemorrhage. Due to the size of cyst, there was labial asymmetry, therefore, labial reconstruction was performed on the left labium majus.

In post-operative follow up, hemoglobin and hematocrit count did not decrease, and there was mild leukocytosis. On the second day, we realized a swelling and ecchymosis on left labia while changing the dressing. Close follow up continued, however the ecchymosis grew, and the tissue appeared necrotic (Figure 1). Usually, excision is the treatment of choice when it comes to necrosis. Considering the patient's age and virginity, and the possible labial loss of normal structure, we discussed the matter with our patient an decided mutually to try hirudotherapy. Risks and benefits of leech therapy were discussed with the patient and an informed consent was obtained.

First, medical leech was put on the affected labia until the leech detached on its own (Figure 2). After the first session, there was immediate improvement of the necrotic tissue, so a 5-day, twice daily therapy was planned (Figure 3). In the first 3 days, the swelling regressed. However, no physical change of appearance was observed on days 4 and 5. While we were contemplating whether to go on with hirudotherapy, a part of the necrotic labium spontaneously split from the tissue healthy underneath (Figure 4). After that, we decided to excise the affected tissue. Excision was performed on the 7th post-operative day. After routine follow up, the patient was discharged. Control examination was performed on the 10th day of discharge. There were no bleeding or signs of infection on the incision site. Hemoglobin levels were stable.

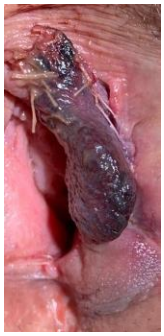

Figure 1: On the second post-operative day the ecchymosis grew and the tissue appeared necrotic

Figure 2: Medical leech was put on the affected labia until the leech detached on its own

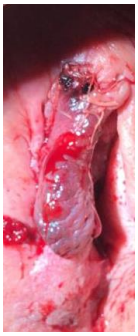

Figure 3: After the first session there was immediate improvement of the necrotic tissue

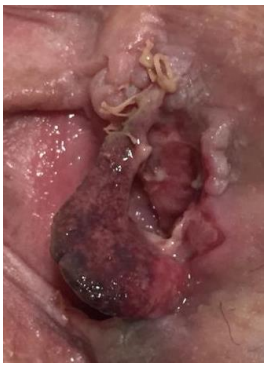

Figure 4: On the 7th post-operative day the necrotic labia detached from the healthy tissue underneath

Discussion

Leech therapy has been long used but it is approved by FDA in 2004. The mechanism of action is yet to be fully clarified. After a leech bite, hyaluronidase and collagenase access the tissues and vascular structures; vasodilatation occurs by the action of histamine-like molecules; platelet functions, kinin activity, and the coagulation cascade are inhibited; and inflammatory reactions are suppressed. Animal experiments also have shown that hirudotherapy is useful on wound/tissue repair [8-11].

Since it is a complementary technique, there is no guidelines or consensus on the duration of leech application and number of simultaneously used leeches. We let the leech detach itself in order to have the maximal amount of tissue to heal and to avoid infection. We used one leech at a time, twice daily.

The total duration of hirudotherapy is not understood or explained. We conducted the therapy for 5 days. The data in the literature varies in a range from one to 22 days [12]. In theory, average duration of hirudotherapy should correspond to neovascularization on the affected site. Leech therapy is highly used in plastic surgery for flap salvage and a systematic review of Herlin et al. stated that the average time of therapy is 6.3 days and generally does not exceed 7 days [3]. We stopped the treatment on the 5th day, due to lack of any macroscopic sign of improvement. It is our opinion that the treatment duration should not be standardized, because data usually depends on case reports, and every condition has unique needs.

Risk of bleeding should be kept in mind, ant the patient must be monitored with vital signs and a complete blood count [3]. There was no blood loss in our case, the hemoglobin and hematocrit counts were stable. The necessity for blood transfusion is related to the number of leeches applied, the duration of their application, patient conditions, and comorbidity. We did not need blood transfusion in our case.

As a natural treatment, leech therapy is not free of complications. Allergies to leeches and its secretions should be considered [13]. Infection is a serious complication which can vary from local infections to bacteremia. A leech should not be forcibly removed, because its jaws may remain in the wound, causing infection, submucosal abscesses, ecchymosis and scarring [14]. Prophylactic antibiotics may reduce the risk of leech-borne infections. We administered antibiotherapy to our patient, and no infectious complications occurred.

Conclusion

Hirudotherapy is a valuable traditional and natural complementary treatment for tissue healing. In our case, we eventually had to excise the necrotic labium, however this may be due to delay or short duration of leech therapy. Use of leeches as a treatment method in gynecology is exceedingly rare, and we wanted our case to set an example. With coming years, more gynecologists may think of leech therapy in similar cases and we may have larger series and more reliable data.

References

1. Whitaker IS, Rao J, Izadi D, Butler PE. Historical Article: Hirudo medicinalis: ancient origins of, and trends in the use of medicinal leeches throughout history. Br J Oral Maxillofac Surg. 2004;42(2):133-7.
2. Mory RN, Mindell D, Bloom DA. The leech and the physician: biology, etymology, and medical practice with Hirudinea medicinalis. World J Surg. 2000;24(7):878-83.
3. Herlin C, Bertheuil N, Bekara F, Boissiere F, Sinna R, Chaput B. Leech therapy in flap salvage: Systematic review and practical recommendations. Ann Chir Plast Esthet. 2017;62(2):1-13.
4. Ahmed T, Anwar M. Clinical importance of leech therapy. Indian Journal of Traditional knowledge. 2009;8(3):443-5.
5. Srivastava A, Sharma R. A brief review on applications of leech therapy. Arch Apll Sci Res. 2010;2(2):271-4.
6. Abdualkader AM, Ghawi AM, Alaama M, Awang M, Merzouk A. Characterization and optimization of lyophilization and storage conditions of Leech saliva extract from the tropical leech Hirudinaria manillensis. Pak J Pharm Sci. 2013;26(3):525-3.
7. Haycox CL, Odland PB, Coltrera MD, Raagi GJ. Indications and complications of medicinal leech therapy. J Am Acad Dermatol. 1995;33(6):1053-5.
8. Abdullah S, Dar LM, Rashid A, Tewari A. Hirudotherapy/leech therapy: applications and indications in surgery. Arch Clin Exp Surg. 2012;1:172–80.
9. Das BK. An overview on hirudotherapy/leech therapy. Ind Res J Pharm Sci. 2014;1:33–45.
10. Hildebrandt JP. Lemke S. Small bite, large impact–saliva and salivary molecules in the medicinal leech, Hirudo medicinalis. Naturwissenschaften. 2011;98:995–1008. [PubMed]
11. Singh A.P. Medicinal leech therapy (hirudotherapy): a brief overview. Complement Ther Clin Pract. 2010;16:213–5.
12. Whitaker IS, Oboumarzouk O, Rozen WM, et al. The efficacy of medicinal leeches in plastic and reconstructive surgery: a systematic review of 277 reported clinical cases. Microsurgery. 2012;32:240-50.
13. Karadag AS, Calka O, Akdeniz N, Cecen I. A case of irritant contact dermatitis with leech. Cutan Ocul Toxicol. 2011;30:234–5.
14. Kunal J, Aarti G, Ridhi N, Sunanda D. Hirudotherapy in Medicine and Dentistry J Clin Diagn Res. 2015 Dec;9(12):ZE05–7.

This paper has been checked for language accuracy by JOSAM editors.
The National Library of Medicine (NLM) citation style guide has been used in this paper.

J Surg Med. 2020;4(11):1098-1100.
DOI: 10.28982/josam.806119

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Sympathectomy with T2-T3 percutaneous radiofrequency thermocoagulation method in upper extremity primary hyperhidrosis cases

Üst ekstremite primer hiperhidrosis olgularında T2-T3 perkütan radiofrekans termokoagülasyon yöntemi ile sempatektomi

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Abstract

Sweating is controlled by the sympathetic nervous system and helps regulate the body's heat and electrolyte balance. Excessive sweating may be observed in about 1% of the population due to a number of reasons. Many methods are used in the treatment of hyperhidrosis, which is important for quality of life. In four patients with primary hyperhidrosis resistant to medical treatment, radiofrequency thermocoagulation of the stellate ganglion with an anterior approach and then the response of radiofrequency thermocoagulation to the T2-T3 sympathetic ganglion were evaluated. We think that it is an advantageous and successful method in terms of being less invasive and cost effective compared to other surgical methods, as the procedure time is short, patient satisfaction, hospitalization time is low. We have seen that stellate and T2-T3 sympathectomy with radiofrequency thermocoagulation method is a useful technique in the treatment of primary hyperhidrosis.

Keywords: Primer hyperhidrosis, Radiofrequency thermocoagulations, T2–T3 sympatectomy, Stellat ganglion radiofrequency

Öz

Terleme sempatik sinir sistemi tarafından kontrol edilir ve vücudun ısı ve elektrolit dengesini düzenlemeye yardımcı olur. Populasyonun %1 kadarında bir takım nedenlerden dolayı aşırı terleme gözlenebilir. Yaşam kalitesi açısından önemli olan hiperhidrozisin tedavisinde pek çok yöntem kullanılmaktadır. Medikal tedaviye dirençli primer hiperhidrozisli dört hastada, stellat ganglionun anterior yaklaşımla radiofrekans termokoagülasyonu daha sonra da T2-T3 sempatik gangliona radiofrekans termokoagülasyonunun yanıtı değerlendirildi. İşlem süresinin kısa olması, hasta memmuniyeti, hastanede kalış süresinin az olması ve iş güç kaybına neden olmaması diğer cerrahi yöntemlere göre hem daha az invaziv olması hem de maliyetinin daha az olması hastanın genel anestezi almaması açısından avantajlı ve başarılı bir yöntem olduğunu düşünüyoruz. Primer hyperhidrosisin tedavisinde radiofrekans termokoagülasyon yöntemi ile stellat ve T2-T3 sempatektominin kesinlikle faydalı bir teknik olduğunu gördük.

Anahtar kelimeler: Primer hiperhidrozis, Radiofrekans termokoagülasyon, T2-T3 sempatektomi, Stellat ganglion radiofrekans

Introduction

Sweating plays a role in maintaining the body's heat balance. It is controlled by the sympathetic nervous system. Excessive sweating can be observed in 1% of the population due to several reasons [1]. It may be generalized or localized (palmar, axillary, plantar, facial), and it is classified according to its etiology as well as where it is observed. The primary type of hyperhidrosis begins in adolescence or before and is uncommon. Rarely, cases of autosomal dominant hyperhidrosis have been reported. Secondary hyperhidrosis can be observed in endocrine diseases such as hyperthyroidism, malignancies, some serious psychiatric diseases, chronic infections, obesity, and menopause. It is common with Reynaud's Disease and Frey's Syndrome. Many methods are used in treatment of hyperhidrosis, including antiperspirants, iontophoresis method, medical treatment, and endoscopic sympathectomy clamping or electrocautery. In addition to these, treatments such as botulinum toxin injection, hypnosis, laser therapy, and radiotherapy are also being tried [2].

In this case report, we aimed to report the results of patients who received radiofrequency thermocoagulation to the stellate ganglion and T2 - T3 sympathetic ganglion.

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Hasta Onamı: Yazarlar çalışmada görüntüleri ile sunulan hastadan yazılı onam alındığını ifade etmiştir.

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 11/29/2020
Yayın Tarihi: 29.11.2020

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How to cite / Atıf için: Yılmaz A, Yılmaz Ö. Sympathectomy with T2-T3 percutaneous radiofrequency thermocoagulation method in upper extremity primary hyperhidrosis cases. J Surg Med. 2020;4(11):1098-1100.

Case presentation

An 18-year-old male patient was admitted to our clinic with complaints of sweating in hands (Case 1). It was learned that his hands and feet sweat excessively since childhood. In physical examination, his hands and feet were red and moist from the ankle, and other system examinations were normal. Reynaud's phenomenon was positive. Different treatments were applied to the patient who visited many clinics with the same complaints. Finally, he had been using pentoxifylline 400 mg three times a day for the last year. The same clinical signs were present in his family, as well. The whole family was admitted to the clinic for examination and treatment. Permission was obtained for the study by the adult patients themselves and the parents of those under the age of 18.

The father (Case 2) was 43 years old and had complaints from childhood. There was no known systemic disease. His hands and feet were also moist from the ankle and he was positive for Reynaud phenomenon. His 17-year-old sister (Case 3) and 14-year-old brother (Case 4) had similar examination results.

First, bilateral stellate ganglion block with triamcinolone and bupivacaine (0.125%) was performed in all cases in different sessions. In all cases, 3-5 °C temperature increase occurred in the same extremity within 30 minutes. Transient Horner syndrome lasting approximately four hours was observed in all cases. In all cases, sweating on hands decreased significantly from the previous 4 hours on average.

Since sweating did not respond to the stellate ganglion block adequately, the second step was thermocoagulation of the stellate ganglion with radiofrequency. First, sensory, and then motor responses were checked in each patient using 18-gauge, 5 cm radiofrequency needles in different sessions, and thermal lesions were created at 80 °C for 1 minute. No complications were encountered in any of the cases during the procedure. In patients with thermal probe implantation, an increase of 5-10 °C developed in the extremities of the treated side within 30 minutes and sweating decreased in the same day. However, this decrease was not permanent.

As a third step, we decided to perform bilateral paravertebral sympathetic ganglion block at T2 and T3 levels for all patients. The patients were monitored, and sedation was achieved by intravenous administration of 2 mg midazolam and 50 microgram fentanyl. In each patient in prone positions, at the threshold of fluoroscopy, using an 18-gauge, 10 cm radiofrequency needle, firstly sensory, and then motor responses were controlled, and thermal lesions were created at 80 °C for 1-3 minutes in separate sessions. 5-10 °C increase in temperature was observed by thermal probes on the treated side in patients.

In all cases, sweating and redness on their hands recurred in third month of follow-up after the procedure, although they were less than before. Sweating did not increase in the following months. The cases are still followed up in our clinic.

Discussion

Although many treatment methods are used to prevent excessive sweating, success rates are not sufficient. Hyperhidrosis is diagnosed by anamnesis and physical examination [1]. Iodized starch spray is sprayed on the sweating area. If there is a change to black, excessive sweating is diagnosed [3].

Regarding the treatment methods, antiperspirant (20-25% alcl hexahydrate and 70-90% alcohol) preparation is applied to dry skin at night and washed off in the morning. The use of the treatment is limited and requires concentrated solutions (such as 30%), which may cause severe skin irritation. For this reason, it is not recommended for application to the face and sensitive skin. It is not an effective treatment for patients with sweating in these areas.

In the iontophoresis method, the patient's hands are submerged in water with 15-18 mA electric current several times a week. The area of use is limited to hands and feet. It is based on the principle of providing low current electricity in water to the skin surface. This process is applied every day for first week or every day for next month until sweating stops. The water used in the process does not contain electrolytes. Iontophoresis is a time-consuming treatment method with rapid recurrence. It is not recommended for pregnant women, individuals with pacemakers, or epilepsy, and may cause skin irritation.

Sedative and anticholinergic drugs are frequently used as medical treatment. It is used in cases of severe hyperhidrosis and side effects such as dry mouth, and constipation can be tolerated by healthy patients. However, it is recommended that patients be consulted to dermatology and other departments before starting this treatment.

Considering the studies related to botulinum toxin type A injection, the average time without sweating is about 5-6 months. The toxin is applied by making many injections to the area with excessive sweating. Although it is a painful and costly procedure with many side effects, it has recently maintained its popularity. Even hypnosis was applied to patient so that the patient did not feel pain while performing this procedure [4,5].

Considering the surgical methods, thoracic sympathectomy can be performed as an outpatient surgery under general anesthesia. T2, T3 sympathectomy can be performed, and the incision scar is distinctive compared to other surgical methods. Complications may include compensatory hyperhidrosis, Horner's syndrome, pneumothorax, hemothorax, and phrenic nerve damage. Video - assisted thoracoscopic sympathectomy has less mortality and morbidity [6]. The scar is smaller, and the side effects are less.

There are studies investigating the difference between resection and ablation, and it is stated that although resection is more successful, many surgeons prefer ablation for reasons such as easy, short operation time, and the ability to be used in recurrent cases [7].

In addition to the sympathectomy method, there are different opinions and studies about location. Although there are studies supporting the success of T2 sympathectomy alone, there are studies showing that T2-T3 sympathectomy is more successful than T2 alone [8,9]. In these cases, it is thought that the success rate can be increased to 99.9% by reprocessing the relapse cases. On the other hand, there are information and studies suggesting that it is effective in the branches originating from T4 in hyperhidrosis and that T4 ganglion blockage is more

successful instead of T3 [10,11]. There are those who use T4 clamping or cutting only [12,13].

Conclusions

The total procedure time in our cases was approximately 15 minutes. Although sweating decreased, it partially returned. The patients stated that they were satisfied with the procedure. We think that it is an advantageous and successful method in terms of being less invasive and cost effective compared to other surgical methods, as the procedure time is short, and patient satisfaction, and hospitalization time are low. We have seen that stellate and T2-T3 sympathectomy with radiofrequency thermocoagulation method is a useful technique in the treatment of primary hyperhidrosis.

References

1. Leung AK, Chan PY, Choi MC, Hydrosis. Int J Dermatol. 1999 Aug;38(8):561-7. doi: 10.1046/j.1365-4362.1999.00609.x.
2. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, et al. Multi-Specialty Working Group on the Recognition, Diagnosis, and Treatment of Primary Focal Hyperhidrosis J Am Acad Dermatol. 2004 Aug;51(2):274-86. doi: 10.1016/j.jaad.2003.12.029.
3. Derma Goldsmith LA. Disorders of Ecrine Sweat Gland. In : Freedberg IM, Eisen AZ, Wolf K, Ausen KF, Goldsmith LA, Katz SI, et al, Editors Fitzpatrik's Dermatology İn General Medicine.5th Ed New York, NY:Mcgraw-Hill;1999.P.800-5
4. Vadoud-Seyedi J. Treatment Of Plantar Hyperhidrosis With Botulinum Toxin Type A. int J Dermatol. 2004 Dec;43(12):969-71. doi: 10.1111/j.1365-4632.2004.02304.x.
5. Lauchli S, Burg G. Treatment Of Hyperhidrosis With Botulinum Toxin A. Skin Therapy Lett. 2003. 8: 1-4
6. Loscertales J, Arroyo Tristán A, Congregado Loscertales M, Jiménez Merchán R, Girón Arjona JC, Arenas Linares C, et al. Thoracoscopic sympathectomy for palmar hyperhidrosis. Immediate results and postoperative quality of life [Article in Spanish] Arch Bronconeumol. 2004 Feb;40(2):67-71. doi: 10.1016/s1579-2129(06)60197-3.
7. Hashmonai M, Assalia A, Kopelman D. Thoracoscopic Sympathectomy For Palmar Hyperhidrosis. Ablate Or Resect? Surg Endosc. 2001;15:435-41.
8. Chiou TS, Chen SC. Intermediate-Term Results Of Endoscopic Transaxillary T2 Sympathectomy For Primary Palmar Hyperhidrosis. Br J Surg. 1999 Jan;86(1):45-7. doi: 10.1046/j.1365-2168.1999.00992.x.
9. Hehir DJ, Brady MP: Long-Term Results Of Limited Thoracic Sympathectomy for Palmar Hyperhidrosis J Pediatr Surg. 1993 Jul;28(7):909-11. doi: 10.1016/0022-3468(93)90694-g.
10. Chang YT, Li HP, Lee JY, Lin PJ, Lin CC, Kao EL, et al. Treatment of palmar hyperhidrosis: T(4) level compared with T(3) and T(2). Ann Surg. 2007 Aug;246(2):330-6. doi: 10.1097/SLA.0b013e3180caa466.
11. Yang J, Tan JJ, Ye GL, Gu WQ, Wang J, Liu YG. T3/T4 Thoracic Sympathictomy And Compensatory Sweating İn Treatment Of Palmar Hyperhidrosis Chinese Registry Of Palmar Hyperhidrosis İnvestigators Chin Med J. 2007;120(18):1574-7. doi: 10.1097/00029330-200709020-00003
12. Lin CC, Wu HH. Endoscopic T4-Sympathetic Block By Clamping (ESB4) İn Treatment Of Hyperhidrosis Palmaris Et Axillaries-Experiences Of 165 Cases. Ann Chir Gynaecol. 2001;90:167-9.
13. Choi BC, Lee YC, Sim SB. Treatment Of Palmar Hyperhidrosis By Endoscopic Clipping Of The Upper Part Of The T4 Sympathetic Ganglion. Preliminary Results. Clin Auton Res. 2003 Dec;13 Suppl 1:I48-51. doi: 10.1007/s10286-003-1112-4.

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