e-ISSN:2602-2079

Volume 3
Issue 12
2019

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

Volume: 3 - Issue: 12

Contents

Review

Case report

/ Pages : 894-897 PDF (/en/download/article-file/907394)
Erhan Okuyan, Zeynep Bayramoğlu, Fethi Karakaya

Complete scintigraphic resolution of a bone metastasis after androgen-deprivation therapy (http://jsurgmed.com/en/issue/50441/598062) / Pages : 898-899 PDF (/en/download/article-file/907391)
Derya Çayır, Mehmet Bozkurt, Salih Sinan Gültekin, Aynur Turan

Bilateral hydronephrosis subsequent to a giant lymphocele after robotic radical prostatectomy (http://jsurgmed.com/en/issue/50441/601013) / Pages : 900-902 PDF (/en/download/article-file/908872)
Erdem Koç, Bahri Gök, Davut Kamacı, Erem Asil, Ali Fuat Atmaca

An unusual catheter malposition following totally implantable venous access port insertion: The catheter tip located into the right axillary vein (http://jsurgmed.com/en/issue/50441/594025) / Pages : 903-905
Ahmet Yüksel, Yusuf Velioğlu, Mustafa Enes Demirel, Erhan Renan Uçaroğlu PDF (/en/download/article-file/914006)

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

J Surg Med. 2019;3(12):820-824.
DOI: 10.28982/josam.588248

Research article
Araştırma makalesi

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

Echocardiographic evaluation of right heart functions in hemodialysis patients

Hemodiyaliz hastalarında sağ kalp fonksiyonlarının ekokardiyografik olarak değerlendirilmesi

İsa Ardahanlı [1], Okan Akyüz [2]

[1] Department of Cardiology, Bilecik State Hospital, Bilecik, Turkey
[2] Department of Nephrology, Bilecik State Hospital, Bilecik, Turkey

ORCID ID of the author(s)
İA: 0000-0002-9309-803X
OA: 0000-0003-2460-9577

Corresponding author / Sorumlu yazar:
İsa Ardahanlı
Address / Adres: Bilecik Devlet Hastanesi, Kardiyoloji Kliniği, Bilecik, Türkiye
e-Mail: isaardahanli@gmail.com

Ethics Committee Approval: This study was approved by Bilecik Health Directorate local ethical committee.
Etik Kurul Onayı: Bu çalışma Bilecik Sağlık Müdürlüğü yerel etik kurulu tarafından onaylandı.

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: 12/02/2019
Yayın Tarihi: 02.12.2019

Abstract

Aim: Volume load assessment is an important problem in patients with chronic renal failure (CRF). Apart from classical volume assessment methods, the number of studies on echocardiographic evaluation of right heart functions is limited. In this study, we aimed to evaluate right heart functions echocardiographically in end-stage renal failure patients receiving hemodialysis (HD) therapy and its utility in volume load determination.

Methods: This case-control study included 49 patients receiving HD treatment as the study group. The control group consisted of 46 healthy individuals whose age and gender were matched. Echocardiographic evaluation was performed for all participants. Tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (SPAB), tricuspid E wave velocity, A wave velocity, E / A ratio, right ventricular ejection fraction (RVEF) and left ventricular ejection fraction (LVEF) were measured.

Results: Right ventricular diastolic diameter (2.55 (0.3) vs 2.30 (0.29) respectively, $P<0.001$) SPAP (37.4 (8.3) vs 19 (6.8), $P<0.001$, respectively) were statistically significant higher in the study group, while TAPSE (1.61 (0.35) vs 2.09 (0.27), $P<0.001$, respectively), A rate, (0.63 (0.27) vs 0.45 (0.26), $P<0.001$, respectively), E / A ratio (0.93 (0.25) vs 1.37 (0.24), $P<0.001$, respectively) were significantly lower. Right ventricular (RV) E velocity was insignificantly lower in the study group ($P=0.523$). There were no statistically significant differences between the groups in terms of age, gender, and body mass index.

Conclusion: In our study, we found that TAPSE was low and SBAP and RV diastolic diameter were high in HD patients. We think that TAPSE and SPAB can be used together with conventional methods for evaluating hypervolemia in HD patients. Further studies are required to explore this clinical tool.

Keywords: Tricuspid annular plane systolic excursion, Systolic pulmonary artery pressure Hemodialysis, Right heart functions

Öz

Amaç: Volüm yükü değerlendirmesi kronik böbrek yetmezliği (KBY) hastalarında önemli bir sorundur. Klasik volüm değerlendirmesi yöntemleri dışında, sağ kalp fonksiyonlarının ekokardiyografik değerlendirmesi ile ilgili yapılmış çalışma sayısı kısıtlıdır. Bu çalışmada hemodiyaliz (HD) tedavisi alan son dönem böbrek yetmezliği hastalarında sağ kalp fonksiyonlarını ekokardiyografik olarak değerlendirmeyi ve volüm yükü tayininde kullanılabilirliğini amaçladık.

Yöntemler: Bu vaka kontrol çalışmasına, çalışma grubu olarak HD tedavisi alan 49 hasta alındı. Kontrol grubu olarak yaş, cinsiyet uyumu sağlanmış 46 sağlıklı birey alındı. Tüm katılımcıların ekokardiyografik olarak değerlendirmesi yapıldı. Triküspit anüler düzlem sistolik hareketi (TAPSE), sistolik pulmoner arter basıncı (SPAB), triküspit E dalga hızı, A dalga hızı, E/A oranı, sağ ventrikül ejeksiyon fraksiyonu (RVEF) ve sol ventrikül ejeksiyon fraksiyonu (LVEF) ölçüldü.

Bulgular: Sağ ventrikül diyastolik çapı (sırasıyla 2.55 (0.3) ve 2.30 (0.29), $P<0.001$) ve SPAP (37.4 (8.3) ve 19 (6.8), $P<0.001$), çalışma grubunda istatistiksel olarak anlamlı derecede yüksek bulundu. Çalışma grubunda TAPSE (sırasıyla 1.61 (0.35) ve 2.09 (0.27), $P<0.001$), A oranı, (sırasıyla 0.63 (0.27) ve 0.45 (0.26), $P<0.001$), E / A oranı (sırasıyla 0.93 (0.25) ve 1.37 (0.24), $P<0.001$). Çalışma grubunda sağ ventrikül E hızı daha düşüktü ancak istatistiksel olarak anlamlı değildi ($P=0.523$). Gruplar arasında yaş, cinsiyet ve vücut kitle indeksi açısından istatistiksel olarak anlamlı fark yoktu.

Sonuç: Çalışmamızda, HD hastalarında TAPSE'nin düşük, SBAP'nin ve sağ ventrikül diyastolik çapının ise yüksek olduğunu tespit ettik. HD hastalarında TAPSE ve SPAB'nin, hipervolemiyi değerlendirmede geleneksel yöntemlerle birlikte kullanılabileceğini düşünüyoruz. Bu klinik aracı keşfetmek için daha ileri çalışmalar gereklidir.

Anahtar kelimeler: Triküspit anüler düzlem sistolik hareketi, Sistolik pulmoner arter basıncı, Hemodiyaliz, Sağ kalp fonksiyonları

How to cite / Atıf için: Ardahanlı İ, Akyüz O. Echocardiographic evaluation of right heart functions in hemodialysis patients. J Surg Med. 2019;3(12):820-824.

Introduction

Cardiovascular diseases (CVD) are still the most common cause of mortality and morbidity in chronic renal failure (CRF) patients [1-4]. Structural and functional abnormalities of the heart are common in patients with end-stage renal disease. The cause of this condition is pressure increase and excessive volume load [5-6]. In patients undergoing hemodialysis, the dry weight, considered to be the ideal weight, is described as the lowest weight that the patient can tolerate, not causing the development of hypotension and hypertension [7]. The first and most important step in the treatment of hypertension (HT) in patients with end-stage renal failure (ESRD) is the provision of hemodialysis (HD) proficiency and access to the patient's actual dry weight. In most hemodialysis patients, hypertension is caused by increased volume, which can be controlled by ultrafiltration. By reducing volume load, hypertension remains refractory in only 5-10% of patients [8]. Cardiovascular events were minimized and cardiovascular mortality and morbidity decreased when the fluid volume control was performed compared to ESRD patients using antihypertensive drugs. In the Tassin series, 20-year survival was 43% in patients who did not use antihypertensive drugs and who were normotensive with strict volume control only. Nevertheless, 5-year survival rate was 40-50% in patients receiving antihypertensive drugs [9]. Adequate and careful evaluation of cardiac functions of patients in this group is very important. The mortality rate in dialysis patients with hypervolemia is four to five times higher than those with normal blood volume [10]. Therefore, the right ventricular functions have recently gained importance in the determination of volume load in HD patients. Since the right ventricle (RV) dysfunction has been shown to be associated with mortality and morbidity in various pathologies, RV is now an important part of the heart that cannot be neglected. Evaluation of the RV has gained importance in recent years, especially after understanding its role in many diseases such as heart failure, pulmonary hypertension and congenital anomalies [11-17]. Many previous studies have shown impaired ventricular function in HD patients. In these studies, the focus is on the left ventricle (LV) functions. There are fewer studies on right heart functions. Several studies have shown impaired right ventricular systolic and diastolic function in HD patients. Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure ≥25 mmHg [18]. Indeterminate or multifactorial mechanisms such as hormonal and metabolic disorders associated with chronic kidney disease (CKD) may cause pulmonary artery vasoconstriction and increased pulmonary vascular resistance in these patients [19]. Right heart catheterization (RHC) is still the gold standard for hemodynamic evaluation of right heart chambers [20-21]. However, as it is an interventional, time-consuming, costly and relatively difficult procedure to be repeated, it is not frequently used in patient follow-up. Therefore, transthoracic echocardiography with good correlation with RHC is recommended for PH screening using derived mean pulmonary artery pressure (mPAP) [22-24]. Similarly, tricuspid annular plane systolic excursion (TAPSE) on M-mod echocardiography provides a simple but specific method for systolic functional evaluation of the RV. And it correlates perfectly with the RV ejection fraction as assessed by radionuclide ventriculography [25]. The aim of this study was to compare the echocardiographically evaluated TAPSE and systolic pulmonary artery pressure (SPAB), an important indicator of RV functions, in HD patients and matched healthy controls.

Materials and methods

Study protocol

Patients between the ages of 18-85 years with sinus rhythm who received systemic HD treatment 3 times a week for at least 6 months were included in this single-center, case-control study. It was conducted on 49 patients followed in the hemodialysis unit of Bilecik State Hospital. 46 healthy individuals who were adjusted for age and gender made up the control group. Participants were informed about the study protocol and gave written informed consent. The local ethics committee approved this study.

The following were exclusion criteria: Patients with known coronary artery disease, Significant valvular disease, LV systolic dysfunction defined as an LVEF <50%, Pericardial disease, Congenital heart disease, Atrial fibrillation, Thyroid dysfunction, Patients with an active infection, Patients with chronic pulmonary disease, Moderate or severe anemia (Hg value <9 gr)

General evaluation and assessments

All participants underwent a detailed clinical, laboratory, and radiological evaluation. Blood pressure, heart rate, demographics, clinical history, laboratory parameters and drug use status were recorded. Blood samples were taken from the antecubital vein in the morning after overnight fasting. Routine serum biochemical variables were analyzed including glucose, serum creatinine, sodium, potassium, calcium, phosphorus, albumin, total protein, liver transaminases, complete blood count, C-reactive protein (CRP), parathyroid hormone (PTH) and lipid profile levels. A 12-lead electrocardiogram (ECG) was obtained from all participants.

Echocardiographic examinations were performed at the Department of Cardiology Echocardiography Laboratory using the EPIQ 7 echocardiography device (Philips, Amsterdam, The Netherlands). The analysis was performed according to the guidelines of the American Society of Echocardiography recommendations. Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septum thickness (IVS), posterior wall thickness (PW), left atrium (LA), Aortic diameter were measured using M-mode in parasternal long-axis imaging [26]. LVEF was measured by Teichoz method [27]. Mitral inflow velocities were evaluated from apical 4-chambered view to evaluate LV's diastolic functions. Right ventricular values were measured from the parasternal long axis and apical 4 chambers. TAPSE, SPAB, tricuspid E wave velocity, A wave velocity, E / A ratio were measured. TAPSE was measured from apical 4-chamber view by placing an M-mode cursor through the lateral tricuspid annulus and measuring the length of longitudinal motion of the annulus at peak systole [28]. SPAB was calculated as 4 x (tricuspid systolic jet) ² + right atrial pressure. Tricuspid regurgitation was measured using continuous-wave Doppler in

apical 4-chamber, parasternal short axis and parasternal long-axis views. The early (E) and late (A) RV inflow velocities were measured by pulsed-wave Doppler by the sample volume between the tricuspid valve in the apical 4-chamber view.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (Statistical Package for Social Sciences Inc., Chicago, Illinois, USA) for Windows. Categorical variables were expressed as percentages. Numerical variables were presented as the arithmetic mean standard deviation. The differences between various groups were analyzed using Student's t-test for the parameters with normal distribution and the Mann–Whitney U test for those without normal distribution. The presence of a linear relationship between the normally distributed parameters was checked using Pearson's correlation test, while Spearman's correlation test was used for nonnormally distributed parameters. *P*-value <0.05 was considered statistically significant.

Results

Forty-nine HD patients and 46 healthy participants were included in the study. The mean weight was 65 (16.3) and mean body mass index (BMI) was 29 (3.4) kg / m^2. The mean systolic blood pressure of all participants was 130 (12) mmHg and the mean diastolic blood pressure was 79 (11) mmHg. Age group was similar, female participants were statistically higher in both the patient group and the control group (P<0.001). BMI was lower in the HD group, but this was not statistically significant. The number of patients with diabetes mellitus and HT history was significantly greater in the HD group (P<0.001 and P<0.001, respectively). Heart rate was higher in the HD group but not statistically significant (P=0.571). The mean HD duration was 56.3 (51.2) months. Demographic and clinical data are shown in Table 1.

As expected in laboratory tests, creatine, urea, phosphorus, potassium, PTH and ferritin values were significantly higher in the HD group. However, albumin, calcium, protein, hemoglobulin and platelet were found to be significantly lower. Although white blood cell (WBC) value was higher in the HD group, it was not statistically significant (Table 2).

LVEF and LVESD were similar in both groups. LVEDD, IVS, PW, LA measured by parasternal long axis were significantly higher in the HD group. RV end-diastolic diameter and SPAP values were significantly higher in the HD group after evaluation of right heart function (P<0.001 and P<0.001, respectively), and TAPSE, measured by M-mode technique, was significantly lower. The RV E velocity was insignificantly lower in HD group (P=0.523). The A velocity, and E/A ratio were significantly lower in the HD group (Table 3).

Table 1: Baseline characteristics of the participants

	Study group (n=49)	Control group (n=46)	*P*-value
Age	64.4 (12.0)	63.7 (8.9)	0.672
Male/ female, n (%)	32/17 (34.7/65.3)	31/15 (67.4/32.6)	<0.001
Hypertension, n (%)	17 (34.6)		
Diabetes mellitus, n (%)	22 (44.8)		
Weight (kg)	65 (17.3)	66 (15)	0.264
Body mass index, kg/ m^2	28.7 (3.5)	29.2 (3.3)	0.480
Pulse rate, beats/m, mean (SD)	80.1(14.7)	77.5(9.2)	0.571
Duration of dialysis, months	56.3 (51.2)		

SD: Standard deviation

Table 2: Laboratory values

	Study group	Control group	*P*-value
Hemoglobin (g/dl)	11.45 (1.26)	13.89 (1.57)	<0.001
Platelet (/mm3)	174.82 (61.50)	289.04 (91.44)	<0.001
WBC	7.84 (2.58)	7.16 (2.47)	0.131
Albumin (g/dl)	3.32 (0.35)	4.43 (0.45)	<0.001
Ferritin(ng/ml)	423 (298.32)	36.65 (59.82)	<0.001
Protein (g/dl)	6.53 (0.77)	7.35 (0.54)	<0.001
Calcium and phosphorus	43.92 (11.59)	33.62 (4.17)	<0.001
Glucose (mg/dl)	127.43 (47.11)	110.22 (8.50)	0.375
Creatinine (mg/dl)	6.56 (2.30)	0.97 (1.12)	<0.001
Urea	123.51 (30.39)	34.99 (41.78)	<0.001
ALT (IU/I)	15.59 (10.48)	22.11 (13.37)	0.004
AST (IU/I)	18 (13)	22 (16)	0.085
TSH	1.58 (0.89)	1.68 (0.87)	0.581
PTH	578.21 (453.45)	36.26 (5.72)	<0.001
CRP	12.15 (16.76)	7.78 (14.72)	0.010
LDL	85.48 (33.95)	125,48 (27.55	<0.001
HDL	38.30 (10.05)	45.49 (9.14	<0.001
TRG	167.85 (102.84)	161.57 (63.86	0.550
Total cholesterol (mg/dl)	157.09 (43.84)	206.45 (36.29	<0.001

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, HDL: high-density lipoprotein, LDL: low-density lipoprotein, PTH: parathyroid hormone, TRG: triglyceride, TSH: thyroid-stimulating hormone, WBC: white blood cell

Table 3: Echocardiographic findings

	Study group	Control group	*P*-value
Left ventricular EF (%)	61.07 (3.46)	62.54 (4.02)	0.324
LV end-diastolic diameter (cm)	4.91 (0.46)	4.63 (0.34)	<0.001
LV end systolic diameter (cm)	3.41 (0.47)	3.13 (0.47)	0.013
Interventricular septum (cm)	1.41 (0.38)	0.97 (0.19)	<0.001
Posterior wall (cm)	1.32 (0.29)	0.93 (0.16)	<0.001
LA diameter (cm)	3.80 (0.31)	3.41 (0.31)	<0.001
PA systolic pressure (mmHg)	37.4 (8.3)	19 (6.8)	<0.001
RV end-diastolic diameter (mm)	2.55 (0.39)	2.30 (0.29)	<0.001
TAPSE	1.61 (0.35)	2.09 (0.27)	<0.001
RV, E (m/s)	0.59 (0.21)	0.62 (0.22)	0.523
RV, A (m/s)	0.63 (0.27)	0.45 (0.26)	<0.001
RV, E/A	0.93 (0.25)	1.37 (0.24)	<0.001

EF: Ejection Fraction, LA: Left atrium, LV: Left ventricle, PA: Pulmonary artery, RV: Right ventricle, TAPSE: Tricuspid annular plane systolic excursion

Discussion

In our study, TAPSE used in the evaluation of right ventricle functions in patients receiving HD therapy was observed to be low and SPAB, high compared to healthy individuals. In case of hypervolemia, the excess blood distributes to the area with the highest compliance. Various parts of the cardiovascular system have different compliances. Compliance of the heart is quite high, but veins have the highest compliance. Therefore, in the presence of hypervolemia, the volumes of these sections increase. When the volume of the venous system and atrium increases, the cardiac output should increase according to the Starling forces. This phenomenon results in people with a normally functioning kidney to discard excess fluid. However, hemodialysis patients cannot successfully complete this process. Although various methods have been proposed for the determination of dry weight in these patients, the applicability and reliability of many of these are limited in clinical practice. We suggest that TAPSE and SPAP may be used in combination with the recommended methods for determining volume load in patients receiving chronic HD treatment. Heart and vascular diseases are the most important cause of mortality and morbidity in CRD patients [29]. Patients receiving dialysis treatment have a higher risk of CVD compared to the community of similar age and sexuality. High risk of cardiovascular death in individuals with ESRD is associated with many factors, which include toxic, metabolic, vascular factors, hypervolemia, hypertension and anemia. Several studies have shown that LV hypertrophy, LV dilatation, decreased EF and diastolic dysfunction may develop as a result of these factors. However, data on the prevalence of RV dysfunction in patients undergoing chronic dialysis are still lacking. Previous cardiac studies in CRF patients have often investigated LV systolic and diastolic functions. There are fewer

studies on RV functions. Diabetic nephropathy is the most common cause of CRF worldwide. Similarly, diabetic nephropathy was the most common etiologic factor in our study. Transthoracic echocardiography is a non-invasive method often used in the evaluation of right ventricular functions because it is easily achievable and inexpensive. However, the complexity of the geometric structure, the anatomical position, the roughness of the endocardial surface and the complex contraction mechanism of the right heart may complicate its evaluation by echocardiography. In order to minimize these difficulties, many echocardiographic methods are utilized together, and many studies are being conducted to develop new methods.

The basis of our study was to investigate the effect of volume burden on heart function by echocardiographic examination in HD patients. The patients included in the study did not have systolic heart dysfunction. In a study by López-Candales et al. [30], TAPSE, which represents the longitudinal functions of the right ventricle, was shown to decrease as a result of both right ventricular and left ventricular dysfunction, which was more pronounced in patients with right ventricular dysfunction. In our study, TAPSE was found to be significantly lower in patients receiving HD treatment. We thought that this could be due to the deterioration of right ventricular functions due to increased volume load. In the study of Kucukdurmaz et al. [31], it was reported that TAPSE decreased significantly in healthy individuals who donated 450 ml blood. In our study, TAPSE was low in HD patients with increased volume load. This was attributed to the hypervolemic status of the patients in our study and the normovolemic status of the subjects in the study of Kucukdurmaz [31]. Lopez-Candales et al. [32] showed that patients with advanced tricuspid regurgitation have a mechanical delay in RV, leading to low TAPSE values. Similarly, in our patient group, the RV diameter was wider than the control group and the rate of tricuspid regurgitation was higher. Akyüz et al. investigated the effects of decreased preload on RV systolic function in HD patients using echocardiographic parameters. They showed that RV Sa velocity was independent of preload, whereas TAPSE value was dependent [33]. Similarly, in our study, TAPSE was found to be lower in patients with HD and volume load compared to the control group. Unlike our study, RV functions were evaluated before and after HD, and TAPSE increased due to decreased volume load after HD. In our study, the control group consisted of healthy individuals. Karavelioglu et al. [34] reported that RV systolic and diastolic functions were impaired in HD patients without hypertension or diabetes mellitus. We obtained similar findings.

PH is common in patients with CRF because several studies based on the echocardiographic evaluation of SPAP have reported a prevalence of 30-60% [35]. Di Lullo et al. [36] reported that about 20% of a cohort of adult hemodialysis patients had impairment of right ventricular function, and low TAPSE values (<15 mm). Also, Momtaz et al. [37] confirmed the high incidence of pulmonary hypertension and subclinical RV dysfunction in HD patients. This was consistent with our study. Tassin series, which was carried out in prolonged HD, correctly determined the dry weight and removed the interdialytic fluid and salt sufficiently in each session, and the patients were found to live about 10 years longer than the patients who underwent standard HD for 12 hours per week. This series demonstrated the importance of accurate volume determination [38,39].

Limitations

One of the limitations of the study was the relatively small number of patients and the fact that it was single-centered. Another important limitation was that right heart catheterization was an invasive procedure for the functional evaluation of RV and RA and not performed due to lack of indication.

Conclusion

In this study, we demonstrated that TAPSE, which is an important indicator of right ventricular function, decreases with volume increase. It is also a less costly, non-invasive method that can be repeated and measured by echocardiography. We believe that it can be used together with other methods in calculating dry weight in ESRD patients receiving HD treatment.

References

1. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995 Jan;47(1):186-92.
2. US Renal Data System 1999 Annual Data Report. Am J Kidney Dis 1999; 34 (2 Suppl1): S1-176.
3. Valderrabano F, Berthoux FC, Jones EHP, Mehls O. Report on management of renal failure in Europe, XXV, 1994. End-stage renal disease and dialysis report. Nephrol Dial Transplant. 1996; 11(Suppl.1):2-21.
4. Meyer KB, Levey AS. Controlling the epidemic of cardiovascular disease in chronic renal disease: a report from the National Kidney Foundation Task Force on cardiovascular disease. J Am Soc Nephrol. 1998;9:S31-42.
5. Paoletti E, Bellino D, Cassottana P, Rolla D, Cannella G. Left ventricular hypertrophy in nondiabetic predialysis CKD. Am J Kidney Dis. 2005;46:320–7.
6. Stewart GA, Gansevoort RT, Mark PB, Rooney E, McDonagh TA, Dargie HJ, et al. Electrocardiographic abnormalities and uremic cardiomyopathy. Kidney Int. 2005;67:217–26.
7. Henderson LW. Symptomatic hypotension during hemodialysis. Kidney Int. 1980 May;17(5):571-6.
8. Blumberg A, Nelp WD, Hegstrom RM, Scribner BH. Extracellular volume in patients with chronic renal disease treated for hypertension by sodium restriction. Lancet. 1967;2:6973.
9. Charra B, Calemard E, Ruffet M. Survival as an index of adequacy of dialysis. Kidney Int. 1992;41:1286-91.
10. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis. 1998;32(5 Suppl 3):112-9.
11. Franco V. Right ventricular remodelling in pulmonary hypertension. Heart Failure Clicic. 2012;8:403-12.
12. Eidem BW, O'Leary PW, Tei C, et al. Usefulness of the myocardial performance index for assessing right ventricular function in congenital heart disease. Am J Cardiology. 2000;86:654-8.
13. Greil GF, Beerbaum P, Razavi R, et al. Imaging the right ventricle. Heart. 2008;94:803-8.
14. Kjaergaard J, Schaadt BK, Lund JO, et al. Quantification of right ventricular function in acute pulmonary embolism: relation to extent of pulmonary perfusion defects. European J Echocardiography. 2008;9:641–5.
15. Maffessanti F, Gripari P, Tamborini G, et al. Evaluation of right ventricular systolic function after mitral valve repair: a two-dimensional Doppler, speckle-tracking, and three-dimensional echocardiographic study. J Am Society Echocardiography. 2012;25:701–8.
16. Oguzhan A, Abaci A, Eryol NK, et al. Colour tissue Doppler echocardiographic evaluation of right ventricular function in patients with right ventricular infarction. Cardiology. 2003;100:41–6.
17. Pleister A, Kahwash R, Haas G, et al. Echocardiography and heart failure: a glimpse of the right heart. Echocardiography. 2014;32:95–107.
18. Simonneau G, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiology. 2013;62:34‑41.
19. Rubin LJ. Pathology and pathophysiology of primary pulmonary hypertension. Am J Cardiology. 1995;75:51A‑54A.
20. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiology. 2013;62:D42‑50.
21. Galiè N, Hoeper MM, Humbert M, et al. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34:1219‑63.
22. Forfia PR, Vachiéry JL. Echocardiography in pulmonary arterial hypertension. Am J Cardiol. 2012;110:16S‑24S.
23. Currie PJ, Seward JB, Chan KL, Fyfe DA, Hagler DJ, Mair DD, et al. Continuous-wave Doppler determination of right ventricular pressure: A simultaneous Doppler‑catheterization study in 127 patients. J Am Coll Cardiol. 1985;6:750‑6.
24. Lanzarini L, Fontana A, Lucca E, Campana C, Klersy C. Noninvasive estimation of both systolic and diastolic pulmonary artery pressure from Doppler analysis of tricuspid regurgitant velocity spectrum in patients with chronic heart failure. Am Heart J. 2002;144:1087‑94.
25. Strange G, Playford D, Stewart S, Deague JA, Nelson H, Kent A, et al. Pulmonary hypertension: Prevalence and mortality in the Armadale echocardiography cohort. Heart. 2012;98:1805‑11.
26. de Simone G, Devereux RB, Ganau A, Hahn RT, Saba PS, Mureddu GF, et al. Estimation of the left ventricular chamber and stroke volume by limited M-mode echocardiography and validation by two-dimensional and Doppler echocardiography. Am J Cardiol. 1996;78:801–7.
27. Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: Echocardiographic-angiographic correlations in the presence of absence of asynergy. Am J Cardiol. 1976;37:7–11.
28. Koestenberger M, Ravekes W, Everett AD, Stueger HP, Heinzl B, Gamillscheg A, et al. Right ventricular function in infants, children, and adolescents: Reference values of the tricuspid annular plane systolic excursion (TAPSE) in 640 healthy patients and calculation of z score values. J Am Soc Echocardiography. 2009;22:715-9.

29. Best PJ, Holmes DR. Chronic kidney disease as a cardiovascular risk factor. Am Heart J. 2003;145:383–6.
30. López-Candales A, Rajagopalan N, Saxena N, Gulyasy B, Edelman K, Bazaz R. Right ventricular systolic function is not the sole determinant of tricuspid annular motion. Am J Cardiol. 2006;98:973-7.
31. Kucukdurmaz Z, Karapinar H, Karavelioğlu Y, Açar G, Gul I, Emiroglu MY, et al. Effect of blood donation mediated volume reduction on right ventricular function parameters in healthy subjects. Echocardiography. 2012;29:451-4.
32. López-Candales A, Dohi K, Bazaz R, Edelman K. Relation of right ventricular free wall mechanical delay to right ventricular dysfunction as determined by tissue Doppler imaging. Am J Cardiology. 2005;96:602-6.
33. Akyüz A, Yıldız A, Akıl MA, et al. Assessment of right ventricular systolic function in patients with chronic renal failure before and after hemodialysis by means of various echocardiographic modalities. Arch Turk Soc Cardiology. 2014;42(8):717-725 doi: 10.5543/tkda.2014.57609.
34. Karavelioğlu Y, Özkurt S, Kalçik M, Karapinar H, Arisoy A. Echocardiographic assessment of right ventricular functions in nondiabetic normotensive hemodialysis patients. Interv Med Appl Sci. 2015;7(3):95-101.
35. Kawar B, Ellam T, Jackson C, Kiely DG. Pulmonary hypertension in renal disease: Epidemiology, potential mechanisms and implications. Am J Nephrol. 2013;37:281-90.
36. Di Lullo L, Floccari F, Polito P. Right ventricular diastolic function in dialysis patients could be affected by vascular access. Nephron Clin Pract. 2011;118:c257-61.
37. Momtaz M, Al Fishawy H, Aljarhi UM, Al-Ansi RZ, Megid MA, Khaled M. Right ventricular dysfunction in patients with end-stage renal disease on regular hemodialysis. Egypt J Intern Med. 2013;25:127–32.
38. Charra B, Bergstrom J, Scribner BH. Blood pressure control in dialysis patients: importance of the lag phenomenon. Am J Kidney Dis. 1998; 32:720–4.
39. Locatelli F, Manzoni C. Duration of dialysis sessions–was Hegel right? Nephrol Dial Transplant. 1999;14:560–3.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):825-828.
DOI: 10.28982/josam.653402

Research article
Araştırma makalesi

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

Investigation of SCUBE-1 levels in pediatric patients with beta-thalassemia

Beta-talasemi majörlü pediatrik hastalarda SCUBE-1 düzeylerinin araştırılması

Can Acıpayam [1], Defne Ay Tuncel [2], Hatice Güneş [3], Nurten Seringec Akkececi [4], Fatma İnanç Tolun [5], Sevcan İpek [6], Ömer Duyuran [6]

[1] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Pediatric Hematology and Oncology, Kahramanmaras, Turkey
[2] Adana Numune Training and Research Hospital, Pediatric Hematology and Oncology, Adana, Turkey
[3] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Pediatrics, Kahramanmaras, Turkey
[4] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Physiology, Kahramanmaras,Turkey
[5] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Biochemistry, Kahramanmaras, Turkey
[6] Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Pediatrics, Kahramanmaras, Turkey

ORCID ID of the author(s)
CA: 0000-0002-6379-224X
DAT: 0000-0002-1262-8271
HG: 0000-0002-6940-0964
NSA: 0000-0003-1915-2350
FİT: 0000-0002-1157-2958
Sİ: 0000-0002-1406-4895
ÖD: 0000-0003-3087-0587

Corresponding author / Sorumlu yazar:
Hatice Güneş
Address / Adres: Sütçü İmam Üniversitesi Kahramanmaraş Tıp Fakültesi, Pediatri Anabilim Dalı, 46050, Kahramanmaraş, Türkiye
e-Mail: drhaticegunes82@gmail.com

Ethics Committee Approval: This study is approved by the Ethics Committee of Kahramanmaraş Sütçü İmam University with the protocol number 163 on 11.10.2017.
Etik Kurul Onayı: Bu çalışma, Kahramanmaraş Sütçü imam Üniversitesi Etik Kurulu tarafından 11.10.2017 tarih ve 163 numaralı protokol ile onaylandı.

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: 12/09/2019
Yayın Tarihi: 09.12.2019

Abstract

Aim: A thrombosis and inflammation marker, Signal peptide-CUB (complement C1r/C1 s)-EGF (epidermal growth factor)-like domain-containing protein 1 (SCUBE-1) is expressed in endothelial cells and activated platelets. We aimed to investigate the levels of this marker in patients with Thalassemia major (TM), a disease which causes a tendency to thrombosis.

Methods: Twenty patients with TM and age and gender-matched twenty healthy controls were included in this prospective case-control study. Other thrombosis markers such as D-dimer and homocysteine were studied in addition to SCUBE-1 in both groups.

Results: The SCUBE1 and D-dimer levels were higher in the TM group compared to the control group (P=0.004, P=0.023, respectively). A significant positive correlation was detected between platelet count and SCUBE1 (r=0.342, P=0.031).

Conclusion: We detected elevated SCUBE1 levels in children with TM compared to the healthy controls, which correlated with platelet count. SCUBE1 may be used as a thrombosis marker in TM in the early stages of the disease.

Keywords: Beta-thalassemia major, Children, SCUBE-1, Thrombosis

Öz

Amaç: Sinyal peptidi-CUB (tamamlayıcı C1r / C1s) -EGF (epidermal büyüme faktörü) benzeri alan içeren protein 1 (SCUBE-1), endotel hücreleri ve aktive olmuş trombositlerde eksprese edilen tromboz ve inflamasyon belirteci olarak kullanılan bir proteindir. Tromboza eğilim yaratan bir hastalık olan talasemi majörde bu belirtecin düzeylerini incelemeyi amaçladık.

Yöntemler: Bu kesitsel vaka-kontrol çalışmasına SCUBE-1 düzeylerini belirleyebilmek için 20 talasemi majorlü hasta ve kontrol grubu olarak da benzer yaş ve cinsiyette 20 sağlıklı çocuk dahil edildi. D-dimer, homosistein gibi diğer tromboz belirteçleri SCUBE-1 ek olarak her iki grupta çalışıldı.

Bulgular: Gruplar arasında SCUBE-1 ve D-dimer düzeyleri açısından anlamlı fark vardı (P=0,004, P=0,023, sırasıyla). Trombosit sayısı ile SCUBE-1 arasında anlamlı pozitif korelasyon tespit edildi (r=0,342, P=0,031).

Sonuç: SCUBE-1 seviyelerinin talasemi majorlü çocuk hastalarda sağlıklılara nazaran yüksek olduğunu ve trombosit sayısı ile korele olduğunu tespit ettik. SCUBE-1 belki erken evrelerde tromboz belirteci olarak kullanılabilir.

Anahtar kelimeler: Beta-talasemi major, Çocuklar, SCUBE-1, Tromboz

How to cite / Atıf için: Acıpayam C, Tuncel DA, Güneş H, Akkececi NS, Tolun Fİ, İpek S, Duyuran Ö. Investigation of SCUBE-1 levels in pediatric patients with beta-thalassemia. J Surg Med. 2019;3(12):825-828.

Introduction

Thalassemia is a hemolytic disorder associated with increased thrombosis incidence [1]. The prevalence of thromboembolic events is reported as 3-3.95% in cases with thalassemia major (TM) [2,3]. The main mechanisms underlying thromboembolism are endothelial cell activation, abnormal erythrocyte cell surface, and platelet activation. It is reported that hypercoagulability detected in thalassemic cases starts in childhood, continues for a lifetime and usually leads to thromboembolic events at older ages. There is a higher risk in patients with splenectomy due to increased abnormal erythrocytes and thrombocytosis [4].

Signal peptide-CUB (complement C1r/ C1s, U egf, and Bmp1)-EGF (epidermal growth factor)-like domain-containing protein-1 (SCUBE-1) is a newly defined marker of platelet activation detected in thrombocyte and endothelial cells. Vascular endothelial cells play a significant role in pathophysiological processes such as cancer metastasis, angiogenesis inflammation, and vascular diseases [5,6]. It is shown that SCUBE-1 is stored in platelet α granules and to move to the cell surface during platelet activation [7,8]. Plasma SCUBE-1 protein is related to platelet and endothelial interactions and may be characteristic of platelet activation during acute ischemic circumstances. It is thought that this interaction between platelet and endothelial cells might have potential as a nonspecific marker of acute ischemia [9].

However, the studies that investigate SCUBE-1 functions are limited [10]. To date, the levels of SCUBE-1 are not studied in β-Thalassemia patients. We aimed to investigate the levels of SCUBE-1 in TM.

Materials and methods

For this cross-sectional and case-control study, we included 20 children with TM and 20 age- and gender-matched healthy children as the control group. TM patients were diagnosed by a pediatric hematologist based on hemoglobin electrophoresis and mutation results. Patients received blood transfusions and chelation therapy, as necessary. Those who had additional chronic, thrombotic, or neoplastic diseases, a major surgical intervention in the last three months or major trauma, those receiving oral or intravenous anticoagulants, those with chronic hepatitis and who were splenectomized were excluded. The control group consisted of healthy children cases who were referred to the outpatient clinic of our hospital, with no previously known chronic diseases, anemia or hemoglobinopathies. All patients' laboratory and demographic data were obtained from the hospital registry. Complete blood counts and routine biochemical parameters were recorded.

All blood samples were obtained under aseptic conditions, centrifuged for 20 minutes at 3500 rpm without any delay to have their plasma was separated and stored at -80 degrees for examination of SCUBE1 levels. Human SCUBE-1 serum levels were determined with ELISA (enzyme-linked immunosorbent assay) method by using the ELISA commercial kit (Shanghai Sunred Biological Technology Co. Ltd.), automatic Elisa reader (Thermo Scientific, Finland) and a software (Skanlt for Multiscan FC 2.5.1). The sensitivity and assay range were 0.852 ng/mL and 1 ng/mL-300 ng/mL, respectively.

Informed written consent was obtained from all patients and their parents; ethical approval was obtained from the local ethics committee before the study.

Statistical analysis

Data management and analysis were performed using SPSS program v.14 (SPSS Inc., Chicago, IL) and a two-sided *P*-value ≤0.05 was considered statistically significant. Baseline and skewness values as well as the mean and standard deviation of variables were calculated. Shao (2002) stated that the distortion and kurtosis values should be within the range of ±3 for the distribution of the data used in the research to be normal [11]. Continuous data were expressed as mean (standard deviation) or median and categorical data were expressed in percentages. The means were compared with an independent sample t-test, and in the case of non-normal distribution, Mann–Whitney U test was used. Chi-square test was utilized for the comparison of categorical data. Correlation analysis was performed with the Pearson correlation test for normally distributed variables and Spearmen correlation test was used for non-normally distributed variables.

Power analysis was used to determine the sample size of the study. Taking into account the statistical parameters of SCUBE1 in the reference studies (group 1: 1.40 (0.25), group 2: 1.22 (0.09)), alpha, beta errors and the power were set at 0.05, 0.20 and 0.80, respectively, to find that twenty individuals per group sufficed [12].

Results

The basic demographic and laboratory findings of the groups are presented in Table 1. There was no statistically significant difference between the groups in terms of age, gender, and body mass index. The SCUBE-1 and D-dimer levels of TM group were significantly higher than the control group (*P*=0.004 and *P*=0.023, respectively) (Figure 1). No difference was found between the homocysteine levels (*P*=0.179). None of the patients had cardiac or endocrinologic involvement.

There was a positive correlation between SCUBE-1 levels and platelet count (r=0.342, *P*=0.031), and a negative correlation between the SCUBE-1 levels and hemoglobin (r=-0.414, *P*=0.008), hematocrit (r=-0.412, *P*=0.008), RBC (r=-0.366, *P*=0.02), and ALT (r=-0.414, *P*=0.008) levels (Table 2). We did not detect any correlation between SCUBE-1, homocysteine and D-dimer values (r=-0.068, *P*=0.677 and r=-0.002, *P*=0.988, respectively).

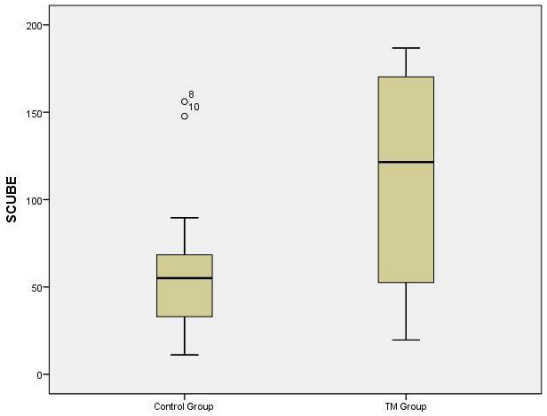

Figure 1: SCUBE-1 levels in patient and control groups

Table 1: Demographic and laboratory data of the study population

	TM group (n=20)	Control group (n=20)	*P*-value
Age, median (IQR), years	11.5(10-13.7)	11.5(10-13.7)	0.900
Gender, male/female	11/9	12/8	0.749*
Body mass index, median (IQR), kg/m^2	16.5(15.2-19.1)	17.1(16.2-22.0)	0.212
Laboratory Findings			
WBC, median (IQR),10^9/L	8.1(6.4-11.6)	8.3(6.6-10.1)	0.752
RBC, mean (SD),10^9/L	3.0 (0.4)	4.09 (0.45)	<0.001
Hb, mean (SD), g/dL	8.2 (1.1)	13.4 (1.20)	<0.001
Hematocrit, mean (SD), %	24.6 (3.6)	39.4 (3.40)	<0.001
MCV, mean (SD), fl	79.8 (4.8)	79.6 (4.70)	0.917
MPV, mean (SD), fl	10.5 (0.7)	9.7 (0.8)	0.002
Platelet Count, median (IQR), 10^9/L	334 (282-467)	327 (313-419)	0.752
Fasting blood glucose, mean (SD), mg/dL	102.9 (13.62)	88.6 (12.8)	0.001
Urea, mean (SD), mg/dL	15.6 (3.57)	12.1(2.7)	0.001
Creatinine, median (IQR), mg/dL	0.4 (0.3-0.4)	0.4 (0.4-0.5)	0.004
AST, mean (SD), U/L	29.9 (11.8)	31.0 (15.9)	0.685
ALT, median (IQR), U/L	16.5 (10.7-26.7)	18 (14-29)	0.752
Ferritin, mean (SD), µg/L	1339.9 (984.7)	-	-
SCUBE-1, median (IQR), ng/mL	121.4 (51.2-173.9)	55.0 (32.5-71.8)	0.004
D-dimer, median (IQR),mg/L	0.2 (0.2-0.3)	0.1 (0.1-0.2)	0.023
Homocysteine, median (IQR), µmol/L	10.3 (7.67-12.0)	9.4 (8.8-10.2)	0.179

*Chi-Square test, ALT: Alanine transaminase, AST: Aspartate transaminase, Hb: Hemoglobin, MCV: Mean corpuscular volume, MPV: Mean platelet volume, RBC: Red blood cell, WBC: White blood cell

Table 2: Correlation coefficients for SCUBE-1

Variables	r	*P*-value
Hemoglobin	-0.414	0.008
Hematocrit	-0.412	0.008
Platelet	0.342	0.031
RBC	-0.366	0.020
ALT	-0.414	0.020

ALT: Alanine aminotransferase, RBC: Red blood cell

Discussion

To the best of our knowledge, this was the first study investigating SCUBE-1 levels in children with TM, and we found that the median SCUBE-1 levels of TM patients were higher than the healthy control group. Furthermore, we demonstrated that there was a positive correlation between SCUBE-1 levels and platelet count.

TM causes a tendency to thromboembolic events such as recurrent or transient ischemic attacks, arterial or venous thrombosis, and stroke [13]. Numerous factors may play a role in the pathogenesis of thromboembolic events in TM. Thrombin formation is facilitated by the asymmetry in membrane phospholipids due to increased phosphatidylserine exposure in red blood cells (RBC), which in turn increases thrombosis [13]. The structural anomalies found in the RBCs of TM patients during the first months of their life increase the life-long risk of thromboembolic events. The other mechanism that causes a tendency to thrombosis is platelet activation. Menichelli et al. [14] demonstrated in vivo platelet activation in children with TM. In the study of Koçak et al. [15] high platelet count found in children with TM increased thrombosis risk. There are many other studies on this issue: Eldor et al. [16] showed increased urine metabolites of thromboxane A2 in TM patients. Similarly, Atichartakan et al. [17] found elevated β-thromboglobulin levels in TM patients. SCUBE-1 protein is stored in the alpha granules of the inactive platelets [18]. By the activation of thrombin, the protein migrates to the surface of platelets, inducing platelet activation, thus increasing the level of SCUBE-1 [19,20]. Dai et al. [21] demonstrated that plasma SCUBE1 levels in acute ischemic stroke patients were higher than the healthy control group. Türkmen et al. [22] showed that SCUBE-1 levels were statistically significantly higher in the 6th hour of mesenteric ischemia compared to the control group. Bolayır et al. [23,24] stated that SCUBE1 levels increased in the initial stages of ischemic stroke and demonstrated an increase in the levels of SCUBE-1 in myocardial infarct. Similarly, we found elevated median levels of SCUBE-1 in children with TM compared to healthy controls. This may be associated with increased thrombotic tendency in TM. We also detected a positive correlation between SCUBE-1 and platelet count, which is known risk factor of thrombosis. This may also contribute to the association of SCUBE-1 with thrombosis.

According to our results, D-dimer and MPV had significantly increased in the TM group. Elevated MPV is another indicator of platelet activation, leading to thrombosis [25,26]. Çıkrıkçıoğlu et al. [27] found higher MPV values in β Thalassemia intermedia. However, we have not detected any correlation between D-dimer and homocysteine levels. This may be related our sample size or the weakness of SCUBE-1 in detecting thrombosis.

Although no thrombotic events were seen in any of our cases during the study period, this does not change the fact that TM poses a risk for thrombosis [13].

The difference between hemoglobin, hematocrit, and RBC in groups was due to the already known TM.

Limitations

The first limitation of this study is our small sample size. The fact that we did this conduct this study among our clinic's regular patients reduced the number of individuals we included in our study. Another limitation is the lack of inclusion of thalassemia patients who experienced thrombotic events, which made it impossible to compare and provide a cut-off value for SCUBE-1. More randomized controlled trials with increased number of patients are needed to illuminate this issue.

Conclusion

Almost all our patients, who had not experienced any thrombotic events, had elevated levels of SCUBE-1, a new thrombosis marker, compared to healthy controls. TM patients should be carefully monitored for any thrombotic events and precautions should be taken.

Acknowledgments

The authors thank the nursing staff of the department for their help and care for the patients.

References

1. Sirachainan N. Thalassemia and the hypercoagulable state. Thromb Res. 2013;132:637-41. doi: 10.1016/j.thromres.2013.09.029.
2. Akar N, Kemahli S, Uysal Z, Cin S. Thromboembolism in beta-thalassemia major. Acta Haematol. 1998;100:166. doi: 10.1159/000040897.
3. Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. Blood. 2002;99:36-43. doi: 10.1182/blood.v99.1.36.
4. Garofoli F, Ciardelli L, Mazzucchelli I, Borghesi A, Angelini M, Bollani L, et al. The red cell distribution width (RDW): value and role in preterm, IUGR (intrauterine growth restricted), full-term infants. Hematology. 2014;19:365-9. doi: 10.1179/1607845413Y.0000000141.
5. Karagüzel E, Menteşe A, Kazaz İO, Demir S, Örem A, Okatan AE, et al. SCUBE1: a promising biomarker in renal cell cancer. Int Braz J Urol. 2017;43:638-643. doi: 10.1590/S1677-5538.IBJU.2016.0316.
6. Bolayır HA, Güneş H, Kıvrak T, Şahin Ö, Akaslan D, Kurt R, et al. The role of SCUBE1 in the pathogenesis of no-reflow phenomenon presenting with ST segment elevation myocardial infarction. Anatol J Cardiol. 2017;18:122-7. doi: 10.14744/AnatolJCardiol.2017.7705.
7. Lindemann S, Gawaz M. SCUBE1-a new scoop in vascular biology? Cardiovasc Res. 2006;71:414-5. doi: 10.1016/j.cardiores.2006.06.005.
8. Tu CF, Su YH, Huang YN, Tsai MT, Li LT, Chen YL, et al. Localization and characterization of a novel secreted protein SCUBE1 in human platelets. Cardiovasc Res. 2006;71:486-95. doi: 10.1016/j.cardiores.2006.04.010.
9. Peacock WF. Will SCUBE1 solve the ischemia marker deficit? J Am Coll Cardiol. 2008;51:2181-3. doi: 10.1016/j.jacc.2008.02.060.
10. Ercan M, Mungan S, Güzel I, Celik HT, Bal C, Abusoglu S, et al. Serum asymmetric dimethylarginine and nitric oxide levels in Turkish patients with acute ischemic stroke. Adv Clin Exp Med. 2019;28:693-8. doi:10.17219/acem/78360.
11. Chow S C, Shao J, Wang H. A note on sample size calculation for mean comparisons based on noncental t-statistics. Journal of Biopharmaceutical Statistics. 2002;12:441-56.
12. Uyanikoglu H, Hilali NG, Yardimciel M, Koyuncu I. A new biomarker for the early diagnosis of ovarian torsion: SCUBE-1. Clin Exp Reprod Med. 2018;45:94-9. doi: 10.5653/cerm.2018.45.2.94.
13. Eldor A, Durst R, Hy-Am E, Goldfarb A, Gillis S, Rachmilewitz EA, et al. A chronic hypercoagulable state in patients with beta-thalassaemia major is already present in childhood. Br J Haematol. 1999;107:739-46. doi: 10.1046/j.1365-2141.1999.01758.
14. Menichelli A, Cianciulli P, Gaviano E, Trua G, Papa G, Giulio S, et al. Platelet activation in thalassemic Children. Pediatric Research. 1991;30:646.

15.Koçak MZ, Dağlı M, Fidan K. Assessment of risk factors affecting thrombosis in patients with essential thrombocytosis. J Surg Med. 2018;2(2):46-9. doi: 10.28982/josam.396881.
16.Eldor A, Lellouche F, Goldfarb A, Rachmilewitz EA, Maclouf J. In vivo platelet activation in â thalassemia major reflected by increased platelet-thromboxane urinary metabolites. Blood. 1991;77:1749-53.
17.Atichartakarn V, Angchaisuksiri P, Aryurachai K, Chuncharunee S, Thakkinstian A. In vivo platelet activation and hyperaggregation in hemoglobin E/β-Thalassemia: a consequence of splenectomy. Int J Hematol. 2003;77:299-303. doi: 10.1007/bf02983790.
18.Gunaydın M, Turkmen S, Sahin A, Sumer A, Mentese A, Turedi S, et al. The diagnostic value of SCUBE1 levels in acute ischemic stroke. Turk J Biochem. 2014;39:10712.
19.Tu CF, Yan YT, Wu SY, Djoko B, Tsai MT, Cheng CJ, et al. Domain and functional analysis of a novel platelet-endothelial cell surface protein, SCUBE1. J Biol Chem. 2008;283:12478-88. doi: 10.1074/jbc.M705872200.
20.Özkan G, Ulusoy S, Menteşe A, Karahan SC, Cansiz M. New marker of platelet activation, SCUBE1, is elevated in hypertensive patients. Am J Hypertens. 2013;26:748-53. doi: 10.1093/ajh/hpt007.
21.Dai DF, Thajeb P, Tu CF, Chiang FT, Chen CH, Yang RB, et al. Plasma concentration of SCUBE1, a novel platelet protein, is elevated in patients with acute coronary syndrome and ischemic stroke. J Am Coll Cardiol. 2008;51:2173-80 doi: 10.1016/j.jacc.2008.01.060.
22.Turkmen S, Mentese S, Mentese A, Sumer AU, Saglam K, Yulug E, et al. The value of signal peptide-CUB-EGF domain-containing protein 1 and oxidative stress parameters in the diagnosis of acute mesenteric ischemia. Acad Emerg Med. 2013;20:257-64. doi: 10.1111/acem.12096.
23.Bolayır A, Gökçe ŞF, Çiğdem B, Bolayır HA, Gülünay A, Çelik VK, et al. Can SCUBE1 be used to predict the early diagnosis, lesion volume and prognosis of acute ischemic stroke? Turk J Biochem. 2018;44:16-24.
24.Bolayır HA, Kıvrak T, Güneş H, Akaslan D, Şahin Ö, Bolayır A. The role of SCUBE1 in the development of late stent thrombosis presenting with ST-elevation myocardial infarction. Rev Port Cardioli. 2018;37:375-81. doi: 10.1016/j.repc.2017.07.015.
25.Ferroni P, Riondino S, Vazzana N, Santoro N, Guadagni F, Davì G. Biomarkers of platelet activation in acute coronary syndromes. Thromb Haemost. 2012;108:1109–23. doi: 10.1160/TH12-08-0550.
26.Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? Curr Pharm Des. 2011;17:47–58. doi: 10.2174/138161211795049804.
27.Cikrikcioglu MA, Celik K, Ekinci I, Nasifov M, Toprak AE, Cetin G, et al. Mean Platelet Volume in Heterozygous Beta Thalassaemia. Acta Haematol. 2017;137:100-5. doi: 10.1159/000455813.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):829-832.
DOI: 10.28982/josam.650233

Research article
Araştırma makalesi

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

Investigation of the relationship between depression and nutritional status of elderly patients in home care

Evde bakım gören yaşlı hastaların nütrisyonel durumları ile depresyon düzeyleri arasındaki ilişkinin incelenmesi

Neşe Karakaş [1], Recep Bentli [2], Betül Fırıncı [3], Bilge Zabcı [4]

[1] İnönü University, Vocational School of Health Services, Department of Health Care Services, Malatya, Turkey
[2] Inonu University, Faculty of Medicine, Department of Internal Medicine, Malatya, Turkey
[3] Inonu University, Faculty of Medicine, Department Of Public Health, Malatya, Turkey
[4] Inonu University Faculty of Health Sciences, Department of Nutrition and Dietetics, Malatya, Turkey

ORCID ID of the author(s)
NK: 0000-0003-0737-0541
RB: 0000-0002-7205-0379
BF: 0000-0001-5685-4142
BZ: 0000-0001-6055-3262

Corresponding author / Sorumlu yazar:
Neşe Karakaş
Address / Adres: İnönü Üniversitesi, Sağlık Hizmetleri Meslek Yüksekokulu, Sağlık Hizmetleri Bölümü, Malatya, Türkiye
e-Mail: nese.karakas@inonu.edu.tr

Ethics Committee Approval: Ethics committee approval was received from the Non-Interventional Research Ethics Committee of İnönü University before beginning the study (Decision Number: 2019/3-19).
Etik Kurul Onayı: Araştırmaya başlamadan önce İnönü Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu'ndan etik kurul onayı alındı (Karar No: 2019 / 3-19).

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: 12/15/2019
Yayın Tarihi: 15.12.2019

Abstract

Aim: Malnutrition and depression are common geriatric disorders. The aim of this study was to determine the prevalence of malnutrition and depression in the elderly, as well as assess the association between depression and malnutrition.

Methods: A cross-sectional study was conducted with 86 elderly patients in the external consultation unit of a public specialty hospital in Malatya. Nutritional status was classified by the Mini Nutrition Assessment (MNA). Depression was assessed using the Geriatric Depression Scale (GDS). Functional autonomy indicators were obtained by Katz Index.

Results: A total of 86 patients, 27 females and 59 males, were included in this study. Among them, 12.8% were classified as in adequate nutritional status, 50.0% were classified as being at risk of malnutrition and 37.2% as malnourished. In this study, depression rate was determined as 79.1% according to the GDS. MNA scores, hand grip strength and folic acid levels of the group diagnosed with depression were statistically significantly lower ($p<0.001$, $P=0.03$, $P=0.04$, respectively).

Conclusion: We suggest routine screening of depression symptoms in addition to the nutritional disorders for the early diagnosis and treatment of malnutrition and depression, however, further studies including more patients are needed.

Keywords: Depression, Malnutrition, Home care

Öz

Amaç: Depresyon ve malnütrisyon yaygın görülen geriatrik sendromlardandır. Bu çalışmanın amacı evde bakım gören yaşlı hastalarda malnütrisyon ve depresyon sıklığını belirleyip, malnütrisyon ve depresyon arasındaki ilişkinin incelenmesidir.

Yöntemler: Kesitsel olarak planlanan çalışmada Malatya devlet hastanesine bağlı evde sağlık hizmetlerinden yararlanan 86 yaşlı hasta dış konsültasyonla değerlendirildi. Hastaların nütrisyonel durumları Mini Nütrisyonel Değerlendirme testi (MNA) depresyon düzeyleri Geriatrik Depresyon Ölçeği (GDS) ile, fonksiyonel durumları KATZ'ın Günlük Yaşam Aktiviteleri indeksi aracılığıyla değerlendirildi.

Bulgular: Araştırma kapsamındaki 86 hastanın, 27'si kadın, 59'u erkekti. Hastaların nütrisyonel durumları incelendiğinde %12,8'inin normal, %50,0'sinin malnütrisyon riski altında ve %37,2'sinde ise malnütrisyon olduğu tespit edildi. Bu çalışmada, GDS'ye göre katılımcıların %79,1'inde depresyon saptanmıştır. Depresyon tanısı alan grubun MNA skorları, el kavrama gücü, folikasit seviyeleri depresyon tanısı almayan gruba göre istatistiksel olarak anlamlı derecede düşüktü (sırasıyla, $P<0,001$, $P=0,03$, $P=0,04$).

Sonuç: Sonuç olarak, rutin tarama malnütrisyonun erken teşhisi ve tedavisi için beslenme bozukluklarına ek olarak depresyon belirtileri olabilir, daha geniş örnekleme grubu ile çalışılması önerilebilir.

Anahtar kelimeler: Malnütrisyon, Depresyon, Evde bakım

How to cite / Atıf için: Karakaş N, Bentli R, Fırıncı B, Zabcı B. Investigation of the relationship between depression and nutritional status of elderly patients in home care. J Surg Med. 2019;3(12):829-832.

Introduction

Since the second half of the twentieth century, the population growth rate has decreased in many countries in parallel with the decrease in the birth rate. This situation, defined as demographic aging, has led to a decrease in the share of children and youth in the population and an increase in the proportion of the elderly population. Turkey is one of the countries that experiences the most rapid demographic aging [1]. The most important social reflection of the demographic aging process is the increase in the need for health and social care in the society. This situation has pushed developed and developing countries to make future plans and develop new care models to meet their long-term needs. As a result of this search, home care appears to be the most effective model [2].

Home Health Services provide physical examination, medical care, treatment, rehabilitation services, and social and psychological support to individuals who need home care due to various diseases, their family members and caregivers [3]. In our country, patients who are more than 65 years of age constitute most of the population and they benefit the most from home health services provided by the Turkish Ministry of Health since 2011 [4,5].

Geriatric syndromes are clinical conditions that may develop due to many different causes, usually present with atypical symptoms and do not belong in a specific category of disease. Depression and malnutrition are common geriatric syndromes. Even though early diagnosis in both syndromes is important in preventing the risk of possible morbidity and mortality, it is often neglected [6-8]. Elderly people who benefit from home health services are generally people with comorbidities, decreased functional and cognitive capacity, dependent in performing activities of daily living. This issue makes this particular patient group prone to geriatric syndromes. Studies on the incidence of malnutrition and depression in elderly patients receiving home health care are extremely limited but it has been reported that the quality of life of the patients who get routine health checks by the home health service is much better [9]. This study was conducted with the aim to determine the prevalence of and relationship between malnutrition and depression among elderly patients receiving home health services in Malatya.

Materials and methods

The universe of this descriptive, cross-sectional study consisted of 101 patients over 65 years of age monitored by the Malatya Provincial Health Directorate Home Health Services as this study took place. No sampling method was used in the study. The aim was to reach the whole universe. 86 (85.14%) patients who volunteered to participate in the study and who had sufficient cooperation and orientation were included in the study.

Data collection tools

The data of the research were collected through the lab results and personal information forms (socio-demographic characteristics, chronic diseases, habits). Mini Nutritional Assessment Test (MNA), Hand Grip Strength Test, Activities of Daily Living Index and Geriatric Depression Scale Charlson Comorbidity Index were used to evaluate the comorbidities of the patients.

Mini Nutritional Assessment test

Turkish validity and reliability of the test was analyzed by Sarıkaya et al. [10]. Normal nutritional status corresponds to 23.5-30 points. Patients are considered under the risk of malnutrition between 17-23 points and malnourished below 17 points.

Hand Grip Strength Test

Hand grip strength of the patients was assessed by a dynamometer (Creative Health Products Inc., T-18). Measurements were determined by testing the dominant hand of the patient three times and taking the highest value recorded. <20 kg in female patients and <30 kg in male patients were accepted as low hand grip strength [11, 12].

KATZ's Activities of Daily Living Index: The index, which is valid and reliable in Turkey, consists of 6 questions regarding bathing, dressing, toilet, movement, discharge and nourishment activities. Patients with total scores between 0-6 points, 7-12 points and 13-18 points are considered dependent, semi-dependent and independent, respectively [13].

Geriatric Depression Scale

Turkish validity and reliability of this test was analyzed by Ertan et al. [14]. Patients with a score of above 5 are considered depressed.

Charlson Comorbidity Index

In this index, which is used to define and rate comorbidity, comorbid diseases are scored according to severity, as 1, 2, 3, 4 from mild disease to severe disease status. Comorbidity grading is done by adding up scores of comorbid diseases [15].

Research ethics

An ethics committee approval was received from the Non-Interventional Research Ethics Committee of İnönü University before beginning the research (Decision Number: 2019/3-19). A written permission was obtained from Malatya Provincial Directorate of Health to carry out the research.

Statistical analysis

SPSS 21.0 (Statistical Package for Social Sciences) statistical software was used to analyze the data obtained as part of the research. Research data showed normal distribution according to Kolmogorov-Smirnov test and homogeneous distribution according to Levene's test ($p>0.05$). Pearson correlation analysis, ANOVA, t test were used in the analysis of the data. $p<0.05$ was considered statistically significant.

Results

The descriptive characteristics of the patients in the study and the distribution of MNA and GDS scores according to these characteristics are presented in Table 1. The average age of the patients was 80.15 (7.98) [min=65, max=100] years; 77.9% were aged 85 and over. 31.4% of the participants were women and 63.9% were single. 62.8% of the group was illiterate, 91.9% were dependent in performing activities of daily living. The Charlson Comorbidity Index score of 10.5% of the patients was above 5. The distribution of average MNA scores differed according to the educational level of the patients and the group that created the difference included patients who had received

primary and higher education (P=0.02). MNA score distributions differed according to the age of the patients and the differing group was that with members older than 85 years (P=0.029). The average MNA scores of the participants who were dependent in activities of daily living were significantly lower (P<0.001). There was no difference between the comorbidity status and mean MNA scores of the patients (P=0.64). The distributions of average GDS scores according to gender, marital status, age, education level and comorbidity status of the participants were not statistically significant (P=0.55, P=0.77, P=0.03, P=0.81, P=0.54, respectively).

Table 1: Distribution of average MNA and GDS scores according to some descriptive characteristics of patients

		n	%	MNA Mean (SD)	t/F	*P*-value	GDS Mean (SD)	t/F	*P*-value
Gender	Female	27	31.4	17.07 (5.3)	0.95	0.34	7.40 (3.46)	-0.60	0.55
	Male	59	68.6	18.23 (5.2)			7.88 (3.36)		
Age	65-74	19	22.1	19 (4.81)	3.714	0.029	6.57 (4.54)	1.119	0.353
	75-84	37	43.0	18.44 (4.68)			7.49 (2.86)		
	Over 85	30	34.9	15.95 (5.71)			8.76 (2.92)		
	Illiterate	54	62.8	18.06 (4.98)	3.734	0.028	7.79 (2.85)	0.203	0.816
Education	Literate/Elementary school	24	27.9	16.14 (5.83)			7.83 (4.35)		
	Above primary school	11	9.3	21.75 (2.79)			7.00 (3.85)		
Marital status	Married	31	36.0	18.69 (4.92)	1.089	0.279	7.87 (3.08)	0.283	0.778
	Single	55	63.9	17.40 (5.42)			7.65 (3.57)		
KATZ	Dependent	79	91.9	17.55 (5.32)	-	0.003	7.86 (3.24)	1.182	0.240
	Semi Dependent	7	8.1	21.50 (2.41)	3.616		6.28 (4.25)		
Charlson	1-2	28	32.6	17.16 (5.46)	0.442	0.644	7.64 (2.66)	0.617	0.542
Comorbidity	3-4	48	55.8	18.21 (8.08)			8.08 (3.41)		
Index	5 and above	9	10.5	17.11 (4.87)			6.77 (4.89)		

SD: Standard deviation

The average MNA score of the patients in the study was 17.87 (5.25) [min: 6.50 - max: 28.00]. Among all, 37.2% were malnourished, and 50.0% were under the risk of malnutrition. The average GDS score of the patients was 7.73 (3.38) [min: 1.00 max: 14]. 79.1% of the participants had depression and 95.0% had low hand grip strength (Table 2). Figure 1 shows the relationship between hand grip strength and MNA scores of the patients. As the nutritional status of the patients in the study worsened their hand grip strength decreased. There was a negative correlation between the MNA scores and the hand grip strengths of the patients (r=0.37, P<0.001).

Table 2: Some descriptive characteristics of patients

		n	%
Nutritional status	MNA	32	37.20
	Risk of MNA	43	50.00
	Normal	11	12.80
Depression	Yes	68	79.10
	No	18	20.90
Hand grip	Low hand grip strength	82	95.30
	Normal	4	4.70
KATZ	Dependent	79	91.90
	Semi Dependent	7	7.10

SD: Standard deviation

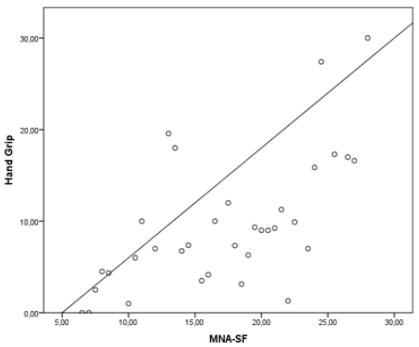

Figure 1: Relationship between hand grip strength and MNA scores

Table 3 shows the correlation between the average scores of KATZ index and GDS, MNA and Hand Grip scores of the patients. As the dependency level of the patients in activities of daily living increased, nutritional status worsened (r=0.21, P=0.04) and hand grip strength weakened (r=0.24, P=0.02). Although the dependence level of the patients included in the study increased their susceptibility to depression, the result was not statistically significant (r=0.15, P=0.16).

Table 4 shows the correlation between the average GDS scores of the participants, MNA and Hand Grip scores. There was a negative correlation (r=-0.37, P<0.001) between nutrition and depression score. In other words, as the nutrition score of the participants decreased, that is, shifted towards malnutrition, their susceptibility to depression increased. There was a negative significant correlation between hand grip strength and depression score (r=-0.243, P=0.01).

As shown in Table 5, the average values of hemoglobin, albumin, B12, ferritin and creatinine were non-significantly (P=0.44, P=0.33, P=0.83, P=0.39, P=0.19, respectively), and folic acid levels were significantly lower in the depressed group of patients (P=0.04). Body mass index, upper arm and calf circumference values of patients did not differ between the groups with and without depression (P=0.92, P=0.39, P=0.82, respectively). The average MNA score and hand grip strength of the patients with depression were significantly lower than those without (P=0.05, P=0.03, respectively).

Table 3: Correlation between KATZ index averages, GDS MNA and Hand Grip averages

		MNA	Hand grip	GDS
KATZ	r	0.21	0.24	-0.15
	P-value	0.043	0.02	0.16
	n	86	86	86

Table 4: Correlation between GDS average scores, MNA and Hand Grip average scores

		MNA	Hand Grip
GDS	r	-0.37	-0.24
	P-value	<0.001	0.012
	n	86	85

Table 5: Comparison between depression status of patients and various parametric variables

	Depression mean (SD)	Depression existent mean (SD)	t	*P*-value
Hemoglobin	12.60 (1.74)	12.15 (2.21)	0.79	0.44
Albumin	3.78 (0.32)	3.69 (0.37)	0.85	0.33
B12	392.38 (213.16)	380.92 (201.78)	0.21	0.83
Folic acid	9.41 (5.63)	6.70 (4.67)	2.08	0.04
Ferritin	117.03 (67.40)	105.60 (97.52)	1.42	0.39
Creatinine	1.27 (0.64)	1.06 (0.57)	1.31	0.19
BMI	29.17(4.87)	28.90 (7.14)	0.09	0.92
Upper middle arm circumference	22.75(6.55)	27.00 (3.00)	0.86	0.39
Calf circumference	39.562 (6.44)	39.00 (9.39)	0.22	0.82
MNA-SF	20.55 (3.89)	17.16 (5.36)	3.01	0.05
Hand grip	14.02 (14.02)	8.72 (7.20)	2.81	0.03

SD: Standard deviation

Discussion

Although the studies conducted with patients over the age of 65 receiving home health care in Turkey are limited, in the available studies, malnutrition and risk of malnutrition rates are reported as 33.1-48.3% and 38.2-39.3%, respectively [16,17]. In a study conducted with elderly patients receiving home health care in Finland, malnutrition rate was reported as 3.0% and malnutrition risk rate as 48.0 % [18]. Although the rate of malnutrition in this study was similar to other studies in our country, it was quite high compared to the that in Finland. Sarcopenia is the loss of skeletal muscle mass and strength with advancing age. Since muscle function is affected by malnutrition early in the process, hand grip strength is recommended to be used as an early diagnosis tool in malnutrition. Bentli et al. [19] reported that hand grip strength decreased as nutritional status deteriorated. In this study, consistent with literature, a positive correlation was determined between hand grip strength and MNA scores. In a systematic review, sarcopenia was reported in at least one-twentieth of the elderly living at home and in one-

third of the elderly living in nursing homes [20]. In our study, 95.3% of the patients were determined as having low hand grip strength. This rate was significantly higher compared to other studies with geriatric patients in literature. The fact that malnutrition rate and low hand grip strength were very high in our study compared to other studies in literature might be due to most patients being bedbound. 91.3 % of the patients in this study were dependent in performing activities of daily living. Their nutritional status worsened as their dependency level increased and their hand grip strength weakened.

The average GDS score of the participants was 7.73 (3.38) and depression was identified in 79.1 % of the participants. The depression rate of the patients in the study was quite high compared to other studies in the literature. In the study they conducted at the nursing home, Göçer et al. [21] determined the depression rate in the study group to be 61.9%, while Balcı et al. [22] reported the depression rate as 7.9% in their study they conducted with elderly people living in the community. As the nutritional score of the patients in the study decreased, shifting towards malnutrition, their susceptibility to depression increased. This result was consistent with the other studies in literature [19,23]. As the hand grip strength of the participants decreased their susceptibility to depression increased. Wangh et al. [24] reported a relationship between sarcopenia and depression. Other studies in literature have reported that depression is affected by the increase in dependence in activities of daily living [23]. Although the dependence level of the patients included in the study increased their susceptibility to depression, the result was not statistically significant. The distributions of average GDS scores according to gender, marital status, age, education level and comorbidity status of the participants were not statistically significant. In contrast to our study, in their study on people older than 60 years who live among society, Balcı et al. [22] reported that women, individuals with low educational levels and those with chronic diseases had increased susceptibility to depression.

MNA score distributions differed according to the age of the patients in the study. The group that differed included individuals over 85 years of age. In a similar study, Saka et al. [25] determined that malnutrition rate was higher in the group with individuals over the age of 85. The average MNA scores of the participants who were dependent in activities of daily living were significantly lower. However, there was no difference between the comorbidity status and average MNA scores of the patients. Yıldız et al. [26] also reported that the increase in the level of dependency in daily living activities adversely affected nutritional status. Similar to other studies in literature, when we categorized the patients in the study according to their educational level, we determined that the nutritional status of the group that had received primary and higher education was better than the illiterate and literate group [22].

Limitations

Our study was conducted at a single center, which limits the generalization of our findings to other institutions or populations with different resources.

Conclusion

Home health care is quite new for our country. Therefore, the number of studies related to this subject in the literature is very few. In this study, the prevalence of malnutrition and depression was determined to be quite high among elderly patients receiving home health care services. Routine screening of elderly patients who benefit from home health care services in terms of nutritional status and depression, providing nutritional education especially to informal caregivers, and having interdisciplinary teams that include nutrition experts and psychologists may improve the quality of life as well as reduce mortality and morbidity of elderly patients receiving home health care. Additionally, early diagnosis of malnutrition and depression may be beneficial in terms of cost effectiveness in health expenditures.

References

1. Çuhadar SG, Lordoğlu K. Aging and issues in turkey during the demographic transformation process. İstanbul University Journal of the Faculty of Political Sciences. 2016;(54):63-80.
2. Genç Y, Barış I. Contemporary approach in elderly care services: strengthening home care services instead of institutional care. Academic Journal of Social Research. 2015;3(10):36-57.
3. Regulation on the Provision of Home Health Services by the Ministry of Health and Its Affiliated Organizations. Ankara, 27.02.2015; Official Gazette Issue: 29280.
4. Karaman D, Kara D, Atar NY. Assessment of disease status and care needs of individuals provided home health care: Zonguldak Case. Gümüşhane University Journal of Health Sciences. 2015;4(3):347-59.
5. Çatak B, Kılınç AS, Badıllıoğlu O, Sütlü S, Sofuoğlu AE, Aslan D. Profile of elderly patients receiving home health care in burdur and home health services. Turkey Journal of Public Health. 2012;10(1):13-21.
6. Ironside PM, Tagliareni ME, McLaughlin B, King E, Mengel A. Fostering geriatrics in associate degree nursing education: an assessment of current curricula and clinical experiences. J Nurs Educ. 2010;49(5):246–52.
7. Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55(5):78.
8. Mete B, Fırıncı B, Doğan E, Pehlivan E. Depression and affecting factors in patients over 50 years of age: A cross-sectional study. J Surg Med. 2019;3(2):149-54.
9. Meriç ÇS., Yabancı AN. Importance of home health care and malnutrition in the elderly. Journal of Nutrition and Diet. 2017;45(3):287-93.
10. Sarıkaya D. Validity study of long and short (MNA-SF) form of Mini Nutritional Assessment (MNA) test in geriatric patients. Medical Thesis, Hacettepe University, Faculty of Medicine, 2013, Ankara.
11. Norman K, Stobaus N, Gonzalez MC, Schulzke JD, Pirlich M. Hand grip strength: outcome predictor and marker of nutritional status. Clin Nutr. 2011;30(2):135-42.
12. Flood A, Chung A, Parker H, Kearns V, O'Sullivan TA. The use of hand grip strength as a predictor of nutrition status in hospital patients. Clin Nutr. 2014;33(1):106-14.
13. Pehlivanoğlu EFO, Özkan MU, Balcıoğlu H, Bilge U, Ünlüoğlu İ. Adaptation to Turkish and reliability of the katz index of activities of daily living for the elderly. Ankara Medical Journal. 2018;18(2):219-23.
14. Ertan T, Eker E. Reliability, validity, and factor structure of the geriatric depression scale in Turkish elderly: Are there different factor structures for different cultures? Int Psychogeriatr. 2000;12:163-72.
15. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis. 1987;40:373-83.
16. Çevik AÇ, Basat AO, Uçak S. Evaluation of nutritional status in elderly patients receiving home health care and examining the effect of nutritional status on laboratory parameters. Konuralp Medical Journal. 2014;6(3):31-7. DOI: 10.18521/ktd.58144
17. Akan H, Ayraler A, Hayran O. Nutritional status of elderly patients admitted to the home health unit. Turkish Family Physician's Journal. 2013;17(3):106-12.
18. Soini H, Routasalo P, Lagström H. Characteristics of the mini-nutritional assessment in elderly home-care patients. Eur J ClinNutr. 2004;58(1):64-70.
19. Bentli R, Karakaş N, Fırıncı B, Deniz S. Nutritional status of elderly people living in nursing homes and some related factors. Medicine Science International Medical Journal. 2019;8(2):430-5.
20. Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, BoirieY, et al. Prevalence and interventions for sarcopenia in aging adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Aging. 2014;43(6):748-59.
21. Göçer S, Günay O. Kayseri'de bir huzurevinde yaşayan yaşlıların günlük yaşam aktiviteleri ve depresif belirti düzeyleri. Euras J Fam Med. 2018;7(3):116-24.
22. Balcı E, Şenol V, Eşel E, Günay O, Elmalı F. Relationship between depression and malnutrition status of individuals 65 years and over. Turkish Journal of Public Health. 2012;10(1):37-43.
23. Ahmadi SM, Mohammadi MR, Mostafavi SA, Keshavarzi S, Kooshesh SM, Joulaei H, et al. Dependence of the geriatric depression on nutritional status and anthropometric indices in elderly population. Iranian Journal of Psychiatry. 2013;8(2):92–6.
24. Wang H, Hai S, Liu Y, Cao L, Liu Y, Liu P, et al. Association between depressive symptoms and sarcopenia in older Chinese community-dwelling individuals. Clinical Interventions in Aging. 2018;13:1605–11. doi:10.2147/CIA.S173146
25. Saka B, Özkuluk H. Evaluation of nutritional status in elderly patients admitted to internal medicine outpatient clinic and the relationship between malnutrition and other geriatric syndromes. Gülhane Journal of Medicine. 2008;50(3):151-7.
26. Yildiz D, Pekel NB, Kilic AK, Tolgay EN, Tufan F. Malnutrition is associated with dementia severity and geriatric syndromes in patients with Alzheimer disease. Turkish Journal of Medical Sciences. 2015;45(5):1078-81.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):833-836.
DOI: 10.28982/josam.651957

Research article
Araştırma makalesi

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

Comparison of external fixation and intramedullary nailing in geriatric patients with intertrochanteric fractures of the femur

Geriatrik femur intertorakanterik kırıklarında, eksternal fiksatör ile intramedüller çivilerin karşılaştırılması

Cihan Adanaş [1], Sezai Özkan [1]

[1] **Van Yuzuncu Yıl University, Dursun Odabaş Medical Center, Department of Orthopedics and Traumatology, Van, Turkey**

ORCID ID of the author(s)
CA: 0000-0002-3652-6077
SÖ: 0000-0003-4444-6939

Abstract

Aim: The healing time of femoral intertrochanteric fractures in the elderly population is prolonged due to the presence of osteoporosis. However, mortality is high because of major causes such as embolism due to long-term bed rest. It is particularly important that these patients be operated and given the freedom to move in the early postoperative period. In this study, we aimed to compare the clinical outcomes of Proximal Femoral Nail (PFN) and External Fixation (EF) in older patients with intertrochanteric fractures of the femur (ITFF).

Methods: This study included 72 patients aged 65 years or older who were diagnosed with ITFF and underwent PFN (n=38) or EF (n=34) between 2011 and 2017. Patient data including demographic characteristics, preoperative ASA score, surgical technique, postoperative complications, and functional outcomes at final follow-up, Harris Hip Score (HHS) and Mean Mobility Score (MMS) scores were recorded for each patient.

Results: The results indicated that both PFN and EF provided equally satisfactory functional outcomes in the patients. EF was found to have major advantages including significantly lower operative times, lower intraoperative blood loss, and administration of sedation only in high-risk patients. PFN was also found to have remarkable advantages such as lower reoperation risk, reduced mortality, and lower risk of superficial wound infection.

Conclusion: Although both PFN and EF were found to have remarkable advantages, PFN seems to be more advantageous in terms of complications. Meaningfully, PFN could be more reliable and effective in the treatment of extracapsular ITFF in old-age patients.

Keywords: External fixation, Femur intertrochanteric fracture, Harris Hip Score, Mortality, Proximal femoral nail

Öz

Amaç: Yaşlı popülasyonda intertrokanterik femur kırıklarının (ITFK) iyileşme süresi osteoporoz varlığı nedeniyle uzar. Bununla birlikte bu hastalarda uzun süreli yatak istirahati sonucu emboli gibi başlıca nedenlerden dolayı ölüm oranı yüksektir. Bu hastaların erken dönemde ameliyat edilmesi ve hareket verilmesi çok önemlidir. Bu çalışmada, ITFK olan yaşlı hastalarda uygulanan Proksimal femoral çivi (PFÇ) ve Eksternal fiksatör (EF) yöntemlerin klinik sonuçlarını karşılaştırmayı amaçladık.

Yöntemler: Çalışmaya 2011-2017 yılları arasında ITFK nedeniyle ameliyat edilen 72 hasta alındı. Bu hastalardan 38 tanesine proksimal femoral çivi, 34 tanesine eksternal fiksatör uygulandı. Hastaların demografik verileri, ameliyat öncesi ASA skoru, cerrahi teknik, ameliyat sonrası komplikasyonlar, final fonksiyonel sonuçlar, Harris kalça skoru ve ortalama kalça hareket skorları herbir hasta için kaydedildi.

Bulgular: Her iki grubun fonksiyonel sonuçları tatminkar olup EF uygulanan grupta ameliyat süresinin daha kısa ve kan kaybının daha az olması, sedasyonla müdahele edilmesi başlıca avantajlarıdır. PFÇ yapılan grupta ise tekrar opere edilme ve mortalite riskinin daha az olması, yüzeyel cilt enfeksiyonlarının olmaması başlıca avantajları olarak görüldü.

Sonuç: PFÇ ile EF'nin karşılaştırıldığı bu çalışmada, PFÇ uygulamasında komplikasyonların daha az olduğu ve bu nedenle ekstrakapsüler ITFK' da Proksimal femoral çivi yönteminin daha güvenli ve daha effektif bir tedavi olduğu kanaatindeyiz.

Anahtar kelimeler: External fiksatör, Femur intertorakanterik kırık, Harris Kalça skoru, Mortalite, Proksimal femoral çivi

Corresponding author / Sorumlu yazar:
Sezai Özkan
Address / Adres: Van Yüzüncü Yıl Üniversitesi, Dursun Odabaş Tıp Merkezi, Ortopedi ve Travmatoloji Anabilim Dalı, Van, Türkiye
e-Mail: doktorsezai@hotmail.com

Ethics Committee Approval: The study was approved by Van Yuzuncu Yıl University ethics committee (no: 2019/16-03).
Etik Kurul Onayı: Çalışma Van Yüzüncü Yıl Üniversitesi Etik Kurulu tarafından onaylandı (no: 2019/16-03).

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: 12/16/2019
Yayın Tarihi: 16.12.2019

How to cite / Atıf için: Adanaş C, Özkan S. Comparison of external fixation and intramedullary nailing in geriatric patients with intertrochanteric fractures of the femur. J Surg Med. 2019;3(12):833-836.

Introduction

Intertrochanteric fractures of the femur (ITFF) are a leading cause of morbidity and mortality in the elderly population. With increasing life expectancy and rising elderly population, ITFF are likely to become a more important public health problem in future [1]. The ITFF patients accompanied by age-related systemic diseases are at increased risk for complications associated with poor prognosis and mortality, including prolonged postoperative hospital stay, deep vein thrombosis, pulmonary embolism, pneumonia, uremia, urinary tract infections, and pressure ulcer [2]. In such patients, the primary goal of treatment is to achieve prompt and lasting union of the fracture and full function of the injured limb with rapid rehabilitation of the patient [3,4]. On the other hand, the primary goal of surgical treatment is to achieve anatomic reduction of the fracture, stable fixation, low mortality, and early mobilization [5,6]. However, achieving and maintaining a stable fixation in geriatric patients can be highly difficult due to osteoporotic bone [7]. Common surgical techniques used in the treatment of ITFF include dynamic hip screw (DHS), PFN, bipolar hemiarthroplasty (BPH), and EF [8]. However, the treatment of ITFF is a gradually increasing problem worldwide and there is still no consensus on an ideal method for the treatment of hip fractures in the elderly population.

To our knowledge, there are a limited number of studies comparing the effectivity of PFN and EF in the treatment of ITFF. In this study, we aimed to compare PFN and EF in the treatment of elderly ITFF patients with regards to functional outcomes, complications, and morbidity and mortality rates.

Materials and methods

Our study included 72 patients aged 65 years or older who were diagnosed with ITFF, underwent PFN (n=38) or EF (n=34) between 2011 and 2017 and had regular follow-up for one year. Patients with incomplete medical records, irregular follow-up, a history of osteoarthritis in hip joint, malignancy-related fractures, chronic kidney failure or metabolic bone diseases, patients that underwent treatment methods other than PFN and EF, and patients aged below 65 years were excluded from the study. The study was conducted in accordance with the Declaration of Helsinki and approved by the local Ethics committee (no: 2019/16-03).

Preoperative patient characteristics including age, gender, anesthetic technique, preoperative waiting period, preoperative ASA score, and fracture type were recorded for each patient in both groups. Postoperative characteristics including follow-up period, complications, and reoperation were also recorded for each patient. Hip functions were evaluated using Harris Hip Score (HHS) and the scores were classified as 'Excellent', 'Good', 'Fair', and 'Poor'.

All the surgical procedures were performed in the same hospital by experienced surgeons. Following surgery, the patients in both groups were prescribed low-molecular-weight heparin and antibiotic prophylaxis. On the first postoperative day, bedside radiography was performed, and patients started strength training of the hip, knee, and ankle. On the second day, the patients practiced weight-bearing activities including weight shifting and short-distance walking. On discharge, the patients were advised to follow up every two weeks and a radiographic examination was performed at each follow-up visit. At 6 months postoperatively, the patients started walking with a full load on the damaged extremity. After achieving adequate bone healing, the external fixator was removed in the outpatient clinic.

Among 72 patients included in the study, 57 patients (33 patients in the PFN group and 25 patients in the EF group) had a final follow-up visit in our clinic (Figure 1 and 2), during which evaluation and scoring were performed. Mean mobility score (MMS) and HHS were used in these evaluations, which included the assessment of walking capacity, pain and physical examination findings [9,10]. On the other hand, 14 out of 72 patients were found to have died before the final follow-up.

Statistical analysis

Data were analyzed using IBM SPSS 22.0 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). Descriptives were expressed as mean (Standard Deviation [SD]). Normal distribution of data was analyzed using the Shapiro-Wilk test. Qualitative variables were compared with the Chi-square test. The group means were compared using Paired Samples t-test and Unpaired Samples t-test. Correlations were determined using Spearman's Correlation Coefficient. A *P*-value of <0.05 was considered significant.

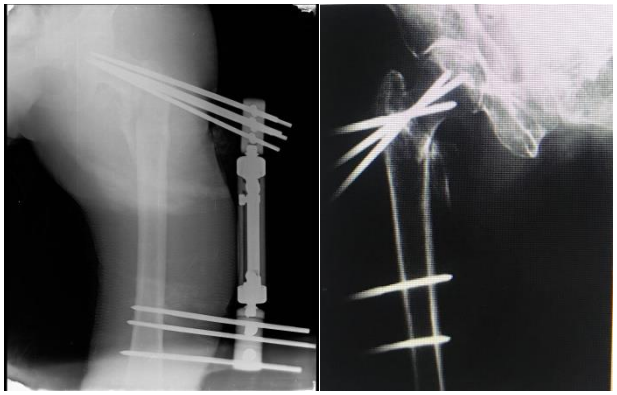

Figure 1: Postoperative X-ray image (EF group)

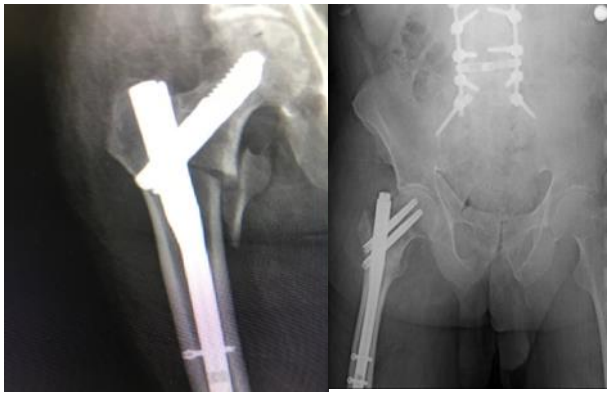

Figure 2: Postoperative X-ray image (PFN group)

Results

Seventy-two patients, including 38 patients who underwent PFN and 34 patients who underwent EF, met the inclusion criteria. No significant difference was found between the two groups with regards to the distribution of demographic characteristics, MMS score before fracture as indicated in the patient history obtained from family members, ASA score measured by the anesthesiologist, and time from injury to surgery ($P>0.05$ for all) (Table 1).

During the intraoperative period, PFN group had significantly more blood loss compared to the EF group (P<0.05). No blood transfusion was required in any patient. Table 2 presents the surgical characteristics of the patients.

An analysis of postoperative complications indicated that the EF group had significantly higher results compared to the PFN group in terms of requirement of reoperation and one-year mortality (P<0.05 for both). Deep tissue infection occurred in 2 patients in the EF group and in no patient in the PFN group. Additionally, the EF group had significantly higher incidences of superficial wound infection and pin-tract infection compared to the PFN group (P<0.05). No heterotopic ossification or avascular necrosis of the femoral head was observed in any of the patients (Table 3).

Length of hospital stay was defined as the time in days from initial presentation to hospital discharge. Mean length of hospital stay was 11.2 (2.3) and 10.8 (2.5) days in the PFN and EF groups, respectively, and no significant difference was found between the groups (P>0.05). In addition, no significant correlation was found between patient ages, ASA scores, operative times, and HHS scores (P>0.05).

No significant difference was found between the groups regarding HHS and MMS scores (P>0.05). One-year mortality was 14.3% in the PFN group and 26.4% in the EF group, which was significantly higher (P<0.05). Table 4 presents the functional outcomes assessed at final follow-up.

Table 1: Preoperative characteristics

	PFN group Mean (SD)	EF group Mean (SD)
Number of patients	38	34
Mean age in years (SD)	72.2 (8.1)	73.1 (7.9)
Female / Male distribution (%)	16/22 (42.1/57.9)	14/20 (41.1/58.9)
Mean mobility score before fracture (SD)	4.2 (1.8)	4.1 (1.9)
Mean ASA score (SD)	2.97 (0.87)	2.82 (0.76)
Mean time (hours) from injury to surgery (SD)	37 (9.5)	35 (10.4)

SD: Standard deviation

Table 2: Surgical characteristics

	PFN group Mean (SD)	EF group Mean (SD)	P-value
Number of patients	38	34	0.216
Operation with spinal anesthesia (%)	26 (68.2)	25 (73.5)	0.313
Mean operation time in minutes (SD)	68.2 (10.7)	47.5 (9.8)	<0.001
Intraoperative blood loss in ml (%)	152 (34.3)	25 (10.2)	<0.001
Number of patients receiving blood transfusion (%)	0	0	0.412

SD: Standard deviation

Table 3: Postoperative complications and mortality rates

	PFN group Mean (SD)	EF group Mean (SD)
Reoperation (%)	2 (5.2)	8 (23.5)
One-year mortality (%)	5 (14.3)	9 (26.4)
Thromboembolic complications	2	3
Superficial wound infection	1	9
Deep wound infection	0	1
Pneumonia	1	0
Neurological complication	1	2
Pressure ulcer	2	6

SD: Standard deviation

Table 4: Functional outcomes at final follow-up

	PFN group Mean (SD)	EF group Mean (SD)
Number of patients	33	25
Harris Hip Score	76.3 (10.2)	70.5 (9.3)
Mean Mobility Score	2.2 (1.32)	1.9 (1.14)
Length of follow-up period in months	13.2 (8.1)	15.3 (8.9)

SD: Standard deviation

Discussion

Hip fractures are likely to become a more important public health problem in the future due to increasing life expectancy. In geriatric patients with osteoporosis, mortality is the second most important complication following hip fractures. Meaningfully, in patients with no risk of mortality, the primary goal of treatment is to restore hip function. However, patients with failed hip function restoration are at increased risk for morbidity and mortality within the first year after surgery due to systemic diseases and reduced joy of life. The treatment of ITFF is mostly achieved using internal and external fixation techniques. Moroni et al. [11] suggested that ideal osteosynthesis technique and materials for osteoporotic pertrochanteric fractures of the femur should achieve good stability and control fracture impaction. Ozdemir et al. [12] and Atici et al. [13] proposed that the ideal surgical technique for the treatment of ITFF should be simple, time-efficient, and effective, leading to minimal trauma and blood loss. In this regard, external fixation or intramedullary nailing following closed reduction is a biological fixation technique that covers all the above-mentioned features and does not affect the fracture hematoma [14]. In this study, we compared two biological fixation techniques which have been rarely compared in the literature.

Literature reviews indicate that there are very few studies comparing PFN and EF. Moreover, there also a limited number of studies comparing other internal and external fixation techniques. In a previous meta-analysis, Parker et al. revealed that there have been only two studies in the literature comparing the clinical outcomes of internal fixation (plate-screw) and EF, and that these two studies reported that the incidence of surgical trauma was lower in the EF group while functional outcomes were similar in both groups [15]. He et al. compared the therapeutic effects of three treatment methods including EF, PFN, and DHS on ITFF and reported that although no significant difference was found among the three groups regarding the union of fracture time and complications, the EF, PFN, and DHS groups provided the best, moderate, and worst outcomes in terms of blood loss, respectively [16]. Wang et al. compared the effectivity of Richard nail, PFN, and EF in a cohort of 321 patients and reported that EF provided the best outcomes regarding complications while PFN yielded the best results in terms of functional outcomes. Moreover, the authors included young-age patients in addition to older patients, which is likely to have contributed to the findings of the study [17]. In our study, the PFN group had better mortality outcomes and pre- and post-operative pin-tract infections compared to the EF group. We consider that the clinical outcomes obtained in the EF group could be associated with the administration of an external fixator that leads to restricted mobility and reduced quality of life in the patients postoperatively.

Functional outcomes following the treatment of ITFF are often unsatisfactory, as shown in numerous studies [18]. These outcomes can be measured using a wide range of scoring systems; therefore, it is often difficult to compare functional outcomes of the patients across different studies. Nevertheless, the primary criteria in the assessment of functional outcomes in old-age patients include restoration of mobility and returning to pre-fracture mobility [12]. To the best of our knowledge, there is no study in the literature comparing the functional outcomes in patients undergoing PFN and EF. However, Pajarinen et al. [19] compared PFN and other internal fixation techniques and reported that the PFN group regained their preoperative walking

ability significantly more rapidly than those treated with other techniques. Ekström et al. [20] also reported that walking ability was significantly better in the patients treated with PFN compared to the patients treated with the other technique. However, both Pajarinen et al. [19] and Ekström et al. [20] revealed that PFN yielded similar functional outcome results with the other treatment techniques. Ozdemir et al. [21] assessed the functional outcomes of patients that underwent external fixation due to ITFF using Foster's criteria and reported that 80% of the patients had anatomically excellent results. Uzun et al. [22] administered PFN in the patients with ITFF and reported that 82% of the patients had good results according to HHS. In this study, early functional outcomes were better in the PFN group compared to the EF group. HHS scores at the 12th postoperative month were higher in the PFN group (76% vs. 70%), although no significant difference was established between the two groups.

Limitations

Our study was limited due to a small patient population and a relatively short follow-up period. It is tempting to consider that conducting longitudinal clinical studies in geriatric patients is often impossible due to their low life expectancy. Another limitation was that all the surgical procedures were not performed by the same surgeon, which is likely to have affected the results of the study. Nevertheless, the use of the same type of implant in all the patients and the single-center nature of the study constitute the major strengths of our study.

Conclusion

The results indicated that both PFN and EF provided equally satisfactory functional outcomes in the patients. EF was found to have major advantages including significantly lower operative times, lower intraoperative blood loss, and administration of sedation only in high-risk patients. PFN was also found to have remarkable advantages such as lower reoperation risk, reduced mortality, and lower risk of superficial wound infection. Depending on these findings, we consider that PFN could be more reliable and effective in the treatment of extracapsular ITFF in old-age patients. Further studies are needed to effectively compare PFN and EF.

References

1. Demirel ME, Ali, I.H. Evaluation of trauma patients admitted to the emergency department of in Mogadishu Training and Research Hospital, Somalia: Cross-sectional study of 1106 patients. J Surg Med. 2019;3:722-4.
2. Baumgaertner MR, Curtin SL, Lindskog DM. Intramedullary versus extramedullary fixation for the treatment of intertrochanteric hip fractures. Clin Orthop Relat Res. 1998:87-94.
3. Atay İM, Aslan, A., Atay, T., Burç,H. Genel ve spinal anestezi uygulanan yaşlı kalça kırığı olgularında deliryum yaygınlığı, risk faktörleri ve bilişsel fonksiyonlar. Turkish Journal of Geriatrics. 2012;5:273-8.
4. Cooper C, Cole ZA, Holroyd CR, Earl SC, Harvey NC, Dennison EM, et al. Secular trends in the incidence of hip and other osteoporotic fractures. Osteoporos Int. 2011;22:1277-88.
5. Hornby R, Evans JG, Vardon V. Operative or conservative treatment for trochanteric fractures of the femur. A randomised epidemiological trial in elderly patients. J Bone Joint Surg Br. 1989;71:619-23.
6. Siegmeth AW, Gurusamy K, Parker MJ. Delay to surgery prolongs hospital stay in patients with fractures of the proximal femur. J Bone Joint Surg Br. 2005;87:1123-6.
7. Seyfettinoglu F, Ersan O, Kovalak E, Duygun F, Ozsar B, Ates Y. Fixation of femoral neck fractures with three screws: results and complications. Acta Orthop Traumatol Turc. 2011;45:6-13.
8. Bhandari M, Devereaux PJ, Swiontkowski MF, Tornetta P, 3rd, Obremskey W, Koval KJ, et al. Internal fixation compared with arthroplasty for displaced fractures of the femoral neck. A meta-analysis. J Bone Joint Surg Am. 2003;85:1673-81.
9. Parker MJ, Palmer CR. A new mobility score for predicting mortality after hip fracture. J Bone Joint Surg Br. 1993;75:797-8.
10. Harris WH. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am. 1969;51:737-55.
11. Moroni A, Faldini C, Pegreffi F, Hoang-Kim A, Vannini F, Giannini S. Dynamic hip screw compared with external fixation for treatment of osteoporotic pertrochanteric fractures. A prospective, randomized study. J Bone Joint Surg Am. 2005;87:753-9.
12. Ozdemir H, Dabak TK, Urguden M, Gur S. A different treatment modality for trochanteric fractures of the femur in surgical high-risk patients: a clinical study of 44 patients with 21-month follow-up. Arch Orthop Trauma Surg. 2003;123:538-43.
13. Atıcı T, Şahin, N., Öztürk, A., Yaray, O. İleri yaşlı (≥65 yaş) yüksek riskli olgularda gelişen intertrokanterik femur kırıklarının eksternal fiksatörle tedavisi. Ulusal Travma Acil Cerrahi Dergisi. 2010;16:413-20.
14. Duramaz A, Sarı, C., Bilgili, G.M., Erçin, E., Kural,C., Avkan, M.C. Outcomes of Four Different Surgical Techniques in the Treatment of Geriatric Intertrochanteric Femur Fractures. Haseki Tıp Bülteni. 2014;52:256-61.
15. Parker MJ, Das A. Extramedullary fixation implants and external fixators for extracapsular hip fractures in adults. Cochrane Database Syst Rev. 2013:CD000339.
16. He SH, Peng JY, Zhao X. The comparison of three operation methods for treatment of femoral intertrochanteric fracture. Zhongguo Gu Shang. 2009;22:6-9.
17. Wang DW, Su EL, Wang WJ, Wang S, Wang BF. Case control study of different fixing methods for intertrochanteric fractures. Zhongguo Gu Shang. 2010;23:769-71.
18. Moroni A, Faldini C, Pegreffi F, Hoang-Kim A, Giannini S. Osteoporotic pertrochanteric fractures can be successfully treated with external fixation. Journal of Bone and Joint Surgery-American. 2005;87a:42-51.
19. Pajarinen J, Lindahl J, Michelsson O, Savolainen V, Hirvensalo E. Pertrochanteric femoral fractures treated with a dynamic hip screw or a proximal femoral nail. A randomised study comparing post-operative rehabilitation. J Bone Joint Surg Br. 2005;87:76-81.
20. Ekstrom W, Karlsson-Thur C, Larsson S, Ragnarsson B, Alberts KA. Functional outcome in treatment of unstable trochanteric and subtrochanteric fractures with the proximal femoral nail and the Medoff sliding plate. J Orthop Trauma. 2007;21:18-25.
21. Özdemir H, Urguden, M., Dabak, T.K., Soyuncu, Y. Treatment of intertrochanteric femoral fractures with the use of a modular axial fixator device. Acta Orthopaedica et Traumatologica Turcica. 2002;36:375-83.
22. Uzun M, Erturer E, Ozturk I, Akman S, Seckin F, Ozcelik IB. Long-term radiographic complications following treatment of unstable intertrochanteric femoral fractures with the proximal femoral nail and effects on functional results. Acta Orthop Traumatol Turc. 2009;43:457-63.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):837-840.
DOI: 10.28982/josam.585425

Research article
Araştırma makalesi

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

Pneumoperitoneum in laparoscopic surgery: Comparison of the effect on gastric and intestinal motility in pediatric and adult rats

Laparoskopik cerrahide pneumoperiton: Pediatrik ve erişkin ratlarda gastrik ve intestinal motilite üzerine etkisinin karşılaştırılması

Umut Alıcı [1], Ahmet Unlu [2], Yasemin Aydın [3], Baran Tokar [1]

[1] Department of Pediatric Surgery, Eskişehir Osmangazi University Medical School, Eskişehir, Turkey
[2] Atatürk Training and Research Hospital, Antalya, Turkey
[3] Department of Physiology, Eskişehir Osmangazi University Medical School, Eskişehir, Turkey

ORCID ID of the author(s)
UA: 0000-0002-3250-724X
AU: 0000-0002-6976-0652
YA: 0000-0003-4992-1153
BT: 0000-0002-7096-0053

Abstract

Aim: There are limited data on how pneumoperitoneum used during laparoscopy affects gastric and intestinal motility in children compared to adults. The aim of this experimental study is to measure and compare the effects of pneumoperitoneum on the gastric and small intestinal motility among children and adult rats.

Methods: The study was conducted with 4 groups: Groups 1 and 2 (n=8 and 7, respectively) comprised pediatric rats while Groups 3 and 4 (n=10 and 10, respectively) included adult rats. Pneumoperitoneum was achieved in Groups 1 and 3. Laparotomy was performed in Groups 2 and 4. The duration of procedure was 90 minutes in all groups. CO_2 (Thermoflator, Karl-Storz, Germany) insufflation pressure was maintained at 5 mHg-0.5 ml/min. Postoperative gastric and intestinal motility studies were performed in all groups. Contractile responses to Acetylcholine and potassium chloride (at a dose range of 10^{-8} to 10^{-3} mM) were recorded (Isometric Transducer, Biopac, USA). Data Collection Analysis System (MP100 Biopac, USA) was used to analyze the data.

Results: The lowest contraction response was obtained in group 1 for both the stomach and intestine. The responses of pediatric groups to potassium chloride and acetylcholine were lower than those of adult groups, but there was no significant difference among the 4 groups (P>0.05).

Conclusion: This study may suggest that in the similar setting for pediatric and adult age groups, pneumoperitoneum does not significantly adversely affect gastric and small intestinal motility in children. Future studies should aim to investigate the effects of pneumoperitoneum on gastric and intestinal motility at different ages, weights, types of anesthesia, intra-abdominal pressures and operative duration.

Keywords: Laparoscopy, Pneumoperitoneum, Gastric motility, Intestinal motility, Child

Öz

Amaç: Literatürde, pnömoperitonun erişkinlere kıyasla çocuklarda mide ve bağırsak hareketliliğini nasıl etkilediği konusunda sınırlı veri bulunmaktadır. Bu deneysel çalışmanın amacı, çocuklarda ve yetişkin sıçanlarda pnömoperitonun gastrik ve ince bağırsak hareketliliği üzerindeki etkilerini ölçmek ve karşılaştırmaktır.

Yöntemler: Çalışma 4 grupta yapıldı. Grup 1'de (n=8) ve 2'sinde (n=7) pediatrik yaşta, grup 3'te (n=10) ve 4'ünde (n=10) yetişkin yaşta sıçanlar vardı. Grup 1 ve 3'te pnömoperiton uygulandı. Grup 2 ve 4'te laparotomi yapıldı. İşlem süresi tüm gruplarda 90 dakika idi. CO_2 insüflasyonu (Thermoflator, Karl-Storz, Almanya) 5 mHg-0,5 ml/dk basınçta uygulandı. Postoperatif mide ve bağırsak motilite çalışmaları tüm gruplarda yapıldı. Asetilkolin ve KCl'ye (10^{-8} ila 10^{-3} mM'lik bir doz aralığında) kontraktil cevaplar kaydedildi (İzometrik Dönüştürücü, Biopac, ABD). Verilerin analizinde Veri Toplama Analiz Sistemi (MP100 Biopac, ABD) kullanılmıştır.

Bulgular: En düşük kasılma cevabı, hem mide hem de bağırsak için grup 1'de elde edildi. Pediatrik grupların potasyum klorid ve asetilkoline verdiği yanıtlar yetişkin gruplardan daha düşüktü, ancak 4 grup arasında anlamlı fark yoktu (P>0,05).

Sonuç: Bu çalışma, pediatrik ve erişkin yaş grupları için benzer bir ortamda, pnömoperitonun çocuklarda mide ve ince bağırsak hareketliliği üzerinde önemli bir olumsuz etki yapmadığını ortaya koyabilir. Gelecekteki çalışmalar, farklı yaşlarda, ağırlıklarda, anestezi tiplerinde, karın içi basınç ve sürelerinde pnömoperitonun mide ve bağırsak hareketliliği üzerindeki etkilerini araştırmayı amaçlamalıdır.

Anahtar kelimeler: Laparoskopi, Pneumoperiton, Gastrik motilite, İntestinal motilite, Çocuk

Corresponding author / Sorumlu yazar:
Umut Alıcı
Address / Adres: Çocuk Cerrahisi Anabilim Dalı, Eskişehir Osmangazi Üniversitesi, Tıp Fakültesi Eskişehir, Türkiye
e-Mail: drualici@gmail.com

Ethics Committee Approval: The approval of the Ethics Committee of Eskişehir Osmangazi University Faculty of Medicine and the Experimental Animal Research Sub-Commission (Resolution 53 dated 15 March 2007) was obtained.
Etik Kurul Onayı: Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Etik Deney Komitesi ve Deneysel Hayvan Araştırmaları Alt Komisyonu'nun onayı (15 Mart 2007 tarihli ve 53 sayılı Karar) alındı.

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: 12/16/2019
Yayın Tarihi: 16.12.2019

How to cite / Atıf için: Alıcı U, Unlu A, Aydın Y, Tokar B. Pneumoperitoneum in laparoscopic surgery: Comparison of the effect on gastric and intestinal motility in pediatric and adult rats. J Surg Med. 2019;3(12):837-840.

Introduction

Laparoscopic abdominal surgery is expected to shorten postoperative recovery time, hospitalization, and duration of return to daily activities. Early postoperative oral intake is one of the major concerns that determine the quality of postoperative follow-up in laparoscopic surgery. Starting early enteral feeding depends on gastrointestinal system (GIS) motility [1].

Pneumoperitoneum via CO_2 insufflation increases intraabdominal pressure (IAP), which may induce motility problems in GIS to possibly result in postoperative ileus and spontaneous ileum perforation [2].

High IAP also increases pressure on the abdominal vena cava, which may cause a decrease in venous blood flow and consequently, the GIS. Clinical and experimental studies show that increased IAP may cause high venous resistance, hypoxic mucosal and neuronal injury and contractility and motility disorders in the gastrointestinal system [2-4]. The intestinal neuronal network, located between the longitudinal and circular muscle layers, releases neurotransmitters responsible for induction of GIS contractility and motility, and it may be damaged by high IAP and significant intraabdominal distension.

Although there are studies investigating the effects of pneumoperitoneum on GIS motility in adults, there is no study on this specific subject in children. In this experimental study, the contractility response of children and adult rats were compared by measuring the effects of pneumoperitoneum on gastric and small intestinal motility.

Materials and methods

The study was conducted at Eskisehir Osmangazi University (ESOGU) Medical and Surgical Research Center (TICAM) with approval of ESOGU Medical School Ethics Committee Sub-Commission on Experimental Animal Research. Forty Sprague-Dowley rats were used. Surgery could not be completed in two rats in group 1 and 3 rats in group 2, which were excluded. Motility study was completed in 35 rats. The ages and weights of rats in Groups 1 (n=8) and 2 (n=7), the pediatric rat groups, ranged between 20-25 days and 49-75 grams, respectively. Groups 3 (n=10) and 4 (n=10) included adult rats aged between 2-3 months that weighed between 300-400 grams. Pneumoperitoneum was achieved in Groups 1 and 3, while laparotomy was performed in Groups 2 and 4.

Surgical procedure and motility study

All rats received 80 mg/kg intramuscular ketamine hydrochloride (Ketalar, Pfizer, USA) and 4 mg/kg midazolam (Dormicum, Roche, Germany). Duration of the procedure was 90 minutes in all groups. Pneumoperitoneum with CO_2 insufflation was achieved by the insufflator (Thermoflator, Karl Storz, Germany) with a flow rate of 0.5 ml/min at 5 mmHg pressure in Groups 1 and 3 with 60 minutes insufflation, 30 minutes desufflation periods. To obtain pneumoperitoneum, insufflator was connected to a 14 G intravascular catheter placed intraperitoneally. At that pressure and flow rate, a marked abdominal distension was preserved throughout the procedure. The insufflation was terminated, and laparotomy was performed to obtain gastric and ileal specimens. A four-cm-long ileal segment that was located 10 cm proximal to cecum and gastric fundus were resected and immersed into the freshly prepared Tyrod solution for the motility study. The experimental animals were sacrificed under anesthesia after removal of tissue samples.

Afterwards, the removed stomach and ileum pieces were placed in the isolated organ bath, fixed at 37 degrees Celsius and receiving a gas mixture of 95% oxygen and 5% CO_2. The same size of bowel and stomach was used in each study. In the isolated organ bath, passive stretching tension of 1 G was applied to each bowel and stomach piece. At the end of this period, 10^{-8} mM of acetylcholine and 10^{-3} mM of potassium chloride were given cumulatively at regular intervals. Contraction responses were recorded by the data acquisition system (MP100 Biopac, USA).

In groups 2 and 4, laparotomy was performed with a 0.5 cm median incision. At the end of 90 minutes, gastric and ileal specimens were resected, and motility studies were performed as described for the groups 1 and 3.

Statistical analysis

Using SPSS 15.0 and SigmaStat 3.1 package programs, two-factor repetitive measurement variance analysis (Two Way Repeated Measures ANOVA), Tukey HSD and Holm-Sidak tests were performed in multiple comparisons.

Results

The lowest contraction response was obtained in group 1 for both the gastric fundus and intestine. The contraction responses of pediatric groups (Group 1 and 2) to potassium chloride and acetylcholine were lower than those of adult groups (Group 3 and 4) in all doses for both the gastric fundus and ileum (Table 1-8) (Figures 1, 2). Statistical comparison of contraction responses of all groups showed that there was no significant difference among the 4 groups (P>0.05).

Table 1: Comparison of ileum contraction responses to potassium chloride

Dose	Group 1 (n=8) Mean (SD) mN	Group 2 (n=7) Mean (SD) mN	Group 3 (n=10) Mean (SD) mN	Group 4 (n=10) Mean (SD) mN
2 mM	0.15 (0.2)	0.14 (0.14)	0.25 (0.5)	0.32 (0.36)
4 mM	0.16 (0.17)	0.25 (0.28)	0.44 (0.34)	0.74 (0.51)
8 mM	0.31 (0.31)	0.51 (0.44)	1.04 (0.59)	1.75 (0.73)
16 mM	0.6 (0.67)	1.19 (1.13)	2.5 (1.91)	3.06 (1.2)
32 mM	0.5 (0.62)	1.24 (1.38)	2.74 (2.05)	2.63 (1.0)

mN: Milinewtons, SD: Standard deviation

Table 2: Comparison of the responses of ileum to potassium chloride in organ baths between groups

Groups	Mean (SD)	*P*-value	Critical level
1-2	0.29 (0.84)	0.41	0.01
1-3	0.38 (1.13)	0.27	0.01
1-4	0.06 (0.18)	0.86	0.05
2-3	0.09 (0.28)	0.78	0.02
2-4	0.23 (0.67)	0.51	0.02
3-4	0.32 (0.95)	0.35	0.01

SD: Standard deviation

Table 3: Comparison of gastric fundus contraction responses to potassium chloride

Dose	Group 1 (n=8) Mean (SD) mN	Group 2 (n=7) Mean (SD) mN	Group 3 (n=10) Mean (SD) mN	Group 4 (n=10) Mean (SD) mN
2 mM	0.12 (0.18)	0.1 (0.09)	0.19 (0.23)	0.47 (0.7)
4 mM	0.21 (0.25)	0.2 (0.15)	0.34 (0.39)	0.68 (0.79)
8 mM	0.32 (0.31)	0.39 (0.21)	0.56 (0.49)	1.75 (0.99)
16 mM	0.6 (0.51)	1.19 (1.13)	2.5 (1.91)	0.81 (1.2)
32 mM	0.35 (0.62)	0.63 (0.24)	1.02 (0.66)	1.43 (0.7)
64 mM	0.74 (0.33)	0.96 (0.41)	2.5 (1.1)	3.14 (0.78)

mN: Milinewtons, SD: Standard deviation

Table 4: Comparison of the responses of gastric fundus to potassium chloride in organ bath between groups

Groups	Mean (SD)	*P*-value	Critical level
1-2	0.01 (0.04)	0.97	0.05
1-3	0.3 (0.86)	0.40	0.02
1-4	0.68 (1.95)	0.06	0.01
2-3	0.28 (0.82)	0.42	0.02
2-4	0.67 (1.92)	0.07	0.01
3-4	0.38 (1.1)	0.29	0.01

SD: Standard deviation

Table 5: Comparison of ileum contraction responses to acetylcholine

Dose	Group 1 (n=8) Mean (SD) mN	Group 2 (n=7) Mean (SD) mN	Group 3 (n=10) Mean (SD) mN	Group 4 (n=10) Mean (SD) mN
-9 mM	0.63 (0.59)	0.74 (0.19)	0.97 (0.85)	1.17 (1.02)
-8 mM	0.61 (0.5)	0.81 (0.38)	1.5 (1.22)	1.9 (0.79)
-7 mM	0.72 (0.53)	0.86 (0.32)	2.19 (1.22)	2.89 (0.74)
5x-7 mM	0.9 (0.68)	1.31 (0.81)	3.14 (1.14)	3.73 (1.91)
-6 mM	0.8 (0.72)	1.25 (0.86)	2.92 (1.44)	1.43 (4.24)
5x-6 mM	1.05 (0.95)	1.64 (1.34)	3.55 (1.77)	5.21 (2.62)
-5 mM	0.76 (0.68)	1.35 (1.29)	3.02 (2.13)	3.92 (1.79)
5x-5 mM	0.72 (0.64)	1.36 (1.45)	3.38 (4.44)	4.31 (1.45)

mN: Milinewtons, SD: Standard deviation

Table 6: Comparison of the responses of ileum to acetylcholine in organ bath between groups

Groups	Mean (SD)	*P*-value	Critical level
1-2	0.48 (1.46)	0.16	0.01
1-3	0.79 (2.42)	0.03	0.01
1-4	0.87 (2.64)	0.02	0.01
2-3	0.32 (0.96)	0.35	0.02
2-4	0.39 (1.18)	0.25	0.02
3-4	0.07 (0.22)	0.83	0.05

SD: Standard deviation

Table 7: Comparison of gastric fundus contraction responses to acetylcholine

Dose	Group 1 (n=8) Mean (SD) mN	Group 2 (n=7) Mean (SD) mN	Group 3 (n=10) Mean (SD) mN	Group 4 (n=10) Mean (SD) mN
-9 mM	0.13 (0.15)	0.45 (0.56)	0.74 (0.55)	0.74 (0.41)
-8 mM	0.19 (0.18)	0.49 (0.57)	0.95 (0.61)	0.97 (0.57)
-7 mM	0.22 (0.14)	0.63 (0.68)	1.14 (0.82)	1.13 (0.74)
5x-7 mM	0.27 (0.16)	0.76 (0.79)	1.49 (1.15)	1.55 (1.05)
-6 mM	0.31 (0.17)	0.83 (0.85)	1.64 (1.28)	1.68 (1.13)
5x-6 mM	0.37 (0.17)	0.99 (0.94)	2.25 (1.46)	2.27 (1.31)
-5 mM	0.41 (0.18)	1.05 (1.0)	2.47 (1.63)	2.56 (1.33)
5x-5 mM	0.48 (0.2)	1.2 (1.06)	3.27 (1.84)	3.4 (1.45)
-4 mM	0.53 (0.19)	1.26 (1.08)	3.40 (1.9)	3.58 (1.5)
5x-4 mM	0.69 (0.25)	1.43 (1.13)	4.04 (1.12)	4.21 (1.61)
-3 mM	0.75 (0.21)	1.49 (1.13)	4.25 (2.17)	4.50 (1.6)

mN: Milinewtons, SD: Standard deviation

Table 8: Comparison of the responses of gastric fundus to acetylcholine in organ bath between groups

Groups	Mean (SD)	*P*-value	Critical level
1-2	0.52 (1.1)	0.18	0.01
1-3	0.65 (1.41)	0.07	0.01
1-4	0.83 (1.64)	0.06	0.01
2-3	0.35 (0.86)	0.41	0.02
2-4	0.44 (0.98)	0.29	0.02
3-4	0.09 (0.25)	0.92	0.05

SD: Standard deviation

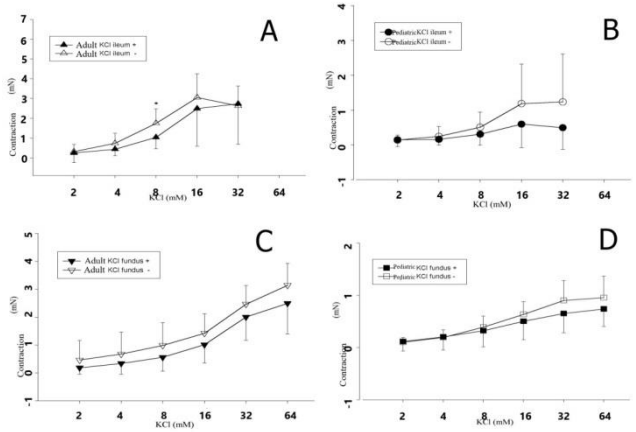

Figure 1: Comparison of cumulative potassium chloride responses in the ileum (A and B) and fundus (C and D) in adult and pediatric groups. Laparoscopy (+), Laparotomy (-)

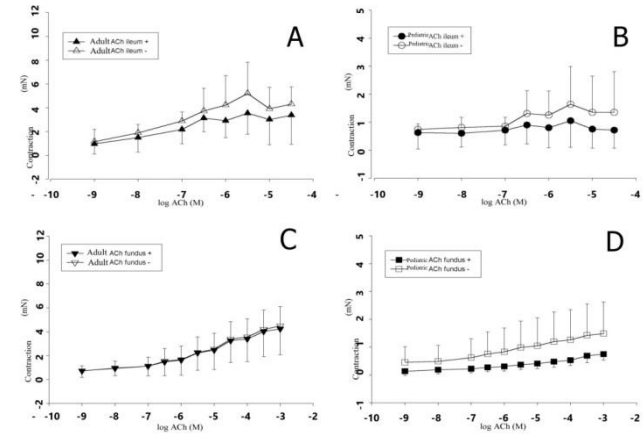

Figure 2: Comparison of cumulative acetylcholine responses in the ileum (A and B) and fundus (C and D) in adult and pediatric groups. Laparoscopy (+), Laparotomy (-)

Discussion

It has been shown that increasing the pressure of pneumoperitoneum from 10 mmHg to 20 mmHg in the pig model reduces mucosal blood flow in the small intestine by 20% to 40% [3]. In the study performed in rats, pneumoperitoneum with up to 20-25 mmHg was reported to cause a 63% decrease in mucosal blood flow [4]. Intraabdominal pressure between 10-15 mmHg in rats reportedly caused a reduction on jejunal mucosal perfusion and consequently caused severe damage to mucosal microcirculation [5]. GIS hypoxia related to high IAP may damage the neuronal structures, which release the neurotransmitters responsible for induction of intestinal contractility and motility [2]. Although those experimental studies have pointed out that high IAP may cause GIS mucosal damage and motility disorders, some other studies have shown that pneumoperitoneum during laparoscopy is not detrimental to GIS motility [6-8]. In most of the laparoscopic procedures, the level of IAP is well tolerated, but variables such as age and size of the patient, level of gas pressure and flow rate and duration of pneumoperitoneum should be considered. In this study, the variables were age and size. Under constant insufflation pressure, flow rate and duration, the effect of pneumoperitoneum on gastric and intestinal motility was investigated for both pediatric and adult ages.

Our results showed that the lowest contraction response for both the stomach and intestine was in group 1 and the contraction responses in both pediatric pneumoperitoneum and laparotomy groups were non-significantly lower than the adult groups. We may hypothesize that lower contraction response might be related to anesthesia and the physiologic stress of the surgery in pediatric groups. Midazolam in combination with ketamine was administered for surgical anesthesia. Ketamine hydrochloride and midazolam may prolong oro-cecal transit time and decrease GIS contractility [9,10]. Findings in our study may suggest that ketamine hydrochloride and midazolam were more effective on motility in pediatric age groups than adult groups. Surgical stress also alters GIS motor function [11,12]. Physiological stress due to surgery might be another factor triggering lower contraction responses in the pediatric groups.

Pneumoperitoneum was best tolerated at a pressure of 2 mmHg and flow rate of 0.5 L/minutes for a model of neonatal minimally invasive surgery in rats [13]. In our study, 5 mmHg of pressure was well tolerated, and the procedure could be completed in Group 1. This may suggest that IAP might be increased up to 5 mmHg in future studies on pediatric rat models.

Our gastric and ileal motility studies showed that the difference in contraction responses between the pediatric and adult pneumoperitoneum groups at the same pressure, flow rate and duration, and that between the pneumoperitoneum and laparotomy groups, were non-significant. These results may suggest that pneumoperitoneum does not adversely affect gastric and small intestinal motility in pediatric age groups. However, this study has some limitations. Further randomized controlled studies should be designed to measure contraction responses at different ages, weights, types of anesthesia, intra-abdominal pressure levels, and operative durations. The effects of pneumoperitoneum on GIS motility in different intraabdominal surgical procedures of children should also be investigated.

References

1. Jimbo T, Masumoto K, Takayasu H, Shinkai T, Urita Y, Uesugi T, et al. Outcome of early discharge protocol after appendectomy for pediatric acute appendicitis. Pediatr Int. 2017;59(7):803-6.
2. Ünsal A.M, İmamoğlu M, Kadioğlu M. The Acute Alterations in Biochemistry, morphology and contractility of rat-isolated terminal ileum via increased intra-abdominal pressure. Pharmacological Research. 2006;53:135-41.
3. Goitein D, Papasavas P, Yeaney W, Gaqne D, Hayetian F, Caushaj P, et al. Microsphere intestinal blood flow analysis during pneumoperitoneum using carbon dioxide and helium. Surg Endosc. 2005;19:541-5.
4. Diebel LN, Dulchavsky SA, Brown WJ. Splanchnic ischemia and bacterial translocation in the abdominal compartment syndrome. J Trauma. 1997;43:852-5.
5. Samel ST, Neufang T, Mueller A, Leister I, Becker H. New abdominal cavity champer to study the impact of increased intraabdominal pressure on microcirculation of gut mucosa by using video microscopy in rats. Crit Care Med. 2002;30:1854-8.
6. Ludwig KA, Frantzides CT, Carlson MA, Grade KL. Myoelectric motility patterns following open versus laparoscopic cholecystectomy. J Laparoendosc Surg. 1993;3:461-6.
7. Naito T, Garcia-Luiz A, Vladisavljevic A, Matsuno S, Gagner M. Gastrointestinal transit and stress response after laparoscopic vs conventional distal pancreatectomy in the canin model. Surg Endosc. 2002;16:1627-30.
8. Hotokezaka M, Dix J, Mentis EP, Schirmer BD. Gastrointestinal recovery after laparoscopic vs open colon surgery. Surg Endosc. 1996;10:485-9.
9. Sparkes AH, Papasouliotis K, Viner J, Cripps PJ, Gruffydd-Jones TJ. Assessment of orocaecal transit time in cats by the breath hydrogen method: the effects of sedation and a comparison of definitions. Res Vet Sci. 1996;60:243-6.
10. Inada T, Asai T, Yamada M, Shingu K. Propofol and midazolam inhibit gastric emptying and gastrointestinal transit in mice. Anesth Analg. 2004;99(4):1102-6.
11. Taché Y, Martinez V, Million M, Wang L. Stress and the gastrointestinal tract III. Stress-related alterations of gut motor function: role of brain corticotropin-releasing factor receptors. Am J Physiol Gastrointest Liver Physiol. 2001;280(2):173-7.
12. Caso JR, Leza JC, Menchén L. The effects of physical and psychological stress on the gastro-intestinal tract: lessons from animal models. Curr Mol Med. 2008;8(4):299-312.
13. Mayer S, Peukert N, Gnatzy R, Gosemann JH, Lacher M, Suttkus A. Physiologic Changes in a Small Animal Model for Neonatal Minimally Invasive Surgery. J Laparoendosc Adv Surg Tech A. 2018;28(7):912-7.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):841-844.
DOI: 10.28982/josam.597751

Research article
Araştırma makalesi

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

The albumin-bilirubin (ALBI) grade as a significant prognostic factor in colorectal cancer patients with liver metastases

Karaciğere metastatik kolorektal kanserde önemli bir prognostik faktör olarak albumin-bilirubin (ALBI) gradı

Nazım Can Demircan [1], Osman Köstek [1], Ali Gökyer [1], Ahmet Küçükarda [1], Muhammet Bekir Hacıoğlu [1], Bülent Erdoğan [1], Sernaz Uzunoğlu [1], İrfan Çiçin [1]

[1] Department of Medical Oncology, Trakya University Faculty of Medicine, Edirne, Turkey

ORCID ID of the author(s)
NCD: 0000-0001-6630-5278
OK: 0000-0002-1901-5603
AG: 0000-0002-1653-6155
AK: 0000-0001-7399-2360
MBH: 0000-0001-8490-3239
BE: 0000-0002-2158-3490
SU: 0000-0001-5387-8309
İÇ: 0000-0002-7584-3868

Corresponding author / Sorumlu yazar:
Nazım Can Demircan
Address / Adres: Trakya Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Anabilim Dalı, Edirne, Türkiye
e-Mail: ncdemircan@gmail.com

Ethics Committee Approval: The approval of the Ethics Committee of Trakya University Faculty of Medicine (14.01.2019, TUTF-BAEK 2018/335) was obtained.
Etik Kurul Onayı: Trakya Üniversitesi Tıp Fakültesi (14.01.2019, TUTF-BAEK 2018/335) Etik Kurulundan onay alındı.

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: 12/22/2019
Yayın Tarihi: 22.12.2019

Abstract

Aim: Colorectal cancer is one of the most common cancers and liver metastases are frequent during its course. Albumin-bilirubin (ALBI) score/grade was shown to predict survival in hepatocellular carcinoma. We aimed to assess the prognostic value of the ALBI score/grade in colorectal cancer patients with liver metastases.

Methods: Medical records of patients with colorectal cancer and synchronous or metachronous liver metastases were reviewed. Serum albumin, total bilirubin, lactate dehydrogenase, carcinoembryogenic antigen and neutrophil-to-lymphocyte ratio at the time of first liver metastasis were determined. ALBI score was calculated from serum albumin and bilirubin and was graded. Multivariate regression models were used to evaluate prognostic factors.

Results: The study included 223 patients. Median overall survival was 23.9, 16.0 and 4.0 months for ALBI grades 1, 2 and 3, respectively (P<0.001). In the first multivariate model, serum albumin was an independent prognostic factor (Hazard ratio=1.97, P=0.001) but total bilirubin was not (Hazard ratio=1.43, P=0.17). In the second multivariate analysis, ALBI grade was a significant predictor of overall survival (Hazard ratio=1.54, P=0.02 for ALBI grade 2 and Hazard ratio=3.85, P<0.001 for ALBI grade 3).

Conclusion: ALBI grade may be a valuable prognostic method to estimate the mortality of patients with colorectal cancer and liver metastases.

Keywords: Albumin-bilirubin grade, Colorectal cancer, Liver metastasis, Prognostic factor

Öz

Amaç: Kolorektal kanser en sık görülen kanserlerden biridir ve hastalık sürecinde karaciğer metastazı sık olarak gelişmektedir. Albumin-bilirubin (ALBI) skoru/gradının hepatoselüler kanserde sağkalımı predikte ettiği gösterilmiştir. Bu çalışmada ALBI skoru/gradının karaciğer metastatik kolon kanserindeki prognostik değerinin araştırılması amaçlanmıştır.

Yöntemler: Kolorektal kanser tanılı ve senkron ya da metakron karaciğer metastazı olan hastaların tıbbi kayıtları incelenmiştir. Karaciğer metastazının saptandığı andaki serum albumin, total bilirubin, laktat dehidrojenaz, karsinoembryonik antijen and nötrofil-lenfosit oranı belirlenmiştir. Albumin ve bilirubin kullanılarak ALBI skoru hesaplanmış ve derecelendirilmiştir. Prognostik faktörler çok değişkenli regresyon modelleri ile değerlendirilmiştir.

Bulgular: Çalışmaya 223 hasta dahil edildi. Medyan genel sağkalım ALBI grad 1, 2 ve 3 için sırasıyla 23.9, 16.0 ve 4.0 ay olarak saptandı (P<0.001). İlk çok değişkenli modelde serum albumin bağımsız bir prognostik faktörken (Tehlike oranı=1.97, P=0.001) total bilirubin değildi (Tehlike oranı=1.43, P=0.17). İkinci çok değişkenli analizde ALBI gradın genel sağkalımı bağımsız olarak predikte edebildiği görüldü (ALBI grad 2 için tehlike oranı=1.54, P=0.02 ve grad 3 için tehlike oranı=3.85, P<0.001).

Sonuç: ALBI gradı karaciğer metastazı olan kolorektal kanser hastalarında mortaliteyi tahmin etmek için değerli bir prognostik metod olabilir.

Anahtar kelimeler: Albumin-bilirubin gradı, Karaciğer metastazı, Kolorektal kanser, Prognostik faktör

How to cite / Atıf için: Demircan NC, Köstek O, Gökyer A, Küçükarda A, Hacıoğlu MB, Erdoğan B, Uzunoğlu S, Çiçin İ. The albumin-bilirubin (ALBI) grade as a significant prognostic factor in colorectal cancer patients with liver metastases. J Surg Med. 2019;3(12):841-844.

Introduction

Colorectal cancer (CRC) stands out as one of the most important causes of cancer-related deaths globally. Liver is the leading site of CRC dissemination, with 15-25% of patients having hepatic metastasis at initial presentation and up to 70% of patients will develop liver metastasis during the disease course [1,2]. Five-year survival of CRC with liver metastasis remains below 10% without curative treatment [1]. Various clinicopathological (e.g. performance status, tumor histology, tumor location) and biochemical (e.g. lactate dehydrogenase, carcinoembryogenic antigen, albumin) factors were identified to indicate prognosis of patients with metastatic CRC [3]. Nevertheless, there is no general consensus on their reliability and validated prognostic markers are still required for these patients.

The albumin-bilirubin (ALBI) score/grade is a novel method based on serum albumin and bilirubin levels that was demonstrated to predict mortality of acute-on-chronic liver failure and acute upper gastrointestinal bleeding in liver cirrhosis before [4,5]. From the oncological perspective, the first assessment of ALBI score/grade was in patients with hepatocellular carcinoma (HCC) and showed that it was an accurate prognostic model to indicate the severity of liver damage and to estimate the long-term survival of these patients [6]. Subsequent studies demonstrated the prognostic value of ALBI score/grade in HCC patients who were treated with different modalities like chemoembolization, radiofrequency ablation, radiotherapy or targeted agents [7-10].

Considering the fact that the prognostic value of ALBI score/grade in cancers except HCC is not elucidated sufficiently yet, we designed this study based on the hypothesis that it could predict survival in CRC patients with established liver metastases as an objective method.

Materials and methods

Study design

This study had a cross-sectional design. Medical files of colon and rectal cancer patients who were evaluated between February 2007 and September 2018 in our clinic were examined. Patients with histologically proven colorectal adenocarcinoma who had liver metastases at the time of diagnosis or developed them later were included. Synchronous or metachronous dissemination to other sites than liver did not preclude from enrollment to the study. Gender, age, primary tumor location and date of first liver metastasis and date of exitus or last visit were acquired from the files. Date of first liver metastasis was accepted as the date of computed tomography, magnetic resonance imaging or positron emission tomography in which liver metastasis was first documented. Having access to the registry system of our institute, we recorded serum albumin, total bilirubin, carcinoembryogenic antigen (CEA), lactate dehydrogenase (LDH) levels and complete blood counts at the time of first liver metastasis (these parameters were routinely tested at baseline and then periodically in our clinic). An approval for this study was granted by Trakya University Faculty of Medicine Clinical Trials Ethics Committee on 14 January 2019 (Protocol code: 2018/334).

Calculation of ALBI scores and categorization of prognostic factors

ALBI score was calculated using the formula of linear prediction model in its original study: ($\log_{10}$ bilirubin x 0.66) + (albumin x -0.085) [2]. Bilirubin and albumin in this equation are measured in μmol/L and g/L, respectively. According to the original research again, patients were assigned into three prognostic groups: ≤-2.60 as ALBI grade 1, >-2.60 and ≤-1.39 as ALBI grade 2 and >-1.39 as ALBI grade 3.

Upper limits of normal for serum total bilirubin, LDH, CEA and lower limit of normal for serum albumin in the institutional laboratory of biochemistry were set as cut-off values. Consequently, patients were categorized into two groups (below and above the cut-off value) for these variables. Neutrophil-to-lymphocyte ratio (NLR) of each patient was calculated using complete blood counts. A receiver operating characteristic (ROC) curve was constructed to determine a cut-off value for NLR and the most sensitive value for prediction of survival was accepted in the case of a statistically significant area under curve (AUC). Simultaneously, distribution of NLR was tested with Kolmogorov-Smirnov method for normality. Patients were also categorized into two groups of primary tumor side for prognostication: Left colon (from rectum to splenic flexure) and right colon (from caecum to hepatic flexure) or transverse colon. Age at the time of liver metastasis was included in the analyses with a cut-off of 65 years.

Statistical analysis

Overall survival (OS) was accepted as the time interval between the detection of liver metastasis and date of exitus or last visit (final update on September 27th, 2018). Probability of survival was tested with Kaplan-Meier method and comparison of survival for each factor was done using a stratified log-rank test. Factors with a *P*-value of <0.05 were selected for multivariate analysis. Cox regression model was utilized to determine independent predictors of survival and their hazard ratios (HRs), these were analyzed in a backward stepwise method. Since ALBI score results from an equation including albumin and bilirubin which are potential prognostic indicators themselves, two separate multivariate models were conducted: Model 1 that included serum albumin and bilirubin without ALBI grade and Model 2 that included ALBI grade without these two variables. Confidence interval (CI) was set as 95% and a 2-sided *P*-value as <0.05 for statistical significance. SPSS software (IBM Corp. Released 2013. IBM SPSS Statistics For Windows, Version 21.0. Armonk, NY: IBM Corp.) was used for all statistical analyses.

Results

Patient characteristics

A total of 223 patients were included in the study. Median age of the patients at the time of documented liver metastasis was 63 (55-70) years. Patients who were 65 years old or older made up 42.2% of the study population. The proportion of male patients was 67.7%. Primary tumor was located in left colon in 79.4% of patients. LDH was above the cut-off value (246 U/L) in 117 patients (52.5%). For CEA, upper limit of normal was 5 ng/mL in our institute and 156 patients (70%) were above this threshold. ROC curve analysis for NLR resulted in a

statistically insignificant AUC (0.567; 95% CI, 0.465-0.668; P=0.20). Therefore, a normality test was done and a median NLR of 2.9 was accepted as the cut-off value considering the distribution was not normal (P<0.001). Percent of patients with a NLR of 2.9 or more was 50.2 in our study.

Fifty-one patients (22.9%) had a serum albumin level lower than 3.5 g/dL and 29 patients (13%) had a serum bilirubin level more than 1.2 mg/dL. ALBI scores of all patients ranged between -0.14 and -3.61 (median: -2.69). ALBI grade was 1 in 126 of the patients (56.5%), 2 in 81 patients (36.3%) and 3 in 16 patients (7.2%). Table 1 summarizes the baseline characteristics of the patients.

Survival outcomes

Median follow-up time in the study was 19.7 months (95% CI, 17.3-22.3). At the final update, death has occurred in 187 patients (83.9%). In patients with ALBI grade 1, 1- and 2-year survival rates were 80% and 50% respectively. For ALBI grade 2, these rates were 62% and 29%, respectively. Patients who had an ALBI grade of 3 had a 1-year survival rate of 25% and 2-year survival rate of only 8%. Median OS in ALBI grade 1, 2 and 3 groups were 23.9, 16.0 and 4.0 months, respectively (P<0.001) (Figure 1).

Univariate analyses of all prognostic factors are shown in Table 2. Besides ALBI grade, advanced age (≥65 years), primary tumor location, higher baseline serum LDH, CEA and total bilirubin levels, a lower baseline serum albumin level and a higher baseline NLR were all found to affect OS significantly. In the multivariate Model 1 including serum albumin and total bilirubin and excluding ALBI grade (displayed in Table 3), age ≥65 years, higher LDH and CEA levels, a higher NLR and a lower albumin level (HR=1.97, P=0.001) were detected as independent prognostic factors while higher total bilirubin was not (HR=1.43, P=0.17). In the multivariate Model 2 excluding serum albumin and total bilirubin, ALBI grade 2 (HR=1.54, P=0.02) and grade 3 (HR=3.85, P<0.001) were both independent predictors of survival after adjusting for other factors (Table 3).

Table 1: Baseline demographical and clinical characteristics of the patients

Variable	Number of patients (%)
Gender	
Male	151 (67.7)
Female	72 (32.3)
Age (years)	
<65	129 (57.8)
≥65	94 (42.2)
Primary tumor location	
Left colon	177 (79.4)
Right or transverse colon	44 (19.7)
Unknown	2 (0.9)
LDH (U/L)	
≤246	95 (42.6)
>246	117 (52.5)
Unknown	11 (4.9)
CEA (ng/mL)	
≤5	37 (16.6)
>5	156 (70)
Unknown	30 (13.4)
NLR	
<2.9	111 (49.8)
≥2.9	112 (50.2)
Albumin (g/dL)	
<3.5	51 (22.9)
≥3.5	172 (77.1)
Total bilirubin (mg/dL)	
≤1.2	194 (87)
>1.2	29 (13)
ALBI grade	
1	126 (56.5)
2	81 (36.3)
3	16 (7.2)

LDH: Lactate dehydrogenase, CEA: Carcinoembryogenic antigen, NLR: Neutrophil-to-lymphocyte ratio

Table 2: Univariate analysis of prognostic factors for overall survival

Factor	OS in months (95% CI)	1-year survival (%)	2-year survival (%)	P-value for OS
Gender				
Male	20.1 (16.9-23.4)	68	42	0.17
Female	18.3 (13.1-23.4)	72	35	
Age (years)				
<65	22.4 (17.5-27.2)	76	48	0.01
≥65	14.1 (10.5-17.8)	61	28	
Primary tumor location				
Left colon	20.4 (17.9-22.9)	75	42	0.006
Right or transverse colon	11.6 (9.5-13.7)	49	28	
LDH (U/L)				
≤246	23.3 (21.0-25.7)	79	48	<0.001
>246	15.8 (12.3-19.3)	62	33	
CEA (ng/mL)				
≤5	24.0 (11.7-36.3)	89	54	0.001
>5	18.8 (16.0-21.6)	68	39	
NLR				
<2.9	23.9 (19.7-28.1)	77	50	<0.001
≥2.9	16.1 (12.4-19.8)	62	29	
Albumin (g/dL)				
<3.5	9.1 (1.6-16.6)	45	18	<0.001
≥3.5	22.0 (19.0-25.0)	77	46	
Total bilirubin (mg/dL)				
≤1.2	21.4 (18.8-24.0)	73	43	<0.001
>1.2	8.5 (0.0-18.5)	45	16	
ALBI grade				
1	23.9 (19.6-28.1)	80	50	<0.001
2	16.0 (11.9-20.1)	62	29	
3	4.0 (3.2-4.9)	25	8	

OS: Overall survival, CI: Confidence interval, LDH: Lactate dehydrogenase, CEA: Carcinoembryogenic antigen, NLR: Neutrophil-to-lymphocyte ratio

Table 3. Multivariate Models 1 and 2 evaluating prognostic factors for overall survival

Factor	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	2.30 (1.60-3.30)	<0.001	2.28 (1.57-3.31)	<0.001
Primary tumor location	1.40 (0.92-2.12)	0.12	1.25 (0.81-1.93)	0.31
LDH	1.47 (1.03-2.11)	0.03	1.47 (1.03-2.10)	0.03
CEA	1.88 (1.19-2.98)	0.007	1.93 (1.22-3.05)	0.005
NLR	1.99 (1.39-2.86)	<0.001	2.09 (1.46-2.99)	<0.001
Albumin	1.97 (1.32-2.95)	0.001		
Total bilirubin	1.43 (0.86-2.37)	0.17		
ALBI grade				
Grade 1			Reference	
Grade 2			1.54 (1.08-2.20)	0.02
Grade 3			3.85 (1.85-8.00)	<0.001

HR: Hazard ratio, CI: Confidence interval, LDH: Lactate dehydrogenase, CEA: Carcinoembryogenic antigen, NLR: Neutrophil-to-lymphocyte ratio

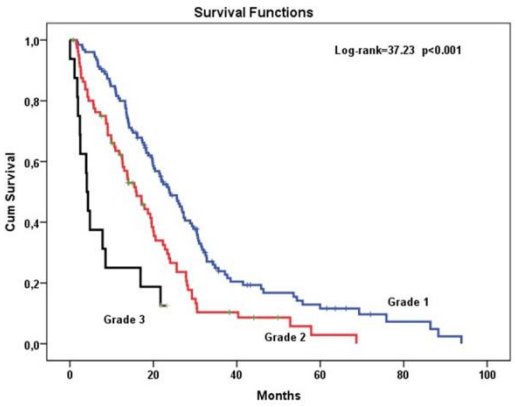

Figure 1: Kaplan-Meier plots stratified by ALBI grade (The horizontal and vertical axes show overall survival and cumulative survival rate, respectively)

Discussion

In our study, we revealed that ALBI grade may be a valuable prognostic tool for CRC patients with liver metastases and can remarkably predict their survival. In addition, advanced age, serum albumin, LDH and CEA levels and NLR were significantly associated with mortality of these subjects. The importance of ALBI grade is related to its potential to identify patients with liver-metastatic CRC who will have unfavorable outcomes at initial presentation.

The validation study of ALBI score/grade in HCC has placed Child-Pugh score, which is a standardized predictive and prognostic model in patients with liver cirrhosis and HCC, as a comparator [6]. Unfortunately, there are no such standard

prognostic models established in CRC yet. Köhne's model including performance status, white blood cell count, serum alkaline phosphatase level and number of metastatic sites was evaluated in two metastatic CRC studies and was shown to be applicable in these patients [11,12]. However, its prognostic value may be controversial because it does not contain serum LDH level which was addressed as an important prognostic factor by many studies regarding metastatic CRC [13-15]. Another simplified model consisting of serum LDH and performance status was shown to discriminate better than Köhne's model but it has not found general use either [13]. In our study, we evaluated other objective prognostic parameters concurrently and observed that ALBI grade was an independent predictor of survival.

Albumin is a nutritional and inflammatory marker produced by the liver, it was first reported as a prognostic factor in CRC by Heys et al. [16]. Subsequent studies highlighted its value in predicting long-term outcomes of CRC patients [17,18]. On the other hand, bilirubin has no known physiologic role but along albumin, it is a major determinant of the hepatic functional status in chronic liver disease and HCC. Limited data exists about the prognostic value of serum bilirubin in CRC. Zhang et al. [19] associated higher serum bilirubin levels with reduced OS in resected stage II and III CRC, while Yang et al. [20] demonstrated its prognostic impact in stage IV disease. After adjusting for other factors in our study, serum albumin independently predicted overall survival whereas total bilirubin did not. In contrast, ALBI grade was an independent negative prognostic factor in a second multivariate analysis, with a 1.5- and 3.9-fold increased risk of death for ALBI grades 2 and 3, respectively. Especially, baseline ALBI grade 3 could predict shorter survival prior to treatment. It is controversial which cut-off value of serum albumin should be used to determine worse prognosis. Therefore, we suggest that ALBI score/grade may be a reliable and universally applicable objective model for estimating outcomes of CRC patients with liver metastases.

LDH is considered as a major prognostic indicator in many published CRC studies. Likewise, CEA is obviously a marker affecting long-term survival of stage IV CRC patients [21]. Our analyses show that higher LDH and CEA are associated with an approximately 1.5- and 1.9-fold increased risk for death in liver-metastatic CRC, respectively. Additionally, A NLR of ≥3 was confirmed to correlate with worse survival in metastatic CRC treated with first-line systemic therapy by Dell'Aquila et al. [22] before. Having used a close cut-off (≥2.9), we have shown that NLR is a markedly significant predictor of overall survival in metastatic CRC with liver metastases as well. On the other hand, impact of age on CRC prognosis has been more arguable than the above-mentioned parameters. Jiang et al. [23] showed in a large study population that younger CRC patients had longer OS in all stages despite presenting with more adverse features. Contrarily, Fu et al. [24] stated that young adults with advanced CRC had worse survival compared to their older counterparts and age was not an independent prognostic factor. Patients who were 65 years old or older had worse OS in our study and advanced age was independently associated with over 2-fold higher risk of death compared to patients younger than 65 years. Although aging is a heterogeneous process, our result may be in part explained by increasing comorbidities and declining of performance status that could contribute to the impact of advanced age on the outcomes of the patients.

Limitations

There were some limitations in this study. We could not evaluate performance status, which is an established prognostic factor in many cancers, because of largely missing data in patient files. Another issue that could be addressed by future studies is how ALBI score/grade would perform in CRC patients with only extrahepatic metastases.

Conclusion

Our study shows that a higher baseline ALBI grade is associated independently with poor overall survival in CRC patients with liver metastases. It may be an useful method in metastatic CRC, for which a generally acceptable prognostic model has to emerge yet.

References

1. Manfredi S, Lepage C, Hatem C. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006;244(2):254-9.
2. Van de Velde C. Treatment of liver metastases of colorectal cancer. Ann Oncol. 2005;16(Supplement 2):144-9.
3. De Divitiis C, Nasti G, Montano M, Fisichella R, Iaffaioli RV, Berretta M. Prognostic and predictive response factors in colorectal cancer patients: Between hope and reality. World J Gastroenterol. 2014;20(41):15049-59.
4. Chen B, Lin S. Albumin-bilirubin (ALBI) score at admission predicts possible outcomes in patients with acute-on-chronic liver failure. Medicine. 2017;96:24(e7142).
5. Zou D, Qi X, Zhu C. Albumin-bilirubin score for predicting the in-hospital mortality of acute upper gastrointestinal bleeding in liver cirrhosis: A retrospective study. Turk J Gastroenterol. 2016;27:180-6.
6. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach—The ALBI Grade. J Clin Oncol. 2015;33:550-8.
7. Hiraoka A, Kumada T, Kudo M, Hirooka M, Tsuji K, Itobayashi E, et al. Albumin-bilirubin (ALBI) grade as part of the evidence-based clinical practice guideline for HCC of the Japan Society of Hepatology: A comparison with the Liver Damage and Child-Pugh Classifications. Liver Cancer. 2017;6:204-15.
8. Ho C, Chiang C, Lee F. Comparison of platelet-albumin-bilirubin (PALBI), albumin-bilirubin (ALBI), and child-pugh (CP) score for predicting of survival in advanced HCC patients receiving radiotherapy (RT). Oncotarget. 2018;9(48):28818-29.
9. Hansmann J, Evers MJ, Bui JT, Lokken RP, Lipnik AJ, Gaba RC, et al. Albumin-bilirubin and platelet-albumin-bilirubin grades accurately predict overall survival in high-risk patients undergoing conventional transarterial chemoembolization for hepatocellular carcinoma. J Vasc Interv Radiol. 2017;28:1224-31.
10. Ho S, Liu P, Hsu C, Chiou Y, Su C, Lee Y, et al. Prognostic performance of ten liver function models in patients with hepatocellular carcinoma undergoing radiofrequency ablation. Sci Rep. 2018;8:843.
11. Díaz R, Aparicio J, Gironés R, Molina J, Palomar L, Segura A, et al. Analysis of prognostic factors and applicability of Köhne's prognostic groups in patients with metastatic colorectal cancer treated with first-line irinotecan or oxaliplatin-based chemotherapy. Clin Colorectal Cancer. 2005;5:197-202.
12. Sanoff HK, Sargent DJ, Campbell ME, Morton RF, Fuchs CS, Ramanathan RK, et al. Five-year data and prognostic factor analysis of oxaliplatin and irinotecan combinations for advanced colorectal cancer: N9741. J Clin Oncol. 2008;26:5721-27.
13. Chibaudel B, Bonnetain F, Tournigand C. Simplified prognostic model in patients with oxaliplatin-based or irinotecan-based first-line chemotherapy for metastatic colorectal cancer: A GERCOR study. The Oncologist. 2011;16:1228-38.
14. Li G, Wang Z, Xu J, Wu H, Cai S, He Y. The prognostic value of lactate dehydrogenase levels in colorectal cancer: a meta-analysis. BMC Cancer. 2016;16:249.
15. Passardi A, Scarpi E, Tamberi S, Cavanna L, Tassinari D, Fontana A, et al. Impact of pre-treatment lactate dehydrogenase levels on prognosis and bevacizumab efficacy in patients with metastatic colorectal cancer. PLoS ONE. 2015;10(8):e0134732.
16. Heys SD, Walker LG, Deehan DJ, Eremin OE. Serum albumin: a prognostic indicator in patients with colorectal cancer. J R Coll Surg Edinb. 1998;43(3):163-8.
17. Lai CC, You JF, Yeh CY, Chen JS, Tang R, Wang JY, et al. Low preoperative serum albumin in colon cancer: a risk factor for poor outcome. Int J Colorectal Dis. 2011;26:473-81.
18. Chandrasinghe PC, Ediriweera DS, Kumarage SK, Deen KI. Pre-operative hypoalbuminaemia predicts poor overall survival in rectal cancer: a retrospective cohort analysis. BMC Clin Pathol. 2013;13:12.
19. Zhang Q, Ma X, Xu Q, Qin J, Wang Y, Liu Q, et al. Nomograms incorporated serum direct bilirubin level for predicting prognosis in stages II and III colorectal cancer after radical resection. Oncotarget. 2017;8(41):71138-46.
20. Yang L, Ge LY, Yu T, Liang Y, Yin Y, Chen H. The prognostic impact of serum bilirubin in stage IV colorectal cancer patients. J Clin Lab Anal. 2018;32(2).
21. Hsu CW, King TM, Chang MC, Wang CH. Factors that influence survival in colorectal cancer with synchronous distant metastasis. J Chin Med Assoc. 2012;75:370-5.
22. Dell'Aquila E, Cremolini C, Zeppola T, Lonardi S, Bergamo F, Masi G, et al. Prognostic and predictive role of neutrophil/lymphocytes ratio in metastatic colorectal cancer: a retrospective analysis of the TRIBE study by GONO. Ann Oncol. 2018;29:924-30.
23. Jiang Z, Wang X, Tan X, Fan Z. Effect of age on survival outcome in operated and non-operated patients with colon cancer: A population-based study. PLoS ONE. 2016;11(1):e0147383.
24. Fu J, Yang J, Tan Y, Jiang M, Wen F, Huang Y, et al. Young patients (≤35 years old) with colorectal cancer have worse outcomes due to more advanced disease. Medicine. 2014;93(23):e135.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):845-847.
DOI: 10.28982/josam.650891

Research article
Araştırma makalesi

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

Hepatitis B, Hepatitis C and HIV seroprevalence among Syrian refugees: A cross-sectional study from a tertiary referral center in Turkey

Suriyeli mülteciler arasında Hepatit B, Hepatit C ve HIV seroprevalansı: Türkiye'deki bir üçüncü basamak merkezinden kesitsel bir çalışma

Ayhanım Tümtürk [1], Bayram Yeşil [2]

[1] Department of Infectious Diseases and Clinical Microbiology, Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey
[2] Department of Gastroenterology, Turkiye Yuksek Ihtisas Training and Research Hospital, Ankara, Turkey

ORCID ID of the author(s)
AT: 0000-0002-0653-6725
BY: 0000-0002-9511-6836

Corresponding author / Sorumlu yazar:
Ayhanım Tümtürk
Address / Adres: Türkiye Yüksek Ihtisas Eğitim ve Araştırma Hastanesi, Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Kliniği, 06230, Altındağ, Ankara, Türkiye
e-Mail: ayhanim06@yahoo.com.tr

Ethics Committee Approval: This study was conducted with the approval of the Ethics Committee (SBÜ Ankara Yuksek Ihtisas Training and Research Hospital, approval number: 25.10.2018-58/29620911-929).
Etik Kurul Onayı: Bu çalışma Etik Kurul onayı ile yapıldı (SBÜ Ankara Yüksek İhtisas Eğitim ve Araştırma Hastanesi, onay numarası: 25.10.2018-58 / 29620911-929).

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: 12/22/2019
Yayın Tarihi: 22.12.2019

Abstract

Aim: Hepatitis B (HBV), Hepatitis C (HCV) and Human Immunodeficiency Virus (HIV) cause serious health problems all over the world. Due to the recent conflicts and war in Syria, many immigrants have entered Turkey in a controlled and / or uncontrolled manner. In this study, we aimed to determine HBV, HCV, and HIV seroprevalence among Syrian migrants who were referred to our hospital.

Methods: This cross-sectional study was performed between 01/01/2015 - 14/05/2018 in Ankara Yuksek Ihtisas Training and Research Hospital. Serum samples from patients were evaluated for positivity of HBV surface antigen (HBsAg), antibodies against HBV surface antigen (anti-HBs), HCV antibody (anti-HCV) and anti-HIV with the Enzyme-Linked Immunosorbent Assay (ELISA) method.

Results: Among 244 patients included in the study, 154 were male (63.11%) and 90 were female (36.89%). Seroprevalences of HBV were 5.84% and 5.55%, respectively, the difference between which was statistically insignificant (P>0.05). Anti-HCV was positive in 6 (2.46%) patients. HCV seroprevalence rates were 1.29% in men, and 4.44% in women. None of these 244 patients had anti-HIV positivity.

Conclusion: In our study, we found that the seroprevalences of HBV and Anti-HIV in Syrian migrants were similar to domestic values, but that of anti-HCV was higher. Age-related incidence rates also differed. We believe that the knowledge of these data is important in terms of planning preventive and therapeutic measures for migrants.

Keywords: Hepatitis B, Hepatitis C, Human immunodeficiency virus, Syrian refugees

Öz

Amaç: Hepatit B (HBV), Hepatit C (HCV) ve İnsan İmmün Yetmezlik Virüsü (HIV) tüm dünyada ciddi sağlık sorunlarına neden olmaktadır. Suriye'deki son çatışmalar ve savaş nedeniyle, birçok göçmen kontrollü ve / veya kontrolsüz bir şekilde Türkiye'ye girmiştir. Bu çalışmada hastanemize başvuran Suriyeli göçmenlerde HBV, HCV ve HIV seroprevalansının belirlenmesi amaçlandı.

Yöntemler: Bu kesitsel çalışma 01.01.2015 - 14.05.2018 tarihleri arasında Ankara Yüksek İhtisas Eğitim ve Araştırma Hastanesi'nde yapıldı. Hastalardan alınan serum örnekleri ELISA (Enzim-Bağımlı İmmunosorbent Testi) yöntemiyle çalışılarak, HBV yüzey antijeni (HBsAg), anti-HBs, HCV antikoru (anti-HCV) ve anti-HIV titreleri araştırıldı.

Bulgular: Çalışmaya alınan 244 hastanın 154'u erkek (%63,11), 90'ı kadındı (%36,89). HBV seroprevalansı erkekler ve kadınlar arasında anlamlı farklılık göstermedi ve sırasıyla %5,84 ve %5,55 olarak bulundu (P>0,05). Anti-HCV pozitif bulunan hasta sayısı 6 (%2,46) 6 idi. HCV seroprevalansı erkeklerde %1,29, kadınlarda %4,44 olarak bulundu. Bu 244 hastanın hiçbirinde anti-HIV pozitifliği tespit edilmedi.

Sonuç: Çalışmamızda Suriyeli göçmenlerde HBV ve Anti-HIV seroprevalansının lokal verilere benzer olduğunu, ancak anti-HCV pozitifliğinin lokal verilere göre daha yüksek olduğu gözlenmiştir. Yaşa bağlı insidans oranları da farklı bulundu. Bu verilerin bilinmesinin, göçmenler için önleyici ve terapötik önlemlerin planlanması açısından önemli olduğuna inanıyoruz.

Anahtar kelimeler: Hepatit B, Hepatit C, İnsan immün yetmezlik virüsü, Suriyeli mülteciler

How to cite / Atıf için: Tümtürk A, Yeşil B. Hepatitis B, Hepatitis C and HIV seroprevalence among Syrian refugees: A cross-sectional study from a tertiary referral center in Turkey. J Surg Med. 2019;3(12):845-847.

Introduction

Migration is a real phenomenon of population dynamics driven by socioeconomic, political, and environmental factors [1]. Due to its geographical location, our country receives many immigrants every year. Especially in recent years due to the conflict and war environment in Syria, a large number of people from this country have migrated permanently or temporarily. These immigrants bring many infectious diseases, which endanger the health of both migrant and host populations [2]. HBV and HCV-induced infections can lead to the development of chronic liver diseases, cirrhosis, and hepatocellular carcinoma. HIV infection can also lead to the development of serious opportunistic diseases. It is important to know the current prevalence of these diseases to create proper health policies for these groups.

Materials and methods

This retrospective study was conducted on 244 Syrian immigrant patients who were referred to Ankara Yuksek İhtisas Training and Research Hospital between 01/01/2015-14/05/2018. The approval for the study was obtained from the local Institutional Ethics Committee. Serum samples from patients were evaluated for positivity of HBV surface antigen (HBsAg), antibodies against HBV surface antigen (anti-HBs), HCV antibody (anti-HCV) and anti-HIV using the ELISA method, which is a popular format of analytic biochemistry assay that uses a solid-phase enzyme immunoassay to detect the presence of a substance, usually an antigen, in a liquid or wet sample.

Statistical analysis

SPSS statistical software v.25 was used for statistical analysis. Mann-Whitney U test was used to compare dependent variables according to gender. Kruskal-Wallis test was used to compare dependent variables according to age groups. *P*-value <0.05 was considered statistically significant.

Results

Hepatitis markers and anti-HIV results of 244 Syrian patients were evaluated, of which 154 were male (63.11%) and 90 were female (36.89%). The mean age of all patients and the age range were 32.6 years (23.249) and 1-94 years, respectively. 78 patients were aged below 15 years (31.97%), 65 were aged between 16-40 years (26.64%), 31 were aged between 41-50 years (12.70%), and 70 were aged above 51 years (28.69%). Anti-Hbs positivity was found in 71 (29.10%) patients. A total of 14 patients, 9 males and 5 females, had HBsAg positivity (5.74%). Seroprevalences of HBV were 5.84% and 5.55%, respectively, the difference between which was statistically insignificant (p=0.952). The mean ages of males and females with HBsAg positivity were 43 (1-63) and 34 (11-55) years, respectively. Anti-HCV was positive in 4 female and 2 male patients (2.46%). HCV seroprevalence was 1.29% in males, and 4.44% in females (*P*=0.123). The mean ages of females and males with anti-HCV positivity were 32 (1-48) and 62 (53 and 71) years, respectively. None of these 244 patients had anti-HIV positivity (Table 1, Table 2).

Table 1: Distribution of HBV, HCV and HIV sero-prevalence according to gender

Serology	Males (n) (%)	Females (n) (%)	*P*-value	Total (n) (%)
Anti-Hbs (+)	50 (32.4%)	21 (23.3%)	0.106	71 (29.1%)
HBsAg (+)	9 (5.8%)	5 (5.5%)	0.952	14 (5.7%)
Anti-HCV (+)	2 (1.2%)	4 (4.4%)	0.123	6 (2.4%)

Table 2: Age distribution of cases possessing HBsAg, anti-Hbs, anti- HCV positivity

Age	Anti-Hbs(+)	HBsAg (+)	Anti-HCV(+)
0-15	32 (41%)	3 (3.8%)	1 (1.2%)
16-40	7 (10.7%)	3 (4.6%)	1 (1.5%)
41-50	4 (12.9%)	1 (3.2%)	2 (6.4%)
>50	28 (40%)	7 (10%)	2 (2.8%)
P-value	<0.001	0.338	0.432

Discussion

In the recent years, millions of people in the world have migrated in the hope of finding better living conditions in developed countries by abandoning their own homeland due to wars, socioeconomic, political and environmental reasons. According to recent statistics, 244 million international immigrants have been reported worldwide [1]. Due to the growing war in the region in recent years, Turkey has opened its doors to many refugees. According to the data provided by General Directorate of Migration, there are 3.567.658 Syrian Refugees living under temporary protection in Turkey as of 2018. About 20% of these refugees are reportedly younger than 5 years and 53% are under 18 years of age. High mobility, poor living conditions, barriers to access to health care, potential public health risks for the new immigrant population and the host population are among the most important public health concerns [2]. The management of health problems of such a large population is also of great importance and therefore, health professionals should be aware of problems with screening, diagnosis and treatment of non-endemic infections [3].

According to the World Health Organization, the global prevalence of viral hepatitis may be as high as 500 million and the annual mortality rate, as much as 1.3 million [4]. The available evidence suggests that the prevalence of HBV and HCV in migrants reflects the countries of origin [1]. This large migration from the areas where viral hepatitis prevalence is high is a major burden on the health systems of host countries. Because of the lack of universal standards for screening, protection and treatment of viral hepatitis, the burden of chronic liver disease and hepatocellular carcinoma is increasing among the immigrant population [2].

Although the majority of Middle Eastern countries have shown that HBV infection, which is a serious public health problem in the region, is moderately or highly endemic, the situation of the Syrian Republic remains unclear [5]. In 1991, HBV vaccine was included in the vaccination program in Syria. In a study conducted on 3168 randomly selected individuals by the Syrian Ministry of Health in 2004, the rate of HCV seroprevalence was 2.1% and hepatitis B surface antigen (HBsAg) was reported as 5.6%. However, there was a significant regional variation in prevalence: The seroprevalence of HBV and HCV in the northern region of the country was reportedly 10.14% and 10.5%, respectively, and the seroprevalence of HBV in the north-eastern region was 10.6% [5,6]. Since 2011, when the conflict began, vaccination rates have fallen significantly [7]. A meta-analysis done by Chemaitelly et al. [8] focused on HCV seroprevalence among the Syrian population and reported a high rate in hemodialysis patients ranging from 48.8% to 75%. They also reported the HCV seroprevalence in drug users and

hemophiliacs, respectively, were %21 and %20.5. The prevalence of HCV in the general population ranged between 0.3% and 0.9% among blood donors. Yazaji et al. [9] reported that anti-HCV positivity was 11.32% in a study of 159 multi-transfusion patients in Syria. In a study conducted by Muselmani and his colleagues [10]. in Syria between 3896 donors, HBsAg was found positive in 66 subjects and anti-Hbc was positive in 63 donorsIn their study in Syria, Antaki et al. [11] stated that the rate of chronic hepatitis B was between 5% and 7%.

Referring to the studies reported from Turkey, HBsAg positivity is between 1.01% - 3.96%, anti-HCV positivity is between 0.4% and 1.57% and it was observed that there are differences between regions (Table 3). In a systematic review of the studies conducted between 1999 and 2009 in our country, it was reported that HBsAg positivity was 4.6% and about 3.3 million people were infected with chronic HBV. The lowest prevalence was in the 0-14 age group (2.8%) and the highest prevalence was in the 25-34 age group (6.3%) [12]. Again, in a study published in our country in 2012, it was reported that the prevalence of anti-HCV was between 0.5% and 1% in participants [13]. In our study, HBsAg was found positive in 5.74% of the Syrian patients who were referred to our hospital, similar to other local data. The highest prevalence was found in the group aged 50 years and older (10%) followed by the group aged between 0-15 (3.85%). Anti HCV (+) was found to be 2.46% in this study. Syria has low prevalence with very low HIV levels. A total of 762 HIV / AIDS cases have been reported between 1987 and 2011 [14]. In our study, we did not find any anti-HIV positivity in any of our patients. In their study among 300 Syrian migrants, Inci and et al reported comparable results: Rates of HBsAg, Anti-HCV (+) and anti-HBs positivity were 3%, 2.3% and 26.6%, respectively. None of the patients had anti-HIV positivity [15].

Hussein et al. [16] conducted a study in Duhok, a region of Southern Iraq, which contains a large number of Syrian refugees, and determined HBsAg positivity as 3.86% among 880 refugees. This rate was 4.43% for men and 3.37% for women. They also reported that they did not encounter any HCV positivity. Kose et al. [17] conducted a study among 171 Syrian children aged between 0-18 years, in which the positivity rates of HBsAg, anti-Hbs, anti-HCV and anti-HIV were 4.2%, 52.8%, 1.8% and 2.2%, respectively. Angeletti et al. [18] studied 48 Syrian refugees in Italy to report that none of the 30 immigrants whose serum samples were obtained were positive for HBV, HCV, or HIV infections. Only 9 cases were positive for anti-Hbs. In another study from Italy conducted among 1212 migrants with low-income groups, HBsAg positivity was reported as 9.6%, anti-HCV positivity as 3.7% and anti-HIV positivity as 1.7% [19].

Table 3: HBV, HCV and HIV prevalence in different cities of Turkey

Study	Year	City	Anti-Hbs (%)	HbsAg (%)	Anti-HCV (%)	Anti-HIV (%)
İnci et al. [20]	2013	Artvin	35.6	3.96	0.85	0.05
Öner et al. [21]	2011	Mersin	-	2.2	0.4	0.2
Denk et al. [22]	2016	Elazig	-	3.71	1.57	0.03
Köse et al. [23]	2015	Izmir	-	1.01	0.51	0.04
Pehlivanoğlu et al. [24]	2011	Istanbul	-	3.27	0.65	-
Çoban et al. [25]	2013	Ankara	43.9	2.54	0.55	-

Limitations

This study has some limitations. First, we were able to research Hepatitis B, Hepatitis C and HIV seroprevalence among Syrian refugees in a single center. Second, the number of patients in study groups is small. Further large-scale, multicenter studies are needed.

Conclusion

The mass migration waves in recent years compel countries to prepare more comprehensive programs in terms of migration health and communicable diseases. It is important for policy makers and health professionals to create comprehensive, evidence-based, and standardized health programs for immigrants to protect both the immigrant health and the health of the host population. Developing appropriate guidance on hepatitis and HIV is a priority.

Although the number of cases in our age group was low, we found differences in the prevalence of HBV and HCV among age groups. We think that it is important to know these local data in order to create appropriate health policies for age groups. Since our study was a retrospective study, the medical history and risk factors of the patients could not be obtained. Therefore, our results may not reflect the serological data of all Syrian migrants. There is a need for multi-center studies in which more Syrian refugees are evaluated.

References

1. Castelli F, Sulis G. Migration and infectious diseases. Clin Microbiol Infect. 2017 May;23(5):283-9.
2. Pottie K, Mayhew AD, Morton RL, Greenaway C, Akl EA, Rahman P, et al. Prevention and assessment of infectious diseases among children and adult migrants arriving to the European Union/European Economic Association: a protocol for a suite of systematic reviews for public health and health systems. BMJ Open. 2017 Sep 11;7(9):e014608.
3. McCarthy AE, Weld LH, Barnett ED, So H, Coyle C, Greenaway C, et al. Spectrum of illness in international migrants seen at GeoSentinel clinics in 1997-2009, part 2: migrants resettled internationally and evaluated for specific health concerns. Clin Infect Dis. 2013 Apr;56(7):925-33.
4. Sharma S, Carballo M, Feld JJ, Janssen HL. Immigration and viral hepatitis. J Hepatol. 2015 Aug;63(2):515-22.
5. Yacoub R, Al Ali R, Moukeh G, Lahdo A, Mouhammad Y, Nasser M. Hepatitis B vaccination status and needlestick injuries among healthcare workers in syria. J Glob Infect Dis. 2010 Jan;2(1):28-34.
6. Bashour H, Muhjazi G. Hepatitis B and C in the Syrian Arab Republic: a review. East Mediterr Health J. 2016 Jul 10;22(4):267-73.
7. WHO, Syrian Arab Republic: Annual Report 2017. 2017.
8. Chemaitelly H, Chaabna K, Abu-Raddad LJ. The Epidemiology of Hepatitis C Virus in the Fertile Crescent: Systematic Review and Meta-Analysis. PLoS One. 2015 Aug 21;10(8):e0135281.
9. Yazaji W, Habbal W, Monem F. Seropositivity of Hepatitis B and C among Syrian Multi-transfused Patients with Hemoglobinopathy. Mediterr J Hematol Infect Dis. 2016 Sep 1;8(1):e2016046.
10. Muselmani W, Habbal W, Monem F. Prevalence of "anti-HBc alone" among Syrian blood donors. J Infect Dev Ctries. 2014 Aug 13;8(8):1013-5.
11. Antaki N, Haffar S, Ali Deeb S, Assaad F, Abou Harb R, Zeibane N, et al. High prevalence of HBV genotype D in Syria and the clinical characteristics of hepatitis B e antigen-negative chronic hepatitis B. Epidemiol Infect. 2010 Jan;138(1):40-4.
12. Toy M, Önder FO, Wörmann T, Bozdayi AM, Schalm SW, Borsboom GJ, et al. Age- and region-specific hepatitis B prevalence in Turkey estimated using generalized linear mixed models: a systematic review. BMC Infect Dis. 2011;11:337.
13. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21:1020-6.
14. Syrian Arab Republic - Global AIDS Response Progress Report 2012. Overview of the AIDS Epidemic in Syria. Country progress report Syrian Republic.
15. İnci A, Sarıcı İŞ, Çalışkan G, Kalaycı MU. Investigation of Frequency of HBsAg, Anti Hbs, Anti HCV and Anti HIV in Refugee Patients from Syria who Admit to a Training and Research Hospital Department of Surgery. Acta Medica Mediterranea, 2017;33:59.
16. Hussein NR, Abdullah IM, Younus OM, Taher AM, Salim AA, Shahab FI. Prevalence of HBV, HCV and HIV Infections Among Syrian Refugees in Kurdistan Region, Iraq. Int J Infect. 2017 April;4(2):e39420.
17. Köse Ş, Ödemis İ, Çelik D, Tatar BG, Akbulut İ, Çiftdoğan DY. Hepatitis A, B, C and HIV seroprevalence among Syrian refugee children admitted to outpatient clinics. Le Infezioni in Medicina. 2017;4:339-43.
18. Angeletti S, Ceccarelli G, Vita S, Dicuonzo G, Lopalco M, Dedej E, et al. Unusual microorganisms and antimicrobial resistances in a group of Syrian migrants: Sentinel surveillance data from an asylum seekers centre in Italy. Travel Med Infect Dis. 2016 Mar-Apr;14(2):115-22.
19. Coppola N, Alessio L, Gualdieri L, Pisaturo M, Sagnelli C, Minichini C, et al. Hepatitis B virus infection in undocumented immigrants and refugees in Southern Italy: demographic, virological, and clinical features. Infect Dis Poverty. 2017 Feb 9;6(1):33.
20. İnci A, Okay M, Güven D. HBsAg, Anti-HBs, Anti-HCV and Anti-HIV Seroprevalence of the Patients Applied to Artvin State Hospital. Viral Hepatitis Journal. 2013;19(1):41-4.
21. Öner S, Yapıcı G, Şaşmaz CT, Kurt AÖ, Buğdaycı R. Hepatitis B, hepatitis C, HIV, and VDRL seroprevalence of blood donors in Mersin, Turkey. Turk J Med Sci. 2011;41(2):335-41.
22. Denk A, Balin ŞÖ. Koroner Anjiyografi Yapılan Hastalarda HBsAg, Anti-HCV ve Anti-HIV Seropozitifliği. Firat Med J. 2016;21(3):125-8.
23. Köse Ş, Ersan G, Liv F. Six-Year Analysis of the Seropositivity of HBV, HCV, HIV, and Syphilis in Volunteer Blood Donors Attending Our Blood Center. Viral Hepat J. 2015;21(1):28-30.
24. Pehlivanoğlu F, Yaşar KK, ŞENGÖZ G. Seroprevalences of Hepatitis B and C in Patients undergoing an Operation. Viral Hepat J. 2011;17:32-6.
25. Çoban M, Sertoğlu E. HBs Ag, Anti-HBs, Anti-HBc Total and Anti-HCV Seroprevalence of the Patients Applied to Beytepe Military Hospital. Viral Hepat J. 2013;19(3):152-5.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):848-851.
DOI: 10.28982/josam.659787

Research article
Araştırma makalesi

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

Effect of hyperemesis gravidarum on maternal renal health: An investigation of the levels of neutrophil gelatinase-associated lipocalin in maternal serum

Hiperemezis gravidarumun maternal böbrek sağlığı üzerine etkisi: Maternal serumda nötrofil jelatinaz ile ilişkili lipokalin düzeylerinin araştırılması

İlknur Çöl Madendağ [1], Mefküre Eraslan Şahin [1], Yusuf Madendağ [2], Erdem Şahin [2], Çiğdem Karakükçü [3]

[1] Department of Obstetrics and Gynecology, Kayseri City Hospital, Kayseri, Turkey
[2] Department of Obstetrics and Gynecology, Erciyes University Medicine Faculty, Kayseri, Turkey
[3] Department of Biochemistry, Kayseri City Hospital, Kayseri, Turkey

ORCID ID of the author(s)
İÇM: 0000-0001-6700-2236
MEŞ: 0000-0001-6484-9132
YM: 0000-0002-7622-2991
EŞ: 0000-0001-9492-6223
ÇK: 0000-0001-9858-3272

Corresponding author / Sorumlu yazar:
İlknur Çöl Madendağ
Address / Adres: Kayseri Şehir Hastanesi, Kadın Hastalıkları ve Doğum Bölümü, Kayseri, Türkiye
Melikgazi Kayseri, Türkiye
e-Mail: ilknurmadendag@gmail.com

Ethics Committee Approval: This study was conducted with the approval of the Ethics Committee of Erciyes University (decision number: 2019/375, 22/05/2019).
Etik Kurul Onayı: Bu çalışma Erciyes Üniversitesi Etik Kurulu (22/05/2019, 2019/375) onayı ile yapıldı.

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: 12/23/2019
Yayın Tarihi: 23.12.2019

Abstract

Aim: Hyperemesis gravidarum (HG) is a severe condition that occurs in 0.8–2.0% of pregnant women and can lead to kidney damage. Within minutes of ischemic perfusion injury, renal distal tubular cells release neutrophil gelatinase-associated lipocalin (NGAL). The aim of this study was to assess the levels of NGAL in maternal serum after HG onset and the association between HG severity, renal ischemia, and subsequent kidney damage.

Methods: In this case-control study, the control group comprised healthy volunteers with similar demographic characteristics. The HG patients were divided into three groups according to disease severity based on the Pregnancy-Unique Quantification of Emesis scale as follows: Mild (≤6); moderate (7–12); and severe (≥13). Demographic parameters, biochemical parameters, and serum NGAL levels were compared among the groups.

Results: Serum glucose, serum blood urea nitrogen, serum creatinine, serum phosphorus, aspartate aminotransferase, and alanine aminotransferase levels were similar among the groups. Serum sodium levels were significantly higher in the severe HG group than in all other HG groups. Urine osmolarity was significantly higher in the moderate and severe HG groups than in the control and mild HG groups. There were no differences in serum NGAL levels among the groups.

Conclusion: Our results suggested that serum NGAL levels were not altered in patients complicated by HG.

Keywords: Neutrophil gelatinase-associated lipocalin, Hyperemesis gravidarum, Dehydration

Öz

Amaç: Hiperemezis gravidarum (HG), hamile kadınların %0,8-2,0'ında meydana gelen ve böbrek hasarına yol açabilen ciddi bir durumdur. İskemik perfüzyon hasarı birkaç dakika içinde, renal distal tübüler hücreler, nötrofil jelatinaz ile ilişkili lipokalini (NGAL) serbest bırakır. Bu çalışmanın amacı HG başlangıcından sonra maternal serumdaki NGAL seviyelerini ve HG şiddeti ile böbrek iskemisi ve böbrek hasarı arasındaki ilişkiyi değerlendirmektir.

Yöntem: Kontrol grubu benzer demografik özelliklere sahip sağlıklı gönüllülerden oluşturuldu. HG hastaları Pregnancy-Unique Quantification of Emesis Ölçeğine göre hastalık şiddetine göre üç gruba ayrıldı: hafif (≤6); orta (7-12); ve şiddetli (≥13). Demografik parametreler, biyokimyasal parametreler ve serum NGAL düzeyleri gruplar arasında karşılaştırıldı.

Bulgular: Serum glukoz, serum kan üre azotu, serum kreatinin, serum fosfor, aspartat aminotransferaz ve alanin aminotransferaz düzeyleri gruplar arasında benzerdi. Serum sodyum seviyeleri şiddetli HG grubunda diğer tüm HG gruplarına göre anlamlı derecede yüksekti. İdrar ozmolaritesi orta ve şiddetli HG gruplarında kontrol ve hafif HG gruplarına göre anlamlı derecede yüksekti. Gruplar arasında serum NGAL düzeylerinde anlamlı fark yoktu.

Sonuç: Bulgularımız HG ile komplike olan hastalarda serum NGAL seviyelerinin değişmediğini göstermiştir.

Anahtar kelimeler: Neutrophil gelatinase-associated lipocalin, Hyperemesis gravidarum, Dehidrasyon

How to cite / Atıf için: Madendağ İÇ, Şahin MA, Madendağ Y, Şahin E, Karakükçü Ç. Effect of hyperemesis gravidarum on maternal renal health: An investigation of the levels of neutrophil gelatinase-associated lipocalin in maternal serum. J Surg Med. 2019;3(12):848-851.

Introduction

It is known that 50–90% of pregnant women between the 4th and 16th gestational weeks experience nausea and vomiting; however, if this becomes severe and requires hospitalization, which occurs in 0.8–2.0% of the women, before the 20th gestational week, the condition is defined as hyperemesis gravidarum (HG) [1,2]. Malnutrition, electrolyte imbalance, and dehydration are the clinical findings associated with HG [4-6]. Sahin et al. [6,7] have reported that severe HG is associated with maternal endothelial dysfunction and increased bone resorption.

Neutrophil gelatinase-associated lipocalin (NGAL), also known as lipocalin-2, is a 25-kDa glycoprotein found in human neutrophil granules [8]. Renal distal tubular cells release NGAL within minutes of ischemic perfusion injury and its levels in serum and urine are biochemical markers which can be used to detect very early stages of acute renal injury [9,10]. It has been reported that the plasma concentration of NGAL increases 3-fold within 2 hours of acute renal injury and 10-fold within 3 hours of ischemic injury [11].

Hypovolemia and dehydration are severe complications of HG and cause an elevation in serum blood urea nitrogen (BUN) and creatinine levels in these patients. It has been observed that serum NGAL levels increase much earlier than either BUN or creatinine in the presence of renal ischemic damage, which enables its early detection [9,10]. The primary objective of the present study was to investigate whether there was ischemic damage in renal tubules by assessing the levels of NGAL in maternal serum coinciding with the onset of HG. The secondary objective was to investigate the association between HG severity, the level of renal ischemia, and subsequent kidney damage.

Materials and methods

This case-control study was approved by the Ethics Committee of Erciyes University (decision number: 2019/375) according to the Declaration of Helsinki and was conducted at Kayseri City Hospital, Kayseri, Turkey.

Pregnant patients between their 5th-12th gestational weeks and aged between 18-35 years who were hospitalized due to HG were included in this study. Healthy volunteers with similar demographic characteristics were included in the study as the control group during their routine antenatal visits. The HG patients were separated into three groups according to disease severity, which was determined using the Pregnancy-Unique Quantification of Emesis scale (PUQE). The PUQE scores are defined as follows: ≤6: mild; 7–12: moderate; and ≥13: severe [12].

The diagnosis of HG was made according to the criteria of the American College of Obstetricians and Gynecologists as follows: 1) 5% weight loss from severe nausea and vomiting compared to pre-pregnancy or vomiting more than three times a day and 2) ketonuria with 3–5% weight loss [3]. The exclusion criteria were as follows: Patients with 1) multiple pregnancies, 2) vestibular diseases, 3) hyperparathyroidism or hyperthyroidism, 4) gastroenteritis, hepatitis, bile duct diseases, 5) urinary stones or pyelonephritis, 6) migraine that may cause nausea and vomiting during pregnancy, 7) chronic kidney, liver, or heart diseases, 8) vascular diseases with known renal involvement, or 9) smoking and alcohol use.

Serum NGAL measurement and data collection.

Venous blood samples were collected from each HG study group when as women with severe HG were hospitalized. Blood samples were collected from the healthy volunteers in the control group during their antenatal visit to the hospital in their first trimester of pregnancy. To measure serum glucose, BUN and creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), potassium (K), and sodium (Na) levels, a 4-mL blood sample was collected into a serum separator tube and analyzed the same day in the Kayseri City Hospital biochemistry clinic. To measure serum NGAL levels, a 2-mL blood sample was collected into a serum separator tube, rapidly centrifuged at 10000 rpm for 10 min, and stored in Eppendorf tubes at -80°C until analyses. The collected samples were analyzed using the enzyme-linked immunosorbent analysis method (CUSABIO TECHNOLOGY, LLC; target name: lipocalin 2; code: CSB-E09408h) in the Biochemistry Clinic at Kayseri City Hospital.

Statistical analysis

An analysis of variance followed by Tukey's post-hoc test using Minitab 16 (https://www.minitab.com/en-us/) was used to compare more than two groups. To compare two groups, the Shapiro–Wilk test was used to determine the normality of the data, and the Levene's test was used to test the assumption of homogeneity of variance. The values are expressed as the mean (SD) or n (%). Parametric comparisons were made using the Student's t-test, and nonparametric comparisons were made using the Mann–Whitney U test. The difference among the groups was considered statistically significant when $p < 0.05$. The number of patients in the current study was referred to in a study by Sahin et al. [7]. Accordingly, the 20 volunteers in each group added up to 80 volunteers.

Results

Among 80 participants in the study, 20 were in the healthy control group and 60 were in the HG groups. The participants were divided into three groups according to disease severity as follows: mild HG group (n=20), moderate HG group (n=20), and severe HG group (n=20). Table 1 provides a comparison of the demographic characteristics of the participants. Maternal age, gestational age at blood draw, body mass index, nulliparity, ethnicity, and education levels were similar among all groups (P=0.852, P=0.752, P=0.661, P=0.806, P=0.868 and P=0.907, respectively).

Table 2 provides a comparison of the biochemical measurements among the four groups. Serum glucose (P=0.068), serum BUN (P=0.559), serum creatinine (P=0.595), serum K (P=0.327), AST (P=0.051), and ALT (P=0.063) levels were similar among the groups. Serum Na levels were significantly higher in severe HG group than in the control and other HG groups (P<0.001). Urine osmolarity was significantly higher in the moderate and severe HG groups than in the control and mild HG groups (P<0.001). Serum osmolarity was significantly higher in all HG groups than in the control group (P<0.001). There was no difference in terms of serum NGAL levels among the groups (Table 2, Figure 1).

Table 1: Comparison of maternal demographic characteristics

	Healthy control (n=20)	Mild HG (n=20)	Moderate HG (n=20)	Severe HG (n=20)	*P*-value
Maternal age (year)	28.50 (2.01)	28.30 (2.29)	28.55 (2.70)	28.3 (2.34)	0.852
Gestational age at blood draw (week)	10.6 (1.3)	10.60 (1.5)	10.25 (1.4)	10.8 (3.0)	0.752
BMI (kg/m^2)	24.3 (1.3)	24.4 (1.1)	24.6 (1.3)	24.1 (1.3)	0.661
Nulliparity (n %)	12 (60%)	10 (50%)	12 (60%)	13 (65%)	0.806
Ethnicity Caucasian (n %)	19 (95%)	18 (90%)	19 (95%)	18 (90%)	0.868
Education high school (n %)	8 (40%)	10 (50%)	9 (45%)	10 (50%)	0.907

HG: hyperemesis gravidarum, BMI: body mass index. Values are expressed as the mean (SD) or n (%)

Table 2: Comparison of maternal biochemical results

	Healthy control (n=20)	Mild HG (n=20)	Moderate HG (n=20)	Severe HG (n=20)	*P*-value
Glucose (mg/dL)	92.8 (11.2)	91.2 (9.4)	94.6 (13.5)	86.3 (20.3)	0.068
BUN (5-15mg/dL)	8.43 (2.86)	9.63 (3.46)	9.80 (3.18)	9.78 (4.43)	0.559
Creatinine (0.5–1.1 mg/dL)	0.56 (0.09)	0.55 (0.07)	0.58 (0.08)	0.59 (0.11)	0.595
Na (136–145 nmol/L)	136.1^a (1.5)	136.4^a (2.0)	137.7^b (2.0)	138.3^b (2.0)	<0.001
K (3–5mEq/L)	3.8 (0.2)	3.8 (0.2)	3.9 (0.3)	3.8 (0.2)	0.327
AST (U/L)	12.4 (4.6)	15.7 (7.2)	15.1 (3.1)	16.8 (5.4)	0.051
ALT (U/L)	11.9 (7.1)	14.7 (6.7)	13.2 (7.5)	17.9 (6.8)	0.063
Serum osmolarity (275–295)	282.2^a (2.6)	288.9^a (5.1)	289.8^b (3.1)	289.9^b (2.2)	<0.001
Urine osmolarity (1010–1020)	1012.1^a (6.6)	1020.6^b (7.2)	1024^c (6.2)	1026^c (4.9)	<0.001
NGAL levels (ng/mL)	327.6 (106.9)	296.1 (130.8)	365.1 (118.2)	332.1 (55.1)	0.250

HG: hyperemesis gravidarum, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, NGAL: neutrophil gelatinase-associated lipocalin. Values are expressed as the mean (SD). Different superscripts indicate statistically significant differences

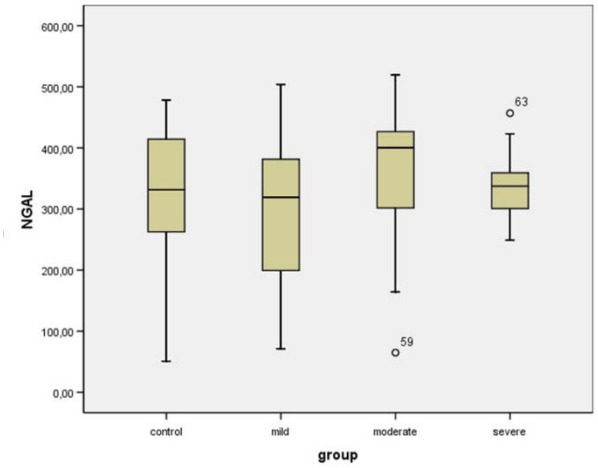

Figure 1: Comparative serum NGAL levels among the four study groups

Discussion

Hypovolemia and dehydration are critical complications of HG that can elevate creatinine levels proportional to disease severity. The aim of our study was to evaluate serum NGAL levels in the presence of HG and investigate the association between disease severity and the levels of renal ischemia.

Although the levels of serum creatinine are widely used to diagnose acute renal failure, it is not an adequate measure of acute renal injury [13] because several factors can regulate these levels, which include its overall generation and its distribution and excretion [13]. With acute renal injury, these levels rise slowly; therefore, new biomarkers must be identified to ensure an early diagnosis. To that end, several authors have evaluated the clinical importance of serum NGAL levels and their connection to dehydration. Antonopoulos et al. [14] have shown that the serum NGAL levels were significantly higher in 12 mildly dehydrated patients than in the healthy controls, 129.4 (25.7) ng/mL and 60.6 (0.4) ng/mL, respectively; however, the leukocyte count, BUN, and serum creatinine levels were not statistically different. Celik et al. [15] have reported that the plasma and urine levels of NGAL in mildly or moderately dehydrated children are higher than those in healthy subjects. It was suggested that these levels can then be used to predict renal impairment in children suffering from mild or moderate dehydration. Tekin et al. [16] have suggested that fasting during long and hot summer days as part of religious practices, such as during Ramadan, leads to fluid deprivation and dehydration, which are related to subclinical maternal renal dysfunction and increased serum NGAL levels.

The results of our study found that serum and urine osmolarity were significantly increased in the moderate and severe HG groups compared to those in the control group, and that serum BUN and creatinine levels were similar among all groups. We did not find any statistical differences in serum NGAL levels among the groups. These results may have been associated with the severity of dehydration and length of time for the disease.

First, it is well documented in the literature that nutritional and metabolic disorders associated with HG severity and prolongation are likely to develop, which increases feto-maternal morbidity [17]. Deficiencies in thiamine, vitamin A, vitamin B6, riboflavin, retinal binding protein, and vitamin K were identified in >60% of HG patients [18]. Wernicke's encephalopathy resulting from thiamine deficiencies [19] and osmotic demyelination syndrome resulting from hyponatremia are other critical metabolic complications [20]. All these complications are related to the extent of HG and occur in patients left untreated. In this study, we included patients who were in the acute period of the disease but who were without metabolic complications.

Secondly, it has been reported that dehydration reduces renal blood flow [14]. During this time, the microvilli of the proximal tubule cells are injured in the prerenal state; however, minimal acute tubular necrosis cannot be detected during this period using routine laboratory tests, such as measuring serum creatinine levels [13]. Prerenal acute kidney injury caused by dehydration may manifest as tubular enzymuria with a concomitant increase in serum NGAL [14]. After examining the pathogenesis of ischemic acute tubular necrosis (ATN), we suggest that patients who become hypotensive after surgery or conditions of sepsis or excess bleeding are at risk of developing ischemic ATN, especially when renal perfusion is either severe or prolonged. In HG patients, inadequate fluid intake activates compensatory mechanisms in response to decreases in renal arterial blood flow and glomerular filtration. These mechanisms provide an adequate volume of blood to vital organs, such as the heart and brain; therefore, we can speculate that these compensatory mechanisms do not adversely affect proximal renal tubule health.

Limitation

Our small sample size is the primary limitation of our study.

Conclusion

The results of the present study showed that serum NGAL levels were not altered in patients with HG.

References

1. Grooten IJ, Mol BW, van der Post JAM, Ris-Stalpers C, Kok M, Bais JMJ, et al. Early nasogastric tube feeding in optimising treatment for hyperemesis gravidarum: the MOTHER randomised controlled trial (maternal and offspring outcomes after treatment of HyperEmesis by refeeding). BMC Pregnancy Childbirth. 2016;16(1):22.
2. Madendag Y, Sahin E, Madendag Col I, Eraslan SM, Tayyar AT, Ozdemir F, et al. The effect of hyperemesis gravidarum on the 75 g oral glucose tolerance test screening and gestational diabetes mellitus. J Matern Fetal Neonatal Med. 2018;31(15):1989–92.
3. Practice Bulletin No. 153: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2015;126(3):e12–e24. https://doi.org/10.1097/AOG.
4. Koudijs HM, Savitri AI, Browne JL, Amelia D, Baharuddin M, Grobbee DE, et al. Hyperemesis gravidarum and placental dysfunction disorders. BMC Pregnancy Childbirth. 2016;16(1):374.

5. Mullin PM, Ching C, Schoenberg F, MacGibbon K, Romero R, Goodwin TM, et al. Risk factors, treatments, and outcomes associated with prolonged hyperemesis gravidarum. J Matern Fetal Neonatal Med. 2012;25(6):632–6.
6. Sahin E, Madendag Y, Eraslan Sahin M, Col Madendag I, Karakukcu C, Acmaz G, et al. Effect of severe hyperemesis gravidarum on maternal vascular endothelial health: evaluation of soluble adhesion molecules. J Matern Fetal Neonatal Med. 2018:1–5.
7. Sahin E, Madendag Y, Sahin ME, Tayyar AT, Madendag IC, et al. Maternal type 1collagen N-terminal telopeptide levels in severe hyperemesis gravidarum. BMC Pregnancy and Childbirth. 2018;18(1):502.
8. Kjeldsen L, Bainton DF, Sengelov H, Borregaard N. Identification of neutrophil gelatinase-associated lipocalin as a novel matrix protein of specific granules in human neutrophils. Blood 1994;83:799-807.
9. Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, et al. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. Kidney Int. 2009;75:285–94.
10. Mishra J, Ma Q, Prada A, Mitsnefes M, Zahedi K, Yang J, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol. 2003;14:2534–43.
11. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005;365:1231–8.
12. Birkeland E, Stokke G, Tangvik RJ, Torkildsen EA, Boateng J, Wollen AL, et al. Norwegian PUQE (pregnancy-unique quantification of Emesis and nausea) identifies patients with hyperemesis gravidarum and poor nutritional intake: a prospective cohort validation study. PLoS One. 2015;10(4):e0119962.
13. Jo SK, Rosner MH, Okusa MD: Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. Clin J Am Soc Nephrol. 2007;2:356–65.
14. Antonopoulos CN, Kalkanis A, Georgakopoulos G, Sergentanis TN Rigopoulos DN: Neutrophil gelatinase-associated lipocalin in dehydrated patients: a preliminary report. BMC Research Notes. 2011;4:435.
15. Çelik T, Altekin E, İşgüder R, Kenesari, Y, Duman M, Arslan N. Evaluation of neutrophil gelatinase-associated lipocalin in pediatric patients with acute rotavirus gastroenteritis and dehydration. Italian J Ped. 2013;39(1):52.
16. Bayoglu Tekin Y, Guvendag Guven ES, Mete Ural U, Yazici ZA, Kirbas A, Kir Sahin F. Evaluation of the effects of fasting associated dehydration on maternal NGAL levels and fetal renal artery Doppler parameters. J Matern Fet Neonatal Med. 2016;29(4):629-32.
17. van Stuijvenberg ME, Schabort I, Labadarios D, Nel JT. The nutritional status and treatment of patients with hyperemesis gravidarum. Am J Obstet Gynecol. 1995;172(5):1585–91.
18. Ismail SK, Kenny L. Review on hyperemesis gravidarum. Best Pract Res Clin Gastroenterol. 2007;21(5):755–69.
19. Chiossi G, Neri I, Cavazzuti M, Basso G, Facchinetti F. Hyperemesis gravidarum complicated by Wernicke encephalopathy: background, case report, and review of the literature. Obstet Gynecol Surv. 2006;61(4):255–68.
20. Corona G, Simonetti L, Giuliani C, Sforza A, Peri A. A case of osmotic demyelination syndrome occurred after the correction of severe hyponatraemia in hyperemesis gravidarum. BMC Endocr Disord. 2014;14:34.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):852-855.
DOI: 10.28982/josam.595537

Research article
Araştırma makalesi

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

Are serum GRP78 levels significant in chronic hepatitis C patients? A case-control study

Kronik hepatit C hastalarında serum GRP78 düzeyleri anlamlı mı? Vaka-kontrol çalışması

Arzu Altunçekiç Yıldırım [1], Selma Cırrık [2], Yeliz Çetinkol [3], Mustafa Kerem Çalgın [3], Tevfik Noyan [4]

[1] Department of Infectious Diseases and Clinical Microbiology, Ordu University School of Medicine, Ordu, Turkey
[2] Department of Physiology, Ordu University School of Medicine, Ordu, Turkey
[3] Department of Medical Microbiology, Ordu University School of Medicine, Ordu, Turkey
[4] Department of Medical Biochemistry, Ordu University School of Medicine, Ordu, Turkey

ORCID ID of the author(s)
AAY: 0000-0003-1141-9838
SC: 0000-0001-8474-0185
YÇ: 0000-0003-4940-4498
MKÇ: 0000-0003-4236-6177
TN: 0000-0002-7733-0177

Abstract

Aims: Glucose-regulated protein 78 (GRP-78) is one of the basic markers of endoplasmic reticulum (ER) stress in tissues. It is known that ER stress develops in the livers of patients infected with hepatitis C. In this study, the aim was to assess serum GRP78 levels which have not previously been investigated as a stress marker in chronic hepatitis C patients (CHC).

Methods: This case control study includes patients with chronic hepatitis C (CHC) infection in our Infectious Diseases clinic (n=60) and a healthy control group without any additional chronic disease (n=60). Serum GRP78 levels were measured with enzyme-linked immunosorbent assay (ELISA), then correlation analysis was performed for serum GRP78 levels with alanine aminotransferase (ALT), aspartate aminotransferase (AST) and HCV-RNA levels.

Results: A significant positive correlation was observed between HCV-RNA, ALT and AST levels in CHC patients (P<0.001 and P=0.008, respectively). Serum GRP78 was identified at similar levels in both the control and HCV subgroups. While a significant positive correlation was identified between serum GRP78 and AST levels (P=0.046), no significant correlation was detected for serum ALT levels.

Conclusion: Though liver injury induced by HCV is shown to cause ER stress, our results showed there was no significant increase in serum GRP78 levels during chronic HCV infection.

Keywords: Glucose-regulated protein 78, Hepatitis C infection, Endoplasmic reticulum stress

Öz

Amaç: Glikozla düzenlenen protein 78 (GRP-78) dokudaki endoplazmik retikulum (ER) stresinin temel göstergelerinden birisidir. Hepatit C ile enfekte hastalarda karaciğerde ER stresinin geliştiği bilinmektedir. Bu çalışmada kronik hepatit C (KHC) hastalarında bir stres belirteci olarak daha önce incelenmemiş olan serum GRP78 düzeylerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmamız, Enfeksiyon Hastalıkları polikliniğimize başvuran Kronik Hepatit C (KHC) enfeksiyonu tanısı almış hasta grubu (n=60) ve ek kronik hastalığı olmayan sağlıklı kontrol (n=60) grubundan oluşan bir vaka kontrol çalışmasıdır. Serum GRP78 seviyesi Enzyme-Linked Immuno Sorbent Assay (ELISA) ile ölçülmüş, ardından GRP78 ile alanin aminotransferaz (ALT), aspartat aminotransferaz (AST), HCV-RNA düzeyleri arasında korelasyon analizi yapılmıştır.

Bulgular: KHC hastalarında HCV-RNA düzeyleri ile ALT ve AST düzeyleri arasında anlamlı bir ilişki izlenmiştir (sırasıyla P<0,001 ve P=0,008). Serum GRP78 hem kontrol hem de HCV alt gruplarında benzer seviyelerde saptanmıştır. Serum GRP78 seviyesi ile AST düzeyleri arasında anlamlı bir pozitif korelasyon saptanırken (P=0,046), serum ALT düzeyleri ile anlamlı bir ilişki saptanamamıştır.

Sonuç: HCV ile indüklenen karaciğer hasarında ER stresinin geliştiği gösterilmiş olmasına rağmen, sonuçlarımız kronik HCV enfeksiyonu sırasında serum GRP 78 düzeyinde anlamlı bir artış olmadığını göstermektedir.

Anahtar kelimeler: Glikozla düzenlenen protein78, Hepatit C enfeksiyonu, Endoplazmik retikulum stres

Corresponding author / Sorumlu yazar:
Arzu Altunçekiç Yıldırım
Address / Adres: Ordu Üniversitesi Tıp Fakültesi, Bucak Mah. Nefsi Bucak Cad. 52200, Ordu, Türkiye
e-Mail: arzaltu@gmail.com

Ethics Committee Approval: The study was approved by Ordu University Faculty of Medicine Ethics Committee (2017-157).
Etik Kurul Onayı: Çalışmaya Ordu Üniversitesi Tıp Fakültesi Etik Kurulu (2017-157) tarafından izin verildi.

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 financial support from the Ordu University Scientific Research Project Fund (BAP; HD-1722).
Finansal Destek: Yazarlar bu çalışmanın Ordu Üniversitesi Bilimsel Araştırma Proje Fonu'ndan (BAP; HD-1722) finansal destek aldığını beyan etmişlerdir.

Published: 12/23/2019
Yayın Tarihi: 23.12.2019

How to cite / Atıf için: Yıldırım AA, Cırrık S, Çetinkol Y, Çalgın MK, Noyan T. Are serum GRP78 levels significant in chronic hepatitis C patients? A case-control study. J Surg Med. 2019;3(12):852-855.

Introduction

Hepatitis C virus (HCV) infection is a widespread and significant public health problem throughout the world. In the last decade, the global seroprevalence in general reached 2.8% and it is estimated there are more than 185 million infected individuals [1]. Due to complications associated with chronic hepatitis C (CHC), nearly 350,000 people die annually [2]. Together with a reduction in the incidence of new cases through the years, it is predicted that secondary mortality from CHC will continue to increase for 20 years [3]. Most people infected with HCV cannot naturally clear the infection and a chronic infection process begins to develop, which may progress to liver cirrhosis and hepatocellular carcinoma (HCC). HCV infection is associated with 15 to 20 times increased risk of HCC development [4,5]. However, the molecular mechanisms related to how HCV infection causes this disease are still not fully understood.

Endoplasmic reticulum (ER) is a quality control center for protein synthesis. Newly synthesized proteins that will be released by cells into the extracellular area or will participate in membrane structures are folded, modified, and combined correctly in ER [6,7]. A variety of physiological, pharmacological, and pathological conditions disrupt ER homeostasis, reducing the capacity to fold proteins. If the work of folding and releasing proteins is not completed effectively in cells, which is defined as "ER stress", it triggers a cell-protective response called unfolded protein response (UPR). The aim of UPR is to increase protein folding capacity, ensuring widening and reorganization of the ER membrane to reduce the stress response. If stress is not solved by severe and adaptive precautions, it may cause programmed cell death (apoptosis) [8-12]. ER stress was shown to play a role in a variety of liver diseases such as non-alcoholic steatohepatitis (NASH), alcoholic liver disease, ischemia reperfusion injury, toxic liver injury and viral hepatitis. HCV and hepatitis B virus (HBV) head the list of viruses inducing ER stress in the liver [13-15].

Replication of the HCV genome within hepatocytes causes accumulation of copious amounts of viral protein and RNA replication intermediate material in ER [16], which induces a significant stress response. The link between development of this stress response and the chronic infection process is not fully known. In mammalian cells, UPR is activated by three ER-stress sensors: RNA-dependent protein kinase-like ER-resident kinase (PERK), activating transcription factor (ATF6) and inositol-requiring enzyme 1 (IRE1). In ER stress, activation of these sensors is completed by separation of GRP78 (glucose-regulated protein), an ER chaperone protein found linked to luminal domains [13]. When ER stress develops, GRP78 expression clearly increases. When sufficient HCV protein accumulates in the ER, it binds to misfolded proteins, is titrated and activates the three pathways to begin UPR. It was shown that both structural and non-structural proteins in HCV trigger ER stress [17].

GRP78, one of the basic markers of ER stress in tissue, is shown to pass into circulation in studies completed recently [19,20]. It was previously shown that an ER stress response develops in hepatitis C patients; however, there was no marker studies that could show ER stress in circulation. This study evaluated the variations in GRP78 levels in circulation of patients with chronic HCV infection.

Materials and methods

Patients

We used serum samples from patients referred to Ordu University School of Medicine Hospital, Infectious Diseases clinic with diagnosis of hepatitis C infection. The hepatitis C patient group (n=60) included anti-HCV positive and HCV RNA positive, HBsAg negative and anti-HIV negative patients. Patients with HCV infections were separated into subgroups according to HCV RNA values as low (20 - $1x10^2$ IU/ml, n=20), moderate ($1x10^3$ - $1x10^5$ IU/ml, n=20), and high HCV-RNA ($1x10^6$ - $1.7x10^8$ IU/ml, n=20). The control group (n=60) included patients with no other chronic disease, and no chronic liver disease, anti-HCV negative, HBsAg negative anti-HIV negative patients. All serum samples were stored at -40 °C until evaluation. All patients and control serum samples had serum GRP78 levels investigated with the ELISA method. The study was conducted in accordance with the Declaration of Helsinki. It was planned retrospectively, and permission was obtained from the local ethics committee (Ordu University Clinical Research Ethics Committee, 2017-157).

Real-Time PCR

The COBAS AmpliPrep automatic extractor system was used for viral nucleic acid extraction. The COBAS AmpliPrep/COBAS Taqman 48 (Roche, Branchburg, NJ, USA) system was utilized to perform real-time PCR analysis for quantitative HCV-RNA. All procedures were performed according to manufacturer's recommendations. The measurement interval for HCV-RNA was 20-$1.7x10^8$ IU/ml.

Detection of GRP78

Analysis of GRP78 in serum used a commercial kit for human-GRP78 protein identification (Elabscience; E-EL-H5586). Using the sandwich-ELISA principle, the measurement interval for this kit was 0.63-40 ng/ml and sensitivity is reported as 0.38 ng/ml. Serum samples and standards were loaded in the appropriate wells of the micro ELISA plate and kit instructions were followed. After spectrophotometric reading at optical density of 450 nm (BioTek, ELx800 brand REF ELX508 SN1310149), serum GRP78 levels were calculated based on a standard graph. Results are presented as ng/ml.

Statistical analysis

Results are given as mean (standard deviation). The one-way ANOVA and Bonferroni post-hoc test were used for statistical assessment. Pearson correlation analysis was used for correlation assessments. $P<0.05$ was considered statistically significant.

Results

This study included a total of 60 chronic HCV patients (34 female and 26 male), with a mean age of 63.03 (14.2) years, and a total of 60 controls (24 female and 36 male), with a mean age 52.97 (19.7) years. Chronic HCV patients were divided into 3 different subgroups according to HCV-RNA levels as low (20 - $1x10^2$ IU/ml, n=20), moderate ($1x10^3$ - $1x10^5$ IU/ml, n=20) and high ($1x10^6$ - $1.7x10^8$ IU/ml, n=20). The mean ages in these subgroups were: 55.40 (16.5) years in the low HCV-RNA group,

66.65 (10.0) years in the moderate HCV-RNA group and 67.05 (12.6) years in the high HCV-RNA group.

ELISA measurements showed serum GRP78 concentration in the control group was 15.09 (10.30) ng/ml. Serum GRP78 was identified as 10.84 (9.6), 12.12 (8.4) and 14.41 (12.0) ng/ml in low, moderate and high HCV-RNA groups, respectively. There was no significant difference when compared with the control group. The value of serum GRP78 was similar in both the control and study subgroups.

There were statistically significant positive correlations between HCV-RNA, ALT and AST levels (P<0.0001 and P=0.008, respectively). However, no significant correlation was detected between HCV-RNA and serum GRP78 levels (P=0.238) (Table 1). A significant positive correlation was established between serum GRP78 and AST (P=0.046), while none was identified with serum ALT levels (Table 2).

Table 1: Correlation between HCV-RNA level and serum ALT, AST, GRP78 levels (n=60)

Correlation	r	R square	*P*-value
HCV-RNA vs. ALT	0.530	0.281	<0.001
HCV-RNA vs. AST	0.352	0.124	0.008
HCV-RNA vs. GRP78	0.161	0.026	0.238

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GRP78: Glucose-regulated protein78

Table 2: Correlation between serum GRP78 level and ALT, AST (n=60)

Correlation	r	R square	*P*-value
GRP78 vs. ALT	0.033	0.001	0.805
GRP78 vs. AST	0.270	0.072	0.046

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GRP78: Glucose-regulated protein78

Discussion

The liver's capacity for protein synthesis is very high and ER stress appears to be one of the important mechanisms in pathophysiology of liver diseases. To date, ER stress was shown to play a role in many liver diseases like alcoholic liver disease, diabetes related steatotic liver disease, toxic liver injury and viral hepatitis. Chronic hepatitis C disease causes cirrhosis and hepatocellular carcinoma, and is characterized by a microenvironment where oxidative stress, inflammation and regeneration processes are dominant in the liver [21]. The oxidative microenvironment and increased protein synthesis are important factors triggering UPR, with hepatitis C virus being one of the leading viruses inducing ER stress in the liver [15].

The HCV genome, coding nearly 3000 amino acids, ensures synthesis of many polypeptides including structural and non-structural proteins. As the host transcription system is used for the virus to replicate, rapid viral replication and accumulation of viral proteins in ER triggers the ER stress response [20]. In HCV, the three ER stress sensors may be activated, and it was found that GRP78 amounts increased significantly in the HCV subgenomic replicon system [7,22]. Studies of biopsy samples obtained from hepatitis C patients showed changes to the ER structure (widening and disorganization) indicating stress with electron microscopy. Additionally, clear increases were identified in proximal sensors (ATF6α, ATF6β, sXBP1, phosphorylated PERK) of the ER stress response and the levels of downstream effectors (GRP78, fosfo-elF2alpha, ATF4) of these sensors [7]. GRP78 shows protective effects against cell death due to cytotoxic T lymphocytes; however, it increases tumoral changes and resistance to antitumor medication [23]. As a result, the increase in GRP78 expression may play a role in HCV infection becoming chronic and carcinogenic.

Another study including HCC patients used immunohistochemistry and the Western Blot method on liver biopsy samples to show increases in ER stress markers of sXBP1, GRP78 and ATF6 [24].

Contrary to these results, there are findings showing that HCV does not cause ER stress. McPherson et al. [25] compared GRP78, GRP94, sXBP1 and EDEM mRNA levels in HCV positive and negative liver biopsies using RT-PCR and observed no significant difference between the two groups. This result may be due to random sampling. They stated they could not identify clear variations in mRNA/protein levels as mixed infected and non-infected hepatocytes were studied. This study simultaneously assessed viral load and UPR correlation, as in our study, and similarly stated there was no correlation.

The ER stress response varies according to whether hepatocytes are infected with HCV or not; as a result, there are other publications stating that random biopsy samples may have different results [7,22].

The association between HCV RNA viral load and liver histology has been researched in many studies. Gretch et al. [26] assessed 121 cases and proposed that hepatic activity index and fibrosis scores were higher among patients with high HCV RNA levels. Magrin et al. [27] concluded that liver histology was worse in patients with low HCV RNA in a 100-case series. Karakuş [28] stated that HCV RNA elevation was a parameter affecting liver histopathology; however, they interpreted different results in studies as indicating the liver injury may not always be shown due to proliferation of HCV in extrahepatic regions. This may explain the lack of connection between GRP78 and HCV RNA in our study.

Currently it is known that transaminase values and liver histopathology may not always comply. In our study, there was a positive correlation identified between AST and GRP78 elevation. AST is known to increase earlier and by higher amounts in ischemic and toxic liver injury [29,30]. However, there is a need for advanced studies to state the correlation with ER stress.

Limitations

Limitations of our study may be listed as the limited number of patients studied and the lack of accompanying histopathologic assessment.

Conclusion

Though ER stress is documented as an important mechanism in chronic liver injury associated with HCV, our results show serum GRP78 concentration does not change during chronic HCV infection, and that there is no significant correlation between parameters associated with HCV and GRP78, other than AST. Considering that random biopsy samples may have different results, identification of a serum/plasma marker for use to assess hepatic ER stress is clinically very important. There is a need for studies about a variety of markers in larger patient groups to explain the molecular mechanisms associated with ER stress in the process extending to chronic disease and cancer in patients infected with HCV and to identify appropriate markers in circulation.

References

1. Hanafiah KM, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. Hepatology. 2013;57(4):1333-42.

2. Messina JP, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG et al. Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. 2015;61:77-87.
3. Razavi H, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology. 2013;57:2164-70.
4. El-Serag HB, Kanwal F, Davila JA, Kramer J, Richardson P. A new laboratory-based algorithm to predict development of hepatocellular carcinoma in patients with hepatitis C and cirrhosis. Gastroenterology. 2014;146:1249-55.
5. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology. 2012;142:1264-73.
6. Düzgün A, Alaçam H, Okuyucu A. Endoplasmic reticulum stress and unfolded protein response. J Exp Clin Med. 2012;29:95-100.
7. Asselah T, Bieche I, Mansouri A, Laurendeau I, Cazals-Hatem D, Feldmann G, et al. In vivo hepatic endoplasmic reticulum stress in patients with chronic hepatitis C. J Pathol. 2010;221(3):264-74.
8. Welihinda AA, Tirasophon W, Kaufman RJ. The cellular response to protein misfolding in the endoplasmic reticulum. Gene Expression. 1999;7:293-300.
9. Hosoi T, Ozawa K. Endoplasmic reticulum stress in disease: mechanisms and therapeutic opportunities. Clinical Science. 2010;118(1):19-29.
10. Hitomi J, Katayama T, Taniguchi M, Honda A, Imaizumi K, Tohyama M. Apoptosis induced by endoplasmic reticulum stress depends on activation of caspase-3 via caspase-12. Neuroscience Letters. 2004;357(2):127-30.
11. Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, et al. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-β. Nature. 2000;403:98-103.
12. Ullman E, Fan Y, Stawowczyk M, Chen HM, Yue Z, Zong WX. Autophagy promotes necrosis in apoptosis-deficient cells in response to ER stress. Cell Death Differ. 2008;15(2):422-5.
13. Dara L, Ji C, Kaplowitz N. The contribution of endoplasmic reticulum stress to liver diseases. Hepatology. 2011;53(5):1752-63.
14. Malhi H, Kaufman RJ. Endoplasmic reticulum stress in liver disease. J Hepatol. 2011;54(4):795-809.
15. Yeganeh B, Moghadam AR, Alizadeh J, Wiechec E, Alavian SM, Hashemi M, et al. Hepatitis B and C virus-induced hepatitis: Apoptosis, autophagy, and unfolded protein response. World J Gastroenterol. 2015;21(47):13225-39.
16. Aizawa Y, Seki N, Nagano T, Abe H. Chronic hepatitis C virus infection and lipoprotein metabolism. World J Gastroenterol. 2015;21(36):10299-313.
17. Chan SW. Unfolded protein response in hepatitis C virus infection. Front Microbiol. 2014;5:1-17.
18. Dash S, Srinivas C, Yucel A, Chandra PK, Ferraris P, Chen V, et al. Hepatitis C Virus Infection Induces Autophagy as a Prosurvival Mechanism to Alleviate Hepatic ER-Stress Response. Viruses. 2016;8:1-29.
19. Khadir A, Kavalakatt S, Abubaker J, Cherian P, Madhu D, Al-Khairi I, et al. Physical exercise alleviates ER stress in obese humans through reduction in the expression and release of GRP78 chaperone. Metabolism. 2016;65(9):1409-20.
20. Delpino A, Castelli M. The 78 kDa glucose-regulated protein (GRP78/BIP) is expressed on the cell membrane, is released into cell culture medium and is also present in human peripheral circulation. Biosci Rep. 2002;22:407-20.
21. Ertuğrul G, Yanaral T. Living donor liver transplantation in hepatocellular carcinoma: A single-center experiences. J Surg Med. 2019;3(4):320-3.
22. Khachatoorian R, French SW. Chaperones in hepatitis C virus infection. World J Hepatol. 2016;8(1):9-35.
23. Chatterjee S, Cheng MF, Berger SJ, Berger NA. Induction of Mr 78,000 Glucose-regulated Stress Protein in Poly(Adenosine Diphosphate-Ribose) Polymerase- and Nicotinamide Adenine Dinucleotide-deficientV79 Cell Lines and Its Relation to Resistance to the Topoisomerase II Inhibitor Etoposide. Cancer Research. 1994;54:4405-11.
24. Shuda M, Kondoh N, Imazeki N, Tanaka K, Okada T, Mori M, et al. Activation of the ATF6, XBP1 and grp78 genes in human hepatocellular carcinoma: a possible involvement of the ER stress pathway in hepatocarcinogenesis. J Hepatol. 2003;38:605-14.
25. McPherson S, Powell EE, Barrie HD, Clouston AD, McGuckin M, Jonsson JR. No evidence of the unfolded protein response in patients with chronic hepatitis C virus infection. J Gastroenterol Hepatol. 2011;26:319-27.
26. Gretch D, Corey L, Wilson J, dela Rosa C, Wilson R, Carithers R Jr, et al. Assessment of hepatitis C virus RNA levels by quantitative competitive RNA polymerase chain reaction: high-titer viremia correlates with advanced stage of disease. J Infect Dis. 1994;169:1219-25.
27. Magrin S, Craxi A, Fabiano C, Simonetti RG, Fiorentino G, Marino L, et al. Hepatitis C viremia in chronic liver disease. Relationship to interferon-alpha or corticosteroid treatment. Hepatology. 1994;19:273-9.
28. Karakuş A. The relationship of metabolic parameters and demographical characteristics in patients with naive chronic hepatitis C between viral load and histological factors [dissertation]. Eskişehir Osmangazi University School of Medicine, Department of Infectious Diseases and Clinical Microbiology; 2016.
29. Zeuzem S, Alberti A, Rosenberg W, Marcellin P, Diago M, Negro F, et al. Review article: management of patients with chronic hepatitis C virus infection and "normal" alanine aminotransferase activity. Aliment Pharmacol Ther. 2006;24(8):1133-49.
30. Giannini EG, Testa R, Savarino V. Liver enzyme alteration:a guide for clinicians. CMAJ. 2005;172:367-79.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):856-860.
DOI: 10.28982/josam.650249

Research article
Araştırma makalesi

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

Which antibiotics should we prefer empirical treatment of urinary tract infections in elderly patients?

Yaşlı hastalarda üriner sistem infeksiyonlarının ampirik tedavisinde hangi antibiyotikleri tercih etmeliyiz?

Nergis Aşgın [1], Şerife Satılmış [2]

[1] Department of Medical Microbiology, Faculty of Medicine, Karabuk University, Karabuk, Turkey
[2] Karabuk University Training and Research Hospital, Medical Microbiology Laboratory, Karabuk, Turkey

ORCID ID of the author(s)
NA: 0000-0001-9739-5675
SS: 0000-0001-5310-3933

Corresponding author / Sorumlu yazar:
Nergis Aşgın
Address / Adres: Karabük Üniversitesi, Tıp Fakültesi, Tıbbi Mikrobiyoloji Anabilim Dalı, Demir çelik kampusu, 78050 Karabük, Türkiye
e-Mail: drnasgin@gmail.com

Ethics Committee Approval: The study was approved by Non-Interventional Clinical Research Ethics Committee of Karabuk University (Date:7.10.2019; No:6/18).
Etik Kurul Onayı: Çalışmaya Karabük Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu (Tarih:7.10.2019; No:6/18) tarafından izin verildi.

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: 12/27/2019
Yayın Tarihi: 27.12.2019

Abstract

Aim: Urinary tract infection (UTI) is a major cause of mortality and morbidity in elderly patients. In this cross-sectional study, we aimed to determine the frequency and antibiotic resistance profile of the bacteria causing UTI and contribute to the empirical treatment options in elderly patients.

Methods: This study included urine culture results from 347 elderly outpatients who were referred to Karabuk Training and Research Hospital between January 2018 and June 2019. The identification and antibiotic susceptibilities of microorganisms were determined using the BD-Phoenix 100 fully automated system, and the extended-spectrum beta-lactamase (ESBL) positivity was analyzed using the combined disk diffusion method. The results were retrospectively analyzed.

Results: The most common pathogens were *Escherichia coli* (58%), *Enterococcus* spp. (18%) and *Klebsiella pneumoniae* (11%). The rate of resistance to ampicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole (TMP-SMX), cefixime, and ciprofloxacin, which are oral antibiotics used in the treatment of UTI, was between 30% and 70%. The rate of resistance to nitrofurantoin was 3%. The gentamicin and piperacillin-tazobactam resistance were 12% and 9%, respectively. The ESBL positivity for *E. coli* and *K. pneumoniae* were 29% and 49%, respectively (P=0.03).

Conclusion: The rates of resistance to oral antibiotics such as ampicillin, amoxicillin-clavulanic acid, TMP-SMX, cefixime, and ciprofloxacin, which are used treatment of UTI, were more than 20%. Therefore, these antibiotics should not be used in the empirical treatment of UTI. Instead, nitrofurantoin may be preferred in the empirical treatment of uncomplicated UTI, or gentamicin and piperacillin-tazobactam, which are parenteral antibiotics that may be used depending on the patient's clinical condition.

Keywords: Antibiotics, *Enterococcus* species, *Escherichia coli*, Nitrofurantoin, Ciprofloxacin, Urinary tract infection

Öz

Amaç: Üriner sistem infeksiyonları (ÜSİ) yaşlı hastalarda önemli bir mortalite ve morbidite nedenidir. Bu kesitsel çalışmada yaşlı hastalarda toplum kaynaklı ÜSİ etkenlerinin sıklığını ve antibiyotik direnç profilini belirleyerek ampirik tedavi seçimine katkıda bulunmayı amaçladık.

Yöntemler: Ocak 2018 - Haziran 2019 tarihleri arasında Karabük Eğitim ve Araştırma Hastanesi'ne ayaktan başvuran 347 yaşlı hastanın idrar kültür sonuçları çalışmaya dahil edilmiştir. Mikroorganizmaların identifikasyonu ve antibiyotik duyarlılıkları BD-Phoenix (Becton-Dickinson, MD,USA) tam otomatize sistem ile, genişlemiş spektrumlu beta-laktamaz varlığı (GSBL) ise kombine disk difüzyon yöntemi ile araştırılmıştır. Sonuçlar retrospektif olarak incelenmiştir.

Bulgular: En sık izole edilen patojenler *Escherichia coli* (%58), *Enterococcus* spp (%18) ve *Klebsiella pneumoniae* (%11) idi. Üriner infeksiyon tedavisinde kullanılan oral antibiyotiklerden ampisilin, amoksisilin-klavulanik asit, trimethoprim-sulfametoksazol (TMP-SMX), sefiksim ve siprofloksasine direnç %30-70 arasında idi. Nitrofurantoin direnci ise %3 idi. Gentamisine %12 ve piperasilin-tazobaktama ise %9 oranında direnç saptandı. GSBL pozitifliği ise *E.coli*'de % 29 iken, *K. pneumoniae* suşlarında %49 idi (P=0.03).

Sonuç: Üriner sistem infeksiyonlarının tedavisinde kullanılan oral antibiyotiklerden ampisilin, amoksisilin-klavulanik asit, TMP-SMX, sefiksim ve siprofloksasine %20'nin üzerinde direnç saptanmıştır. Bu nedenle ÜSİ' nın ampirik tedavisinde bu antibiyotikler kullanılmamalıdır. Onun yerine komplike olmayan ÜSİ' da nitrofurantoin, parenteral antibiyotiklerden ise gentamisin ve piperasilin-tazobaktam hastanın klinik durumuna göre tercih edilebilir.

Anahtar kelimeler: Antibiyotik, *Enteroccus türleri, Escherichia coli,* Nitrofurantoin, Siprofloksasin, Üriner sistem infeksiyonları

How to cite / Atıf için: Aşgın N, Satılmış Ş. Which antibiotics should we prefer empirical treatment of urinary tract infections in elderly patients? J Surg Med. 2019;3(12):856-860.

Introduction

The elderly population has increased due to the rise in life expectancy worldwide. People over 65 years of age are considered to be elderly. Elderly people constitute one-sixth of the world's population. However, this rate increases to one-third in outpatient visits [1]. The elderly population in Turkey has been on the rise over the years. The rate of the elderly population was 4.3% in 1990, whereas this rate increased to 8.8% in 2018 [2].

Elderly people are more susceptible to infections due to comorbid conditions as well as anatomical and physiological changes associated with aging. In the literature, approximately one-third of the infections observed in elderly patients have been reported as urinary tract infections (UTIs) [1,3,4]. It has been estimated that UTIs cause 100,000 hospitalizations, 1 million emergency room visits, and 7 million outpatient admissions in the USA [3,5]. On the other hand, increasing drug resistance has been a major public health threat worldwide. Infections associated with multi-drug resistant bacteria occur more frequently in elderly patients who reside in nursing homes. UTIs have been reported to account for 15.5% of hospitalizations and 2% of mortalities in elderly patients [3]. Advanced age is a major risk factor for UTIs. Comorbid conditions such as increased urinary incontinence, urinary retention, increased urinary catheterization, and diabetes mellitus (DM) associated with aging lead up to the development of UTI [4,6]. In addition, decreased cognitive functions, along with decreased personal hygiene, dementia, immunodeficiency, and malnutrition can also facilitate the development of the infection [3,4,6]. The fact that elderly patients are more sensitive to the side effects of drugs and chronic comorbidities (chronic liver and renal failure, DM) can limit treatment options [4,5]. In the treatment of UTI in elderly patients (where urine culture test is not available), the empirical treatment is recommended to be chosen based on local antibiotic resistance data [3,7].

In this study, we aimed to determine the prevalence and antibiotic resistance pattern of bacterial causes of community-acquired UTI and contribute to the choice of empirical treatment in elderly patients who were admitted to our hospital's outpatient clinic.

Materials and methods

This cross-sectional study included urine culture results obtained from patients aged over 65 years who were referred to Karabuk Training and Research Hospital between January 2018 and June 2019. The results of the inpatients, patients younger than 65 years, and repetitive patients were excluded. The distribution of uropathogens causing UTIs and their antibiotic susceptibilities were retrospectively examined. The ethics approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Karabuk University. (Date: 7 October 2019, no: 6/18).

The urine samples sent to the microbiology laboratory were cultured on Columbia agar with 5% sheep blood (RTA laboratories, Kocaeli, Turkey), eosin-methylene blue agar (RTA laboratories, Kocaeli, Turkey) and using a sterile plastic ring loop with a urine sample capacity of 0.01 mL, and then incubated for 18–24 hours at 35°C under aerobic conditions. The culture samples were evaluated in accordance with the Society of Clinical Microbiology guidelines [8]. The identification and antibiotic susceptibility of bacteria were determined using the BD-Phoenix 100 (Becton-Dickinson, Sparks, MD, USA) fully automated microbiology system. Antibiotic susceptibility results were evaluated based on the European Committee on Antimicrobial Susceptibility Testing guidelines [9]. The presence of the extended-spectrum beta-lactamase (ESBL) enzyme was analyzed using the combined disk diffusion method [9]. *Escherichia coli* ATCC 25922 and *S. aureus* ATCC 29213 strains were used as quality control strains.

Statistical analysis

The data were statistically analyzed using SPSS software version 22.0 (IBM Corporation, Chicago, IL, USA). The descriptive statistics were expressed as number, percentage and median value. Pearson's chi-squared test was used for comparison of descriptive data between groups. The *P*-value ≤0.05 was considered statistically significant within a 95% confidence interval.

Results

Among 347 patients, 157 (45%) were male, and 190 (55%) were female. The median age of the patients was 74 (65–94) years. *Escherichia coli* was isolated in 58% (n= 202) of the urine cultures, and the distribution of the isolated bacteria is shown in Table 1. The most common pathogen was *E. coli* (58%), followed by *Enterococcus* spp. (18 %) and *K. pneumoniae* (11 %). The antibiotic resistance profiles of *E. coli* and *K. pneumoniae* (the most frequently isolated gram-negative pathogens) strains are shown in Table 2.

Table 1: Distribution of microorganisms isolated from urine cultures of elderly patients

Microorganisms	n (%)
Gram-negative bacteria	
Escherichia coli	202(58)
Klebsiella pneumoniae	37(11)
Enterobacter spp.	9(3)
Proteus mirabilis	7(2)
Pseudomonas aeruginosa	7(2)
Gram-positive bacteria	
Enterococcus spp.	62(18)
Streptococcus agalactiae	13(4)
Staphylococcus spp.	5(1)
Other	
Candida spp.	5(1)
TOTAL	347(100)

Table 2: Antibiotic susceptibilities of E. coli and K. pneumoniae isolates

Antibiotics	*E. coli* (n=202)	*K. pneumoniae* (n=37)	*P*-value
	n (%)	n (%)	
Ampicillin	125(62)	*	NA
Amoxicillin-clavulanic acid	104 (52)	26(70)	0.05
Trimethoprim-sulfamethoxazole	70 (35)	11(30)	0.69
Ciprofloxacin	85(42)	18(49)	0.57
Cefixime	75(37)	20(54)	0.08
Nitrofurantoin	6(3)	**	NA
Ceftriaxone	59(29)	18(49)	0.03
Ceftazidime	56(28)	18(49)	0.02
Gentamicin	25(12)	6(16)	0.72
Piperacillin-tazobactam	18(9)	7(19)	0.12
ESBL	59(29)	18(49)	0.03

* Intrinsic resistant, ** no EUCAST recommendation, NA: not applicable, ESBL: Extended spectrum beta-lactamase

K. pneumoniae strains were found to be more resistant compared with the *E. coli* strains in all the antibiotic groups. The rates of resistance to amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole (TMP-SMX), cefixime, and ciprofloxacin, which are oral antibiotics, ranged between 30% and 70% in both groups. The rates of resistance to the third-generation cephalosporins ranged between 28% and 49%, whereas the rate of resistance to nitrofurantoin was 3% in *E. coli* strains. The rates

of resistance to gentamicin in *E. coli* and *K. pneumoniae* strains were 12% and 16%, respectively (P=0.72).

The production of ESBL in *K. pneumoniae* strains was significantly higher than *E. coli* strains (P=0.03). The antibiotic resistance was relatively high in ESBL-positive *E. coli* strains. The rates of resistance to ciprofloxacin, TMP-SMX, gentamicin, and piperacillin-tazobactam were 92%, 59%, 30%, and 25%, respectively. The lowest rate of resistance was seen to nitrofurantoin with 7%.

Among 62 *Enterococcus* spp. strains, 48 (77%) were isolated from the male patients; 95% of the strains (n=59) were *E. faecalis*, and 5% were *E. faecium*. The rate of resistance to ciprofloxacin in the *E. faecalis* strains was 55%. The rates of resistance to ampicillin, amoxicillin-clavulanic acid, and nitrofurantoin were found to be at low levels of 8%, 5%, and 10%, respectively. The high level of gentamicin resistance (HLGR) rate was 48%. All the strains were found to be susceptible to vancomycin, linezolid, and teicoplanin.

Discussion

Due to the increased elderly population worldwide, the diagnosis and treatment of diseases in this age group have become more significant. UTI is a significant cause of mortality and morbidity in elderly patients. UTI is one of the most significant causes of sepsis in elderly patients, and the rate of mortality associated with urosepsis has been reported as 33% [1]. The elderly population's visits to the outpatient clinic due to UTI have been reported to be three times more than in the young population [3]. This has been commonly associated with age-related bladder dysfunction, urethral catheterization, and bladder obstruction due to benign prostatic hyperplasia, particularly in men [1,4]. In addition, antibiotic resistance is higher in elderly patients compared with young patients due to repetitive antibiotic treatments and urinary interventions [4].

In the literature, *E. coli* has been reported as the most common pathogen for UTI in both the elderly and other groups such as children, adults, and pregnant women [3,4,6,11]. In this study, the most frequently isolated pathogen was *E. coli* (58 %). Similarly, Ulug et al. [6] reported the rate of *E. coli* isolated as a causative agent of UTI was 64% in 401 elderly patients. This rate was 32% in elderly patients admitted to the emergency room and diagnosed with UTI in the study by Ginde et al. [12], 69% in elderly patients who resided in nursing homes in the study by Sundwall et al. [11], and 54% in the study by Das et al. [13].

There is no agreement in the literature regarding the choice or duration of antibiotics in the treatment of UTI in elderly patients. Therefore, empirical treatment protocols should be established based on local antibiotic resistance profiles. As the Infectious Diseases Society of America has identified *E. coli* as the most common causative agent of UTI, it recommends that the local antibiotic resistance pattern of *E. coli* be monitored by active surveillance and that antibiotics with a rate of resistance below 20% are to be preferred for empirical treatment [3,7]. Due to the limited number of studies on the antibiotic resistance profile of uropathogens in elderly patients in Turkey, the results of the studies consisting of adult age groups have also been included in the discussion.

In our study, the rate of resistance to ampicillin in *E. coli* strains was 62%. This rate is between 52% and 77% in the other studies conducted in Turkey [14-16], whereas it has been reported to be 32% in the study by Fagan et al. (Norway) [17] and 46% in the study by Sanchez et al. (USA) [8]. Due to its high rates of resistance, ampicillin is no longer an empirical treatment option in UTI in Turkey and worldwide.

In this study, the rate of resistance to amoxicillin-clavulanic acid in *E. coli* strains was 52%. This rate has been reported to be 33% in elderly patients in the study by Ulug et al. [6] and between 6.5% and 32% in the studies consisting of various groups in Turkey [14,15,19,20]. Sanchez et al. [18] have found a rate of resistance of 7% against amoxicillin-clavulanic acid in *E. coli* strains in elderly patients.

In the present study, the rates of resistance to cefixime in *E. coli* and *K. pneumoniae* strains were 37% and 54%, respectively. The data on the resistance to cefixime, which is a third-generation oral cephalosporin, is limited. A rate of resistance of 8%–26% [10,21-23] and 10% [20] has been reported in pediatric patients and pregnant women in Turkey, respectively. Kacmaz et al. [24] have found a rate of resistance of 6% against cefixime in community-acquired *E. coli* strains. In our study, high resistance to cefixime may be due to the fact that our study group consisted of elderly patients. Generally, it is considered that antibiotic resistance is higher in the elderly population compared with that in young people. This may be associated with repetitive antibiotic treatments and urinary interventions [4].

In this study, the rate of resistance to TMP-SMX in *E. coli* and *K. pneumoniae* strains was 35% and 49%, respectively. This rate has been reported to vary between 19-58% in the other studies conducted in Turkey [6,14,16,19]. Similarly, high rates of resistance have been reported in the studies from Brazil (35%) [5] and the USA (60%) [13]. On the contrary, the study by Fagan et al. [17] (Norway) has found rates of resistance of 24% and 19%, respectively.

Although TMP-SMX has previously been used in prophylaxis and maintenance treatment in patients with UTI, it is no longer a treatment option for UTI.

In the present study, the rate of resistance to ciprofloxacin in *E. coli* and *K. pneumoniae* strains were 42% and 49%, respectively. Rates of resistance between 10%-41% have been reported in the other studies conducted in Turkey [6,15,16,19]. We believe that the overuse of fluoroquinolones in the treatment of infections other than UTI in our hospital resulted in high fluoroquinolone resistance. In a multi-center study conducted on elderly patients, the rates of resistance to ciprofloxacin in *E. coli* strains have been reported to be 30% in Canada and 44% in the USA [25]. Sanchez et al. [18] have found rates of resistance of 11% in adults and 30% in elderly patients. Fagan et al. [17] have reported relatively low rates of resistance in *E. coli* and *K. pneumoniae* strains, which were 8% and 3%, respectively.

A study conducted in Spain has found that the prevalence of fluoroquinolone-resistant *E. coli* increased with age over 60 years [4]. A history of hospitalization and quinolone use have also been reported as independent risk factors [13,26]. Marquez et al. [5] have reported that the rate of resistance to

fluoroquinolone is 21% in *E. coli* strains isolated from elderly women residing in nursing homes, and the history of UTI, vaginitis, and DM are risk factors for UTI.

In our study, the prevalence of ESBL in *K. pneumoniae* was significantly higher than *E. coli* and were 49% and 29%, respectively (P=0.03). These rates were 27% and 2% in the study by Caliskan et al. [15] and 29% and 24% in the study by Gulcan et al. [27]. In community-acquired *E. coli* isolates, Tasbakan et al. [19] have found ESBL prevalence to be 13%, whereas Uyanik et al. [28] have found it to be 26%. Lob et al. [25] have reported the prevalence of ESBL in elderly patients diagnosed with UTI to be 13% in Canada and 23% in the USA. The prevalence of ESBL is also increasing in community-acquired infections. Rodriguez et al. [29] have reported that advanced age, being male, the presence of DM, and the use of fluoroquinolones in the past two months are risk factors in community-acquired ESBL-producing *E. coli* infections. In addition, in May 2016, the United States Food and Drug Administration reported severe adverse reactions such as fluoroquinolone-induced QT prolongation, delirium, and seizures [1]. Therefore, the use of fluoroquinolone in patients at risk should be limited. In this study, the presence of ESBL was higher than in other studies [14-16]. This may be due to our patient group consisting of elderly patients and fluoroquinolone being excessively prescribed.

The use of nitrofurantoin is prominent in the treatment of UTI associated with ESBL-positive isolates. However, nitrofurantoin is only recommended in uncomplicated UTI [3,4]. In the current study, the rate of resistance to nitrofurantoin in *E. coli* strains was 3%. However, this rate was higher in ESBL-positive *E. coli* strains (8%). The other studies in Turkey have reported rates of resistance to nitrofurantoin between 14%-40% in ESBL-positive *E. coli* strains [15,27,30]. The rates of resistance to nitrofurantoin have been reported to be 2% in the study by Fagan et al. (Norway) [17] and 7% in the study by Das et al. (USA) [13].

In the present study, the second most common pathogen was *E. faecalis*. The majority of strains were isolated from male patients. Gulcan et al. [27] found that *Enterococcus* spp. was significantly high in male patients aged over 65 years in the study group. In this study, the rate of resistance to ampicillin was low (8%), and the HLGR rate was relatively high (48%). Similarly, Gulcan et al. [27] reported resistance to ampicillin to be 7% and the HLGR rate to be 37%. Also, Kutlu et al. [31] reported the rate of resistance to ampicillin and HLGR rate to be 5.6% and 44.7%, respectively. In our study, the rate of resistance to nitrofurantoin was 10%, whereas no resistance to vancomycin, linezolid, and teicoplanin was found. Kutlu et al. [31] reported resistance to nitrofurantoin 4.8% and vancomycin to be 1.5%. On the basis of our results, nitrofurantoin may be preferred in the treatment of UTI caused by enterococci.

Limitations

There are some limitations to this study; since it is a retrospective study based on laboratory data, the data on the clinical characteristics and treatments of patients were not available. In addition, as the reference method, the agar dilution test could not be performed, the susceptibility of fosfomycin to *Enterobacterales* spp. was excluded.

Conclusion

In the present study, the rates of resistance to ampicillin, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, cefixime, and ciprofloxacin, which are oral antibiotics used in the treatment of UTI in elderly patients, were found to be >20%. Therefore, these antibiotics should not be used in the empirical treatment of UTI. Instead, nitrofurantoin may be preferred in the empirical treatment of uncomplicated UTI. Gentamicin and piperacillin-tazobactam, which are parenteral antibiotics, may also be used depending on the clinical condition of the patient. Since the antibiotic resistance profile of each region is different, the empirical treatment protocols should be established on the basis of the antibiotic resistance data, and the resistance profiles should be monitored through active surveillance.

References

1. Gbinigie OA, Ordonez-Mena JM, Fanshawe TR, Pluddemann A, Heneghan C. Diagnostic value of symptoms and signs for identifying urinary tract infection in older adult outpatients: systematic review and meta-analysis. J Infection. 2018;77(5):379-90.
2. Turkey General Directorate of Public Health. https://hsgm.saglik.gov.tr/depo/birimler/kronik-hastaliklar-engelli-db/hastaliklar/Yasli_Sagligi/raporlar_istatistikler/TUIK_Yasli_Istatistik_2018.pdf Accessed 15 Oct 2019.
3. Cortes-Penfield NW, Trautner BW, Jump RL. Urinary tract infection and asymptomatic bacteriuria in older adults. Infect Dis. Clin. North Am. 2017;31(4):673-88.
4. Nicolle LE. Urinary tract infections in the older adult. Clin Geriatr Med. 2016;32(3):523-38.
5. Marques LPJ, Flores JT, Junior ODOB, Rodrigues GB, de Medeiros Mourao C, Moreira RMP. Epidemiological and clinical aspects of urinary tract infection in community-dwelling elderly women. Braz J Infect Dis. 2012;16(5):436-41.
6. Ulug M, Gul I. Investigation of the Results of Urine Cultures and Approaches to Empirical Antibiotic Treatment of Community-Acquired Urinary Tract Infections in Elderly Patients. Klimik Derg. 2012; 25:71-6.
7. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines or the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):103-20.
8. The Guide to Analysis and Presentation of Antibiotic Susceptibility Data. Available at: https://www.klimud.org/public/uploads/content/files/Antibiyotik%20Duyarl%C4%B1l%C4%B1k%20Verilerin%20Analizi%20ve%20Sunumu%20RRehberi.pdf Accessed 11 Oct 2019.
9. European Committee on Antimicrobial Susceptibility Testing. Breakpoint tables for interpretation of MICs and zone diameters. Version 8.1, (2018). Available at http://www.eucast.org/ast_of_bacteria/previous_versions_of_documents/ Accessed 14 Oct 2019.
10. Asgin N, Cakmakliogullari EK. In-vitro antibiotic resistance profile of E. coli strains isolated from community-acquired pediatric urinary tract infections in Karabuk province. J Contemp Med. 2017;7(3):241-5.
11. Sundvall PD, Ulleryd P, Gunnarsson RK. Urine culture doubtful in determining etiology of diffuse symptoms among elderly individuals: a cross-sectional study of 32 nursing homes. BMC Fam Pract.2011;12(1):36.
12. Ginde AA, Rhee SH, Katz ED. Predictors of outcome in geriatric patients with urinary tract infections. J Emerg Med. 2014;27(2):101-8.
13. Das R, Perrelli E, Towle V, Van Ness PH, Juthani-Mehta M. Antimicrobial susceptibility of bacteria isolated from urine samples obtained from nursing home residents. Infect Control Hosp Epidemiol. 2009;30(11):1116-9.
14. Coskun USS, Coskun G. Determination of the Prevalence and Antibiotic Susceptibilities of Extended Spectrum Beta-Lactamase Positive Escherichia coli Strains Isolated from Urine of Outpatient Patients of a State Hospital. Kocatepe Tıp Derg. 2015;16(1):25-30.
15. Caliskan E, Dede A, Aytar AA, Biten G, Kas E. The Evaluation of Resistance Rates to Various Antibiotics and Extended Spectrum Beta-lactamase Positivity of Esherichia coli and Klebsiella spp. Strains Isolated from Outpatients with Urinary Tract Infection. ANKEM Derg. 2015;29(2):47-53.
16. Duman Y, Gucluer N, Serindag A, Tekerekoglu MS. Antimicrobial Susceptibility of E. coli Strains and Presence of Extended-Spectrum Beta Lactamase. Fırat Tıp Derg. 2010;15(4):197-200.
17. Fagan M, Lindbaek M, Grude N, Reiso H, Romoren M, Skaare D, et al. Antibiotic resistance patterns of bacteria causing urinary tract infections in the elderly living in nursing homes versus the elderly living at home: an observational study. BMC Geriatrics. 2015;15:98.
18. Sanchez GV, Adams SJ, Baird AM, Master RN, Clark RB, Bordon JM. Escherichia coli antimicrobial resistance increased faster among geriatric outpatients compared with adult outpatients in the USA, 2000–10. J Antimicrob Chemother. 2013;68(8):1838-41.
19. Tasbakan MI, Pullukcu H, Sipahi OR, Yamazhan T, Arda B, Ulusoy S. A pooled analysis of the resistance patterns of Escherichia coli strains isolated from urine cultures in Turkey: a comparison of the periods 1997-2001 and 2002-2007. Turkish J Med Sci. 2011;41(3):557-64.
20. Asgin N, Eroglu S, Cakmakliogullari EK. Which Antibiotics Should be First Line Options for Empirical Treatment of Urinary Tract Infections During Pregnancy? ANKEM Derg. 2018;32(3):94-102.
21. Caktır DA. The Distribution of the Factors Causing Childhood Urinary Tract Infections and Investigation of Antibiotic Susceptibility (dissertation) Istanbul; 2008.
22. Yasar KK, Pehlivanoglu F, Sengoz G. Distribution of gram-negative microorganisms and their antibiotic resistance in urinary tract infections of children. Medical Bulletin of Zeynep Kamil. 2010;41(3):137-41.
23. Coban B, Ulkü N, Kaplan H, Topal B, Erdogan H, Baskın E. Five-year assessment of causative agents and antibiotic resistances in urinary tract infections. Turk Pediatr Ars. 2014;49(2):124-9.
24. Kacmaz B, Aksoy A, Sultan N. The Investigation of Resistance to Oral Antibiotics in Escherichia coli Isolates Obtained from Urine. Turk Hij Den Biyol Derg. 2007;64(1):11-5.
25. Lob SH, Nicolle LE, Hoban DJ, Kazmierczak KM, Badal RE, Sahm DF. Susceptibility patterns and ESBL rates of Escherichia coli from urinary tract infections in Canada and the United States, SMART 2010–2014. Diagn Microbiol Infect Dis. 2016;85(4):459-65.
26. Smithson A, Chico C, Ramos J, Netto C, Sanchez M, Ruiz J, et al. Prevalence and risk factors for quinolone resistance among Escherichia coli strains isolated from males with community febrile urinary tract infection. Eur J Clin Microbiol Infect Dis. 2012;31:423–30.
27. Gulcan A, Aslanturk A, Gulcan E. The Microorganisms Isolated from Urine Culture and Their in Vitro Antibiotic Susceptibility. Abant Med J. 2012;1(3):129-35.
28. Uyanık MH, Hancı H, Yazgı H. In-vitro Activity of Fosfomycin Trometamol and some other Antibiotics to Escherichia coli Strains Isolated from Community-acquired Urinary Tract Infections. ANKEM Derg. 2009;23(4):172-6.
29. Rodriguez-Bano J, Navarro MD, Romero L, Martínez-Martínez L, Muniain MA, Perea EJ et al. Epidemiology and clinical features of infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in nonhospitalized patients. J Clin Microbiol. 2004;42(3):1089-94.
30. Bayram Y, Eren H, Berktas M. Distribution of Bacterial Pathogens in Urine Samples and Resistance Patterns of ESBL positive and negative Escherichia coli Isolates against Fosfomycin and other Antimicrobials. ANKEM Derg. 2011;25(4):232-6.

31. Kutlu O, Arabacı Ç. Antibiotic susceptibility pattern of Enterococcus isolates in a five-year period at a tertiary care hospital. J Surg Med. 2019;3(9):644-7.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):861-864.
DOI: 10.28982/josam.595773

Research article
Araştırma makalesi

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

Is there any relationship between propofol induction dose and duration of seizure for repetitive electroconvulsive therapies?

Tekrarlanan elektrokonvulsif tedavilerde propofol indüksiyon dozu ve nöbet süresi arasında ilişki var mıdır?

Çiğdem Yıldırım Güçlü [1], Ahmet Onat Bermede [1], Başak Ceyda Meço [1], Zekeriyya Alanoğlu [1], Neslihan Alkış [1]

[1] Ankara University, School of Medicine, İbn-i Sina Hospital, Department of Anesthesiology and Intensive Care Unit, Ankara, Turkey

ORCID ID of the author(s)

ÇYG: 0000-0002-8416-3418
AOB: 0000-0002-8598-6264
BCM: 0000-0003-2951-9634
ZA: 0000-0003-4967-5829
NA: 0000-0003-0469-2318

Corresponding author / Sorumlu yazar:
Çiğdem Yıldırım Güçlü
Address / Adres: Sancak mah. 525. Sok. 15/7, Çankaya, Ankara, Türkiye
e-Mail: drcigdemyldrm@yahoo.com.tr

Ethics Committee Approval: The study was approved by Ankara University Ethic Committee (14835, 7/16/2013, Clinical trial ID: NCT02394847).
Etik Kurul Onayı: Çalışmaya Ankara Üniverrsitesi Tıp Fakültesi Etik Kurulu (14835, 16.07.2013, Clinical trial ID: NCT02394847) tarafından izin verildi.

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: 12/28/2019
Yayın Tarihi: 28.12.2019

Abstract

Aim: Anesthetic agents have been used during electroconvulsive therapy for years, but selecting the agent remains a challenge. Anesthetics may play a negative role on seizure duration, which directly affects the success of the treatment. This study is designed to see the relationship of repetitive sessions, anesthetic dose, and seizure duration.

Methods: A total of 73 ECT treatments for 11 patients were evaluated for this prospective-cohort study. After premedication, propofol was administered slowly until the patient lost eyelash reflex. The duration of the seizure, propofol dose administered, and the time between the end of the procedure and full recovery (as decided by Aldrete score) were recorded.

Results: The mean seizure time was 25.5 (10.2) seconds. There was a statistically significant correlation between seizure duration, the number of sessions and propofol dose, and no correlation between the time to reach an Aldrete score of 10 and both the number of sessions and propofol dosing.

Conclusion: An increased propofol dosage may be needed during ECT as the number of session increases, but this increase does not affect recovery time.

Keywords: Electroconvulsive therapy, Propofol, Seizure

Öz

Amaç: Elektrokonvülsif tedavi için yıllardır anestezik ajanlar kullanılmıştır, ancak ajanın seçiminde bir zorluk vardır. Anestezikler, tedavinin başarısını doğrudan etkileyen nöbet süresi üzerinde olumsuz rol oynayabilir. Bu noktada, bu çalışma tekrarlayan seanslarda anestezik doz ve nöbet süresi arasındaki ilişkiyi görmek için tasarlanmıştır.

Yöntemler: Bu prospektif-kohort çalışmada toplam 11 hasta, 73 EKT tedavisi değerlendirildi. Premedikasyondan sonra, hastanın kirpik refleksi kaybolana dek yavaş yavaş propofol uygulandı. Nöbet süresi, uygulanan propofol dozu kaydedildi. İşlemin bitimi ile tam derlenme (Aldrete skoru ile karar verildi) arasındaki süre de kaydedildi.

Bulgular: Ortalama nöbet süresi 25,5 (10,2) saniye idi. Nöbet süresi, seans sayısı ve propofol dozu arasında istatistiksel olarak anlamlı bir korelasyon vardı. Aldrete skoru 10'a ulaşma süresi ile seans sayısı ve propofol dozu arasında korelasyon saptanmadı.

Sonuç: Seans sayısı arttıkça EKT sırasında artmış bir propofol dozu gerekebilir, ancak bu artış iyileşme süresini etkilemediği görülmüştür.

Anahtar kelimeler: Elektrokonvülsif tedavi, Propofol, Nöbet

How to cite / Atıf için: Güçlü ÇY, Bermede AO, Meço BC, Alanoğlu Z, Alkış N. Is there any relationship between propofol induction dose and duration of seizure for repetitive electroconvulsive therapies? J Surg Med. 2019;3(12):861-864.

Introduction

Electroconvulsive therapy (ECT) is a valuable option in the treatment of many psychiatric disorders. The procedure is performed following the administration of short-term general anesthesia using a neuromuscular-blocking agent by placing two electrodes on the temples and/or the forehead of the patient and delivering electrical pulses between the electrodes in order to induce a generalized convulsion [1].

Anesthetics have been used during ECT since the 1950s. The anesthesia is used to avoid unpleasant feelings that the patient may have during convulsion inducement [2]. No guidelines exist for the strategies regarding choice, and potential switching of narcotic agents throughout a course of ECT. While choosing the agent, it is suggested to consider a patient's individual risk factor profile, co-existing diseases, and concomitant medication [3]. Currently, propofol is one of the most favorable anesthetic agents used during ECT due to its rapid recovery and minor hemodynamic effects, however, little is known about its long-term usage in ECT patients [4].

This study is designed to evaluate the effect of repeated ECTs on propofol induction dose, seizure time and recovery parameters within the treatment period of patients undergoing ECT.

Materials and methods

Eleven patients who were scheduled for ECT treatment for depression (n=5) and schizophrenia with depression (n=6) were included this study. A total of 73 ECT treatments were evaluated after Institutional Ethics Committee approval (Ankara University Ethic Committee, 14835) and written informed consent forms were obtained. The study was performed in accordance with the most recent version of the Helsinki Declaration.

Exclusion criteria

The exclusion criteria for this study included (1) presence of any serious concomitant diseases, such as cardiovascular disease, cerebrovascular disorders, intracranial hypertension, respiratory tract diseases, or severe fractures, (2) presence of hypertension, glaucoma, arterial aneurysm, or cerebrovascular malformation, (3) presence of a foreign body, such as a pacemaker, intracranial electrode, or clips, (4) positive seizure history, (5) history of substance abuse or dependence, including alcohol abuse, (6) ASA IV–V status, (7) history of serious adverse effects related to anesthetics (8) coexistence of a mental disorder other than major depression, such as dementia and bipolar disorder, and (9) pregnancy.

Anesthesia and ECT administration

All chronic antidepressant medication was continued. After premedication with intravenous atropine sulfate (0.25 mg), propofol was administered slowly until the patient showed loss of the eyelash reflex. Then, succinylcholine, 1 mg/kg, was administered. Ventilation was assisted with 100 % oxygen in all patients during the procedure. The duration of the seizure and the administered propofol dose were recorded. After the procedure, the patient was awakened and followed-up during recovery until Aldrete score reached 10. The time between the end of the procedure and full recovery (as decided by Aldrete score) were also noted.

The seizure threshold was determined according to half-age method (% energy=half the age [5]. A suprathreshold electrical stimulus was given via bifrontotemporal electrodes with a Thymatron System IV, ECT Instrument (Somatics, Lake Bluff, IL, USA). EEG electrodes were placed on the mastoid processes, and frontal leads were placed bilaterally on the midforehead directly above the eyes to allow two-channel (bihemispheric) recordings. Recording gain was set according to the manufacturer's recommendations. The duration of the motor seizure was defined as the time from the ECT stimulus to cessation of tonic–clonic motor activity in the 'isolated' arm.

All treatments were administered using the Thymatron System IV (Somatics, LLC, Lake Bluff, Ill; maximum energy 200%, 1008 mC, stimulus frequency 1 m/s) after induction with propofol, with the dosage determined by the anesthesiologist. The delivery of the electrical stimulus was bilateral. Stimulus dose titration was used to establish individual seizure thresholds. The dosage was set at 1.5 times the seizure threshold for bilateral treatment and at 6 times the seizure threshold for unilateral treatment. Dosage was adjusted during ECT to maintain a seizure duration of at least 20 seconds as measured with the cuff method, or 25 seconds on the electroencephalogram (EEG). An adequate seizure was defined as seizure duration of at least 20 seconds as measured with the cuff method, or 25 seconds on the EEG [6].

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 11.5 (SPSS, Chicago, IL, USA). Distribution of continuous variables was analyzed with the one-sample Kolmogorov–Smirnov test, and all data were distributed normally. Comparisons among groups with respect to seizure duration and recovery parameters were evaluated using one-way analysis of variance (ANOVA) with the Bonferroni post hoc test. Repeated ANOVA with Bonferroni post hoc tests were used to compare baseline and follow-up HR and MAP measurements. Side effects among groups were evaluated using the Chi square test. A two tailed *P*-value of 0.05 was considered statistically significant. The results were expressed as mean (SD). Power calculations based on a pilot study with 10 patients were used to detect a significant difference in the seizure duration (a=0.05, power=0.80).

Results

Eleven patients were enrolled in the study and received a total of 73 sessions of ECT. The demographic and clinical characteristics are summarized in Table 1 and 2. The mean age was 37.2 years. Most of the patients were male (n: 9, 81.8%). The mean seizure time was 25.5 (10.2) minutes, with a minimum of 7 and maximum of 54 minutes. The patients had at least 1 and at most 15 sessions of ECT.

There was a statistically significant correlation between seizure duration and the number of sessions as well as propofol dose (*P*=0.020, *P*=0.027, respectively). The mean increase in the number of sessions was 1 time for every 0.6 sec decrease in seizure duration (95% confidence interval [CI], 1.83; *P*=0.05). The mean increase in propofol dose was 1 mg per 0.08 sec

decrease in seizure duration (95% confidence interval [CI], 1.08; *P*=0.05).

The mean propofol dose of the total 73 sessions is 110.89 (28.3) mg. The propofol need increased with the number of sessions (Figure 1). The mean seizure duration was 25.5 (10.2) sec. The mean time passed to achieve the Aldrete score of 10 was 10.9 (4.8) min. The time passed to reach an Aldrete score of 10 and duration of seizure did not any increase with the number of sessions (Figure 2 and 3). The mean dose of all sessions, seizure duration and time passed to reach an Aldrete score of 10 are summarized in Table 3.

The correlations between the time to reach an Aldrete score of 10 and both the number of sessions and propofol dose were statistically insignificant with p values of 0.308 and 0.627, respectively. The number of sessions and propofol dose did not impact the time to reach an Aldrete score of 10. The correlation between seizure duration and the time to reach Aldrete score of 10 was statistically insignificant (*P*=0.126).

Table 1: Patient characteristics

Patient characteristics	
Age (years) mean (SD)	37.2 (16.3)
Gender (n)	M: 9 F: 2
Height (cm) (SD)	173.3 (6.1)
Weight (kg) (SD)	76.1 (7.4)
Diagnosis (n)	1:7
	2:2
	3:2

Table 2: Clinical characteristics of the patients

Clinical characteristics	mean (SD)	min-max
t seizure (sec)	25.5 (10.2)	7-54
sessions (n)	4.86 (3.3)	1-15
propofol dose	110.8 (28.3)	80-200
t Aldrete(min)	10.95 (4.84)	5-20

Table 3: The propofol dosage (in mg), seizure duration (in sec), time to reach an Aldrete score of 10 (in min) according to the sessions

sessions	N of patients	Propofol dose(mg) Mean (SD)	Seizure duration(sec) Mean (SD)	T Aldrete (min) Mean (SD)
1	11	114.55(35)	28.2 (13.9)	11.6 (5)
2	11	105.45 (0.7)	32.6 (13.4)	12.2 (4.4)
3	10	109.5 (29.4)	22.2 (8.4)	11 (5.3)
4	8	110 (32)	23 (5.5)	11.1 (5)
5	7	101.43 (18.6)	27.2 (7.6)	9.4 (4.7)
6	5	112 (30.3)	26.6 (8.8)	9 (5.1)
7	5	106 (24)	25.4 (10.9)	10.6 (5.7)
8	5	114 (36.4)	18.2 (6.4)	12.8 (6)
9	5	108 (27.7)	24 (7.8)	12 (5.8)
10	1	120	27	9
11	1	120	14	8
12	1	130	12	7
13	1	140	30	6
14	1	150	21	8
15	1	130	23	11
Total	73	110.8 (8.3)	25.5 (10.2)	10.9 (4.8)

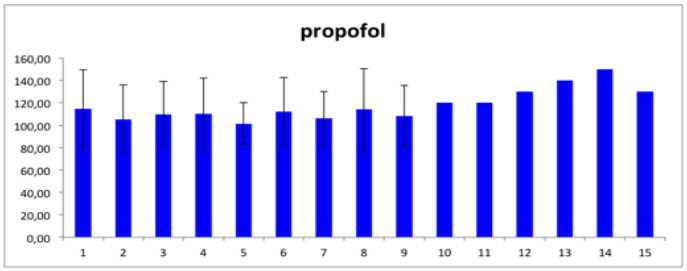

Figure 1: Propofol dosage according to the sessions (X axis: propofol dose, Y axis: number of sessions)

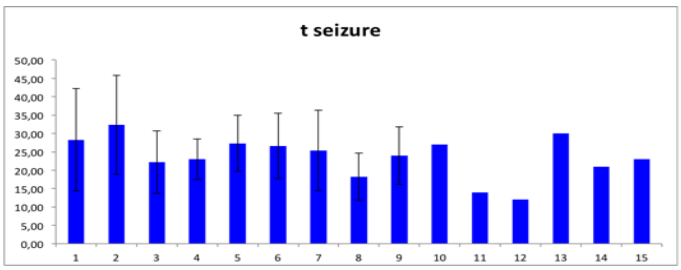

Figure 2: Seizure duration according to the number of sessions (X axis: seizure duration in seconds, Y axis: number of session)

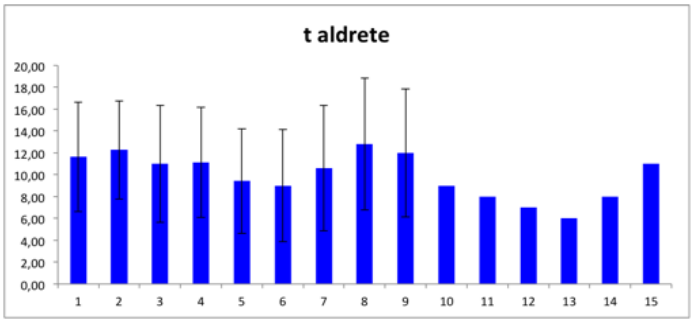

Figure 3: Time spent until reaching an Aldrete score of 10, according to the sessions (X axis: time until reaching Aldrete score of 10 in minutes, Y axis: number of sessions)

Discussion

This study was designed to investigate the relationship between repetitive ECT therapies, seizure duration and recovery time, as measured by the Aldrete score. The results of the study showed that there are statistically significant but weak negative correlations between propofol dose and both seizure duration and number of sessions. According to our results, the number of sessions and propofol dose does not affect recovery time, and there was no significant correlation between seizure duration and recovery time.

Electroconvulsive therapy is an alternative treatment for many psychiatric disorders. The aim of the procedure is to induce cerebral seizures, which may lead to changes in drugs' pharmacokinetics. Anesthesia has been used for electroconvulsive therapy since the 1950s. Many anesthetic agents have been compared to find the best option. Propofol seems to be most popular one in current clinical use with the advantages of decreased risk of hypertension and tachycardia, as well as faster recovery from anesthesia. However, there are challenges regarding correct dosage, duration of seizure and recovery with these patients. Data on cognitive functioning, although limited, generally indicate no reduction in cognition related to propofol use [7].

The anticonvulsant properties of certain anesthetic agents have repeatedly been shown to negatively impact seizure parameters [8-11]. This study also showed comparable results to the literature.

Many alternative methods like hyperventilation, using low dose of anesthetics and a combination of anesthetics have been assessed to prolong the duration of seizure [12]. In this study, we tried to find the optimal dose of propofol when used alone. There are studies regarding exceptionally low doses of propofol (0.75-1 mg/kg), but the current study used higher doses for loss of eyelash reflex [8].

The effectiveness of the procedure depends on duration of the seizure. When compared with other anesthetic agents, propofol seems to achieve a shorter duration of seizure, but questions remain about the efficacy of the treatment. The duration of the seizure may be related to the dose of propofol because of its antiepileptic properties. The findings of this study conclude that increase in propofol dose results in a decrease in seizure duration as expected. As the number of the sessions increase, so does the need for higher doses of propofol.

Another critical issue is the rapid and full recovery from anesthesia after ECT. Anesthetic agents used for ECT have long been evaluated from this perspective. When compared with other

agents, propofol has many advantages including rapid recovery [7]. As the propofol dose increases with increasing sessions, the effect on recovery becomes questionable. There is no positive relationship between recovery time and both propofol dosage and number of sessions.

Limitations

The limitation of the study is the absence of anesthetic depth monitoring, such as bispectral index monitoring (BIS) or entropy. The use of BIS or entropy during the ECT procedure would yield more accurate results regarding the dose of propofol.

Conclusion

Propofol is a suitable alternative as an anesthetic agent in the ECT procedure. An increased propofol dosage may be needed during ECT as the number of sessions increases, but this increase does not affect recovery time. The best maintenance of satisfactory and suitable anesthesia for ECT should utilize the guidance of anesthetic depth monitoring.

References

1. Fink M, Taylor MA. Electroconvulsive therapy. JAMA. 2007;298(3):330–2.
2. Steven RJ, Tovel RM, Johnson JC, Delgado E. Anesthesia for electroconvulsive therapy. Anesthesiology. 1954;15(6):623–36.
3. Wagner KJ, Mollenberg O, Rentrop M, Werner C, Kochs EF. Guide to anesthetic selection for electroconvulsive therapy. CNS Drugs. 2005;19:745–75.
4. Ding Z, White PF. Anesthesia for electroconvulsive therapy. Anesth Analg. 2002;94:1351–64.
5. Petrides G, Fink M. The ''half-age'' stimulation strategy for ECT dosing. Convuls Ther. 1996;12:138–46.
6. Abrams R. Electroconvulsive Therapy. New York, NY: Oxford University Press; 2002.
7. An den Broek WW, Leentjens AFG, van Vliet IM, et al. Hand-boek Elektroconvulsietherapie. Assen, the Netherlands: Koninklijke Van Gorkum. 2005.
8. Rasmussen KG. Propofol for ECT Anesthesia a Review of the Literature. J ECT. 2014;30:210–5.
9. Van Waarde JA, van Oudheusden LJ, Verwey B, Giltay EJ, van der Mast RC. Clinical predictors of seizure threshold in electroconvulsive therapy: a prospective study. Eur Arch Psychiatry Clin Neurosci. 2013;263:167–75.
10. Bundy BD, Hewer W, Andres FJ, Gass P, Sartorius A. Influence of anesthetic drugs and concurrent psychiatric medication on seizure adequacy during electroconvulsive therapy. J Clin Psychiatry. 2010 Jun;71(6):775–7.
11. Janouschek H, Nickl-Jockschat T, Haeck M, Gillmann B, Grözinger M. Comparison of methohexital and etomidate as anesthetic agents for electroconvulsive therapy in affective and psychotic disorders. J Psychiatr Res. 2013;47:686–93.
12. Yalcin S, Aydogan H, Selek S, Kucuk A, Yuce HH, Karababa F, et al. Ketofol for electroconvulsive therapy anesthesia, two stones for one bird. J Anesth. 2012;26:562–7.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):865-869.
DOI: 10.28982/josam.661757

Research article
Araştırma makalesi

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

Retinal nerve fiber layer thickness in patients with essential tremor and Parkinson's disease

Esansiyel tremoru ve Parkinson hastalığı olan hastalarda retina sinir lifi tabaka kalınlığı

Halit Fidancı [1], Nevra Öksüz [2], Şeyda Öztürk [2], Ufuk Adıgüzel [3], Şükrü Hakan Kaleağası [2], Okan Doğu [2]

[1] Department of Neurology and Clinical Neurophysiology, Adana City Training and Research Hospital, Adana, Turkey
[2] Department of Neurology, Faculty of Medicine, Mersin University, Mersin, Turkey
[3] Department of Ophthalmology, Faculty of Medicine, Mersin University, Mersin, Turkey

ORCID ID of the author(s)
HF: 0000-0001-6573-9090
NÖ: 0000-0003-4825-7457
ŞÖ: 0000-0001-5105-5800
UA: 0000-0001-6618-1359
ŞHK: 0000-0003-2709-3051
OD: 0000-0002-2126-9792

Corresponding author / Sorumlu yazar:
Halit Fidancı
Address / Adres: Adana Şehir Eğitim ve Araştırma Hastanesi, Nöroloji Anabilim Dalı, Klinik Nörofizyoloji Bilimdalı, Adana, Türkiye
e-Mail: dr.halitfidanci@gmail.com

Ethics Committee Approval: Ethical approval for this study was obtained from the ethical committee of the Faculty of Medicine in Mersin University (number: 2013/339).
Etik Kurul Onayı: Çalışmaya Etik kurul onayı Mersin Universitesi Etik Kurulu'ndan alınmıştır (no: 2013/339).

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

Financial Disclosure: This study was funded by the scientific research projects fund of Mersin University (number: BAP-TFDTB(HF)2014-1TU).
Finansal Destek: Bu çalışma, Mersin Üniversitesi'nin bilimsel araştırma projeleri fonu tarafından finanse edilmiştir (sayı: BAP-TFDTB(HF)2014-1TU).

Published: 12/29/2019
Yayın Tarihi: 29.12.2019

Abstract

Aim: Essential tremor (ET) and Parkinson's disease (PD) are common movement disorders. In PD, visual problems such as impaired color vision and decreased visual acuity have been reported. Studies have shown that retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) is decreased in PD and some neurodegenerative diseases. Due to the similarities of ET and PD, we aimed to evaluate RNFL measured by OCT in ET and PD patients.

Methods: PD, ET and control groups were formed in this prospective case-control study. Each group included 30 individuals, and 180 eyes were examined. In these groups, RNFL quadrants, macula and fovea were evaluated with OCT. In the ET group, tremor severity was included in the analyses. The severity of disease in PD was assessed with the Unified Parkinson's Disease Rating scale and the Hoehn and Yahr scale.

Results: In the control, ET and PD groups, the mean RNFL thicknesses of the right eye were 93.2 (8.1), 86.7 (9.7), 86.8 (10.2) µm, respectively. These values were lower in the PD and ET groups compared to the control group (P=0.026, P=0.025). There was no correlation between disease severity and RNFL thickness in ET.

Conclusion: Decreased RNFL thickness in ET may indicate that ET is a neurodegenerative disease, such as PD. There may be subclinical retinal impairment in ET.

Keywords: Essential tremor, Optical coherence tomography, Parkinson's disease, Retinal nerve fiber layer

Öz

Amaç: Esansiyel tremor (ET) ve Parkinson hastalığı (PH) yaygın hareket bozukluklarındandır. PH'de renkli görmede bozulma ve görme keskinliğinde azalma gibi görme sorunları bildirilmiştir. Çalışmalar, optik koherens tomografi (OKT) ile ölçülebilen retina sinir lifi tabaka (RSLT) kalınlığının PH ve bazı nörodejeneratif hastalıklarda azaldığını göstermiştir. ET ve PH hastalığının benzer özellikleri olması nedeniyle, ET ve PH hastalarında OKT kullanarak RSLT'yi değerlendirmeyi amaçladık.

Yöntemler: Bu prospektif vaka-kontrol çalışmasında PH, ET ve kontrol grupları oluşturuldu. Her grupta 30 kişi mevcuttu ve 180 göz incelendi. Bu gruplarda, RSLT kadranları, makula ve fovea OKT ile değerlendirildi. ET grubunda titreme şiddeti analizlere dahil edildi. PH'de hastalığın şiddeti Birleşik Parkinson Hastalığı Değerlendirme Ölçeği ve Hoehn ve Yahr ölçeği ile değerlendirildi.

Bulgular: Kontrol, ET ve PH gruplarında sağ gözün ortalama RSLT kalınlığı sırasıyla 93,2 (8,1), 86,7 (9,7), 86,8 (10,2) µm idi. PH ve ET gruplarında bu değerler kontrol grubuna göre daha düşüktü (P=0,026, P=0,025). ET'de hastalık şiddeti ile RSLT kalınlığı arasında ilişki bulunmadı.

Sonuç: ET'de azalmış RSLT kalınlığı, ET'nin PH gibi bir nörodejeneratif hastalık olduğunu gösterebilir. ET'de subklinik retinal bir etkilenme olabilir.

Anahtar kelimeler: Esansiyel tremor, Optik koherens tomografi, Parkinson hastalığı, Retinal sinir lifi tabakası

How to cite / Atıf için: Fidancı H, Öksüz N, Öztürk Ş, Adıgüzel U, Kaleağası ŞH, Doğu O. Retinal nerve fiber layer thickness in patients with essential tremor and Parkinson's disease. J Surg Med. 2019;3(12):865-869.

Introduction

Essential tremor (ET) and Parkinson's disease (PD) are common movement disorders with similar clinical features. PD is characterized by rest tremor, rigidity, bradykinesia, and postural instability. Postural and kinetic tremor is typical in ET. Rest tremor can be seen in ET as the disease progresses. Nonmotor clinical features are seen in both diseases. Visual impairments including impaired contrast sensitivity, decreased visual acuity and impaired color vision is one of the nonmotor symptoms in PD [1,2]. It was shown that the concentration of retinal dopamine decreased in PD [2-5]. In PD, it is thought that some visual impairments may develop as a result of dopamine deficiency in retina. Although the correlation between the retinal nerve fiber layer (RNFL) thickness measured by optical coherence tomography (OCT) and the dopamine present in retinas is not fully established, studies have shown that RNFL thickness in PD patients is also thinner compared to controls, as in other neurodegenerative diseases such as Alzheimer's disease [6-9]. ET, including postural and kinetic tremor, is a chronic progressive disease that typically progresses slowly over time. Clinical progression in ET, development of rest tremor and ataxia in some patients, the risk of developing PD and the presence of Lewy bodies in brainstem in autopsy studies show that ET has similar aspects to PD [10-13]. Some nonmotor symptoms such as cognitive impairment or neuropsychiatric problems are seen in ET as in PD [14,15]. In the literature, there are very few researches on visual functions in ET, and color vision abnormalities have not been detected [16,17]. The studies determining RNFL thickness with OCT in ET had different results [18-20]. However, we did not find any study comparing RNFL thickness in both PD and ET patients. In addition, few studies on RNFL thickness in ET did not investigate whether there was a correlation between RNFL thickness and tremor severity. In our study, we wanted to evaluate RNFL thickness in ET and PD with OCT based on their similar characteristics.

Materials and methods

Subjects

Healthy individuals who were referred to the Neurology Department of the Faculty of Medicine in Mersin University between September 2013 and May 2014, patients with definite ET diagnosis according to the Washington Heights-Inwood Genetic Study of ET (WHIGET) diagnostic criteria and patients with definite PD diagnosis according to the United Kingdom Brain Bank diagnostic criteria were included in this prospective case-control study. Ethical approval for this study was obtained from the ethical committee of the Faculty of Medicine in Mersin University (year: 2013, number: 2013/339). Written consent was obtained from all participants. The age of onset of idiopathic PD was taken into consideration and participants were included in the study if the age of the participants was over 40 years in all groups. Individuals with Parkinsonism-causing toxic substance exposure, history of encephalitis, meningitis or head trauma and those with diabetes mellitus, thyroid disease, vasculitis, retinal detachment, glaucoma and cataract were excluded from the study. The severity of postural, kinetic and rest tremor was evaluated in ET patients. Postural tremor severity was scored after 30 seconds of observation, with arms extended straight forward. It was scored as 0 for no tremor, 1 for mild, 2 for moderate amplitude and 3 for high amplitude and severe cases. Kinetic tremor was scored by pouring water from glass to glass, using spoon, drinking and finger-nose test. It was scored as 0 for no tremor, 1 for mild degree, 2 for moderate amplitude, 3 for high jump mode and 4 for extremely high amplitude. While evaluating tremor severity, the value on the extremity with the most severe tremor was recorded. ET patients were separated in subgroups as with and without rest tremor. In ET patients with rest tremor, frequency of rest tremor was lower than the frequency of postural tremor, and rest tremor did not occur at the early stages of the disease. Patients with a family history of PD were not included in the ET group. In the PD group, disease severity was measured by the Hoehn and Yahr scale (HYS) and Unified Parkinson's Disease Rating Scale (UPDRS). PD patients with a suspected or definite history of ET were not included. All PD patients were included in the study during on periods. Patients in the PD group were receiving dopaminergic or levodopa therapy. An experienced ophthalmologist examined participants, and those with findings consistent with ophthalmologic conditions that would affect the retina were not included in the study. Visual acuity using Snellen chart was 20/30 or higher in all subjects. Intraocular pressure of all subjects was lower than 21 mmHg.

OCT examination

Carl Zeiss Cirrus 4000 OCT was used to measure RNFL and macular thickness. Each individual focused on a bright point set by OCT. OCT examination consisted of three circular scans with a diameter of 3.4 mm centered on optic disk. The software was enabled to measure the thickness data of each quadrant automatically. RNFL superior (RNFLs; $46\text{-}135^0$), inferior (RNFLi; $226\text{-}315^0$), nasal (RNFLn; $136\text{-}225^0$), temporal (RNFLt; $316\text{-}45^0$) quadrants thickness and foveal thickness values were obtained in the evaluation of both eyes and these values were recorded as micron (μm), and the macular cube volume was recorded as cubic millimeter (mm^3). Mean of RNFL (RNLFm; 360^0) and central foveal thickness were also calculated. RNFLm values were obtained by averaging RNFLs,i,n,t quadrants. Because a small number of studies reported that asymmetry may be present in OCT measures, both eyes of the individuals were examined with OCT [18-21].

Statistical analysis

The distribution of the variables was checked by the Kolmogorov-Smirnov test. ANOVA (Tukey test), Kruskal-Wallis and Mann-Whitney U tests were used in the analysis of quantitative data; the Chi-squared test was used in the analysis of qualitative data, and Spearman's correlation was used in the correlation analysis. Bonferroni correction was used for post-hoc analysis and multiple comparisons. Considering the previous studies and power analysis (95% confidence interval and level 0.05 type 1 error), it was planned to include 30 participants in each group [8,9,18]. *P*-value <0.05 was considered statistically significant. Statistical Package for the Social Sciences (SPSS IBM Corp; Armonk, NY, USA) 22.0 was used to perform the statistical analysis.

Results

Each group included 30 individuals, and a total of 180 eyes were examined. Mean age (standard deviation) was detected as 61 (11.3) years in ET patients, 62 (10.4) years in PD patients and 60.5 (11.9) years in the control group. 12 ET patients (40%), 11 Parkinson's patients (36.7%) and 16 patients (53.3%) in the control group were females. There was no difference between the groups with respect to age and gender. Family history of ET was present in 19 ET patients (63.3%) and family history of PD was present in 8 PD patients (26.7%). Demographic features of PD and ET patients are shown in Table 1. The mean durations of the disease in Parkinson's and ET patients were 4.1 (2.4) and 8.7 (5.4) years, respectively. Postural and kinetic tremor severities in the ET group were shown in Table 1. There was a positive correlation between kinetic tremor severity (most affected side considered) and duration of disease in the ET group (P=0.15, r=0.440). Five ET patients had rest tremor without bradykinesia or rigidity or re-emergent tremor or jaw tremor. Asymmetric clinical findings were present in 20 patients with ET and 25 patients with PD. The mean HYS score was 2.1 (0.9) in the PD group. UPDRS mental status, daily life, motor examination and treatment complication scores were 4.6 (2.3), 15.6 (10.3), 20.3 (10.8) and 2.7 (4.3), respectively. The mean UPDRS total score was 43.2 (25.4). There was a significant positive correlation between the duration of the disease and the HYS of the patients (P=0.019, 0.425). There was also a significant positive correlation between the duration of the disease and UPDRS mental status, daily living activities and scores related to treatment complications (P=0.019, r=0.426; P=0.002, r=0.534; P=0.002, r=0.537, respectively). A similar positive correlation was found between UPDRS total score and the duration of the disease (P=0.004, r=0.509).

The RNFLs, i, n, t, m values among groups are shown in Table 2. Right RNFLm was 93.3 (8.1), 86.7 (9.7) and 86.8 (10.2) μm in the control, ET and PD groups, respectively, and significantly lower in the ET and PD groups compared to the control group (P=0.025 and P=0.026 with Bonferroni correction, respectively). The mean RNFL thickness of the right eyes among groups was shown in Figure 1. Similarly, the left RNLFn of ET patients was thinner than the left RNLFn of PD patients and controls (Table 2). In the control, PD and ET groups, mean of macular volumes were 10.0 (0.7), 9.7 (0.6) and 9.7 (1.0) mm^3, respectively, and mean values of foveal thickness were 263.2 (16.3), 266.6 (19.7) and 262.7 (12.1) μm, respectively, and there was no significant difference between the groups (table 2).

In the PD group, a negative correlation was found between HYS scores and RNFLn in the right eye (P=0.005, r=-0.498). There were also negative correlations between right RNFLn and UPDRS mental (P=0.007, r=-0.484), daily life (P=0.005, r=-0.498), motor (P=0.018, r=-0.429) and total (P=0.018, r=-0.429) scores. A negative correlation between RNFLi and UPDRS motor score in the left eye was found (P=0.015, r=-0.442). There was no correlation between macular volume and UPDRS / HYS scores in PD patients. No correlation was found between RNFL parameters, foveal thickness, and tremor severity in the ET group.

Table 1: Demographic characteristics and disease severity of PD, ET and Control groups

	PD group	ET group	Control group	*P*-value
Age mean (SD) (years)	62 (10.4)	61 (11.3)	60.5 (11.9)	0.901
Gender (female/male)	11 / 19	12 / 18	16 / 14	0.387
Duration of disease mean (SD) (years)	4.1 (2.4)	8.7 (5.4)	-	
Side of onset* (right/left/bilateral)	14 / 11 / -	11 / 6 / 7	-	
HYS scores mean (SD)	2.1 (0.9)	-	-	
UPDRS total scores mean (SD)	43.2 (25.4)	-	-	
Postural tremor severity mean (SD) (right/left)	-	2.1 (0.6)/ 2.1 (0.7)	-	
Kinetic tremor severity mean (SD) (right/left)	-	2.5 (0.9) / 2.3 (0.9)	-	

PD: Parkinson's disease, ET: essential tremor, HYS: Hoehn and Yahr scale, SD: standard deviation, *: the side of onset of symptoms was unknown in some patients

Table 2: Comparison of RNFL thickness in PD, ET and Control groups

	PD group Mean(SD)	ET group Mean (SD)	Control group Mean (SD)	*P*-value
RNFLm (μm)				
Right eye	86.8 (10.2)	86.7 (9.7)	93.2 (8.1)	0.010
Left eye	85.7 (12.9)	84.5 (15.9)	91.7 (8.9)	0.076
RNFLs (μm)				
Right eye	103.6 (18.1)	103.5 (16.1)	110.1 (16.5)	0.206
Left eye	103.9 (25.5)	105.3 (25.1)	112.1 (17.3)	0.341
RNFLi (μm)				
Right eye	113.7 (20.3)	112.5 (20.0)	123.7 (15.3)	0.064
Left eye	110.7 (23.9)	108.3 (25.9)	118.0 (21.8)	0.266
RNFLn (μm)				
Right eye	70.2 (9.1)	68.3 (11.7)	73.4 (12.7)	0.216
Left eye	65.1 (12.4)	64.7 (14.7)	73.2 (12.5)	0.023
RNFLt (μm)				
Right eye	59.9 (12.9)	62.3 (8.9)	65.3 (14.8)	0.243
Left eye	60.2 (18.3)	59.9 (15.2)	63.7 (10.2)	0.554
Foveal thickness (μm)				
Right eye	257.6 (13.9)	267.8 (24.2)	260.8 (18.3)	0.156
Left eye	268.2 (16.5)	266.0 (24.3)	264.9 (19.5)	0.089
Macular volume (mm^3)				
Right eye	9.7 (1.1)	9.6 (0.7)	9.9 (0.7)	0.162
Left eye	9.7 (1.1)	9.8 (0.6)	10.0 (0.7)	0.407

SD: standard deviation, RNFLs/i/n/t/m: retinal nerve fiber layer thickness superior / inferior / nasal / temporal / mean. Anova Tukey and Kruskal-Wallis tests were used. P<0.05 was considered statistically significant.

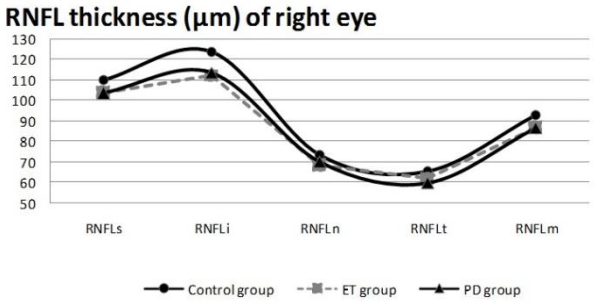

Figure 1: Mean RNFL thickness value of right eyes among groups (RNFLs/i/n/t/m: Retinal nerve fiber layer thickness superior / inferior / nasal / temporal / mean)

Discussion

Inzelberg [8] first showed that RNFL of PD patients measured by OCT was thinner than that of controls. Similar results of other studies supported this result [9, 22-24]. In a meta-analysis, it was found that all RNLF quadrants might be thinner in PD patients than in controls with different OCT devices. However, subgroup analysis showed a statistically significant decrease in RNFLt thickness and RNFLm thickness in all OCT types [25]. Akin to these previous studies [8,25,26], in our study, peripapillary RNFL thickness in all quadrants was thinner in Parkinson's patients compared to the controls. Although all these findings were not significant, right RNFLm thickness was significantly smaller compared to the controls. Although temporal quadrant was thought to be affected early in neurodegenerative diseases [27], it was lower than the control group in our study, but this was not significant. We think that, if the number of patients increase, this difference will become more significant. Interestingly, we also found similar decreases in

RNFL thickness in the ET group. We found few studies in the literature where RNFL of ET patients was assessed by OCT [18-20]. One of these studies was a pilot study with a small number of patients where it was found that foveal thickness decreased in ET patients compared to the controls, but this difference was not statistically significant [18]. Although we did not find such a result, it may indicate that retinal involvement may be present in ET patients. Similar to our results, Tak et al. found that RNFL was thinner in ET patients compared to the control group [19]. However, in another study, RNFL thickness of ET patients was not significantly different compared to the control group, in contrast to our results [20]. This may be due to methodological differences, such as the age of the patients included in the study. We have difficulty in explaining these different results, but we believe that more studies on this topic will result in clearer findings.

In a small number of studies, color vision impairment was not detected in ET [16,17], but the retinal thinning we found may indicate a subclinical visual effect. It is known that there is a retinal dopamine deficiency in PD [3,4]. Retinal dopamine deficiency leads to decreased visual contrast sensitivity. OCT can measure RNFL thickness but does not measure the amount of dopamine. It is not known whether dopamine deficiency affects the RNFL thickness or whether there is a correlation between the RNFL and the amount of dopamine. In addition, lack of direct connection between dopaminergic amacrine cells and ganglion cells suggests that dopamine deficiency alone may not be responsible for the reduction of RNFL thickness [3,4,28]. However, the improvement of retinal activity measured by electroretinogram or improvement of color vision with levodopa treatment suggests that dopamine has a significant retinal effect [29,30]. Lewy bodies (LB) or phosphorylated α-synuclein may have contributed to this retinal involvement. As is well known, LB and other pathological findings occur in brainstem and olfactory nucleus before they occur in substantia nigra, and these pathological findings are spread from brainstem to the cortex and other regions, as described in the Braak staging [31]. LB are not specific to PD but also occur in other neurodegenerative diseases such as corticobasal degeneration and Lewy body dementia. Alpha-synuclein, which plays a role in dopamine release, is important in the formation of LB. Phosphorylated alpha-synuclein was found in the retinas of PD patients, which is thought to be a biomarker of PD [32,33]. Visual problems seen in PD can be caused by LB or phosphorylated α-synuclein present in retina. In postmortem studies performed on ET patients, LB were detected in brainstem [11]. Decrease in RNFL thickness determined by OCT may also occur in ET as a result of these pathologies. Regardless of the cause, RNFL thickness in measured by OCT decreased in neurodegenerative disorders such as PD, Alzheimer's disease and multiple sclerosis. Similar to these neurodegenerative diseases, the presence of thinner RNFL suggests that ET may be a neurodegenerative disease.

As expected, there was a correlation between disease severity identified by UPDRS, HYS in PD, tremor grade in ET and the duration of illness. The correlation between RNFL thickness, macula or fovea and severity of PD has been determined in some studies [6,22]. Satue et al. [6] found a negative correlation between HYS and macular parameters. We did not find such a correlation. In our study, an inverse correlation was found between RNFLn, RNFLi and UPDRS scores in PD patients. Jimenéz et al. [34] found a negative correlation between UPDRS scores and average RNFL thickness. Unlike the PD group, we did not obtain a similar correlation in the ET group. In fact, this finding was not surprising, because the severity of tremor was based on motor symptoms, and a retinal pathology that may be present in ET may be a nonmotor symptom.

Limitations

There were some limitations of our study. First, some of the ET patients may develop PD. The risk of developing PD in ET patients can be four times higher than controls [35]. The prevalence of rest tremor in ET varies between 1% and 50% [36,37]. Five ET patients (16.7%) had rest tremor in our study. It should be noted that the ET patients included in our study were > 40 years old and had a longer duration of disease. There were no re-emergent tremor, jaw tremor, bradykinesia or rigidity in ET patients included in our study. However, there may be a possible overlap between ET and PD. Second, all PD patients were receiving dopaminergic or levodopa therapy, and these treatments may affect RNFL thickness. In addition, the PD group was not divided into subgroups according to treatment.

Conclusion

In conclusion, our study has shown that RNFL thickness measured by OCT was reduced in ET as in neurodegenerative diseases such as PD and Alzheimer's disease. This finding may indicate that ET is a neurodegenerative disease and subclinical retinal impairment occurs in ET.

References

1. Biousse V, Skibell BC, Watts RL, Loupe DN, Drews-Botsch C, Newman NJ. Ophthalmologic features of Parkinson's disease. Neurology. 2004;62:177–80.
2. Bodis-Wollner I. Retinopathy in Parkinson disease. J Neural Transm. 2009;116(11):1493-501.
3. Bodis-Wollner I. Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. Trends Neurosci. 1990;13:296–302.
4. Witkovsky P. Dopamine and retinal function. Doc Pohthalmol 2004;108(1):17-40.
5. Harnois C., Di Paolo T. Decreased dopamine in the retinas of patients with Parkinson's disease. Investigative Ophthalmology&Visual Science. 1990;31(11):2473–75.
6. Satue M, Seral M, Otin S, Alarcia R, Herrero R, Bambo MP, et al. Retinal thinning and correlation with functional disability in patients with Parkinson's disease. British Journal of Ophthalmology. 2014;98(3):350–5.
7. Satue M, Obis J, Rodrigo MJ, Otin S, Fuertes MI, Vilades E, et al. Optical Coherence Tomography as a Biomarker for Diagnosis, Progression and Prognosis of Neurodegenerative Diseases. J Ophtalmol. 2016;2016:8503859.
8. Inzelberg R, Ramirez JA, Nisipeanu P, Ophir A. Retinal nerve fiber layer thinning in Parkinson disease. Vision Res. 2004;44:2793–7.
9. Kirbas S, Turkyilmaz K, Tufekci A, Durmus M. Retinal nerve fiber layer thickness in Parkinson disease. J Neuroophthalmol. 2013;33:62–5.
10. Louis ED, Honig LS, Vonsattel JP, Maraganore DM, Borden S, Moscowitz CB. Essential tremor associated with focal nonnigral Lewy bodies: a clinicopathologic study. Arch Neurol. 2005;62(6):1004-7.
11. Louis ED, Faust PL, Vonsattel JP, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain. 2007;130(12):3297-307.
12. Louis ED. Essential Tremor: From Bedside to Bench and Back to Bedside. Curr Opin Neurol. 2014;27(4):461-7.
13. Jankovic J. Essential tremor: a heterogenous disorder. Mov Disord. 2002;17:638.
14. Louis ED, Benito-León J, Bermejo-Pareja F. Self-reported depression and anti-depressant medication use in essential tremor: cross-sectional and prospective analyses in a population-based study. Eur J Neurol. 2007;14(10):1138–46.
15. Lee SM, Kim M, Lee HM, Kwon KY, Koh SB. Nonmotor symptoms in essential tremor: Comparison with Parkinson's disease and normal control. J Neurol Sci 2015;349(1-2):168-73
16. Oh YS, Kim JS, Chung SW, Song IU, Kim YD, Kim YI, et al. Color vision in Parkinson's disease and essential tremor. Eur J Neurol. 2011;18(4):577-83.
17. Louis ED, Gerbin M, Viner AS. Color vision: a study of essential tremor cases versus controls. Eur J Neurol. 2012;19 (8):1136-9.
18. Cubo E, Tedejo RP, Rodriguez Mendez V, Lopez Pena MJ, Trejo Gabriel Y Galan JM. Retina Thickness in Parkinson's Disease and Essential Tremor. Movement Disorders. 2010;25(14):2461-2.
19. Tak AZA, Şengül Y, Karadağ AS. Evaluation of thickness of retinal nerve fiber layer, ganglion cell layer, and choroidal thickness in essential tremor: can eyes be a clue for neurodegeneration. Acta Neurol Belg. 2018;118(2):235-41.
20. Turkel Y, Ornek N, Dag E, Ornek K, Alpua M, Ogurel T, et al. Retinal nerve fiber layer thickness in patients with essential tremor. Neurology Asia. 2017;20(4):363-6.
21. Shrier EM, Adam CR, Spund B, Glazman S, Bodis-Wollner I. Intraocular asymmetry of foveal thickness in Parkinson's disease. J Ophtalmol. 2012;728457
22. Altintas O, Iseri P, Ozkan B, Caglar Y. Correlation between retinal morphological and functional findings and clinical severity in Parkinson's disease. Doc Ophthalmol. 2008;116:137–46.
23. Rohani M, Langroodi AS, Ghourchian S, Falavarjani KG, SoUdi R, Shahidi G. Retinal nerve changes in patients with tremor dominant and akinetic rigid Parkinson's disease. Neurol Sci. 2013;34(5):689-93.
24. Archibald NK, Clarke MP, Mosimann UP, Burn DJ. Retinal thickness in Parkinson's disease. Parkinsonism Relat Disord. 2011;17:431–6.
25. Yu JG, Feng YF, Xiang Y, Huang JH, Savini G, Parisi V, et al. Retinal Nerve Fiber Layer Thickness Changes in Parkinson Disease: A Meta-Analysis. PLoS One. 2014:9(1);e85718.

26. Moschos MM, Tagaris G, Markopoulos I, Margetis I, Tsapakis S, Kanakis M, et al. Morphologic Changes and Functional Retinal Impairment in Patients with Parkinson Disease without Visual Loss. Eur J Ophthalmol. 2011;21(1):24-9.
27. Garcia-Martin E, Pueyo V, Ara JR, Almarcegui C, Martin J, Pablo L, et al. Effect of optic neuritis on progressive axonal damage in multiple sclerosis patients. Mult Scler. 2011;17(7):830-7.
28. Frederick JM, Rayborn ME, Laties AM, Lam DM, Hollyfield JG. Dopaminergic neurons in the human retina. J Comp Neurol. 1982;210:65–79.
29. Peppe A, Stanzione P, Pierelli F, De Angelis D, Pierantozzi M, Bernardi G. Visual alterations in de novo Parkinson's disease: pattern electroretinogram latencies are more delayed and more reversible by levodopa than are visual evoked potentials. Neurology. 1995;45:1144–8.
30. Büttner T, Kuhn W, Patzold T, Przuntek H. L-Dopa improves colour vision in Parkinson's disease. J NeuralTransm Park Dis Dement Sect. 1994;7:13–9.
31. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of the brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003;24:197-211.
32. Ortuño-Lizarán I, Beach TG, Serrano GE, Walker DG, Adler CH, Cuenca N. Phosphorylated α-synuclein in the retina is a biomarker of Parkinson's disease pathology severity. Mov Disord. 2018; 33(8):1315-24.
33. Beach TG, Carew J, Serrano G, Adler CH, Shill HA, Sue LI, et al. Phosphorylated α-synuclein-immunoreactive retinal neuronal elements in Parkinson's disease subjects. Neurosci Lett. 2014;571:34-8.
34. Jiménez B, Ascaso FJ, Cristobal JA, Lopez del Val J. Development of a prediction formula of Parkinson disease severity by optical coherence tomography. Mov Disord. 2004;29(1):68-74.
35. Benito-Leon J, Louis ED, Bermejo-Pareja F. Risk of incident parkinson's disease and parkinsonism in essential tremor: a population based study. J Neurol Neurosurg Psychiatry. 2009;80(4):423-5.
36. Louis ED, Hernandez N, Michalec M. Prevalence and correlates of rest tremor in essential tremor: cross-sectional survey of 831 patients across four distinct cohorts. Eur J Neurol. 2015;22(6):927-32.
37. Thenganatt MA, Louis ED. Distinguishing essential tremor from Parkinson's disease: bedside tests and laboratory evaluations. Expert Rev Neurother. 2012;12(6):687-96.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):870-872.
DOI: 10.28982/josam.638664

Research article
Araştırma makalesi

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

Outcomes of robot-assisted transperitoneal pyeloplasty: Case series

Robot yardımlı transperitoneal piyeloplasti sonuçları: Vaka serisi

İbrahim Karabulut [1], Ali Haydar Yılmaz [2], Fatih Kürşat Yılmazel [1], Fatih Özkaya [3]

[1] Education and Research Hospital, Deparment of Urology, Erzurum, Turkey
[2] Bilecik State Hospital, Department of Urology, Bilecik, Turkey
[3] Atatürk University, Medical Faculty, Deparment of Urology, Erzurum, Turkey

ORCID ID of the author(s)
İK: 0000-0001-6766-0191
AHY: 0000-0001-5797-0655
FKY: 0000-0001-8744-5317
FÖ: 0000-0002-7776-4231

Abstract

Aim: Ureteral pelvic junction (UPJ) obstruction, which restricts the passage of urine from the pelvis to the ureter may cause progressive destruction of the kidney if left untreated. Causes of UPJ obstruction include various intrinsic and extrinsic factors. Symptomatic UPJ obstruction should be treated without delay. We herein aimed to present the results of robot-assisted pyeloplasty (RAP) that we performed in our clinic.

Methods: Data of 15 patients who underwent RAP between January 2017 and 2019 in our clinic were examined. The diagnosis of ureteropelvic junction obstruction (UPJO) was based on intravenous pyelography (IVP), and diuresis renography (DTPA) was performed during follow-up. Dismembered pyeloplasty was performed on all patients with the DaVinci XI 4-arm robotic system. The results were retrospectively evaluated.

Results: The mean age of all patients was 41.3 (8.2) years. There were 7 males and 8 females. None of the cases had previously undergone pyeloplasty. While 6 of the patients had intrinsic obstruction, 9 had extrinsic obstruction associated with aberrant vascular compression. The mean operation time and duration of anastomosis were 155.3 (29.8) and 33.4 (8.1) minutes, respectively. The mean amount of intraoperative bleeding was 48 (10.2) ml. The mean hospital stay was found as 3.6 (1.1) days. There was no conversion to open surgery in any of the patients. None of the patients had intraoperative or postoperative complications. The mean follow-up time was 12.7 (5.4) months. Postoperative IVP and DTPA of all the patients were found to have improved.

Conclusion: RAP is a minimally invasive method with successful surgical and functional outcomes in the treatment of UPJO.

Keywords: Robotic Surgery, Ureteropelvic Obstruction, Pyeloplasty

Öz

Amaç: Üretero pelvik bileşke (ÜPB) darlıkları idrarın renal pelvisten üretere geçişini kısıtlayan ve gerekli durumlarda tedavi edilmezse kademeli olarak böbrek fonksiyonlarında kayıba yol açabilen bir durum olarak kabul edilir. ÜPB darlıklarını dıştan başı yada iç tıkanıklığa bağlı olabilir. Semptomatik ÜPB darlıkları tedavi edilmelidir. Biz bu çalışmamızda kliniğimizde robot yardımlı piyeloplasti (RYP) yaptığımız hastaların sonuçlarını sunmayı amaçladık.

Yöntemler: Kliniğimizde Ocak 2017 - 2019 tarihleri arasında RYP yaptığımız 15 hastanın verileri incelendi. Üretero pelvik bileşke darlığı (UPBD) tanısı, intravenöz piyelografi (IVP) ve diürez renografisi (DTPA) ile hasta muayenesi veya olası kontrolleri takiben yapıldı. Da Vinci XI 4 kollu robotik sistem kullanan tüm hastalara dismembred piyeloplasti yapıldı. Sonuçlar retrospektif olarak değerlendirildi.

Bulgular: Hastaların yaş ortalaması 41,3 (8,2) idi. Cinsiyet dağılımı 7 erkek, 8 kadındı. Tüm işlemler birincil olgularda yapıldı. Hastaların 6' sında intrinsik obstrüksiyon, 9' unda dıştan dammar basısına bağlı ekstrinsik obstrüksiyon vardı. Ortalama ameliyat süresi 155,3 (29,8) dakika idi. Ortalama anastomoz süresi 33,4 (8,1) dakika idi. İntraoperatif kanama miktarı 48 (10,2) cc olarak bulundu. Ortalama hastanede kalış süresi 3,6 (1,1) gündü. Hiçbir hastada açık cerrahi müdahale olmadı. Hiçbir hastada intraoperatif veya postoperatif komplikasyon gözlenmedi. Ortalama takip süresi 12,7 (5,4) aydı. Postoperatif IVP ve DTPA tüm hastaların düzeldiği tespit edildi.

Sonuç: Çalışmamızda tespit edildiği gibi, RYP UPBD tedavisinde başarılı cerrahi ve fonksiyonel sonuçları olan minimal bir invaziv yöntemdir.

Anahtar kelimeler: Robotik Cerrahi, Üreteropelvik obstrüksiyon, Piyeloplasti

Corresponding author / Sorumlu yazar:
Ali Haydar Yılmaz
Address / Adres: Bilecik Devlet Hastanesi, Üroloji Kliniği, Bilecik, Türkiye
e-Mail: alicerrahcom@yahoo.com

Ethics Committee Approval: Ethical approval was obtained from the ethics committee of Health Sciences University, Erzurum Education and Research Hospital (2019/13-129).
Etik Kurul Onayı: Etik onay, Sağlık Bilimleri Üniversitesi, Erzurum Eğitim ve Araştırma Hastanesi etik kurulundan alınmıştır (2019/13-129).

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: 12/29/2019
Yayın Tarihi: 29.12.2019

How to cite / Atıf için: Karabulut İ, Yılmaz AH, Yılmazel FK, Özkaya F. Outcomes of robot-assisted transperitoneal pyeloplasty: Case series. J Surg Med. 2019;3(12):870-872.

Introduction

Incidence of ureteropelvic junction obstruction (UPJO), the most common congenital anomaly of the urinary system, is about 1 in 20000 live births [1]. By its mechanism of occurrence, UPJO can develop due to intrinsic, extrinsic, and secondary causes. Intrinsic UPJO may occur due to changes in collagen content and the amount in muscle cells in the intercellular area or retardation of circular muscular development. The most common causes of extrinsic UPJO include lower polar vessels leading to aberrant, accessory, or early branching polar veins, which cause mechanic obstruction through external compression in ureteropelvic junction or upper part of ureter [2]. Secondary UPJO is often associated with severe vesicoureteral reflux.

The aim of UPJO treatment is to ensure appropriate transport of urine from renal pelvis, to improve renal functions if possible and to help relieve symptoms. Dismembered pyeloplasty, introduced by Anderson and Hynes, meets all these criteria, and is considered the gold-standard therapy today [3]. However, with open surgery-associated morbidities and developments especially in laparoscopic surgery, laparoscopic pyeloplasty has become the standard therapeutic approach in several European countries and the USA [4,5]. With recent technological developments, laparoscopic surgery is now being replaced by robotic surgery for its advantages such as easier intracorporal suturing and 3-D imaging [6,7].

The aim of this study was to evaluate the surgical and functional outcomes of UPJO patients who underwent robot-assisted pyeloplasty in our clinic, in line with the literature.

Materials and methods

A total of 15 patients who underwent robot-assisted pyeloplasty in our clinic between January 2016 and 2019 were included in the study. Approval was obtained from the ethics committee of Health Sciences University, Erzurum Education and Research Hospital (App. No. 2019/13-129). The same experienced surgical team performed all surgeries. Demographic data, intraoperative parameters and postoperative follow-up results of the patients were evaluated. The diagnosis of UPJO was based on patient complaints, urinary system ultrasonography (USG) and intravenous pyelography (IVP) results. Deterioration in renal functions and degree of obstruction were evaluated with diuresis renography (DTPA). For postoperative evaluation, T ½ being under 20 min. in DTPA or complete or nearly complete excretion at the 2nd-hour IVP images were considered clinical success. Patients who had previously undergone renal or upper abdominal surgery and those with bleeding diathesis were excluded from the study. Da Vinci XI (Intuitive Surgical Inc., USA) robot was used in all cases. Anderson-Hynes dismembered pyeloplasty was performed with the transperitoneal approach. All results were retrospectively evaluated.

Surgical preparation

Detailed consents were obtained from all patients prior to the surgical procedure. Anticoagulant and/or antiaggregant medication were discontinued after consultation with the relevant departments. Complete urine analysis and urine cultures were obtained from all patients to exclude urinary system infections. All patients underwent general anesthesia (GA). Bladders were catheterized with Foley catheters suitable for urethral calibration. Following surgical site cleaning, the patients were positioned with a 60^0 angle for flank approach. Pneumoperitoneum was achieved with a Veress needle or the Hasson technique through an incision approximately 1 cm lateral to the umbilicus. A 12 mm camera port was placed through the first entry point. Next, trocars were placed 4 cm cranio-medially to the spina iliaca anterior superior (SIAS) and in the intersection point of the mid-clavicular line and arcus costalis respectively under direct vision. The assistant port was placed 2 cm medially to the intersection of lines through the camera and final ports. Port placement was performed in the same way for the right or left kidneys. A trocar was placed about 2 cm below the SIAS under direct vision if the 4th arm was to be used, depending on the surgical choice. Docking was achieved by approaching the robotic unit from the back of the patient.

Surgical technique

Adhesions within the abdomen in the surgical site were removed with blunt and sharp dissections. Colon was medialized by freeing along Toldt's line. Ureter was found in the retroperitoneal region to access the renal pelvis with its guidance. All patients were subjected to Anderson-Hynes dismembered pyeloplasty. If the cause of UPJO was an aberrant vascular compression (Figure 1), anterior transposition of the pelvis was ensured to protect the vessel. All compressing tissues were excised. Severely enlarged, excessive pelvic tissue was excised and prepared for to anastomosis (Figure 2). A 4.8F, 28 cm-long ureteral stent was placed anterogradely (Figure 3). The ureteral stent was inserted into the abdomen via the 10-mm assistant port and pushed towards bladder through the open ureter with the help of the robotic arms. Ureteropelvic anastomosis was performed in the form of continuous suturation with 4/0 Vicryl sutures. Gerota's fascia was closed onto the pelvis following the anastomosis. In the final stage, intraabdominal gas pressure was decreased to perform hemostasis. Drain without a vacuum was placed in the surgical site to finalize the procedure. Port entries were closed anatomically.

Postoperative follow-up

All patients were mobilized on the first postoperative day and oral feeding was initiated following bowel movements. Foley catheters of the patients were removed after the amount of drained fluid had dropped below 50 ml. Once the drainage of fluid stopped following the removal of a foley catheter, patients' drains were removed, then they were discharged. Ureteral stents were removed with the help of a flexible cystoscope under local anesthesia at the 1st postoperative month. The patients were evaluated with IVPs or DTPAs performed in the 3rd month.

Statistical analysis

Descriptive statistics were used for the analysis of data. Continuous variables were presented as mean and standard deviation, and categorical data as number and percentages.

Results

The mean age of the patients included in the study was 41.8 years (Table 1). There were 7 are males and 8 females. Flank pain was detected in 9 of the patients. 3 had pyelonephritis. UPJ was detected incidentally in 3 patients. 3 surgical arms were utilized in all patients. The mean duration of

operation and anastomosis were 155 and 33.4 minutes, respectively. The mean amount of bleeding was 48 ml. Stasis stones were found in 3 patients. Stones were removed to ensure appropriate conditions before the anastomosis. Severely enlarged pelvic tissue that might affect urine transit time was found in 7 patients and excised to accommodate the pelvis to anastomosis. External aberrant vascular compression on the ureter was observed in 9 patients. None of the patients had intraoperative or postoperative complications. The mean hospital stay was 3.6 days, and the mean follow-up duration was 12.7 months. In postoperative follow-ups, 9 patients were evaluated with DTPA and 6 with IVP. DTPA evaluation revealed that $T_{1/2}$ had improved compared to the preoperative period and dropped below 20 minutes. During IVP imaging, complete or nearly complete excretion from the kidney was observed in the late images obtained at the 2nd hour.

Table 1: Demographic, preoperative and postoperative data

	Patient (n=15)
Age mean (SD) (year)	41.3 (8.2)
Gender (male/female)	7/8
Side (Right/Left)	6/9
UPO etiology	9
Aberrant vascular compression	6/15
Intrinsic Obstruction	
Operation time mean (SD) (minutes)	155.3(29.8)
Duration of anastomosis mean (SD) (minutes)	33.4 (8.1)
Amount of intraoperative bleeding mean (SD) (ml)	48 (10.2)
Stay hospital time mean (SD) (day)	3.6 (1.1)
Follow-up time mean (SD) (month)	12.7 (5.4)

SD: Standard derivation, UPO: Ureteropelvic obstruction

Discussion

Open pyeloplasty has managed to remain the gold-standard technique in UPJO treatment with a success rate of 90-100% for years [8,9]. Despite successful results, there has been a search for alternative minimal invasive treatments due to long recovery time associated with open surgery and high morbidity. With the development of laparoscopic surgery in parallel with technological developments, pyeloplasty found its place among surgeries as of 1993. Success rates of laparoscopic pyeloplasty are comparable to open surgery. In addition, it has various advantages such as lower morbidity and shorter recovery time [9,10]. Studies have shown that success rates of laparoscopic pyeloplasty were 88-100% [11]. Despite all these positive developments, widespread use of laparoscopic pyeloplasty has been limited due to long learning curve and difficulty of intracorporal suturing.

Robotic surgery began to be used in pyeloplasty due to advantages such as 3-D imaging, convenient intra corporal suturing techniques and mobility. A comparison between the urological use of robotic surgery (robot-assisted radical prostatectomy, robot-assisted pyeloplasty, robot-assisted partial nephrectomy) and open and laparoscopic methods found that robotic and laparoscopic methods had lower mortality and morbidity and shorter hospital stay while robotic surgery cost higher [12]. In another study comparing RAP with open and conventional laparoscopic pyeloplasty, RAP was found to be an efficient procedure with shorter hospital stay, shorter recovery time, lower morbidity and with successful surgical outcomes and robotic methods were criticized for their higher costs [13,14]. All these studies have shown that robotic pyeloplasty has important advantages such as high success rates, low amount of bleeding and shorter hospital stay [15-20]. Today, lack of obstruction and presence of urinary drainage are considered success indicators in the 3rd-month DTPA and/or IVP examinations during post-pyeloplasty follow-up [21]. In our study, none of the patients had obstructive findings in their postoperative 3rd-month follow-ups, either.

An important disadvantage that can be encountered during robot-assisted pyeloplasty is that it is not possible to use fluoroscopy due to the robotic tower. Failing to fluoroscopically evaluate patients, who have undergone stone extraction or ureteral stent placement, in terms of residual stone and stent's location during the procedure would cause that any problem that can be solved at the moment cannot be detected, leading to morbidity [22]. A study on this situation found extended duration of urinary drainage associated with the migration of ureteral stent to kidney in 3 patients and presence of residual stone in 2 patients after the RAP follow-ups of 86 patients in total. In our study, no stent migration and no residual stone in the patients with stasis stone was observed in the perioperative period. We believe that the reason is that our series had a small number of patients. Limited number of patients and lack of long-term follow-ups are limitations of our study.

Conclusion

RAP is an efficient minimally invasive treatment method in ureteropelvic junction obstructions with shorter hospital stay, lower morbidity rates and high successful surgical outcomes.

References

1. Tripp BM, Homsy YL. Neonatal hydronephrosis-the controversy and the management. Pediatr Nephrol. 1995;9:503-9.
2. Nakada SY, Hsu THS. Management of Upper Urinary Tract Obstruction. editor-in-chief, Wein AJ; editors, Kavoussi LR, Partin AW, Novick AC, Peters CA. Campbell-Walsh Urology, 10th Edition. Philadelphia: W.B. Saunders Elsevier; 2012.p.1122-3.
3. Poulakis V, Witzsch U, Schultheiss D, Rathert P, Becht E. History of ureteropelvic junction obstruction repair (pyeloplasty). From Trendelenburg (1886) to the present. Urologe A. 2004;43:1544-59.
4. Özmerdiven G, Kaygısız O, Çiçek Ç, Günseren KÖ, Vuruşkan H. The effect of laparoscopy courses in laparoscopy practice after urology resident training: A questionnaire-based observational study. J Surg Med. 2019;3:725-8.
5. Symons JS, Palit V, Bi yani CS, Cartledge JJ, Browning AJ, Joyce AD. Minimally invasive surgical options for ureteropelvic junction obstruction: a significant step in the right direction. Indian J Urol. 2009;25:27-33.
6. Albqami N, Janetschek G. Laparoscopic pyeloplasty. Ann Urol.2006;40:363-7.
7. Jarrett TW, Chan DY, Charambura TC, Fugita O, Kavoussi LR. Laparoscopic pyeloplasty: the first 100 cases. J Urol.2002;167:1253-56.
8. Eden CG. Minimally invasive treatment of ureteropelvic junction obstruction: a critical analysis of results. Eur Urol. 2007;52:983-9.
9. Schuessler WW, Grune MT, Tecuanhuey LV, Preminger GM. Laparoscopic dismembered pyeloplasty. J Urol. 1993;150:1795-9.
10. Miyake H, Kawabata G, Gotoh A, Fujisawa M, Okada H, Arakawa S, et al. Comparison of surgical stress between laparoscopy and open surgery in the field of urology by measurement of humoral mediators. Int J Urol. 2002;9:329-33.
11. Canes D, Berger A, Gettman MT, Desai MM. Minimally invasive approaches to ureteropelvic junction obstruction. Urol Clin North Am. 2008;35:425-39.
12. Yu HY, Hevelone ND, Lipsitz SR, Kowalczyk KJ, Hu JC. Use, costs and comparative effectiveness of robotic assisted, laparoscopic and open urological surgery. J Urol. 2012;187:1392-8.
13. Başataç C, Boylu U, Önol FF, Gümüş E. Comparison of surgical and functional outcomes of open, laparoscopic and robotic pyeloplasty for the treatment of ureteropelvic junction obstruction. Turkish Journal of Urology. 2014;40:24-30.
14. Canda AE, Atmaca AF, Balbay MD. Robotic Pyeloplasty: Step by Step Surgical Technique. Adv Robot Autom. 2013;2:1-5.
15. Gupta NP, Nayyar R, Hemal AK, Mukherjee S, Kumar R, Dogra PN. Outcome analysis of robotic pyeloplasty: a large single-centre experience. BJU Int. 2010;105:980-3.
16. Patel V. Robot-asisted laparoscopic dismembered pyeloplasty. Urology. 2005;66:45-9.
17. Lucas SM, Sundaram CP, Wolf JS Jr, Leveillee RJ, Bird VG, Aziz M, et al. Factors that impact the outcome of minimally invasive pyeloplasty: Results of the Multi institutional Laparoscopic and Robotic Pyleoplasty Collaborative Group. J Urol. 2012;187:522-7.
18. Minnillo BJ, Cruz JA, Sayao RH, Passerotti CC, Houck CS, Meier PM. Longterm experience and outcomes of robotic assisted laparoscopic pyeloplasty in children and young adults. J Urol. 2011;185:1455-60.
19. Thom MR, Haseebuddin M, Roytman TM, Benway BM, Bhayani SB, Figenshau RS. Robot-assisted pyeloplasty: outcomes for primary and secondary repairs, a single institution experience. Int Braz J Urol. 2012;38:77-83.
20. Niver BE, Agalliu I, Bareket R, Mufarrij P, Shah O, Stifelman MD. Analysis of robotic-assisted laparoscopic pyleloplasty for primary versus secondary repair in 119 consecutive cases. Urology. 2012;79:689-94.
21. Pohl HG, Rushton HG, Park JS, Belman AB, Majd M. Early diuresis renogram findings predict success following pyeloplasty. J Urol. 2001;165:2311-5.
22. Ener K, Altınova S, Canda AE, Özcan MF, Asil E, et al. Outcomes of robot-assisted laparoscopic transperitoneal pyeloplasty procedures: a series of 18 patients.Turk J Urol. 2014;40(4):193-8.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):873-876.
DOI: 10.28982/josam.658773

Research article
Araştırma makalesi

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

Novel markers for mortality in patients with acute pancreatitis: NLR and PLR at the 48th hour

Akut pankreatitli hastalarda mortalite göstergesi olarak yeni belirteçler: 48. saat NLR ve PLR

Mehmet Suat Yalçın [1], Serkan Yalaki [2]

[1] Department of Gastroenterology, Department of Internal Medicine, Aksaray University Education and Research Hospital, Aksaray, Turkey
[2] Department of Gastroenterology, Mersin City Education and Research Hospital, Mersin, Turkey

ORCID ID of the author(s)
MSY: 0000-0003-1054-1882
SY: 0000-0001-8137-0924

Abstract

Aims: In recent years, simple, effective, and rapid laboratory markers have become important to predict acute pancreatitis prognosis. In this study, we aimed to demonstrate whether there was a difference in predicting AP-related mortality between current scores and indirect markers of systemic inflammation, namely, red cell distribution width (RDW), mean platelet volume (MPV), platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR) obtained at the 48th hour.

Methods: We retrospectively reviewed files of AP patients admitted to Gastroenterology Department of two hospitals to include the acute phase reactant values of 667 patients obtained at the 48th hour. CRP_0 indicates CRP value at presentation while CRP, RDW, MPV, NLR and PLR indicate values at the 48th hour. In all patients, Ranson score, Atlanta score, NLR and PLR values were calculated.

Results: The patients were classified into 2 groups as survivors (n=641; 96.1%) and non-survivors (n=26; 3.9%). Both NLR and PLR were found to be significantly higher in the non-survivor group (P<0.001 and P=0.02). Both NLR and PLR were weakly and positively correlated to mortality.

Conclusion: Based on our results, MPV was not correlated with mortality, while RDW was weakly and positively correlated. However, we found that NLR and PLR values obtained at the 48th hour after presentation are effective parameters in predicting mortality in AP. These easily accessible and low-cost tests may be used for closer monitoring of these patients when necessary.

Keywords: Acute pancreatitis, NLR, PLR, Atlanta score

Öz

Amaç: Son yıllarda akut pankreatit prognozunu öngörmede basit, etkili ve hızlı laboratuvar belirteçleri önem kazanmıştır. Bu çalışmada, mevcut skorlarla sistemik inflamasyonun dolaylı belirteçleri arasında AP ile ilişkili mortalite tahmininde bir fark olup olmadığını ortaya koymak amaçlandı (48. saatte RDW, MPV, PLR ve NLR).

Yöntemler: Bu çalışmada, Gastroenteroloji Bölümü'ne başvuran Akut pankreatitli hastaların dosyaları geriye dönük olarak incelendi. Genel olarak, 667 hastanın verileri dahil edildi. 48. saatte akut faz reaktan değerleri çalışmaya alındı. CRPo başvuru sırasındaki CRP'yi gösterirken CRP, RDW, MPV, NLR ve PLR 48. saatte değerleri gösterir. Tüm hastalarda Ranson skoru, Atlanta skoru, NLR ve PLR değerleri hesaplandı.

Bulgular: Hastalar sağ kalanlar (n=641; %96,1) ve ölenler (n=26; %3,9) olarak 2 gruba ayrıldı. Hem NLR hem de PLR, hayatta kalan grupta anlamlı olarak yüksek bulundu (sırasıyla P<0,001 ve P=0,02). NLR ile mortalite arasında zayıf, pozitif bir korelasyon vardı. Yine PLR ile mortalite arasında zayıf ve pozitif bir korelasyon vardı.

Sonuç: Çalışmamızda MPV değeri ile mortalite arasında ilişki saptanmazken, RDW ile mortalite arasında zayıf-pozitif bir ilişki olduğu görüldü. Başvurunun 48. Saatinde elde edilen NLR ve PLR değerlerinin mortaliteyi gösteren etkili parametreler olduğunu saptadık. Bu ulaşılması kolay ve düşük maliyetli testler, gerektiğinde hastaları daha yakından takip etmek amacıyla kullanılabilir.

Anahtar kelimeler: Akut pankreatit, NLR, PLR, Atlanta skoru

Corresponding author / Sorumlu yazar:
Mehmet Suat Yalçın
Address / Adres: Aksaray Üniversitesi Eğitim ve Araştırma Hastanesi, Gastroenteroloji Kliniği, Aksaray, Türkiye
e-Mail: mehmetsuatyalcin@aksaray.edu.tr

Ethics Committee Approval: Ethical approval was obtained from the local Ethics Committee.
Etik Kurul Onayı: Etik onay, yerel Etik Kuruldan alınmıştır.

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: 12/29/2019
Yayın Tarihi: 29.12.2019

How to cite / Atıf için: Yalçın MS, Yalaki S. Novel markers for mortality in patients with acute pancreatitis: NLR and PLR at the 48th hour. J Surg Med. 2019;3(12):873-876.

Introduction

One of the most common disorders of gastrointestinal system, acute pancreatitis (AP) is an acute, inflammatory process of the pancreas with significant variability in clinical presentation and severity. The inflammation may cause local damage within the pancreas, release several cytokines, result in systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). In most cases, the disease has a mild course and good prognosis; however, 15 - 20% of patients present with severe AP with high morbidity and mortality rates [1]. Despite advances in the diagnosis and management, AP remains to be an important cause of in-hospital mortality and increased overall costs [2]. The AP-related early mortality generally occurs due to MODS caused by SIRS within the first 2 weeks while almost one-half of patients die due to peripancreatic necrosis, infection, or secondary MODS after 2 weeks [1]. Thus, it is crucial to identify patients with potentially severe AP and establish management plans accordingly. Today, several scoring systems have been proposed to assess and classify the severity of AP [3].

In the recent years, simple, effective, and rapid laboratory markers have become important to predict AP prognosis. These markers rely on inexpensive laboratory tests such as neutrophil-lymphocyte ratio (NLR), red blood cell distribution width (RDW), mean platelet volume (MPV) and platelet-lymphocyte ratio (PLR), which are direct or combined markers of systemic inflammation. The elevation of NLR within the first 48 hours of admission is considered a negative prognostic marker and associated with severe AP [4]. Previous studies have shown that NLR may predict AP severity in patients with hypertriglyceridemia and biliary pancreatitis [5]. In a recent study, it was found that NLR and PLR were effective in predicting both AP severity and mortality [1].

In this study, it was aimed to demonstrate whether there was a difference in predicting AP-related mortality between current scores (e.g. Atlanta score, Ranson score, CRP at presentation, CRP at the 48th hour) and indirect markers of systemic inflammation (PLT, MPV, PLR and NLR at the 48th hour).

Materials and methods

In this study, we retrospectively reviewed files of AP patients admitted to the Gastroenterology Clinic of Mersin City Hospital between March 2016 and August 2019 and the Gastroenterology Clinic of Aksaray Teaching and Research Hospital between June 2017 and September 2019. Among 824 patients, 157 patients were excluded due to incomplete data. Overall, data from 667 patients were included.

AP diagnosis was made in the presence of two of following three criteria: i) abdominal pain compatible with disease; ii) serum amylase and/or lipase levels greater than three times the upper limit of normal range, and iii) characteristic findings in abdominal imaging studies [6]. Demographic characteristics were examined in all included patients. Clinical (blood pressure, respiration rate, heart rate) and laboratory parameters (white blood cell count, neutrophil count, lymphocyte count, hemoglobin level, platelet count, RDW, MPV, hematocrit, liver and kidney function tests, electrolyte, arterial blood gases) were assessed and recorded in all patients. As CRP values obtained at the 48th hour were found to be correlated with disease severity in previous studies, we included acute phase reactant values at the 48th hour [7]. CRP_0 indicates CRP at presentation while CRP, RDW, MPV, NLR and PLR indicate values obtained at the 48th hour of presentation. In all patients, Ranson score, Atlanta score, NLR and PLR values were calculated [8, 9].

The revised Atlanta score is a parameter that indicates the severity of the disease, according to which the patients were classified into 3 groups as mild AP (MAP), moderate AP (MSAP) and severe AP (SAP). MAP was defined as disease with no-organ failure and no local or systemic complications. MSAP was defined with the presence of local or systemic complications and/or temporary organ failure which resolved within 48 hours. SAP was defined as disease with persistent organ failure (>48 hours) [9].

We evaluated whether there were significant differences between Ranson score, Atlanta score, RDW, MPV, CRP, NLR and PLR values of survivors and non-survivors. Correlation and ROC curve analyses were performed upon detection of a significant difference.

Statistical analysis

All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) for Windows version 20 (IBM SPSS Inc., Chicago, USA). The data distribution was assessed by Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation while continuous variables with skewed distribution were presented as median (min-max). The categorical variables were presented as percentages. For inter-group comparisons, categorical variables were assessed using Chi-square test while continuous variables with normal distribution were assessed with the t test. Continuous variables with abnormal distribution were evaluated with the Mann Whitney test. Spearman's correlation analysis was used to assess correlation among data. The Receiver Operator Characteristics (ROC) analysis was performed and Area under Curve (AUC) was compared to determine the predictive values of NLR, PLR, RDW, CRP and AP severity scores. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated based on cut-off values. A two-sided p value was used. A p-value <0.05 was considered as statistically significant.

Ethical approval

This study was approved by the Local Ethics Committee and conducted in accordance with the Helsinki Declaration.

Results

Overall, 667 patients were included to the study, and classified into 2 groups as survivors (n=641; 96.1%) and non-survivors (n=26; 3.9%). Table 1 presents the demographic characteristics of the two groups. Among 641 survivors, 211 (32.9%) were male and 430 (67.1%) were female, with an overall mean age of 54.64 years. 26 non-survivors comprised 10 (38.4%) males and 16 (61.6%) females with an overall mean age of 77.88 years. There was no significant difference in gender distribution between groups (P=0.55). Mean age was significantly higher among non-survivors when compared to

survivors (*P*<0.001). A weak positive correlation was detected between age and mortality (rs=0.23; *P*<0.001).

In the etiology of AP, biliary causes were most common reason detected in 473 patients (70.9%), followed by idiopathic AP in 102 patients (15.2%) (Table 2).

Table 2 presents the distribution of AP severity scores according to groups. Atlanta score determined that mortality increased with the severity of the disease (*P*<0.001). There was a significant difference in Ranson scores between survivor and non-survivor groups (1.37 vs. 2.65; *P*<0.001). Both Atlanta and Ranson scores were significantly higher in the non-survivor group. A weak, positive correlation was detected between Ranson scores and mortality (rs=0.20; *P*<0.001).

Table 3 presents the distribution of laboratory parameters according to groups. No significant difference was detected in CRP_0 values (*P*=0.631) while there was significant difference in CRP values obtained at the 48^{th} hour between groups (*P*<0.001). A weak, positive correlation was detected between CRP and mortality (rs=0.16; *P*<0.001).

There were no significant differences in PLT and MPV values between the survivor and non-survivor groups (*P=0.054* and *P=0.126*, respectively). A significant difference was detected in RDW values between groups (*P*=0.006). A weak, positive correlation was found between RDW and mortality (rs=0.11; *P*=0.01).

Both NLR and PLR were found to be significantly higher in the non-survivor group (*P*<0.001; and *P*=0.02, respectively), and weakly but positively correlated with mortality (rs=0.19, 0.19; *P*<0.001, *P*<0.001, respectively).

The ROC analysis was performed and AUCs were compared to assess the predictive values of NLR, PLR, RDW, CRP and AP severity scores (Figure 1). The AUC values for NLR, Atlanta score, Ranson score, CRP, RDW and PLR were found as 0.79, 0.88, 0.80, 0.72, 0.68 and 0.68, respectively. The Atlanta and Ranson scores had the highest predictive values for mortality (AUC: 88% and 80%, respectively). The cut-off value for NLR was calculated as 12 with a sensitivity of 64% and a specificity of 80% (AUC: 0.79; *P*<0.001). The cut-off value for PLR was 352 with a sensitivity of 52% and a specificity of 87% (AUC: 0.68; *P*=0.002).

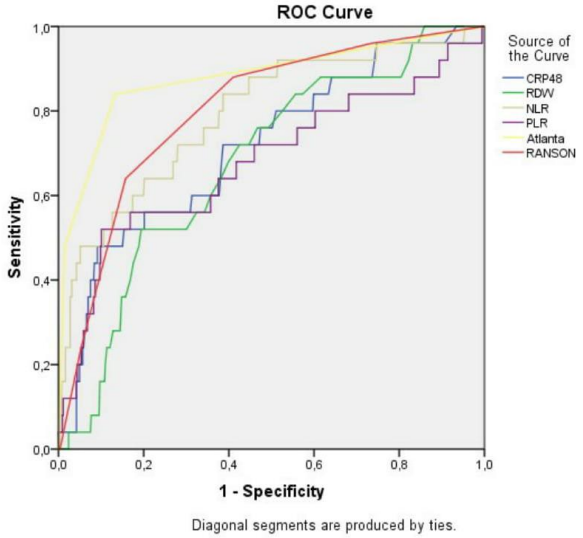

Figure 1: ROC analyse for NLR, Ranson score, Atlanta score, CRP48, PLR and RDW. NLR AUC: 0.79, Ranson Score AUC: 0.80, Atlanta Score AUC: 0.88, CRP48 AUC: 0.71, PLR AUC: 0.68, RDW AUC: 0.67

Table 1: Demographic findings of groups

Groups	Survivors (n=641)	Non-survivors (n=26)	*P*-value
Age (year)	54.64	77.88	<0.05
Gender (M/F)	211/430	10/16	>0.05

M: Male, F: Female

Table 2: Etiology of acute pancreatitis and distribution of severity scores by groups

Etiology	Survivors (n=641)	Non-survivors (n=26)	*P*-value *
Biliary	451	22	N/A
Hypertriglyceridemia	37	0	
Alcohol	32	0	
İdiopathic	99	3	
Others	48	1	
Severity scores			
Atlanta score			
MAP	502	0	<0.001
MSAP	91	3	
SAP	48	23	
Ranson score			
0-3	473	0	<0.001
4-6	101	5	
≥7	67	21	

N/A: Not applicable, * Mann-Whitney u test

Table 3: Laboratory values of groups

	Survivors (n=641)	Non-survivors (n=26)	*P*-value *
Glucose (mg/dl)	151.4	155.2	0.759
Creatinine (mg/dl)	0.88	1.42	0.007
ALT (U/L)	171.4	116.8	0.24
AST (U/L)	188.14	349.5	0.001
LDH	379.3	515.4	0.006
WBC (µL)	12143	16411	<0.001
Hgb	13.0	12.7	0.567
Platelet (µL)	257730	233720	0.138
CRPo (mg/L)	4.14	6.28	0.631
CRP (mg/L)	16.8	44.4	<0.001*
MPV (fl)	8.5	9.0	0.226*
RDW (%)	15.6	16.3	0.006
Neutrophile (µL)	9514	13991	<0.001
Lymphocyte (µL)	1700	1194	0.006
NLR	8.0	19.7	<0.001*
PLR	196.8	342.3	0.02
ALP (u/L)	156	157	0.983
GGT (u/L)	264	209	0.337
Albumin (g/L)	4.5	3.6	0.733
T. bilirubin (mg/dL)	2.1	3.2	0.675
Calcium (mg/dL)	9.0	8.8	0.361
Ranson score	1.37	2.65	<0.001*

* Mann-Whitney u test, MPV: mean platelet volume, RDW: red cell distribution width, PLR: platelet to lymphocyte ratio, NLR: neutrophile to lymphocyte ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gama glutamyl transferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, CRP: c-reactive protein, WBC: white blood cell

Discussion

Our study showed that mortality increased with increasing NLR, PLR, Atlanta and Ranson scores. Significant differences in CRP, NLR, PLR, Atlanta and Ranson scores were observed between patient groups. Atlanta and Ranson scores, NLR, PLR, CRP and RDW values all positively correlated with mortality. ROC analyses showed that the Atlanta scoring system had highest AUC value for prediction of mortality in AP, followed by the Ranson score. NLR, CRP, PLR and RDW values showed a weak, positive correlation with mortality while RDW had the lowest AUC value. Our findings were generally consistent with the previous studies in the literature; however, AUC for RDW was found to be lower than those in previous studies [1]. In the United States, acute pancreatitis is the most common diagnosis at discharge among gastrointestinal system disorders and associated with a major burden. It has an annual cost of about 2.6 billion dollars for healthcare system [10]. The mortality rate is about 1% among all AP cases while it may reach 20-30% in severe disease [11]. There is no single prognostic index for assessment of severity in AP; disease severity and mortality are generally evaluated using clinical data, imaging studies and biochemical parameters [12]. In AP, early mortality occurs due to SIRS, resulting in MODS, while delayed mortality is generally due to sepsis and its complications [13]. Therefore, it

is important to diagnose and treat the disease early, perform accurate risk assessment for stratification into high or low risk categories, and to admit patients with organ dysfunction to the intensive or intermediate care units [14].

It is well-known that inflammatory markers can be used for prognostication in many diseases including cancer [15, 16]. NLR was introduced as a simple parameter that can assess systemic inflammation and stress in critically ill patients. Wang et al. [17] showed that NLR has a high discrimination capacity for acute pancreatitis caused by severe hypertriglyceridemia. In a study by Jeon and Park, it was shown that elevated baseline NLR was associated with SAP and organ failure [18]. In a study on 359 patients, Li et al. [19] concluded that NLR had the highest AUC value when compared to RDW, CRP, lymphocyte-monocyte ratio and prognostic nutrition index. Ilhan et al. [20] compared 30 patients with pregnancy-induced AP with 30 healthy pregnant women to show that NLR was significantly increased in AP group but PLR did not change when compared to controls. Azab et al. [21] reported that NLR was superior than WBC in prediction of ICU presentation and longer hospital stay. They reported that the cut-off value was around 4.7.

A recent study proposed that NLR-PLR combination could be an effective marker for prediction of AP severity and prognosis [22]. In our study, it was found that both NLR and PLR were associated with mortality. This finding is compatible with studies indicating a correlation between AP severity, NLR and PLR. However, our findings are inconsistent with the study by İlhan et al. [20] regarding the correlation between PLR and mortality.

In ROC analysis, AUC value was calculated as 0.88 for Atlanta score, 0.78 for Ranson score, 0.77 for NLR and 0.68 for RDW. The sensitivity and specificity of the predictive value of NLR for mortality were calculated as 64% and 80%, respectively, at a cut-off value of >12. The cut-off value for PLR was calculated as 325 with 52% sensitivity and 87% specificity. In our study, it was concluded that NLR and PLR values at the 48th hour are significant markers for prediction of mortality in patients with AP.

CRP and Ranson scores were correlated with mortality in our study. This finding is consistent with the findings of one of the studies conducted by Başak et al. [23].

Limitations

Lack of comparison with NLR and PLR values obtained at the 24th hour may be the limitation of our study.

Conclusion

Morbidity and mortality are closely related with disease severity in AP. It is highly important to predict patients likely to develop severe disease. Thus, rather than complex scoring systems, simple markers can be helpful to determine disease severity in early periods. We believe that NLR and PLR values obtained at the 48th hour can be useful for predicting mortality in AP. Further and larger studies are needed to calculate standardized cut-off values. The addition of NLR and PLR values into hemogram results will facilitate use of these parameters by clinicians.

References

1. Zhou H, Mei X, He X, Lan T, Guo S. Severity stratification and prognostic prediction of patients with acute pancreatitis at early phase. Medicine (Baltimore). 2019 Apr;98(16):e15275.
2. Han C, Zeng J, Lin R, Liu J, Qian W, Ding Z, et al. The utility of neutrophil to lymphocyte ratio and fluid sequestration as an early predictor of severe acute pancreatitis. Sci Rep. 2017;7:10704.
3. Tee YS, Fang HY, Kuo IM, Lin YS, Huang SF, Yu MC. Serial evaluation of the SOFA score is reliable for predicting mortality in acute severe pancreatitis. Medicine (Baltimore). 2018;97:e9654.
4. Suppiah A, Malde D, Arab T, Hamed M, Allgar V, Smith AM, et al. The prognostic value of the neutrophil-lymphocyte ratio (NLR) in acute pancreatitis: identification of an optimal NLR. J Gastrointest Surg. 2013;17:675–81.
5. Cho SK, Jung S, Lee KJ, Kim JW. Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio can predict the severity of gallstone pancreatitis. BMC Gastroenterol. 2018 25;18(1):18.
6. Mitchell RM, Byrne MF, Baillie J. Pancreatitis. Lancet. 2003;361:1447–55.
7. Larvin M. Assessment of clinical severity and prognosis. In: The Pancreas, Beger HG, Warshaw AL, Buchler MW, et al (Eds), Blackwell Science, Oxford 1998. p.489.
8. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Localio SA. Objective early identification of severe acute pancreatitis. The American Journal of Gastroenterology. 1974;61:443–51.
9. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
10. Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ, Camargo CA Jr. Direct medical costs of acute pancreatitis hospitalizations in the United States. Pancreas. 2007;35:302–7.
11. Whitcomb DC. Clinical practice. Acute pancreatitis. The New England Journal of Medicine. 2006;354:2142–50.
12. Wang D, Yang J, Zhang J, Zhang S, Wang B, Wang R, et al. Red cell distribution width predicts deaths in patients with acute pancreatitis. Journal of research in medical sciences. 2015;20:424–8.
13. Mutinga M, Rosenbluth A, Tenner SM, Odze RR, Sica GT, Banks PA. Does mortality occur early or late in acute pancreatitis? Int J Pancreatol. 2000;28:91–5.
14. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013;108:1400-15;1416.
15. Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, et al. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow Inflammation Outcome Study. European Journal of Cancer. 2011;47:2633–41.
16. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Review of Cardiovascular Therapy. 2013;11:55–9.
17. Wang Y, Fuentes HE, Attar BM, Jaiswal P, . Evaluation of the prognostic value of neutrophil to lymphocyte ratio in patients with hypertriglyceridemia-induced acute pancreatitis. Pancreatology. 2017;17:893–7.
18. Jeon TJ, Park JY. Clinical significance of the neutrophil-lymphocyte ratio as an early predictive marker for adverse outcomes in patients with acute pancreatitis. World J Gastroenterol. 2017;23:3883–9.
19. Li Y, Zhao Y, Feng L, Guo R. Comparison of the prognostic values of inflammation markers in patients with acute pancreatitis: a retrospective cohort study. BMJ Open. 2017;7:e013206.
20. İlhan M, İlhan G, Gök AF, Bademler S, Atmaca FV, Ertekin C. Evaluation of neutrophil-lymphocyte ratio, platelet-lymphocyte ratio and red blood cell distribution width-platelet ratio as early predictor of acute pancreatitis in pregnancy. J Matern Fetal Neonatal Med. 2016;29:1476–80.
21. Azab B, Bhatt VR, Phookan J, Murukutla S, Kohn N, Terjanian T, et al. Usefulness of the neutrophil-to-lymphocyte ratio in predicting short- and long-term mortality in breast cancer patients. Annals of Surgical Oncology. 2012; 19: 217–24.
22. Kaplan M, Ates I, Oztas E, Yuksel M, Akpinar MY, Coskun O, et al. Early predictor of acute pancreatitis: PLR-NLR combination. J Med Biochem. 2018;37(1).
23. Başak F, Hasbahçeci M, Şişik A, Acar A, Tekesin K, Baş G, et al. Can C-reactive protein levels increase the accuracy of the Ranson score in predicting the severity and prognosis of acute pancreatitis? A prospective cohort study. Turk J Gastroenterol. 2017;28(3):207-13.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):877-881.
DOI: 10.28982/josam.590825

Review
Derleme

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

Indoor air pollution

Kapalı ortam hava kirliliği

Duygu Kavuncuoğlu [1], Zahide Koşan [1]

[1] Department of Public Health, Ataturk University Faculty of Medicine, Erzurum, Turkey

ORCID ID of the author(s)
DK: 0000-0002-0546-5478
ZK: 0000-0002-1429-6207

Abstract

Clean air is one of the essential preconditions of life. Approximately 4.3 million people die due to indoor air pollution every year. The majority of these deaths are due to stroke (34%), ischemic heart disease (26%), and chronic obstructive pulmonary disease (22%). The principal indoor air pollutant particulate materials are carbon monoxide, tobacco smoke, formaldehyde and volatile organic compounds, nitrogen dioxide, asbestos, radon, and biological pollutants (micro-organisms and allergens). The prevention of indoor air pollution and use of clean energy sources must be regarded as an opportunity to improve health, particularly that of mothers and children, reduce poverty, and achieve environmental sustainability.

Keywords: Air pollution, Indoor air pollution, Sick building syndrome

Öz

Temiz hava hayatın temel şartlarından biridir. Her yıl kapalı ortam hava kirliliği nedeniyle 4.3 milyon insan yaşamını kaybetmektedir. Bu ölümlerin, çoğu inme (%34), iskemik kalp hastalığı (%26) ve kronik obstrüktif akciğer hastalığı (%22) kaynaklıdır. Başlıca kapalı ortam hava kirleticileri partiküler madde, karbonmonoksit, tütün dumanı, formaldehit ve uçucu organik bileşikler, nitrojen dioksit,assbest, radon, biyolojik kirleticiler (mikroorganizmalar ve allerjenler) olarak sıralanabilir. Kapalı ortam hava kirliliğinin engellenmesi ve temiz enerji kaynaklarının kullanılması, özellikle anne-çocuk sağlığı olmak üzere sağlığı iyileştirmek, yoksulluğu azaltmak ve çevresel sürdürülebilirliğin sağlanması için bir fırsat olarak değerlendirilmelidir.

Anahtar kelimeler: Hava kirliliği, Kapalı ortam hava kirliliği, Hasta bina sendromu

Corresponding author / Sorumlu yazar:
Duygu Kavuncuoğlu
Address / Adres: Atatürk Üniversitesi Tıp Fakültesi, Halk Sağlığı Anabilim Dalı, Yakutiye, Erzurum, Türkiye
e-Mail: duygu_koylu@hotmail.com

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: 12/08/2019
Yayın Tarihi: 08.12.2019

How to cite / Atıf için: Kavuncuoğlu D, Koşan Z. Indoor air pollution. J Surg Med. 2019;3(12):877-881.

Introduction

Clean air is an essential precondition for life. Air quality in homes, schools, day care centers, health institutions and other private and public buildings where humans spend much of their lives is a basic determinant of healthy living and well-being [1].

The presence of harmful biological, physical and chemical agents such as carbon monoxide, sulfur dioxide, nitrogen oxides, formaldehyde, cigarette smoke, radon, asbestos, volatile organic compounds, various micro-organisms, and allergens, with their deleterious effects on human health, in closed environments such as homes, non-industrial workplaces, and official buildings, is defined as 'indoor pollution' [2,3].

Hazardous materials deriving from structural components of buildings and internal equipment, forming for reasons such as fuel consumption for day-to-day activities such as cooking and heating, can result in severe health problems, even with fatal consequences. Approximately 4.3 million people die due to indoor air pollution every year. The majority of these deaths are due to stroke (34%), ischemic heart disease (26%) and chronic obstructive pulmonary disease (22%) [1].

Social and economic prosperity levels are closely associated with indoor air pollution markers. There are considerable differences between developing and industrialized countries. Indoor air pollution is related to the characteristics of the structure concerned, the materials used in its construction, the heating system and fuel use, ventilation, the behaviors of the residents, and external environmental conditions [1].

Approximately 3 billion people worldwide use solid fuels (such as wood, plant wastes, charcoal, coal, and manure) to meet their basic domestic energy requirements. The majority of these live in low- and moderate-income countries. Components of indoor air pollution far exceed acceptable levels in housing in which such fuels are used without adequate ventilation. Exposure is high among women and children who spend the most time close to domestic ranges particularly used for heating and/or cooking [4]. According to World Health Organization (WHO) data, more than 50% of pneumonia-related deaths among children under five years are associated with indoor air pollution [1].

In addition to fuel-based pollutants, various other elements such as asbestos, wood protection materials, volatile organic compounds, paints, adhesives, resins, polishing materials, perfumes, spray gases, and cleaning materials also cause indoor pollution [5].

Indoor air pollution also varies between rural and urban regions, in association with economic conditions and lifestyle. For example, dust and organic particles are more common in agricultural areas, and pollutants such as mites and fungi, in urban dwellings. Regional climatic conditions, architectural factors (construction materials, structure, and room distribution and characteristics), and particularly the ventilation of homes must also be considered since they are also effective. People living in urban areas who spend the majority of their time indoors are exposed to a relatively higher level of indoor air pollution.

The acute health impacts of indoor air pollutants include an increased incidence of mucosal damage, cough, wheezing, increased thoracic pressure, airway susceptibility to allergens, and pneumonia, as well as middle ear infection, trachea-bronchiolitis, and asthma flare-ups. In the chronic period, air pollution has an adverse impact on child growth, causes increasing susceptibility to chronic obstructive lung diseases including asthma by leading to pulmonary function disorder, and diseases such as ischemic heart disease, stroke, lung cancer, cataract, and tuberculosis. Air pollution has also been linked to low birth weight in newborns [6].

Another effect on health of indoor air pollution is described as sick building syndrome. During the energy crisis in the 1970s, thermal insulation began being used to maintain environmental heat in buildings. This gave rise to increasing indoor air pollution because of inadequate ventilation in some buildings. Pollution caused by construction materials and other environmental pollutants was trapped inside buildings and increased to levels capable of producing symptoms in susceptible individuals. Sick building syndrome refers to a series of symptoms emerging in a closed environment and resolving when leaving that environment, and affecting the majority of individuals living in the building [7-9]. Probable causes include problems concerning building architecture, work-related factors, building repairs being carried out in a manner incompatible with the original design, insufficient ventilation, inadequate maintenance, and chemical and biological pollutants. In 1982, the WHO listed the symptoms observed in sick building syndrome under five categories: ear, nose and throat damage, skin damage, idiopathic hypersensitivity reactions, taste and smell-related findings, and neurological or general health symptoms [7,10].

The principal indoor air pollutants are as follows:

Particulate matter

The combustion of fossil fuels (such as coal), organic materials (such as wood and peat), and other substances such as rubber and plastic, motorized vehicles, power station emissions, and forest fires are the principal sources of particulate matter (PM). The pathogenicity of PMs is determined by their size, compounds, origins, solubility, and capacity to produce reactive oxygen. PMs with an aerodynamic diameter less than 10 μm have been found to have a greater effect on human health.

According to U.S. Environmental Protection Agency (EPA) standards, the recommended mean annual threshold for PM_{10} (breathable particles ≤ 10 micrometers in diameter) is 50 $\mu g/m^3$. Several studies have shown that biomass used as fuel causes very high particle levels in homes, that the mean 24-h PM_{10} value in environments with open fires is 1000 $\mu g/m^3$ and can even exceed 10,000 $\mu g/m^3$ when specimens are collected during open fire use. Considering that this occurs daily in homes using biomass, mean pollution levels are approximately 20 times higher than the limit recommended by the EPA. There are two important components showing individuals' exposure to indoor pollution; environmental pollutant density and length of exposure of each individual to this. Women, young girls up to the age when they begin to walk, and girls from the time when they begin to acquire culinary skills are known to be exposed to greater indoor pollution, about at least 3-5 hours a day. Exposure to pollutants may be prolonged in some societies and in cold regions [11].

The PM group defined as $PM_{2.5}$ has small diameters and larger surface areas. They can thus pass through nasal filtration, be carried by air currents to the farthest points of the respiratory canal and accumulate there [12]. $PM_{2.5}$ can cause asthma and respiratory tract infections, adversely affects pulmonary functions, and can even lead to cancer [13-15]. Studies have determined a positive correlation between $PM_{2.5}$ levels and respiratory tract disease prevalence, hospitalization rates, and daily death rates [16,17]. These relations are more marked in the elderly, pregnant women, babies, adolescents, subjects with a history of cardiopulmonary disease and other susceptible populations [18-20]. One study of a seven-year period in the USA (from 2000 to 2007) showed that every 10 μg / m^3 decrease in $PM_{2.5}$ extended life spans by 0.35 years [21].

Carbon monoxide

Carbon monoxide (CO) is a colorless, odorless gas produced by the insufficient combustion of fossil-based fuels. Any situation involving inadequate combustion can produce carbon monoxide, such as gas, kerosene, wood- coal-burning stoves, chimneys, cooking ranges, leaking stove pipes and chimneys, room and water heaters, vehicle exhaust in closed garages, and tobacco smoke.

Mean threshold levels set by the US Environmental Protection Agency (EPA) are 50 ppm for 8 hours, 75 ppm for 4 hours, and 125 ppm for one hour, although there is no agreed standard for indoor air CO.

The affinity of CO for hemoglobin (Hb) is 240-270 times greater than that of oxygen, and it reduces the capacity of Hb to transport oxygen to tissues. Intoxication results in tissue hypoxia, and multiple organs, particularly the central nervous and cardiovascular systems are affected with their high metabolic rates. Intervention may be delayed since symptoms of exposure are not specific. Exposure to CO is particularly hazardous to babies and individuals with a history of asthma or heart disease. At low levels, fatigue and chest pain are exacerbated in individuals with chronic heart disease. At higher levels of exposure, breathing CO causes symptoms such as headache, dizziness, and loss of strength in healthy individuals. CO can also cause sleepiness, nausea, vomiting, confusion, and disorientation. Very high levels of exposure can result in loss of consciousness and death, and may produce irreversible sequelae [22].

Carboxyhemoglobin (COHb) measurement confirms that exposure has taken place, although there is no correlation between severity of intoxication and COHb levels. Normal COHb levels are 3-8% in smokers and 1-3% in non-smokers. The half-life of COHb is 4 h at room temperature, 1 h with 100% O_2, and 20-30 min with hyperbaric oxygen.

Tobacco smoke

Tobacco smoke consists of more than 3800 different substances such as CO, carbon dioxide, oxides of nitrogen, polyaromatic hydrocarbons, and numerous toxic materials. The PM rate in air is 2-3 times higher in homes where the residents smoke [23,24].

Environmental tobacco smoke components are divided into the smoke exhaled by the smoker, and smoke disseminated from the tip of the cigarette. Non-smokers exposed to environmental tobacco smoke are exposed to the majority of toxins and various additional substances emitted by active smokers. For example, levels of N-nitrosodimethylamine, a proven carcinogenic substance in animals, in main smoke are 20-100 times higher than those in subsidiary smoke [25], and a 'passive' smoker 50 cm from a cigarette can breathe more than ten times the active carbonyl compounds inhaled by the active smoker [26]. Smoking one pack a day contributes approximately 20 μg/m^3 to 24-h indoor particle levels. In addition, it has been concluded that the moment a cigarette is lit, it has a probable increasing effect of 500-1000 μg/m^3 on short-term particle concentrations [27].

Health impacts associated with exposure to tobacco smoke range from nose and throat irritation, worsening of asthma symptoms in children and adults, and lower respiratory tract diseases to lung cancer [8,28-31]. One case-control study of 191 individuals in the USA concluded that approximately 17% of lung cancers among non-smokers were associated with exposure to environmental tobacco smoke at early ages [32].

Formaldehyde and volatile organic compounds

The sources of indoor formaldehyde vary among different countries; the main sources in developing countries are solid fuels used indoors, insect repellents, and furniture, while in developed countries they are domestic cleaning products and deodorants, glues and resins, tobacco smoke, carpets, furniture and paint materials, and insulating foams. A colorless gas with a pungent odor, formaldehyde can result in a burning sensation in the eyes and throat, nausea, and respiratory difficulty. High concentrations can trigger attacks in asthma patients. Chronic formaldehyde inhalation causes damage to the nasal and other respiratory tract mucosa, and an increased incidence of lung and nasopharyngeal cancer [33].

Organic chemicals are widely used in domestic products such as paint, varnish, sealing wax, cosmetic products, wood preservers, cleaning materials and disinfectants, moth repellents, sprays, and hobby materials. In addition, fuel can also be made from organic chemicals. All these products result in the release of a specific quantity of organic chemicals during use and in the area concerned. Mean indoor levels of various organic compounds are 2-5 times higher than external levels. The effects on health of volatile organic products can vary significantly; some are highly toxic, while others have no known health impacts. Exposure to volatile organic compounds can lead to symptoms such as irritation of the eyes, nose and throat, headache, loss of coordination, nausea, dizziness and eye disorders, and to impaired memory and liver, kidney, and central nervous system damage [34]. Chronic exposure to benzene can lead to bone marrow depression and associated hematological diseases and leukemia [35].

Nitrogen dioxide

The best-known sources of indoor nitrogen dioxide (NO_2) are gas and oil stoves used for cooking and cigarette smoke. The current WHO air quality guideline recommends a mean indoor annual value of 40 μg/m^3 for NO_2. Indoor NO_2 levels in winter are 2-3 times higher than external levels, while the two are approximately equal in summer. NO_2 is a non-water-soluble gas. At low levels it can be expelled via mucus secretions on the upper respiratory tract but reaches the lower respiratory tract after being inhaled. If inhaled at high levels, cough,

wheezing, respiratory failure, nausea, dyspnea, fatigue and anxiety may be seen [36].

A mean increase equivalent to 28 μg/m^3 in indoor NO_2 has been determined in homes using solid fuels compared to electricity, increasing the risk of respiratory difficulty in children by 20%.

Asbestos

Asbestos is a general term referring to the group of hydrated silicate minerals with an incombustible filament structure that occur in various forms [8]. In the 1970s, asbestos was widely used in various areas of industry, due to its electrical and thermal insulation properties, such as the production of pipe insulation, cement slabs, tiles, paint, and wallpaper. Concerns over the health effects of exposure to asbestos have led to legal measures prohibiting its use in many countries [37]. Exposure to asbestos generally involves respiration of the fibers and causes diseases such as lung cancer, mesothelioma, and asbestosis [38,39]. In order for asbestos fibers to affect health, they need to remain in the respiratory passages for approximately one year, and those less than 1 μm in diameter and greater than 5-10 μm in length have been shown to be particularly hazardous [37].

Radon

Radon is a colorless, odorless, radioactive gas arising from the natural breakdown of thorium and uranium in rock and soil. Radon exposure represents more than 50% of annual radiation exposure of natural origin [40]. The most important sources of indoor radon are various structural materials, emissions from the soil, rock and natural fissures beneath and around the building, and well water [41]. Radon general involves no health risk in the open air, since outdoor levels are quite low. However, it may accumulate at dangerous levels in closed environments. Differences in air pressure between the inside of a building and the surrounding soil also play a significant role in radon emissions. If the air pressure in a house is greater than that in the soil beneath, then the radon remains outside. However, if it is lower than that of the surrounding soil (as is generally the case), then the internal pressure behaves like a vacuum cleaner attracting radon gas. Since radon is emitted from the soil, geological data for the area can help predict potential indoor radon levels. Cell culture, animal experiments, and epidemiological cohort and case-control studies have proven that radon causes cancers such as leukemia and lung cancer. Radon has been classified as a Group 1 carcinogen by the International Agency for Research on Cancer [42-45]. Approximately 14,000 adults die from radon-related cancer in the USA every year. In light of the latest scientific data, the World Health Organization recommends a reference level of 100 Bq/m^3 in order to reduce health risks associated with indoor radon exposure to a minimum [41].

Biological Pollutants (micro-organisms and allergens)

Domestic animals, their fur and secretions, moisturizers, ventilation systems, drainage pipes, and pipes can constitute indoor growth areas for micro-organisms, fungi, and algae. Moisture is essential for dust mites, fungi, and bacteria to multiply. Rain or subterranean water entering a building and accumulating on internal surfaces can facilitate the growth of micro-organisms. These micro-organisms can then cause various contagious diseases, allergic reactions, and toxic effects in those living in that environment. Adequate air flow is essential to prevent moisture problems associated with water vapor produced and exhaled by humans and domestic animals, or from cooking and cleaning. Legionella can be present and grow in ventilation system water discharge channels, stagnant water pipes, and shower pipes, and is one of the agents involved in pneumonia in humans. Higher number of people in an indoor environment facilitate the spread of infectious diseases. Mites found in floor furnishings, bed surfaces and beddings may lead to asthma, particularly in children. Pollen in the air can also lead to asthma [1–5].

Conclusion

Understanding the hazards posed by substances giving rise to indoor air pollution constitutes the first step to preventing adverse health effects and identifying the requisite precautionary measures [46]. Education and establishing individual awareness and sensibility are therefore particularly important. Education will help in the search for diverse ways of managing energy better, protecting children in the home, and reducing risks. Individuals must also be educated about using clean alternative energy sources instead of the direct burning of biomass fuel. However, in addition to the public, politicians and administrators must also reinforce their commitment and awareness of the health impacts of indoor pollution.

Fuel use is affected by sociocultural and economic factors. Habits, availability and most importantly, affordability influence fuel selection. Most low-income families directly employ biomass fuel for cooking, since this is the cheapest and simplest option available. The use of accessible, economical, and clean energy sources must be encouraged. Stoves used for heating and/or lighting, and which are traditionally smoky and leaky, must be replaced with those that are fuel efficient, non-smoke emitting, and have reliable means of eliminating indoor pollutants. Importance must be attached to adequate ventilation during the construction of dwellings, and appropriate architectural measures must be introduced for homes with inadequate ventilation.

The prevention of indoor air pollution and the use of clean sources of energy must be regarded as an opportunity to improve health, particularly that of mothers and children, to reduce poverty, and to achieve environmental sustainability. Indoor air pollution can only be controlled through coordinated and determined endeavor on the part of different sectors associated with health, energy, the environment, and rural and urban regeneration. The prevention of indoor air pollution will result in economic and social regeneration.

References

1. Indoor air pollution. 14.01.2018]; Available from: https://www.who.int/features/qa/indoor-air-pollution/en/.
2. Myers I, Maynard RL. Polluted air—outdoors and indoors. Occup Med (Lond). 2005;55(6):432-8.
3. McKenzie JF, Pinger RR, Kotecki JE. An introduction to community health. London: Jones & Bartlett Publishers; 2011.
4. Kurmi OP, Semple S, Steiner M, Henderson GD, Ayres JG. Particulate matter exposure during domestic work in Nepal. Annals of occupational hygiene. 2008;52(6):509-17.
5. Cooke TF. Indoor Air Pollutants: A Literature Review. Reviews on Environmental Health. 1991;9(3):137-60.
6. Kırımhan S, Boyabat N. Erzurum'da hava kirliliği-Son rapor. Atatürk Üniversitesi Çevre Sorunları Sempozyumu–5, Erzurum, 1983;12:6-8.
7. Spellman FR. The science of air: concepts and applications. Boca Raton, Fla: CRC Press; 2016:300.
8. Maroni M, Seifert B, Lindvall T. Indoor air quality: a comprehensive reference book. Vol. 3. Amsterdam: Elsevier; 1995.
9. Wang LK, Pereira NC; Hung YT. Advanced air and noise pollution control; Totowa, New Jersey: Humana Press; 2005.

10.Chang CC, Ruhl RA, Halpern GM, Gershwin ME. The sick building syndrome. I. Definition and epidemiological considerations. 1993;30(4):285-95.
11.Raaschou-Nielsen O, Andersen ZJ, Beelen R, Samoli E, Stafoggia M, Weinmayr G, et al. Air pollution and lung cancer incidence in 17 European cohorts: prospective analyses from the European Study of Cohorts for Air Pollution Effects (ESCAPE). The Lancet Oncology. 2013;14(9):813-22.
12.Xing YF, Xu YH, Shi MH, LianXing YX. The impact of PM2. 5 on the human respiratory system. J Thorac Dis. 2016;8(1):E69-74.
13.Samoli E, Analitis A, Touloumi G, Schwartz J, Anderson HR, Sunyer J, et al. Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. Environmental Health Perspectives. 2004;113(1):88-95.
14.Ostro B, Broadwin R, Green S, Feng WY, Lipsett M. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. Environmental Health Perspectives. 2005;114(1):29-33.
15.Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB, et al. Air pollution–associated changes in lung function among asthmatic children in Detroit. Environmental Health Perspectives. 2005;113(8):1068-75.
16.Zanobetti A, Franklin M, Koutrakis P, Schwartz J. Fine particulate air pollution and its components in association with cause-specific emergency admissions. Environ Health. 2009;8(1):58.
17.Dominici F, Peng RD, Bell ML, Pham L, McDermott A. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. JAMA. 2006;295(10):1127-34.
18.Huynh M, Woodruff TJ, Parker JD, Schoendorf KC. Relationships between air pollution and preterm birth in California. 2006;20(6):454-61.
19.Martinelli N, Girelli D, Cigolini D, Sandri M, Ricci G, Rocca G, et al. Access Rate to the Emergency Department for Venous Thromboembolism in Relationship with Coarse and Fine Particulate Matter Air Pollution. PLoS ONE. 2011;7(4):e34831.
20.de Oliveira BFA, Ignotti E, Artaxo P, do Nascimento Saldiva PH, Junger WL, Hacon S. Risk assessment of PM 2.5 to child residents in Brazilian Amazon region with biofuel production. Environ Health. 2012;11(1):64.
21.Correia AW, Pope CA, Dockery DW, Wang Y, Ezzati M, Dominici F. The effect of air pollution control on life expectancy in the United States: an analysis of 545 US counties for the period 2000 to 2007. Epidemiology. 2013 Jan;24(1):23-31.
22.Indoor Air Quality (IAQ). https://www.epa.gov/indoor-air-quality-iaq. Accessed 7 December 2018.
23.Güler Ç. Kapalı Ortam Hava Kirliliği. Mesleki Sağlık ve Güvenlik Dergisi (MSG). 2015; 3(12):25-32.
24.Gold D. Indoor air pollution. Clinics in Chest Medicine. 1992;13(2):215-29.
25.Jenkins RA, Tomkins B, Guerin MR. The chemistry of environmental tobacco smoke: composition and measurement. CRC Press; 2000.
26.Schlitt H, Knoppel H. Carbonyl compounds in mainstream and sidestream tobacco smoke. Present and Future of Indoor Air Quality. 1989:197-206.
27.Spengler JD, Dockery DW, Turner WA, Wolfson JM, Ferris BG. Long-term measurements of respirable sulfates and particles inside and outside homes. Atmospheric Environment (1967). 1981;15(1):23-30.
28.Jones A. Asthma and domestic air quality. Social Science & Medicine. 1998;47(6):755-64.
29.Forastiére F, Corbo GM, Michelozzi P, Pistelli R, Agabiti N, Brancato G, et al. Effects of environment and passive smoking on the respiratory health of children. International journal of epidemiology. 1992;21(1):66-73.
30.Arshad SH, Matthews S, Gant J, Hide DW. Effect of allergen avoidance on development of allergic disorders in infancy. The Lancet. 1992;339(8808):1493-7.
31.National Research Council. Environmental tobacco smoke: measuring exposures and assessing health effects. National Academies Press; 1986.
32.Janerich DT, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, et al. Lung cancer and exposure to tobacco smoke in the household. New England Journal of Medicine. 1990;323(10):632-6.
33.Formaldehyde. https://www.epa.gov/formaldehyde. Accessed 19 March 2019.
34.Indoor Air Quality (IAQ). https://www.epa.gov/indoor-air-quality-iaq. Accessed 19 March 2019.
35.Wallace LA. Human exposure to volatile organic pollutants: implications for indoor air studies. Annual Review of Energy and the Environment. 2001;26(1):269-301.
36.Shima M, Adachi M. Effect of outdoor and indoor nitrogen dioxide on respiratory symptoms in schoolchildren. 2000;29(5):862-70.
37.Jones AP. Indoor air quality and health. Atmospheric Environment. 1999;33(28):4535-64.
38.McDonald JC. An epidemiological view of asbestos in buildings. Toxicology and Industrial Health. 1991;7(5-6):187-93.
39.Ohar J, Sterling DA, Bleecker E, Donohue J. Changing patterns in asbestos-induced lung disease. Chest. 2004;125(2):744-53.
40.United Nations Scientific Committee on the Effects of Atomic Radiation, Sources and Effects of Ionizing Radiation. New York, NY United Nations; 2006.
41.World Health Organization WHO Guidelines for indoor air quality: selected pollutants, 2010. http://www.euro.who.int/__data/assets/pdf_file/0009/128169/e94535.pdf. Accessed 15 December 2018.
42.Hussain SP, Kennedy CH, Amstad P, Lui H, Lechner JF, Harris CC. Radon and lung carcinogenesis: mutability of p53 codons 249 and 250 to 238 Pu alpha-particles in human bronchial epithelial cells. Carcinogenesis. 1997;18(1):121-5.
43.Weaver DA, Hei TK, Hukku B, McRaven JA, Willey JC. Cytogenetic and molecular genetic analysis of tumorigenic human bronchial epithelial cells induced by radon alpha particles. Carcinogenesis. 1997;18(6):1251-7.
44.Collie CG, Strong JC, Humpherys JA, Timpson N, Baker ST, Eldered T, et al. Carcinogenicity of radon/radon decay product inhalation in rats–effect of dose, dose rate and unattached fraction. International Journal of Radiation Biology. 2005;81(9):631-47.
45.National Research Council, Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. Health risks from exposure to low levels of ionizing radiation: BEIR VII phase 2. National Academies Press; 2006.
46.Household air pollution and health. https://www.who.int/news-room/fact-sheets/detail/household-air-pollution-and-health. Accessed 7 December 2018.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):882-884.
DOI: 10.28982/josam.590383

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

Appendiceal intussusception, a peroperative surprise: A case report

Peroperatuvar sürpriz; Appendiks intussusepsiyonu: Olgu sunumu

Baha Arslan [1], Tuğba Han Yılmaz [1], Varlık Erol [1], Hüseyin Gülay [1]

[1] Başkent University School of Medicine, Zubeyde Hanim Training and Research Hospital, Department of General Surgery, İzmir, Turkey

ORCID ID of the author(s)

BA: 0000-0003-4461-4904
THY:0000-0002-9590-0276
VE: 0000-0002-7337-4973
HG: 0000-0002-0442-6178

Abstract

Intussusception of the appendix is very uncommon and when encountered, it may alter surgical procedures. For this reason, it should be kept in mind that appendiceal intussusception may occur in every patient diagnosed with acute appendicitis. It is critical to consider appendiceal intussusception in patients presenting with recurrent nausea, vomiting and chronic abdominal pain.

Keywords: Intussusception of appendix, Acute appendicitis, Surgical procedures

Öz

Apendiks intussepsiyonu nadir görülse de cerrahların ister ameliyat öncesi ister ameliyat sırasında karşılaştıklarında cerrahi işlem basamaklarını değiştirebilecek bir durumdur. Bu nedenle akut apandisit tanısı alan her hastada karşlaşılabileceğinin bilincinde olunması aynı zamanda tekrarlayan bulantı kusma ve kronik karın ağrılı hastalarda intussepsiyonun da akla getirilmesi önemlidir.

Anahtar kelimeler: Apendiks intussusepisyonu, Akut apandisit, Cerrahi prosedür

Introduction

Acute appendicitis (AA) is the most common condition encountered by general surgeons and emergency physicians that necessitates emergency surgery. Therefore, its differential diagnosis needs to be established precisely. Today, clinical scoring and imaging techniques are used for the diagnosis of AA. However, when imaging techniques are unavailable, the diagnosis of a substantial number of patients are based on anamnesis and laboratory analyses, after which they are operated on [1,2]. We herein present the diagnostic and therapeutic approach to a case diagnosed with AA based on clinical, laboratory, and ultrasonographic (US) findings, in which Type III intussusception of the appendix was determined during surgery.

Corresponding author / Sorumlu yazar:
Baha Arslan
Address / Adres: Başkent Üniversitesi Tıp Fakültesi, Zubeyde Hanım Eğitim ve Araştırma Hastanesi, Genel Cerrahi Anabilim Dalı, Caher Dudayev Bulvarı No: 175 Bostanlı, Karşıyaka, İzmir, Türkiye
e-Mail: drbaha112@gmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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: 12/5/2019
Yayın Tarihi: 05.12.2019

How to cite / Atıf için: Arslan B, Yılmaz TH, Erol V, Gülay H. Appendiceal intussusception, a peroperative surprise: A case report. J Surg Med. 2019;3(12):882-884.

Case presentation

A 29-year-old male patient was admitted to our Emergency Service with severe nausea, vomiting, and abdominal pain lasting for 2 days. His physical examination revealed extensive abdominal tenderness together with defense and rebound positivity in the right lower quadrant. His laboratory findings were normal except for a leukocyte count of 17000 /mL. On US, appendix diameter had increased to 11 mm and there was enhanced echogenicity in the surrounding mesenteric tissue. The patient was operated on with a pre-diagnosis of AA. The surgical procedure was initiated with a McBurney incision. Appendix, curved on its own mesentery, was visibly inflamed and adherent to the ileal mesentery, which was separated with sharp and blunt dissections with bleeding control. Meanwhile, a mass-like formation was palpated at the point where appendix is attached to the cecum (Figure 1). Cecum was mobilized. The mass-like formation was considered an appendiceal intussusception (AI). When the appendix was slightly suspended after the division of the serosa, it was observed that the mass-like formation disappeared by sliding back to the appendix (Figure 2). Appendectomy was performed at the base of the cecum. Pathological examination revealed a material 7.3 cm in length and 1.3 cm in diameter with its serosa surrounded by purulent exudate and the appendix wall showing bleeding on serial sections, which was consistent with AA. Written and verbal informed consent form obtained from patient.

Figure 1: Palpable mass at the point where appendix attaches to the cecum

Figure 2: Reduction of intussusception after opening the serosa

Discussion

Acute appendicitis is the most common condition encountered in 6% of the general population during evaluation of acute surgical abdomen [1,2]. Differential diagnoses of patients visiting emergency services due to abdominal pain may range from urinary tract infections to peptic ulcer perforation, and from AA to ectopic pregnancy. Detailed medical history and physical examination are helpful in differentiating between various conditions.

The scoring systems used for diagnosis of AA establish a cost-effective control mechanism and save time by preventing unnecessary testing. Among these, Alvarado and RIPASA scoring systems are well known and widely used [1,2].

Appendix intussusception was defined in 1858 by Mckidd [3] during the post-mortem examination of a 7-year-old male patient. Afterwards, in 1897, Whright and Renshaw [4] and Pitts and McGraw [5] reported the successful surgery of a 13-year-old male patient. In 1963, Collins published a review investigating the surgical and autopsy examinations of 71000 appendices in a 40-year period and reported the prevalence of AI to be 0.01% [6]. In their literature review, Chaar et al. [7] determined 190 cases of AI reported between 1993 and 2009 worldwide.

The classification of AI, which was first defined in 1910 by Moschowitz [5], was modified in 1941 by McSwain [8] (Table 1).

Table 1: Classification of appendix intussusception modified in 1941 by McSwain [8]

Type I	The proximal end of the appendix invaginates into the appendix and intussusception occurs into the appendix.
Type II	Invagination begins anywhere on the appendix and intussusception of the adhered tissue occurs.
Type III	Invagination occurs from the junction of the appendix and cecum to the cecum. Intussusception occurs into the cecum.
Type IV	There occurs retrograde intussusception. The proximal appendix invaginates into the distal appendix.
Type V	Complete invagination of the appendix into the cecum from progression of type I, type II or type III.

In the review by Chaar et al. [7] only 32% of the patients were diagnosed during the preoperative period and 63% of the patients presented with chronic abdominal pain increasing and decreasing in intensity, intermittent nausea and vomiting, and occasional rectal bleeding for weeks or months. They reported that 11% were diagnosed by histopathological examination of the specimen and 57% were diagnosed peroperatively. Moreover, while 19% had inflammation only, 33% had endometriosis, 19% had mucocele, 11% had adenoma, 7% had carcinoid tumor, and 6% had adenocarcinoma. In that review, the surgical procedures performed on the patients ranged from appendectomy to right hemicolectomy [7].

The medical history of our case revealed complaints for 2 days. The patient described pain initially starting with nausea and vomiting. Besides, the patient was operated on without need for an additional analysis as his US confirmed the clinical and laboratory findings. During the surgery, a mass-like formation was detected in the cecum.

The review by Chaar et al. [7] opted us to think about two issues. First, whether the simple tests are adequate in establishing the diagnosis of AA and second, what should the decision of the resection margin be based on in such a case?

Rational use of clinical and laboratory findings when imaging modalities are unavailable is helpful in deciding on the surgical treatment of patients with acute abdomen. Rational use of either Alvarado or RIPASA scoring system is important for clinicians. Monitoring of clinical and laboratory parameters would be instructive in suspicious cases. While US examination is adequate in centers where imaging systems are available, in clinically suspicious cases, it is recommended to perform US

first, and computed tomography (CT) second. Laboratory and imaging techniques can be performed at intervals together with clinical follow-up in un-diagnosed cases [9].

Levine et al. [9] stated that in addition to US examination being user-dependent, CT also has pitfalls in diagnosing AA. Therefore, they emphasized that clinicians needed to act considering clinical examination, laboratory analyses, and imaging techniques all together. Although various facilities now initially perform CT for diagnosis, many other centers prefer US as the first choice, akin to this case. However, CT can be preferred when the diagnosis of appendicitis cannot be established [9].

With regards to the decision of resection margin, it has been demonstrated that malignancy or malignancy-related situations are the causes of AI in nearly 40% of the cases; however, potential burden of the surgical procedure on the patient should also be taken into account [10]. Obviously, it will be difficult to distinguish an AI caused by an inflammatory scar from an AI caused by malignancy. Although experience plays a significant role in peroperative evaluation, surgeons should act knowing that each surgeon has the potential of making mistakes. In this case, we preferred appendectomy alone for the patient who underwent surgery for AA, because AA was the primary cause of acute abdomen, it was an early diagnosis, the patient's blood parameters were stable and serosal thickening had newly developed in the base of the appendix. After this decision, examination of the pathologic frozen section during the surgery could have provided early diagnosis of malignancy and, if necessary, enabled surgery to be extended. Since pathological examination of frozen section is not available in our center, the treatment decision was based on the definite pathological findings.

Atkinson et al. [10] defined the clinical presentation of AI in four groups: patients presenting with classical signs of AA, those presenting with a clinical picture of intussusception, those with prolonged clinical history including recurrent pain in the right lower quadrant, vomiting, and rectal bleeding, and those not primarily determined to have AI clinically but incidentally detected to have AI during colonoscopy or radiological examination.

In patients suffering predominantly from nausea and vomiting, as was in the present case, or in those suffering predominantly from clinically overt intussusception, contrast-enhanced CT can be performed to better understand the intraabdominal event even when US suggests AA [11]. However, clinicians decide surgery without need for CT taking cost-effectiveness and necessity of rational use of time into account and due to the likelihood of overlooking AI as it is a rare condition.

According to the evaluation in the review by Chaar et al. [7], considering the malignancy-related situations in 40% of AI patients, it is the surgeon's decision to choose preventive approach by performing aggressive surgery for cases detected during surgery. Availability of pathological examination of frozen sections would be helpful to decide rapidly about the treatment in these patients. For the centers where frozen pathology is unavailable, we believe that there are two different alternatives: One of them is performing appendectomy after correcting AI and taking actions according to the definite pathology findings and the other is completing the procedure with extensive resection from the cecum and waiting for the definite pathology findings. In fact, both approaches can be considered inconvenient since malignancy is pointed out as the primary cause of intestinal intussusception in adult cases. Moreover, surgical intervention should also minimize mortality and morbidity. In our case, it was observed that intussusception was corrected as the serosa was divided, after which appendectomy was performed.

Another issue to be questioned is the potential pitfalls when laparoscopic appendectomy is planned in a similar case. The comfort of laparoscopic surgery for both the surgeons and patients cannot be underestimated. However, it is obvious that unavailability of palpation during laparoscopic surgery would make the intraoperative recognition of undiagnosed intussusception difficult for the surgeon. In addition, unrecognized intussusception would be associated with postoperative complications as well. For this reason, the guidance of collaborative radiologists is always valuable.

Conclusion

Surprising situations resulting from frequent emergency conditions such as AA might be the starting point of long-lasting efforts for both the patient and the surgeon. Intussusception should also be kept in mind among other pathological parameters as well as appendicitis in cases presenting with abdominal pain in the right lower quadrant and confirmation by CT and surgical planning are required in suspicious cases.

References

1. Alvarado A. A practical score for the early diagnosis of acute appendicitis. Ann Emerg Med. 1986;15:557-64.
2. Chong CF, Adi MI, Thien A, Suyoi A, Mackie AJ, Tin AS, et al. Development of the RIPASA score: a new appendicitis scoring system for the diagnosis of acute appendicitis. Singapore Med J. 2010;51:220-5.
3. McKidd J. Case of invagination of caecum and appendix. Edinburgh Med J. 1858;4:793-7.
4. Wright GA, Renshaw K. Chronic intussusception of the appendix into the cecum, operation recovery. Br Med J. 1897;12:1470-1
5. Moschcowitz AV. Intussusception of the appendix. Med Rec NY. 1910;8:1087-95.
6. Collins DC. 71,000 human appendix specimens. A final report, summarizing forty years' study. Am J Proctol. 1963;14:265-81.
7. Chaar CI, Waxelman B, Zuckerman K, Longo W. Intussusception of the appendix: a comprehensive review of the literature. Am J Surg. 2009;198:122-8.
8. McSwain B. Intussusceptionof the Appendix. South Med. 1941;34:263.
9. Levine CD, Aizenstein O, Wachsberg RH. Pitfalls in the diagnosis of appendicitis. Br J Radio. 2004;l77:792-9.
10. Atkinson GO, Gay BB, Naffis D. Intussusception of the appendix in children. AJR Am J Roentgenol. 1976;126:1164-8.
11. Yeni M, Peksöz R, Dablan A, Dişçi E. A rare acute abdomen case: Acute appendicitis in the patient with situs inversus totalis. J Surg Med. 2019;3(10):766-8.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):885-887.
DOI: 10.28982/josam.652654

Case report
Olgu sunumu

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

A rare case: Asymptomatic spontaneous pneumobilia

Nadir bir olgu: Asemptomatik spontan pnömobilya

Selman Yeniocak [1], Adem Az [1], Eda Canıpek [2], Büşra Ekinci Biçkici [3], Merve Metiner [1], Ahmet Demirel [4]

[1] University of Health Sciences, Haseki Training and Research Hospital, Emergency Department, Istanbul, Turkey
[2] Istanbul University, Faculty of Medicine, Department of Radiology, Istanbul, Turkey
[3] University of Health Sciences, Haseki Training and Research Hospital, Department of General Surgery, Istanbul, Turkey
[4] University of Health Sciences, Okmeydanı Training and Research Hospital, Emergency Department, Istanbul, Turkey

ORCID ID of the author(s)
SY: 0000-0002-1124-396X
AA: 0000-0002-7204-6185
EC: 0000-0003-0814-4597
BEB: 0000-0002-9767-839X
MM: 0000-0002-2377-1903
AD: 0000-0002-7905-5850

Corresponding author / Sorumlu yazar:
Selman Yeniocak
Address / Adres: Haseki Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, Acil Servis, İstanbul, Türkiye
e-Mail: selmanyeniocakacil@hotmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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.

Bu olgu, 15-17 Şubat 2019 tarihinde 23. İstanbul Acil Tıp Kış Sempozyumu (Kritik Bakım)'nda sözlü olarak sunulmuştur.

Published: 12/18/2019
Yayın Tarihi: 18.12.2019

Abstract

Pneumobilia, or aerobilia, is defined as the presence of gas in the biliary system. It may occur for various reasons, including recent enterobiliary system interventions, sphincter of oddi dysfunction, and enterobiliary fistula and anastomoses. A 61-year-old male patient presented to our emergency department due to nausea and vomiting. He had no history of drug use other than proton pump inhibitor medication, nor of alcohol or substance use. Although no history of previous medical intervention was present, gas (pneumobilia) was detected in the intrahepatic biliary ducts. We suspected that the incidentally detected pneumobilia in this patient, who also suffered from food poisoning, developed spontaneously in association with peptic ulcer and might have derived from a thin, asymptomatic enterobiliary fistula. Depending on its cause, pneumobilia may not require emergency surgery. The possibility of enterobiliary fistula should not be overlooked in patients presenting to the emergency department with chronic peptic ulcer symptoms.

Keywords: Pneumobilia, Gas in intrahepatic bile ducts, Saber sign, Hepatic portal vein gas

Öz

Aerobilia olarak da bilinen pneumobilia, biliyer sistemde gaz olması olarak tanımlanır. Son zamanlarda yapılmış enterobilier sistem girişimleri, Oddi sfinkter disfonksiyonu, enterobilier sistem fistül ve anastomozları gibi değişik nedenlerle gelişebilir. Altmış bir yaşında erkek hasta bulantı kusma şikayeti ile acil servise başvurdu. Proton pompa inhibitörü ilacı dışında herhangi bir ilaç, alkol veya madde kullanım öyküsü olmayan hastada, daha önce herhangi tıbbi girişim işlemi geçirmemiş olmamasına rağmen intrahepatik safra yollarında gaz (pneumobilia) tespit edildi. Besin zehirlenmesi de olan hastada tesadüfen tespit edilen pneumobilia'nın, peptik ülsere bağlı spontan gelişmiş, asemptomatik enterobilier ince bir fistülden kaynaklanmış olabileceği düşünüldü. Pneumobilia, geliştiği nedene bağlı olarak acil cerrahi girişim gerektirmeyebilir. Kronik peptik ülser şikayetleri ile acil servise müracaat eden hastalarda enterobilier fistül gelişmiş olabileceği gözardı edilmemelidir.

Anahtar kelimeler: Pneumobilia, İntrahepatik safra yollarında gaz, Saber işareti, Hepatik portal ven gazı

Introduction

Pneumobilia, or aerobilia, is defined as the presence of gas in the biliary system. The condition has a broad etiological spectrum, including recent enterobiliary system interventions, drugs and structural causes leading to sphincter of Oddi dysfunction, spontaneous and surgical enterobiliary fistulae, malignancy, and rarely infections and biliary-bronchopleural fistula [1]. We report a case presenting to the emergency department with nausea and vomiting and diagnosed with rare spontaneous pneumobilia, together with the current literature.

How to cite / Atıf için: Yeniocak S, Az A, Canıpek E, Biçkici BE, Metiner M, Demirel A. A rare case: Asymptomatic spontaneous pneumobilia. J Surg Med. 2019;3(12):885-887.

Case presentation

A 61-year-old male patient, from whom verbal consent for this case report was obtained, presented to our emergency department due to nausea and vomiting. On arrival, his general condition was average, and he was conscious and cooperative. Arterial blood pressure was 100/60mmHg, heart rate 88/min, and body temperature 36.7°C, and respiration was normal. Peptic ulcer was present in his medical history, and he had been using proton pump inhibitors (PPIs) irregularly for 7-8 years. He had no history of alcohol or substance use, nor of previous medical intervention. The patient reported occasional recurrence of epigastric pain, with partial improvement after taking PPIs, that nausea and vomiting began a few hours after eating in the evening, and that no diarrhea occurred. No positive signs other than epigastric tenderness not radiating to the back were present at physical examination. Normal sinus rhythm was present at echocardiography (EKG). No pathological finding was determined at lung x-ray. Symptomatic intravenous (IV) 10 mg metoclopramide and 40 mg pantoprazole were administered with fluid infusion. At blood tests, glucose was 165 mg/dl (range 74-106 mg/dl), amylase 164 U/L (range 28-100U/L), and gamma glutamyl transferase (GGT) 71 U/L (<55). Hepatic enzymes, bilirubin values, C-reactive protein and other biochemical parameters were within normal reference ranges. Leukocyte value at complete blood count was 12.770/mm3 (range 3980-10.200/mm3). Blood gas oxygen saturation was 95.9%, carbon dioxide pressure was 43.1 mmHg, and pH was 7.49. Abdominal ultrasound (USG) revealed gas in the intrahepatic bile ducts (pneumobilia). The gall bladder and choledochal duct wall were normal, and no dilation was determined (Figure 1). Air was observed in the intrahepatic bile ducts at both non-contrast and oral and iv with-contrast computerized tomography (CT), but no stone, mass, fistula, perforation or stenosis were observed in the hepatobiliary and enterobiliary tract. No appearance of air or fluid was encountered in the abdomen (Figure 2). We suspected that the patient's acute onset symptoms were due to food poisoning, but that the pneumobilia observed might derive from the asymptomatic, fine enterobiliary fistula developing in association with peptic ulcer present in his previous history. The general surgery department was consulted, but no condition requiring emergency surgery was determined. The peptic ulcer again improved following symptomatic treatment. The patient was discharged, and polyclinic check-up visits were advised for advanced tests and treatment.

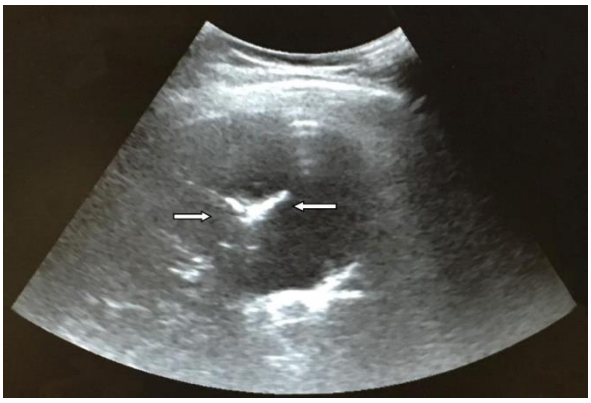

Figure 1: The image of the pneumobilia on the ultrasound of the patient

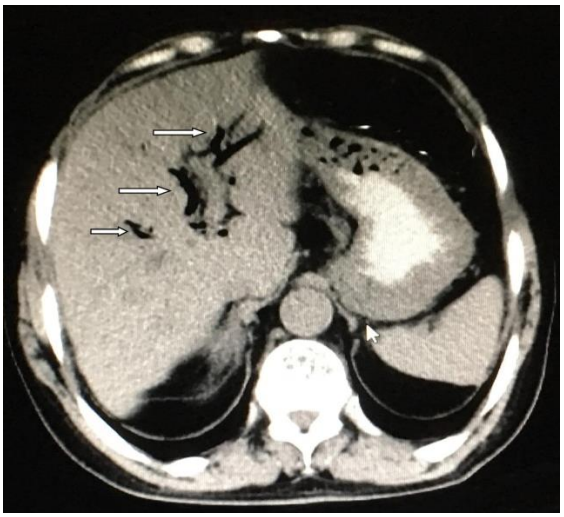

Figure 2: The image of the pneumobilia on the CT of the patient

Discussion

Pneumobilia is a rare condition. Due to the limited number of studies available, we found no up-to-date data concerning its incidence. Yamashita et al. [2] noted a relation between pneumobilia and the enterobiliary system, and reported the presence of spontaneous bilioenteric fistula in 33 (1.9%) out of 1929 patients with existing biliary disease, and that 15 (44%) of these patients with bilioenteric fistula presented due to pneumobilia.

In their retrospective study, Lassandro et al. [3] determined pneumobilia detection rates of 37.04% at abdominal x-ray, 55.6% at abdominal ultrasound, and 88.89% at abdominal CT. In the present case, the air in the patient's intrahepatic bile ducts could not be detected at x-ray imaging, but was clear at USG and CT.

Radiologically, pneumobilia can be confused with hepatic portal vein gas. The air in pneumobilia is in the direction of the bile flow, and has fewer branches. On x-ray images this is known as the sabre sign, and is a reliable indication at differential diagnosis. In contrast, portal venous gas is retrograde to the bile flow, extending both to the hepatic hilum region and toward Glisson's capsule, and exhibits a tree-like appearance in the peripheral branches [4,5]. Hepatic artery calcification can also mimic pneumobilia [6].

Our scan of the literature various case reports of pneumobilia development. It has been reported in association with emphysematous cholecystitis, emphysematous pyelonephritis, hepatic abscess, and intestinal tuberculosis [1,7,8]. Some case reports have shown that it can develop in association with metastatic colon cancer, as well as lymphoma, and may be associated with malignancy [9,10]. Gallstone is one important cause of pneumobilia, representing one in four bowel obstructions, and pneumobilia has been detected in 89% of these ileus cases [3]. Gallstone can also lead to pneumobilia without causing ileus [1]. One report described pneumobilia caused by choledochogastric fistula developing in association with congenital gall bladder agenesis [11]. Pneumobilia can also develop as a complication of invasive diagnostic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), or following surgical procedures [1]. It may develop in association with blunt and penetrating traumas, and there is a case report of cardiopulmonary resuscitation-related

development. This was thought to derive from the retrograde passage of air to the biliary system due to increased intra-abdominal pressure associated with blunt trauma [12-14].

Incidentally-detected pneumobilia can be assessed as a guide to diagnosis. In one case, enterobiliary fistula was suspected due to pneumobilia detected incidentally at USG in a case presenting due to diarrhea, and cholecystocolic fistula was determined with endoscopic cholangiopancreatography [15]. In another case, pneumobilia was observed incidentally in a patient presenting due to peptic ulcer symptoms persisting despite long-term medication. Cholecystoduodenal fistula was detected at endoscopy performed in order to identify the source of the pneumobilia [16]. In the present case, acute onset nausea and vomiting symptoms were attributed to food poisoning. However, the history of chronic peptic ulcer and irregular PPI use suggested that the enterobiliary fistula may have developed in association with peptic ulcer. No enterobiliary fistula was observed at multislice spiral computed tomography performed with both oral and iv contrast material.

Both diagnosis and treatment can be performed with endoscopic procedures in some patients with pneumobilia thought to be associated with enterobiliary fistula that cannot be detected at CT. The defective region can be closed by inserting an endobiliary prosthesis with ERCP. Magnetic resonance cholangiopancreatography (MRCP) can show the site of the bile leak and fistula in detail in a non-invasive manner [17,18]. No endoscopic or magnetic resonance imaging was performed in the emergency department in the present case. Some gastrobiliary fistulas identified endoscopically have been reported to close spontaneously with anti-ulcer treatment [19]. Emergency surgery was not considered. The patient was discharged, and polyclinic check-up visits were advised for advanced tests and treatment.

Conclusion

The etiological cause can be evaluated by establishing a relation between incidentally detected pneumobilia and detailed history and clinical findings, and the decision whether emergency surgical intervention is required can be made accordingly. The possibility of enterobiliary fistula should also be considered in patients presenting to the emergency department with symptom of chronic peptic ulcer, and these should be referred to the polyclinic for advanced tests.

References

1. Haouimi A, Gaillard F. Pneumobilia. Available from: https://radiopaedia.org/articles/pneumobilia
2. Yamashita H, Chijiiwa K, Ogawa Y, Kuroki S, Tanaka M. The internal biliary fistula-reappraisal of incidence, type, diagnosis and management of 33 consecutive cases. HPB Surg. 1997 June;10(3):143-7.
3. Lassandro F, Gagliardi N, Scuderi M, Pinto A, Gatta G, Mazzeo R. Gallstone ileus analysis of radiological findings in 27 patients. Eur J Radiol. 2004 Apr;50(1):23-9.
4. Rajković Z, Papes D, Altarac S, Arslani N. Abdominal pain and two x-rays: spot the difference. Ann R Coll Surg Engl. 2012 Mar;94(2):e95.
5. Lewandowski BJ, Withers C, Winsberg F. The air-filled left hepatic duct: the saber sign as an aid to the radiographic diagnosis of pneumobilia. Radiology. 1984 Nov;153(2):329-32.
6. Kane RA. Clue for distinguishing hepatic arterial calcifications from pneumobilia. J Clin Ultrasound. 2002 Sep;30(7):455.
7. Wu CC, Hung SF. Severe emphysematous pyelonephritis combined with pneumobilia. Emerg Med J. 2012 Nov;29(11):938.
8. Alvi AR, Zaidi M. A unique variant of intestinal tuberculosis. J Coll Physicians Surg Pak. 2008 Oct;18(10):657-9.
9. Antony A, Kramer S, Tzimas D, Saitta P. Pneumobilia Resulting From Choledochoduodenal Fistula Secondary to Metastatic Colon Adenocarcinoma. ACG Case Rep J. 2016 Jan;3(2):112-4.
10. Jabr FI. Large B-cell lymphoma of the duodenal papilla presenting as pneumobilia. Gastrointest Endosc. 2006 Oct;64(4):669-70.
11. Shirbur SN, Ramachandran H, Gokhale S, Falleiro J. Unusual Biliary Fistula. Med J Armed Forces India. 2001 Apr;57(2):167-8.
12. Okan I, Tali S, Özsoy Z, Deniz Ç, Acu B, Yenidoğan E, et al. The development of pneumobilia after blunt trauma. Ulus Cerrahi Derg. 2015 Jul;32(3):224-5.
13. Sandhu SS, Sampley SK, Chhabra K. Pneumobilia After Penetrating Trauma Abdominal Wall with no Injury to the Biliary Tree- A Case Report. Indian J Surg. 2013 Jun;75(Suppl 1):428-9.
14. Ladurner R, Kotsianos D, Mutschler W, Mussack T. Traumatic pneumobilia after cardiopulmonary resuscitation. Eur J Med Res. 2005 Nov;10(11):495-7.
15. Dutta U, Nagi B, Kumar A, Vaiphei K, Wig JD, Singh K. Pneumobilia--clue to an unusual cause of diarrhea. Trop Gastroenterol. 2002 Jul-Sep; 23(3):138-40.
16. Chaouch MA, Nacef K, Ghannouchi M, Khalifa MB, Chaouch A, Abdelkafi M, et al. Choledochoduodenal fistula due to peptic duodenal ulcer diagnosed by X-barium meal study: interest of medical treatment. Pan Afr Med J. 2018 Mar;29:177.
17. Abiad F, Sidani M. Biliary-colonic fistula through a cysticduct stump. Int Surg. 2000 Jul-Sep;85:231-3.
18. Çalışkan YK, Kalaycı MU. Can failure of choledochal cannulation in endoscopic retrograde cholangiopancreatography be prevented? J Surg Med. 2018 June;2(3):253-6.
19. Thyssen EP, Weinstock LB, Balfe DM, Shatz BA. Medical treatment of benign gastrocolic fistula. Ann Intern Med. 1993 Mar;118:433-5.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):888-890.
DOI: 10.28982/josam.592917

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

Anterior chest wall reconstruction for cutaneous involvement of Hodgkin's lymphoma

Hodgkin lenfomasının deri tutulumu için anterior göğüs duvarı rekonstrüksiyonu

Ariffuddin Ishak [1], Arman Zaharil Mat Saad [1], Wan Azman Wan Sulaiman [1], Azlan Husin [2], Ahmad Sukari Halim [1]

[1] Reconstructive Surgery Unit, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Malaysia
[2] Department of Internal Medicine, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Malaysia

ORCID ID of the author(s)

AI: 0000-0002-4256-7393
AZMS: 0000-0002-4003-6783
WAWS: 0000-0002-0600-9765
AH: 0000-0003-0899-0443
ASH: 0000-0001-8999-6403

Abstract

Hodgkin lymphoma with initial thoracic involvement is common and it is more frequently localized in the mediastinum, followed by lung parenchyma and the pleura. However, skin involvement of Hodgkin's lymphoma is extremely rare. We report this case to illustrate a rare and unique presentation of a potentially curable disease, with resistance to standard treatment. Free tissue transfer was used as an adjunct to provide a better quality of life for the patient with Hodgkin lymphoma complicated with extensive anterior chest wall ulceration exposing lung and pericardium.

Keywords: Hodgkin lymphoma, Cutaneous, Anterior chest wall, Reconstruction

Öz

Torasik tutulum gösteren Hodgkin lenfoma yaygındır ve mediastende daha sık lokalize olur, bunu akciğer parankimi ve plevra izler. Ancak Hodgkin lenfomanın cilt tutulumu oldukça nadirdir. Bu vaka sunumunda, tedavi edilebilir bir hastalığın nadir ve tedaviye dirençli prezentasyonunu sunmaktayız. Akciğer ve perikardiyumun teşhir olduğu yaygın göğüs ön duvarı ülserasyonu komplikasyonu ile başvuran Hodgkin lenfomalı hastanın yaşam kalitesini arttırmak amacıyla serbest doku transferi yapıldı.

Anahtar kelimeler: Hodgkin lenfoma, Kütanöz, Anterior göğüs duvarı, Rekonstrüksiyon

Introduction

Hodgkin's lymphoma (HL) encompasses 20 to 30% of all lymphomas [1]. The cutaneous involvement in Hodgkin's disease is almost always secondary to visceral or nodal involvement and is a rare condition, occurring in only 0.5 to 3.4% of the cases that typically occurs late in the progression. This unusual condition is believed to have declined in incidence in recent decades, likely due to improved treatment of patients with Hodgkin's disease who received modern combined chemotherapy, radiation therapy, and the role of peripheral blood stem cell transplantation [2].

Hodgkin's lymphomas are usually treated medically, with surgery being utilized for local control. Commonly, the cytotoxic chemotherapy is preferred for the treatment of malignant lymphoma. In well-chosen cases, surgical treatment can significantly contribute to a good outcome and better quality of life [3].

The patient described in this case report is unique whereby she presented with huge anterior chest wall ulceration which was successfully treated by using a combination of chemotherapy and free tissue transfer.

Corresponding author / Sorumlu yazar:
Ariffuddin Ishak
Address / Adres: Reconstructive Sciences Unit, School of Medical Sciences, Heath Campus, Universiti Sains Malaysia, 16150 Kubang Kerian Kelantan, Malaysia
e-Mail: ariffuddin_ishak@yahoo.com.my

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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: 12/20/2019
Yayın Tarihi: 20.12.2019

How to cite / Atıf için: Ishak A, Saad AZM, Sulaiman WAW, Husin A, Halim AS. Anterior chest wall reconstruction for cutaneous involvement of Hodgkin's lymphoma. J Surg Med. 2019;3(12):888-890.

Case presentation

A 40-year-old woman was diagnosed with stage IV (liver) mixed cellularity subtype Hodgkin lymphoma with bulky mediastinal mass in January 2006. She completed ABVD (Adriamycin, Bleomycin, Vinblastine, Dacarbazine) regimen and achieved partial remission with a significant residual anterior mediastinal disease. There was a delay in the commencement of salvage chemotherapy as she eventually was lost to follow-up for a year and presented back with anterior chest wall ulceration (Figure 1). Two months prior to presentation, she had skin ulceration over the anterior chest wall preceded by persistent discharging sinus. The infected wound secreted copious amount of foul smelling discharge. There was no constitutional symptom.

Clinically, the wound measured 15x12 cm with 4 cm depth with sloughy wound bed, exposed and eroded sternal cartilage with foul smelling serous discharge. Multiple cervical nodes were palpable. She had no sign of upper airway obstruction. Chest CT scan demonstrated multiple enlarged calcified nodules seen within the mediastinum, extensive sternal bone destruction, and extension to the anterior chest wall, exposing right pleura and pericardium, from the level of T2 to T11 costal cartilage. No lung involvement and no osteomyelitic changes were seen. Biopsies of cutaneous lesions revealed histological subtypes of Hodgkin disease consistent with those observed in the lymph nodes.

She underwent wound debridement and excision of the inflamed margin with preservation of thoracic cage. The wound bed was covered with pedicled omental and supercharged pedicled transverse rectus abdominis myocutaneous (TRAM) flap and concurrent chemoport insertion on right upper chest (Figure 2A, 2B, and 2C). Postoperatively, it was complicated with wound infection and dehiscence resulting in partial flap loss (Figure 3). The wound was then re-debrided prior to secondary coverage with free latissimus dorsi myocutaneous flap using perforators from internal thoracic as recipient vessel (Figure 4). During the recovery period, multiple sinuses developed on the lateral aspect of the flaps with continuous serous discharge. It took almost six months of regular dressing with concurrent treatment with monoclonal antibody targeting CD30 antigen on Hodgkin cells, brentuximab vedotin monotherapy for the wound to finally heal.

Upon completion of four cycles of brentuximab, her mediastinal disease slightly increased in size with presence of new lung nodules and hence her treatment has now switched to GDC (Gemcitabine, Carboplatin, Dexamethasone) protocol palliative chemotherapy. There is no evidence of cutaneous disease recurrence at one year of follow-up and she is able to resume most of her daily house chores (Figure 5).

Figure 1: Huge ulceration over the anterior chest wall

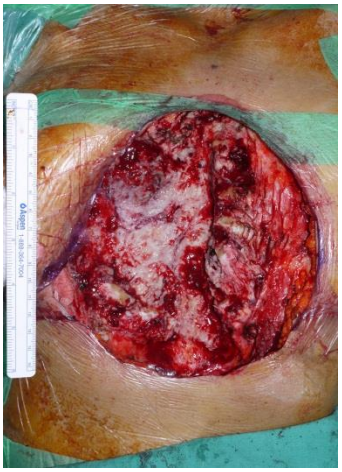

Figure 2A: Wound bed preparation

Figure 2B: Pedicled omental flap and pedicled TRAM flap dehiscence

Figure 2C: Flap inset

Figure 3: Wound breakdown after the first operation

Figure 4: Free latissimus dorsi myocutaneous flap to cover the wound

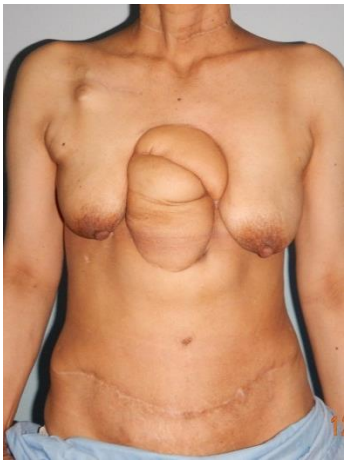

Figure 5: Final result after 1 year post-operatively

Discussion

Most patients with HL present with asymptomatic superficial lymphadenopathy. The usual locations of the disease include cervical (more than 80%), supraclavicular and mediastinal lymph nodes (more than 50%) while sub-diaphragmatic presentations, bone marrow, and hepatic involvement are rare.

Secondary cutaneous HL occurs in 0.5 to 3.4% of cases and is almost always secondary to visceral or nodal involvement. Histologically, it resembles nodal disease [1]. The mechanisms for the skin involvement in HL are unknown but suggested to be retrograde lymphatic spread derived from tumour-involved lymph nodes, direct extension into the skin by tumour cells in underlying lymph nodes, or haematogenous spread of the tumour [6]. The commonest clinical presentation usually involves a single or multiple dermal or subcutaneous nodules. Cutaneous involvement usually denotes stage IV disease, and it carries an ominous prognosis [1].

Our patient demonstrated an exceptional manifestation of mediastinal Hodgkin's lymphoma, an initial appearance with an anterior chest wall ulceration without symptoms of upper airway compression. The invasion to the sternum may have been directly from the anterior mediastinal lymph nodes.

The advent of more effective treatment options has improved the 5-year survival rates (81%) that are unmatched in any other cancers over the past four decades. Every patient with newly diagnosed HL has a possibility of being cured with the proper treatment [5]. However, 20–30% with advanced disease will be refractory to initial treatment. In the management of refractory disease, salvage chemotherapy is used, followed by autologous stem-cell transplantation and high dose chemotherapy [7].

There are several case reports and case series depicting the behaviour and treatment of the cutaneous involvement of HL but none so far describing the incorporation of free tissue transfer in the management of HL [2,4,8,9].

Prior to commencement of surgical management of this patient, histological diagnosis is warranted to rule out different malignancies in patients presenting with a mediastinal mass invading the anterior chest wall. Possible tumours include carcinoma and sarcoma of primary sternal tumour or the breast itself.

The ultimate goal in chest reconstruction is to eliminate dead space, preserve adequate chest wall solidity and deliver coverage while preserving form and function [10].

The chest wall defect can be categorized as superficial and deep whereby the superficial defects that involve only the soft tissues of the chest wall, without exposure of vital structures are comparatively easier to manage and can be treated effectively with skin grafts or local flaps. Full thickness defects exposing bone and cartilage, or even vital structures, for example lungs, heart, or a major vessel, necessitates different reconstructive options [11].

In this patient, the defect was wide, exposing the eroded sternum and adjacent ribs. The wound bed was sloughy with a copious amount of serous discharge. Thus, local infection was treated with regular dressing and all devitalized soft tissues debrided prior to coverage with vascularized soft tissue flaps.

The patient was underweight and cachexic, and not enough tissue bulk was available to fill the defect of a large area within the deep cavity, hence the need for an additional procedure. This was achieved by usage of vascularized omental flap to cover the bottom half of the defects [12].

The supercharged pedicled transverse rectus abdominis muscle flap provides an additional bulk for resurfacing the chest wall and cutaneous coverage to completely seal the defect. Therefore, both flaps were able to be raised through a single incision, involving an adjacent surgical field to the defective area.

The wound dehiscence caused her to lose a quarter of the coverage of the wound subsequently causing the upper part of the initial defect to be exposed due to gravitational effect and wound contraction. The free latissimus dorsi myocutaneous flap was used to salvage the remaining defect. The development of the sinuses on the lateral part of the flaps were treated with regular flushing and frequent dressing changes until it was fully healed.

Post-operatively, the patient was started on brentuximab. It is indicated in relapsed Hodgkin lymphoma and relapsed systemic anaplastic large-cell lymphoma after FDA accelerated approval, based on the result of two single-arm trials [13]. Unfortunately, her disease progressed after completion of four cycles. She was then started on GDC (Gemcitabine, carboplatin, dexamethasone) therapy and the treatment is still on-going. Despite that, she regained part of her quality of life without the troublesome wound on her chest.

Conclusion

Although the cutaneous involvement of Hodgkin lymphoma is rare and the prognosis is thought to be extremely poor, our case among others demonstrates that a good response to current treatment and surgical management does offer an aide in the management of extensive cutaneous involvement in Hodgkin's disease.

References

1. Elder DE, Elenitsas R, Rosenbach M, Murphy GF, Rubin AI, Xu X. Levers Histopathology of the Skin. Wolters Kluwer; 2015
2. Introcaso CE, Kantor J, Porter DL, Junkins-Hopkins JM. Cutaneous Hodgkins disease. Journal of the American Academy of Dermatology. 2008;58(2):295–8.
3. Nishiyama N, Inoue K, Nakatani S, Hamba H, Kinoshita H. Malignant lymphoma presenting as a large mass in the anterior chest wall. Osaka City Medical Journal. 2000 Dec;46(2):105-10.
4. Erkılıç S, Erbağcı Z, Koçer NE, Bayazıt YA, Camcı C. Cutaneous involvement in Hodgkin's lymphoma: report of two cases. The Journal of Dermatology. 2004 Apr;31(4):330-4.
5. Gobbi PG, Ferreri AJ, Ponzoni M, Levis A. Hodgkin lymphoma. Critical Reviews in Oncology/Hematology. 2013 Feb 1;85(2):216-37.
6. Hsia CC, Howson-Jan K, Rizkalla KS. Hodgkin lymphoma with cutaneous involvement. Dermatology Online Journal. 2009 May 1;15(5).
7. Townsend W, Linch D. Hodgkin's lymphoma in adults. The Lancet. 2012 Sep 1;380(9844):836-47.
8. Rich BS, McEvoy MP, Honeyman JN, La Quaglia MP. Hodgkin lymphoma presenting with chest wall involvement: a case series. Journal of Pediatric Surgery. 2011 Sep 1;46(9):1835-7.
9. Dhull AK, Soni A, Kaushal V. Hodgkin's lymphoma with cutaneous involvement. BMJ Case Reports. 2012 Nov 29;2012:bcr2012007599.
10. Losken A, Thourani VH, Carlson GW, Jones GE, Culbertson JH, Miller JI, Mansour KA. A reconstructive algorithm for plastic surgery following extensive chest wall resection. British Journal of Plastic Surgery. 2004 Jun 1;57(4):295-302.
11. Cohen M, Ramasastry SS. Reconstruction of complex chest wall defects. The American Journal of Surgery. 1996 Jul 1;172(1):35-40.
12. Skoracki RJ, Chang DW. Reconstruction of the chest wall and thorax. Journal of Surgical Oncology. 2006 Nov 1;94(6):455-65.
13. de Claro RA, McGinn K, Kwitkowski V, Bullock J, Khandelwal A, Habtemariam B, et al. US Food and Drug Administration approval summary: brentuximab vedotin for the treatment of relapsed Hodgkin lymphoma or relapsed systemic anaplastic large-cell lymphoma. Clinical Cancer Research. 2012 Nov 1;18(21):5845-9.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):891-893.
DOI: 10.28982/josam.652699

Case report
Olgu sunumu

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

A rare case of newly diagnosed multiple myeloma presenting to the emergency department with acute paraplegias

Multipl myelom'un acil servise prezentasyonu

Sunay Yıldırım [1], Selman Yeniocak [1], Mesut Ayer [2], Adem Az [1], Muhammed Furkan Özden [1], Ahmet Demirel [3]

[1] University of Health Sciences, Haseki Training and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey
[2] University of Health Sciences, Haseki Training and Research Hospital, Department of Hematology, Istanbul, Turkey
[3] University of Health Sciences, Okmeydanı Training and Research Hospital, Department of Emergency Medicine, Istanbul, Turkey

ORCID ID of the author(s)

SY: 0000-0003-1268-7113
SY: 0000-0002-1124-396X
MY: 0000-0003-1977-0104
AA: 0000-0002-7204-6185
MFÖ: 0000-0003-1027-0015
AD: 0000-0002-7905-5850

Corresponding author / Sorumlu yazar:
Selman Yeniocak
Address / Adres: Haseki Eğitim ve Araştırma Hastanesi, Sağlık Bilimleri Üniversitesi, Acil Servis, İstanbul, Türkiye
e-Mail: selmanyeniocakacil@hotmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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.

Bu olgu, 28-30 Haziran 2019 tarihli İstanbul 2.Uluslararası Hipokrat Tıp ve Sağlık Bilimleri Kongresi'nde sözlü olarak sunulmuştur.

Published: 12/27/2019
Yayın Tarihi: 27.12.2019

Abstract

Multiple myeloma (MM), neoplastic proliferation of monoclonal plasma cells in bone marrow, constitutes 1% of cancers. We discuss a rare case of newly diagnosed MM presenting to the emergency department with sudden strength loss in both legs and inability to walk, together with the current literature. Impaired balance and 2/5 strength loss in the bilateral lower extremities was determined in a 42-year-old man presenting due to weakness in both legs and inability to walk, noticed on waking in the morning. At blood tests, uric acid was 8.4 mg/dl, total protein 98.8 g/L, globulin 60.8 g/L. Magnetic resonance imaging revealed a mass between T_2 and T_4 vertebrae. At mass biopsy immunohistochemical investigation, lesion cluster of differentiation (CD)38, CD138, endomysial antibody, kappa and lambda cells exhibited immune reactions. Serum IgA was 0.27 g/L, IgM 0.28 g/L, IgG 44.36 g/L, beta-2 microglobulin 4.78 mg/L, lambda light chain 0.230 g/L, and kappa light chain 5.25 g/L. Mass biopsy revealed plasma cell tumor, with atypical plasma cells at 52%, which was compatible with MM at bone marrow aspiration biopsy. Neoplastic plasma cell proliferation should be considered for differential diagnosis in sudden strength loss in the lower extremities.
Keywords: Emergency medicine, Multiple myeloma, Plasmacytoma, Acute paraplegia

Öz

Kemik iliğinde monoklonal plazma hücrelerinin neoplastik proliferasyonu olan multipl myelom (MM), tüm kanserlerin %1'ini oluşturur. Bu yazıda ani gelişen her iki bacakta kuvvet kaybı ve yürüyememe şikayeti ile acil servise müracaat eden hastada tespit edilen ve nadir görülen yeni tanı MM literatür eşliğinde tartışmayı amaçladık. Sabah fark ettiği her iki bacakta kuvvet kaybı ve yürüyememe şikayeti ile acil servise başvuran 42 yaşında erkek hastanın alt ekstremitelerinde 2/5 kuvvet kaybı ile beraber dengesini sağlamada bozukluk tespit edildi. Kan tetkiklerinde ürik asit 8,4 mg/dl, total protein 98,8 g/L, globülin 60,8 g/L olarak tespit edildi. Manyetik rezonans görüntülemede torakal $(T)_2$-T_4 vertebralar arasında kitle izlendi. Kitle biyopsisi immünohistokimyasal çalışmada lezyona ait hücreler cluster of differentiation (CD)38, CD138, endomysial antibody, kappa ve lambda ile immün reaksiyon gösterdiği gözlendi. Serum IgA 0,27 g/L, IgM 0,28 g/L, IgG 44,36 g/L, beta-2 mikroglobulin 4,78 mg/L, lambda hafif zincir 0,230 g/L, kappa hafif zincir 5,25 g/L olduğu tespit edildi. Kitlenin biyopsi incelemesi plazma hücreli tümör, kemik iliği aspirasyon biyopsisi ise MM ile uyumlu ve atipik plazma hücreleri %52 olduğu tespit edildi. Hastada MM düşünüldü. Alt ekstremitelerde ani gelişen kuvvet kaybı şikayetiyle acil servise müracaat eden hastalarda ayırıcı tanıda plazma hücrelerinin neoplastik proliferasyonu olabileceği düşünülmelidir.
Anahtar kelimeler: Acil tıp, Multipl miyelom, Plazmasitom, Akut parapleji

Introduction

Multiple myeloma (MM), the neoplastic proliferation of monoclonal plasma cells in bone marrow, constitutes 1% of all cancers and approximately 10% of hematological malignancies. The most common clinical presentation is bone pain, while pathological fractures, recurrent bacterial infections, and kidney failure are less common. Plasmacytoma is a solitary neoplasm of monoclonal plasma cells [1,2]. Clinical findings associated with spinal cord or nerve-root compression are observed, depending on the location [3]. This report discusses a case of plasmacytoma associated with rare MM determined in a patient presenting to the emergency department with acute onset loss of strength in the bilateral lower extremities and inability to walk, in the light of the current literature.

How to cite / Atıf için: Yıldırım S, Yeniocak S, Ayer M, Az A, Özden MF, Demirel A. A rare case of newly diagnosed multiple myeloma presenting to the emergency department with acute paraplegia. J Surg Med. 2019;3(12):891-893.

Case presentation

A 42-year-old man, from whom verbal consent for this case report was obtained, presented to the emergency department due to loss of strength in the bilateral lower extremities and inability to walk, which he noticed on waking in the morning. On arrival, the patient's general condition was average, he was lucid and cooperative, and vital signs were normal. No history of disease or trauma was present. He described a sensation of numbness in the bilateral plantar regions at night, followed by onset of pain in the bilateral proximal of the lower extremities, but he was able to walk with support. By morning he reported becoming unable to walk or to support his body weight in a standing position. He also reported that the feeling of numbness in the soles experienced at night had spread as far as the umbilical region. The patient reported no urine or fecal incontinence. Physical examination revealed 2/5 loss of strength in the bilateral lower extremities and impaired balance, as if the patient were about to fall forward from a standing position. Deep tendon reflexes were hyperactive in the bilateral lower extremities. At blood tests, uric acid was 8.4 mg/dl (range 3.5-7.2), creatinine 0.99 mg/dl (range 0.67-1.17), calcium (Ca^{++}) 9.9 mg/dl (range 8.4-10.5), potassium (K^{+}) 3.7 mEq/L (range 3.5-5.1), total protein 98.8 g/L (range 66-83), albumin 38 g/L (range 35-52), globulin 60.8 g/L (range 15-37), lactate dehydrogenase (LDH) 285 U/L (range <247), C-reactive protein (CRP) 27 mg/L (range 0-5), sedimentation 38 mm/hour (range 0-30), and hemoglobin 13.6 g/dl (range 14.1-18.1). No pathology was determined in the cranial computerized tomography (CT) or magnetic resonance imaging (MRI). Spinal CT revealed extensive medullary lytic lesions in the cervical $(C)_7$, and thoracic $(T)_{2,4, \text{ and } 11}$ vertebrae, in all lumbar vertebrae, in the bilateral ileac bones and the sacrum. Spinal MRI revealed a mass lesion, T1 hypointense and T2 mildly hyperintense, with contrast involvement, 5 cm in length and with an anteroposterior diameter of 9.2 mm, compressing the cord from the right posterolateral to the anterior region, with an extra-axial location in the right half of the posterior spinal canal at the T_2 vertebra level, extending inferiorly to the T_4 vertebra level. Nodular lesions, T1 hypointense and T2 hyperintense, and exhibiting contrast involvement, were observed in the $T_{10,11}$ vertebral corpi (Figure 1). The patient was transferred to the neurosurgery department for surgery. Biopsy material was collected with excision of the thoracic intradural extramedullary mass and sent to the pathology laboratory. The relation with MM was investigated in consultation with the hematology department. Peripheral smear result was reportedly normal. At immunohistochemical study, cells from the lesion exhibited cluster of differentiation (CD) 38, CD138, endomysial antibody (EMA), and immune reaction with kappa and lambda. Serum IgA was 0.27 g/L (range 0.7-4), IgM 0.28 g/L (range 0.4-2.3), IgG 44.36 g/L (range 1-16), beta-2 microglobulin 4.78 mg/L (range 0,8-2,4), serum free kappa light chain 5.25 g/L (range 1,7-3,7), and serum free lambda light chain 0.230 g/L (range 0.9-2.1). Lambda light chain in 24-h urine was <3.720 mg/L (range <10), and the kappa light chain value was <6.690 mg/L (range <15). The mass biopsy was reported as an IgG/Kappa monotypic plasma cell tumor. Bone marrow aspiration was compatible with MM, and atypical plasma cells were determined at 52% (Figure 2). Plasmacytosis arising from MM was suspected, and the patient was discharged with polyclinic treatment and follow-up.

Figure 1: Plasmocytoma transverse (a), sagittal (b) and vertebral nodular lesion (c) images at MRI

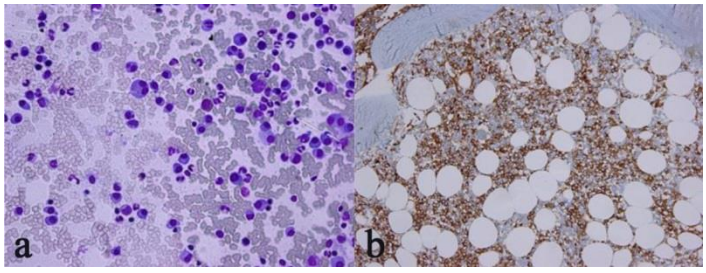

Figure 2: a) Plasma cells in bone marrow aspiration biopsy preparate (Giemsa X400) and b) IgG involvement (immunohistochemical X400)

Discussion

Plasma cell tumors arise from B-lymphocytes as a result of the proliferation and accumulation of plasma cells that synthesize immunoglobulin [4]. These include MM, monoclonal gammopathy of undetermined significance, plasma cell leukemia, solitary plasmacytoma, Waldenström macroglobulinemia, primary amyloidosis (AL), heavy chain disease, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, M Protein, and Skin Changes) syndrome, Type I and II cryoglobulinemia, and light chain deposition disease [5,6]. MM is a lymphoproliferative disease that causes malignant proliferation of immunoglobulin-secreting plasma cells which most commonly involves bone marrow (42%). The annual incidence in the USA is 3-4/100,000 [7]. Although not enough is known about the etiology, chronic exposure to viral agents and radiation has been implicated [8]. No etiological cause was determined in our patient.

The most commonly involved bones in MM are the vertebrae in particular, along with the calvarium, pelvis, rib, scapula, humerus and femur [9,10]. Diffuse involvement was observed in the vertebral column in our patient. The most common findings in MM are osteolytic bone lesions, osteoporosis, and resultant pain. Anemia-related symptoms and findings, infections resulting from immune paralysis, a disposition to hemorrhage due to various types of hemostasis impairment, polyneuropathy, paraplegia and quadriplegia

resulting from vertebral fractures, root compression symptoms, symptoms of hyperviscosity syndrome, and hyperuricemia may also be seen [11]. Despite the absence of back pain, we attributed the acute onset pain and strength loss in the bilateral lower extremities to spinal cord compression due to spinal plasmacytosis. Hyperuricemia was also present, but no bone fracture was determined.

Direct radiography is still the primary diagnostic technique in determining destructive osseous lesions in the diagnosis of MM. Small, distinct lytic lesions with well-demarcated margins, and staple-like holes are observed at radiography. CT is a more sensitive diagnostic technique in showing osseous lesions. Lytic lesions at CT exhibit expansile masses with a soft tissue component, diffuse osteopenic bone fractures, and osteosclerosis. MRI assists CT in terms of mass staging and spread [12]. No pathology was observed at x-ray in our case, while CT revealed medullar lytic lesions, and MRI revealed a spinal mass and nodular lesions.

Plasmacytoma constitutes 3% of plasma cell disorders. Clinical findings vary, depending on the location, while laboratory findings are similar to those of MM. However, prognosis is better in comparison to MM [13]. It frequently involves the thoracolumbar region, and particularly the vertebral body [14]. The lesion arises from regions of bone marrow function. Diagnosis is confirmed by tissue biopsy in addition to clinical and laboratory findings, as in the present case [15].

With the spread of plasma cells in bone marrow caused by myeloma, it restricts erythropoiesis, while generally normocytic normochromic anemia or rarely macrocytic or microcytic anemia occur as a result of obstruction of erythropoiesis by means of release of interleukin-6 by bone marrow stromal and endothelial cells. Hypercalcemia is an important finding of diagnostic value in myeloma, measures the tumor burden and indicates organ damage, and is seen in 18-30% of cases. Increases in creatinine values exceeding 2 mg/dl are seen in 25% of patients with MM at time of diagnosis. In other words, kidney failure of varying degrees of severity is present in approximately half of patients. Serum LDL elevation is seen in between 7% and 11% of newly diagnosed MM cases. Myeloma plasma cells exhibit CD 38-, CD 138-, and CD 79a-positivity [15]. Mild, asymptomatic anemia was present in our patient. No hypercalcemia or kidney failure were observed, but LDL levels were elevated. Myeloma plasma cells also exhibited immune reaction with CD38 and CD138.

Diagnostic criteria for MM were revised by the International Myeloma Working Group (IMWG) in 2014, and were defined as clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary and serum M protein (monoclonal immunoglobulin) IgG ≥3 g/dL, IgA >1 g/dL and presence of a myeloma-defining event, in other words, one or more CRAB features or findings (elevated serum calcium level, renal failure, anemia, and bone lesions) or one or more SLiM criteria (clonal bone marrow plasma >60%, involved/uninvolved serum-free light chain ratio >100, presence of more than one focal lesion 5 mm in size or larger at whole-body MRI) [16]. Our patient was assessed as stage 2 according to the International Staging System.

In addition to various classic chromosome analysis tests, structural changes in chromosomes, which are related to risk levels in MM patients, can be determined using molecular cytogenetic tests such as polymerase chain reaction and fluorescent in situ hybridization. Chemotherapy and autologous stem cell transplantation are performed in the treatment of MM. Prognosis depends on various factors, but is generally poor [16].

Conclusion

The possibility of neoplastic proliferation of plasma cells should be considered for differential diagnosis in patients presenting to the emergency department with sudden onset loss of strength in the lower extremities and no history of trauma.

References

1. Rajkumar SV. Multiple myeloma. Curr Probl Cancer. 2009 Jan-Feb;33(1):7-64.
2. Bolaman AZ. Diagnosis of multiple myeloma and criteria for response. Turkiye Klinikleri J Hem Onc Special Topics. 2008 July;1:1-4.
3. Günçag D. Hemolitik Anemiler. In: Dinçol G, Pekçelen Y, Atamer T, Sargın D, Nalçacı M, Aktan M, Beşışık SK, Eds. Klinik Hematoloji, İstanbul: Nobel Tıp Kitabevi. 2003:87-152.
4. Tesei F, Caliceti U, Sorrenti G, Canciullo A, Sabbatini E, Pileri S, et al. Extramedullary plasmocytoma (EMP) of the head and neck: a series of 22 cases. Acta Otorhinolaryngol. 1995 Dec;15:437-42.
5. International Myeloma Working Group. Criteria for the classifi cation of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol. 2003 Jun;121:749-57.
6. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratifi cation and response assessment of multiple myeloma. Leukemia. 2009 Jan;23:3-9.
7. Oymak FS, Karaman A, Soyuer I, Karaman H, Gülmez I, Demir R, et al. Multipl Miyelomada Akciğer ve Göğüs Duvarı Tutulumu. Tüberküloz ve Toraks Dergisi. 2003 Jan;51(1):27-32.
8. Ersoy O, Sanlier T, Yigit O, Halefoglu AM, Ucak S, Altuntaş Y. Extramedullary plasmacytoma of the maxillary sinus. Acta Otolaryngol. 2004 Aug;124:642-44.
9. Kocaeli H, Köseoğlu BG, Bilgiç B. Mandibulada Multiple Myeloma (İki Olgu Sunumu) AÜ Diş Hek Fak Derg. 2005 Apr;32(2):135-45.
10. Önal MB, Kırçelli A, Civelek E. (2018). Solitary involvement of multiple myeloma in the upper thoracic spine, and anterior approach to thoracic region without full sternotomy: A case report. Journal of Surgery and Medicine. 2018 Sept;2(3):403-5.
11. Alkan Ö, Kızılkılıç E, Yıldırım T, Kasar M, Kızılkılıç O, Yeral M, et al. Multipl Myelomda İntrakranial Tutulum. Türk Nöroloji Dergisi. 2008 Oct;14(5):328-32.
12. Angtuaco EJ, Fassas AB, Walker R, Sethi R, Barlogie B. Multiple myeloma: clinical review and diagnostic imaging. Radiology. 2004 Apr;231(1):11-23.
13. Di Micco P, Di Micco B. Up-date on solitary plasmacytoma and its main differences with multiple myeloma. Exp Oncol. 2005 Mar;27(1):7-12.
14. Cervoni L, Celli P, Salvati M, Tarantino R, Fortuna A. Solitary plasmacytoma of the spine: Relationship of IgM to tumor progression and recurrence. Acta Neurochir (Wien). 1995 Sep;135(3-4):122-5.
15. İliçin G, Biberoğlu K, Süleymanlar G, Ünal S (ed). İç Hastalıkları. 2rd ed. Güneş Kitabevi. 2003;1943-9.
16. Türk Hematoloji Derneği Multipl Myelom Tanı ve Tedavi Kılavuzu. Sürüm 1. 02-Ekim, 2016;1-4.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):894-897.
DOI: 10.28982/josam.600546

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

Undiagnosed placenta previa percreta presenting as an obstetric emergency to the district hospital with inexperienced surgeons: Case report and review of the literature

İlçe hastanesine obstetrik acil olarak başvuran tanı konulmamış plasenta previa perkreata: Vaka sunumu ve literatürün gözden geçirilmesi

Erhan Okuyan [1], Zeynep Bayramoğlu [2], Fethi Karakaya [1]

[1] Department of Obstetrics and Gynecology, Batman Maternity and Child's Health Hospital, Batman, Turkey
[2] Department of Pathology, Konya Education and Research Hospital, Konya, Turkey

ORCID ID of the author(s)
EO: 0000-0001-9636-9539
ZB: 0000-0001-7075-8819
FK: 0000-0001-5620-6794

Corresponding author / Sorumlu yazar:
Zeynep Bayramoğlu
Address / Adres: Konya Eğitim ve Araştırma Hastanesi, Patoloji Anabilim Dalı, Konya, Türkiye
e-Mail: drzeynepbayramoglu@hotmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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: 12/28/2019
Yayın Tarihi: 28.12.2019

Abstract

Placenta previa, a placental implantation anomaly where the placenta is located close to the internal os, has an incidence of 0.5%. One of the most important complications of placenta previa is the presence of placenta percreta. Nowadays, the incidence of placenta percreta has increased due to the increase in the number of cesarean sections. Maternal morbidity in such cases comprise massive transfusion, development of disseminated intravascular coagulation, uterine rupture, cystostomy, fistula formation, ureteral stricture, intensive care unit admission, infection, prolonged hospitalization, adult respiratory distress syndrome, renal failure, septicemia and even death. The aim of this research is to report how the inexperienced surgeons who were caught unprepared reacted in the case of undiagnosed placenta previa percreta. We aimed to make this case report a guide to saving the life of mother with placental previa percreta and baby under inadequate hospital conditions. Similar cases may be encountered by every young surgeon at any time.

Keywords: Cesarean Hysterectomy, Undiagnosed plasenta previa percreta, Inadequate Hospital Conditions

Öz

Plasenta previa, plasentanın servikal internal os'a yakın olduğu ve insidansının %0,5 olarak bildirildiği plasenta implantasyonu anomalisidir. Plasenta previa'nın en önemli komplikasyonlarından biri plasenta perkreata'nın eşlik etmesidir. Dünyada yapılmaya devam eden primer sezaryen nedeniyle plasenta previa perkreata insidansı artmaktadır. Plasenta previa perkreata tanısı konulan olgularda; maternal ve fetal morbidite ve mortalite çok yüksektir ve çoklu organ yetmezliğine ilerleyebilecek yıkıcı olaylara neden olabilir. Bu araştırma tanı konmamış plasenta previa perkreata durumunda; hazırlıksız ve deneyimsiz yakalanan cerrahların nasıl tepki verdiğini rapor etmeyi amaçlamaktadır. Bu olgu sunumunu; yetersiz hastane koşullarında her genç cerrahın her an karşılaşabileceği tanı konmamış plasenta previa perkreata vakalarında anne ve bebeğin hayatını kurtarmak için bir rehber haline getirmeyi amaçladık.

Anahtar kelimeler: Sezaryen Histerektomi, Tanı konulmamış plasenta previa perkreata, Yetersiz hastane koşulları

Introduction

Placenta previa, a placental implantation anomaly where the placenta is located close to the internal os, has an incidence of 0.5%. One of the most important complications of placenta previa is the presence of placental percreta. Nowadays, the incidence of placenta percreta has increased due to the increase in the number of cesarean sections. Accurate prenatal diagnosis and implementation of preplanned management strategies of abnormally invasive placentation is fundamental because it has been shown to reduce maternal and fetal morbidity associated with this condition, such as severe hemorrhage, need for blood transfusion, peripartum hysterectomy, intraoperative and postoperative complications [1,2]. Intra- and postsurgical outcomes of women affected by abnormally invasive placentation are directly related to the depth and topography of placental invasion in placenta percreta. Those showing parametrial invasion are at the highest risk of morbidity [3,4]. The placenta begins to form 13-15 days after ovulation. With the onset of the fetal period, the villi covering the decidua capsularis degenerate to form the chorion leave, while the villi above the decidua basalis proliferate to form the placenta. Normal implantation of the placenta is necessary for successful pregnancy and is regulated very strictly by cytokines, steroid hormones, immunological factors, prostaglandins, and some other mediators. Placental adhesion anomalies are characterized histopathologically by defects in the decidua or fibrous Nitabuch layer and penetration of trophoblasts into the myometrium and adjacent organs. There are three different subtypes of trophoblasts depending on the depth of invasion. In placenta accreta vera, the placenta invades the decidual layer of the myometrium [5].

How to cite / Atıf için: Okuyan E, Bayramoğlu Z, Karakaya F. Undiagnosed placenta previa percreta presenting as an obstetric emergency to the district hospital with inexperienced surgeons: Case report and review of the literature. J Surg Med. 2019;3(12):894-897.

In placenta increta, placental villi invade more deeply within the myometrium [6]. Placenta percreta is diagnosed when the placenta invades the serosa and even beyond, in some cases. Placenta accreta is diagnosed in about 1:533 pregnancies among which placenta accreta vera constitutes about 75%-80%, placenta increta, 17%, and placenta percreta, the remaining 5%. Overall, the incidence of placenta percreta is extremely low but the diagnosis of this rare disorder is increasing due to the increased number of cesarean deliveries performed in the past few years globally [6]. In cases where placenta percreta is complicated by bladder invasion, mortality rates can be as high as 9.5% and 24% among mothers and newborns, respectively. Both ultrasonography and MRI have good sensitivity and specificity for prenatal diagnosis of placenta accreta. According to American College of Obstetricians and Gynecologists, cesarean hysterectomy is the widely acknowledged method to manage placenta accreta spectrum, during which the placenta is left in situ after delivery of the fetus because any attempts to remove the placenta is associated with a substantial danger of hemorrhage. Another way to manage placenta percreta includes the conservative approach, where the uterus and the placenta are left in-situ at time of cesarean delivery, which was shown to decrease blood loss, the need for transfusion, and the incidence of disseminated intravascular coagulation through uterus involution [7,8]. We wanted to shed light on the rare case of placenta previa percreta, which was overlooked in the population with low health literacy despite having regular pregnancy controls. The presented case is highly interesting in our opinion, since the patient is referred to the hospital from 70 kilometers far with the diagnosis of placental detachment and the surgeons who accept the case urgently began the operation without preparation for this fatal case. It also includes the surgeons who were caught unprepared for the case and who made the right decision of cesarean hysterectomy and the events that followed until discharge.

Case presentation

A 31-year-old patient who had previously delivered by cesarean section twice was referred to Batman Maternity and Children's Diseases Hospital by ambulance from the district hospital approximately 70 kilometers away with a preliminary diagnosis of detached placenta. On admission, the patient was semi-conscious, had excessive vaginal bleeding with an arterial blood pressure of 70/40 mmHg. The ultrasonographic examination performed on arrival revealed a live breech-like fetus with a fetal heart rate of 90 beats/minute whose measurements were consistent with approximately 36-37 weeks of gestation. The placenta had completely blocked the cervical internal os and the anterior bladder uterine line was not clearly visualized. In doppler ultrasonography, there were many lacunae in the placenta along with hypervascularized areas, and the sonolucent area between the placenta and myometrium was undistinguishable. Placenta previa percreta was considered for preliminary diagnosis. The second surgeon was called for immediate assistance, blood and blood products were urgently prepared before surgery. Cystostomy could not be performed due to lack of time and equipment. The abdomen was entered through an umbilical median incision, and the placenta was observed to have invaded the uterus with full thickness at the uterine cervical line and bladder border. Uterus was vertically incised, and a single live 3000-gram-weighing female baby was delivered, after which placenta and its attachments were left in. After placental cord ligation, we decided on performing hysterectomy, however, on the second look, we observed that the placenta invaded the bladder and uterine serosa, former incision scars could not be visualized and intestinal adhesions were present at the level of bilateral uterine arteries (Figure 1). The bladder was separated from the uterus by sharp dissections after bleeding control. Upon the arrival of the desired blood and blood products at the 40th minute of the operation, blood transfusion was initiated. The bladder was filled with approximately 200 ml of methylene blue and checked for bladder injury. After making sure there was no bladder damage, intestinal adhesions were divided by sharp dissection at the level of uterine arteries. Bilateral ureters were visualized by retroperitoneal dissection, and finally hysterectomy was started at the 80th minute of operation. Two hours into the surgery, hysterectomy was performed (Figure 2). After bleeding control and checking for bladder damage, parietal peritoneum, fascia, and skin were closed anatomically and the patient was hospitalized at the gynecology service. The operation took 2.5 hours and 4 units of erythrocyte suspension and 1 unit of fresh frozen plasma were transfused. The patient's hemoglobin value was 6.7 mg/dL at the first postoperative hour, and vital signs were stable. Macroscopic examination of serial uterine sections revealed a placenta-like irregular hemorrhagic tissue with a size of 9x8x4.5 cm fully invading the uterine wall. Upon microscopic examination, the placental villi were observed to interdigitate directly with the uterine myometrium, without an intervening decidual plate. On the first postoperative day, 5 units of erythrocyte suspension and 1-unit fresh frozen plasma were transfused, and the patient was mobilized at 8th postoperative hour. On the 2nd postoperative day, the hemodynamically stable patient had passed gas and stool, and her bladder catheter was removed after bladder exercise. The patient was discharged on the third postoperative day after hemodynamic stability was observed for 48 hours with no complications.

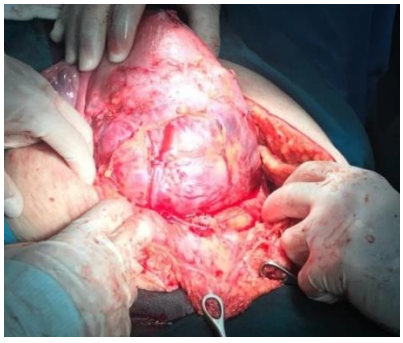

Figure 1: Placenta previa percreta with bladder invasion

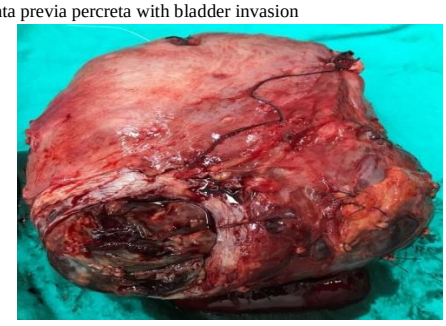

Figure 2: Hysterectomy material

Discussion

Medline, PubMed and Cochrane databases were scanned for randomized controlled trials in undiagnosed placenta previa percreta. Written informed consent was obtained from the patient.

Based on the literature, the risk factors for abnormal invasive placentation(AIP) include obesity, age >35 years, smoking before or during pregnancy, prior uterine surgery, abortion and uterine curettage, in vitro fertilization (IVF) pregnancy, little time interval between a previous cesarean section (CS) and a subsequent pregnancy, placenta previa and prior CS, the latter two being the strongest risk factors for the occurrence of AIP according to the meta-analysis of Iacovelli et al. [9] in 2018. Placenta percreta is the most uncommon and dangerous form of abnormal placentation and most common cause of hysterectomies associated with childbirth. The diagnosis of this condition can be made during pregnancy by ultrasound and/or magnetic resonance imaging (MRI). MRI is not the first-choice examination due to high cost, lesser accessibility, and inconvenience. It is mostly used when the diagnosis of placenta percreta cannot be confirmed or denied by ultrasound examination, as well as before planned surgical treatment. MRI is now described as an examination that better predicts topography and placental tissue invasion [10]. A meta-analysis including 876 articles with large case series published by D'Antonio et al. in 2018 identified that the most common ultrasonographic features of placenta accreta in the first trimester of pregnancy were low implantation of the gestational sac close to a previous uterine scar, which was observed in 82.4% (95% CI, 46.6–99.8%) of cases, and anechoic spaces within the placental mass (lacunae), which was observed in 46.0% (95% CI, 10.9–83.7%) [11]. The presence of lacunar spaces (irregular vascular areas similar to “Swiss cheese” in the placental implantation area) within the placenta and an increase in their number during 15–20th weeks of pregnancy are highly significant predictive signs of placenta accreta (79% sensitivity and 92% positive predictive value). The more lacunar spaces are present, the more likely the placental invasion into the nearby tissue [12]. The criteria of placental invasion as seen in Doppler ultrasonography include abnormal hypervascularization of the tissue (myometrium and the bladder gap), enlarged diffusion lacunar spaces throughout the whole placenta reaching the myometrium and the cervix, low resistance of arterial blood flow, increased venous flow to blood vessels, and the locally extinct vascular tone in the hypoechogenic sub-placental gap. It is incredibly important to identify pathological blood flow between the uterus and the bladder wall. This is one of the best indicators for the invasive placental abnormalities. The sensitivity and specificity of color Doppler imaging in the diagnosis of placenta previa accreta are reportedly 82.4% and 96.8%, respectively, with an 87.5% positive and a 95.3% negative predictive value [13]. A novel pathological feature of abnormal fetal vasculature in placenta accreta spectrum disorders (PASD) was described by Konstantinidou et al. [14] in 2019. The histopathological examination of eleven PASD- hysterectomy specimens and subsequent review of the corresponding MRIs revealed the presence of large fetal vascular trunks extending deep towards the placental periphery, demonstrating deficient branching along their course ('stripped-fetal-vessel' sign). To their knowledge, this was the first report to describe the pattern of abnormal fetal vasculature in correlation with MRI in PASD. The management is usually an elective cesarean delivery with hysterectomy, but this approach often causes massive hemorrhage and may cause injury to the adjacent organs due to the morbidly adherent placenta, thus should be performed under multidisciplinary conditions with experienced surgical teams. Conservative management is usually followed by uterine and pelvic devascularization to reduce risk of bleeding. Placental tissue is either allowed to undergo spontaneous autolysis or its expulsion is aided with methotrexate. These patients are at elevated risk of emergency peripartum hysterectomy due to uncontrolled secondary postpartum hemorrhage, severe sepsis due to uterine infection and placental necrosis. Most publications in the literature include surgical procedures performed under elective conditions.

Our literature search revealed no large case series on the emergency management and resulting complications of placenta percreta by inexperienced surgeons. In 2019, Stanleigh et al. [15] compared elective management using the ProActive peripartum multidisciplinary approach (PAMA) with urgent management of their PASD series of 72 cases. PAMA protocol eliminated urgent deliveries and reduced the associated significant hemorrhage-related maternal morbidity, with no increase in the rate of hysterectomy or adverse neonatal outcome. Maternal mortality rate in the literature was %7-10, except for one article from India by Aggarwal et al. [16], in which it was noted as %30. The author attributed this high rate to the population of patients with low socioeconomic status, as there were no previous scans and no regular follow-up. As long as primary cesarean rates continue to increase, we will likely encounter more difficult cases, such as isthmoceles and placental adhesion abnormalities, more frequently [17]. In our case, we confirmed the diagnosis of the patient with a preliminary diagnosis of placental detachment at the district hospital during the operation. Although there was no urology specialist, vascular surgeon or intensive care unit in our hospital, we managed to save the mother and the baby by performing emergency surgery under our current conditions. We aimed to make this case report a guide to saving the life of mother with placental previa percreta and the baby under inadequate hospital conditions. Similar cases can be confronted by every young surgeon at any time.

Conclusion

Undiagnosed placenta previa percreta is a serious, life-threatening condition. Early preoperative diagnosis is the key to saving the patient’s life. A tertiary-level hospital has greater antenatal diagnostic and management tools. Increasing health literacy in patients primarily in developing countries will play a life-saving role in such mortal cases. Previous cesarean section is an important risk factor of placental invasion abnormalities thus there is a need to keep the primary cesarean section rates down. Placenta previa percreta should be managed in tertiary centers and operated under elective conditions with multidisciplinary experienced teams.

References

1. Sumigama S, Itakura A, Ota T, Okada M, Kotani T, Hayakawa H, et al. Placenta previa increta/percreta in Japan: a retrospective study of ultrasound findings, management, and clinical course. J Obstet Gynaecol Res. 2007;33:606–11.
2. Tikkanen M, Paavonen J, Loukovaara M, Stefanovic V. Antenatal diagnosis of placenta accreta leads to reduced blood loss. Acta Obstet Gynecol Scand. 2011;90:1140–6.
3. Oyelese Y, Smulian JC. Placenta previa, placenta accreta, and vasa previa. Obstet Gynecol. 2006;107:927–41.
4. Belfort MA. Placenta accreta. Am J Obstet Gynecol. 2010;203:430–9.
5. Ibrahim MA, Liu A, Dalpiaz A, Schwamb R, Warren K, Khan SA. Urological Manifestations of Placenta Percreta. Curr Urol. 2015;8(2):57-65.
6. Hudon L, Belfort MA, Broome DR. Diagnosis and management of placenta percreta: a review. Obstet Gynecol Surv. 1998;53:509–17.
7. Wright JD, Pri-Paz S, Herzog TJ. Predictors of massive blood loss in women with placenta accreta. Am. J. Obstet. Gynecol. 2011;205(38):1-6.
8. Sentilhes. Maternal outcome after conservative treatment of placenta accreta. Obstet. Gynecol. 2010;115(3):526–34.
9. Iacovelli A, Liberati M, Khalil A, Timor-Trisch I, Leombroni M, Buca D, et al. Risk factors for abnormally invasive placenta: a systematic review and meta-analysis. J Matern Fetal Neonatal Med. 2018 Jul;22:1-11. DOI:10.1080/14767058.2018.1493453.
10. Berkley EM, Abuhamad AZ. Prenatal Diagnosis of Placenta Accreta Is Sonography All We Need? Ultrasound Med. 2013;32:1345–50.
11. D'Antonio F, Timor-Tritsch IE, Palacios-Jaraquemada J, Monteagudo A, Buca D, Forlani F, et al. First-trimester detection of abnormally invasive placenta in high-risk women: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2018Feb;51(2):176-83. DOI: 10.1002/uog.18840. Review.
12. Rac MW, Dashe JS, Wells CE, Moschos E, McIn-tire DD, Twickler DM. Ultrasound predictors of placental invasion: the Placenta Accreta Index. Am J Obstet Gynecol. 2015 Mar;212(3):343:e1-7.
13. Chou MM, Ho ESC, Lee YH. Prenatal diagnosis of placenta previa accreta by transabdominal color Doppler ultrasound. Ultrasound Obstet Gynecol. 2000;15:28–35.
14. Konstantinidou AE, Bourgioti C, Fotopoulos S, Souka E, Nikolaidou ME, Zafeiropoulou K, et al. Stripped fetal vessel sign: a novel pathological feature of abnormal fetal vasculature in placenta accreta spectrum disorders with MRI correlates. Placenta. 2019 Jul 9. pii: S0143-4004(19)30515-6. DOI: 10.1016/j.placenta.2019.07.005.
15. Stanleigh J, Michaeli J, Armon S, Khatib F, Zuckerman B, Shaya M, et al. Maternal and neonatal outcomes following a proactive peripartum multidisciplinary management protocol for placenta creta spectrum as compared to the urgent delivery. Eur J Obstet Gynecol Reprod Biol. 2019 Jun;237:139-44. doi: 10.1016/j.ejogrb.2019.04.032. Epub 2019 Apr 19.
16. Aggarwal R, Suneja A, Vaid NB, Yadav P, Sharma A, Mishra K.Morbidly adherent placenta: a critical review. J Obstet Gynaecol India. 2012 Feb;62(1):57-61. DOI: 10.1007/s13224-012-0149-5.Epub 2012 Apr 20.
17. Karlı P, Şahin B, Kara F. The incidence of isthmocele may be higher than reported. J Surg Med. 2018;2(3):283-7.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):898-899.
DOI: 10.28982/josam.598062

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

Complete scintigraphic resolution of a bone metastasis after androgen-deprivation therapy

Androjen-Deprivasyon tedavisi ile regrese olan kemik metastazının sintigrafik değerlendirmesi

Derya Çayır [1], Mehmet Bozkurt [1], Salih Sinan Gültekin [1], Aynur Turan [2]

[1] University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital, Nuclear Medicine Department, Ankara, Turkey
[2] University of Health Sciences Dışkapı Yıldırım Beyazıt Training and Research Hospital, Radiology Department, Ankara, Turkey

ORCID ID of the author(s)
DÇ: 0000-0002-7756-3210
MB: 0000-0002-8325-5249
SSG: 0000-0003-2458-3530
AT: 0000-0001-6654-3129

Corresponding author / Sorumlu yazar:
Derya Çayır
Address / Adres: Sağlık Bilimleri Üniversitesi Dışkapı Yıldırım Beyazıt Eğitim ve Araştırma Hastanesi, Nükleer Tıp Bölümü, 06110, Ankara, Türkiye
e-Mail: drderyaors@hotmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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.

This study was accepted as an e-poster at the 30th Annual National Congress of Turkish Association of Nuclear Medicine, April 2018, Antalya, Turkey.

Published: 12/28/2019
Yayın Tarihi: 28.12.2019

Abstract

^{99m}Tc-methylene diphosphonate (MDP) whole body bone scintigraphy is a frequently used imaging method for the evaluation of the bone metastases of prostate cancer. Nuclear medicine imaging modalities are very valuable in terms of functional assessment and treatment response assessment of the malign lesions that cannot be detected by anatomic imaging methods. However, it is known that some scintigraphic studies may have a relatively limited role in defining resolution and anatomical details of the lesion, compared to some radiological imaging modalities. Androgen-deprivation therapy (ADT) alone is rarely effective for the treatment of bone metastases, on that account combined systemic therapies are often preferred. Here we present a rare case of prostate cancer with radiologically undetectable bone metastasis evident on scintigraphy that has disappeared after 18 months of ADT.

Keywords: Whole body scan, Prostate cancer, Metastasis, Tomography

Öz

^{99m}Tc-metilen difosfonat (MDP) tüm vücut kemik sintigrafisi prostat kanserinin kemik metastazlarını değerlendirmede sıklıkla kullanılmaktadır. Anatomik görüntüleme yöntemleri ile saptanamayan malign lezyonların fonksiyonel olarak izlenebilmesi ve tedaviye yanıtının değerlendirilebilmesi açısından nükleer tıp tetkikleri çok değerlidir. Bununla birlikte sintigrafik yöntemlerin rezolüsyon ve anatomik detayları belirlemede bazı radyolojik tetkiklere göre sınırlı olabildiği bilinmektedir. Kemik metastazlarının tedavisinde sıklıkla kombine sistemik tedaviler tercih edilmekte olup, androjen-deprivasyon tedavisi (ADT) tek başına nadiren etkilidir. Burada bilgisayarlı tomografi ile saptanamayan, 18 ay ADT ile regrese olan kemik metastazlı nadir prostat kanserli bir olguyu sunuyoruz.

Anahtar kelimeler: Tüm vücut görüntüleme, Prostat kanseri, Metastaz, Tomografi

Introduction

The most common indication of ^{99m}Tc-MDP bone scintigraphy is to detect osteoblastic bone metastases of various malignities. It is cost-effective, accessible, without known contraindications, and highly sensitive [1]. Since metabolic changes in bone show up earlier than anatomical changes, bone scintigraphy may detect bone pathologies sooner than anatomic imaging modalities [2]. We herein present a case with prostate cancer who had a radiologically undetectable bone metastasis evident on scintigraphy which disappeared after androgen-deprivation therapy (ADT).

How to cite / Atıf için: Çayır D, Bozkurt M, Gültekin SS, Turan A. Complete scintigraphic resolution of a bone metastasis after androgen-deprivation therapy. J Surg Med. 2019;3(12):898-899.

Case presentation

A 68 year-old male patient diagnosed with prostate adenocarcinoma (Gleason score 4 + 5) was admitted to our department. He presented with high serum prostate-specific antigen level [(PSA): 43.17 ng/mL (N:0-4)]. 99mTc-MDP in whole-body bone scintigraphy and Single Photon Emission Computed Tomography (SPECT) imaging revealed a focal activity in the coccygeal area (Figure 1). Computed tomography (CT) was performed for accurate differential diagnosis of possible sacrum fractures. Trauma history was insistently questioned, no history of trauma was evident in anamnesis. There was no significant finding on CT, except for degenerative changes in the sacroiliac region (Figure 2). ADT was initiated after the diagnosis of sacral metastasis. After 18 months of treatment, serum PSA level decreased to 1.1 ng/mL, and the 99mTc-MDP whole body bone scintigraphy revealed no lesions in the coccygeal area (Figure 3). A written informed consent was obtained from the patient.

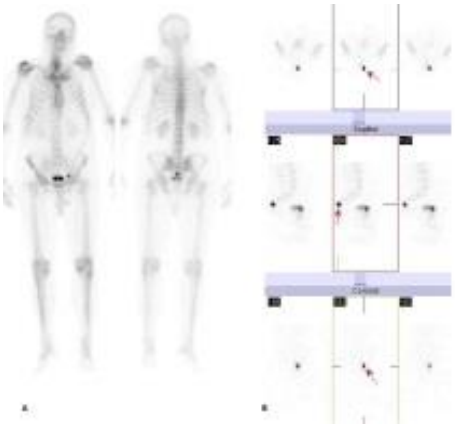

Figure 1: ^{99m}Tc-MDP in whole-body bone scintigraphy (A) and Single Photon Emission Computed Tomography (SPECT) (B) imaging showed a focal activity in the coccygeal area (arrows)

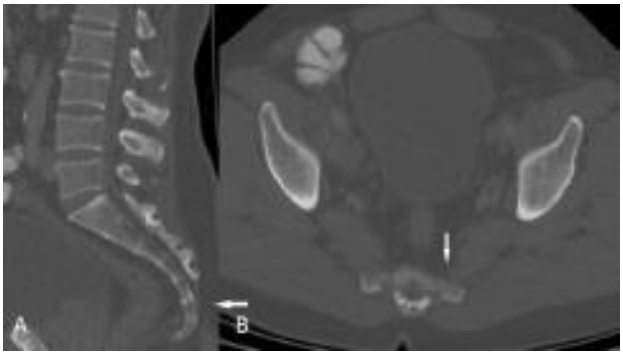

Figure 2: Computed tomography (CT) revealed no significant finding except degenerative changes in the sacroiliac region (A; sagittal plane, B; transaxial plane, arrows).

Figure 3: ^{99m}Tc-MDP whole body bone scintigraphy revealed no lesion in the coccygeal area

Discussion

Prostate cancer is the most common malignancy in elderly men [3]. Ordinarily, the skeletal system is the most frequent target of metastases in castration-resistant prostate cancer, with an estimate of involvement around 90% [4]. On account of suspected bone metastases, high PSA level is an important, widely available serum marker. A serum PSA level above 10 ng/ml, and/or a Gleason score above 8 should prompt investigation for bone metastases [5]. Radiologic imaging modalities, such as CT and magnetic resonance imaging (MRI) provide structural and anatomical details of the bone. Nevertheless, the results are more significant whenever the anatomical imaging methods and the functional evaluation tests are correlated. Surgical castration with subsequent androgen-deprivation therapy (ADT) has been favored for treatment of metastatic prostate cancer since the 1940s [6]. The treatment of bone metastases of prostate cancer includes bisphosphonates, radiotherapy, chemotherapy, hormone therapy, surgery, radionuclide therapy, immunotherapy, and palliative treatments [7]. Antiandrogen therapies (such as bicalutamide, flutamide, nilutamide, and enzalutamide) alone are mainly used in locally advanced prostate cancer, however, they are rarely effective for treating bone metastases of prostate cancer [8]. Our patient received bicalutamide 50 mg/day after the diagnosis of sacral metastasis. At the end of 18 months of treatment, his PSA levels had decreased, and bone scintigraphy showed no radioactivity uptake in the pelvic area, consistent with a complete resolution of the bone metastasis.

^{99m}Tc-MDP whole body bone scintigraphy has advantages over other anatomical imaging modalities regarding the functional evaluation of new bone metastases and the progression or response assessment of previously diagnosed bone metastases in patients with prostate cancer. Therefore, in asymptomatic patients with prostate cancer and high serum PSA levels, bone scintigraphy might play a role in identifying metastatic lesions, despite normal findings on anatomic studies.

References

1. Van den Wyngaert T, Strobel K, Kampen WU, Van den Wyngaert T, Strobel K, Kampen WU, et al. The EANM practice guidelines for bone scintigraphy. Eur J Nucl Med Mol Imaging. 2016;43:1723-38.
2. Bozkurt MF, Dede Z, Burak Z, Ak I, Bekis R, Degirmenci B, et al. Procedure Guideline For Bone Scintigraphy. Turk J Nucl Med. 2001;10:97-102.
3. Kölükçü E, Beyhan M, Atılgan D. Factors affecting complications of transrectal ultrasound-guided prostate biopsy: A cohort study with 403 patients in a single center. J Surg Med. 2019;3(2):183-6.
4. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin. 2010;60:277-300.
5. O'Sullivan JM, Norman AR, Cook GJ, Fisher C, Dearnaley DP. Broadening the criteria for avoiding staging bone scans in prostate cancer: a retrospective study of patients at the Royal Marsden Hospital. BJU Int. 2003;92:685-9.
6. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res. 1941;1:293-7.
7. Cornford P, Bellmunt J, Bolla M, Briers E, De Santis M, Gross T, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017;71:630-42.
8. Mcleod DG, Iversen P, See WA, Morris T, Armstrong J, Wirth MP, et al. Bicalutamide 150 mg plus standard care vs standard care alone for early prostate cancer. BJU International. 2006;97:247-54.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):900-902.
DOI: 10.28982/josam.601013

Case report
Olgu sunumu

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

Bilateral hydronephrosis subsequent to a giant lymphocele after robotic radical prostatectomy

Robotik radikal prostatektomi sonrası dev lenfosele bağlı gelişen bilateral hidronefroz

Erdem Koç [1], Bahri Gök [1], Davut Kamacı [2], Erem Asil [2], Ali Fuat Atmaca [1]

[1] Ankara Yildirim Beyazit University School of Medicine, Ankara Hospital, Department of Urology, Ankara, Turkey
[2] Ankara City Hospital, Department of Urology, Ankara, Turkey

ORCID ID of the author(s)
EK: 0000-0003-3439-2105
BG: 0000-0002-2295-234X
DK: 0000-0002-3454-6154
EA: 0000-0001-6966-5076
AFA: 0000-0002-0794-2135

Corresponding author / Sorumlu yazar:
Erdem Koç
Address / Adres: Ankara Şehir Hastanesi Üroloji Kliniği, Bilkent Street 3, Ankara 06800, Türkiye
e-Mail: drerdemkoc@gmail.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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: 12/29/2019
Yayın Tarihi: 29.12.2019

Abstract

Lymphocele, one the most common complications after pelvic lymph node dissection, is usually observed between postoperative 2nd-12th months as a subclinical complication. We aimed to present a bilateral hydronephrosis case resulting from a giant lymphocele which developed during the early postoperative period after robot assisted radical prostatectomy (RARP) and pelvic lymph node dissection. Cystography was performed on the 7th postoperative day following RARP and extended lymph node dissection. Due to the left sided deviation of the bladder in cystographic images, non-contrast computed tomography (CT) was obtained, which revealed bilateral hydronephrosis and a giant lymphocele in the right pelvic region. The clinical status improved dramatically after percutaneous catheter drainage of the lymphocele. To the best of our knowledge, this is the first bilateral hydronephrosis case in the literature, which developed due to a giant lymphocele that occurred during the early postoperative period after transperitoneal surgery and had an asymptomatic clinical course despite increased creatinine levels. The findings improved dramatically by percutaneous catheter drainage.

Keywords: Hydronephrosis, Lymphocele, Prostate carcinoma, Robotic surgery

Öz

Lenfosel, pelvik lenf nodu diseksiyonu sonrası meydana gelen en sık komplikasyondur ve genellikle postoperatif 2.-12. aylarda görülmekle birlikte subklinik seyreder. Biz bu olgu sunumunda, robot yardımlı radikal prostatektomi (RYRP) ve genişletilmiş pelvik lenf nodu diseksiyonu sonrası oluşan dev lenfosele bağlı olarak gelişen bilateral hidronefroz vakasını sunmayı amaçladık. Robotik radikal prostatektomi ve genişletilmiş pelvik lenf nodu diseksiyonu sonrası postoperatif 7. günde çekilen sistografide mesanenin sol tarafa deviye izlenmesi nedeniyle kontrastsız bilgisayarlı tomografi (BT) çekildi. BT'de sağ pelvik bölgede bilateral hidronefroz ve dev lenfosel izlendi. Lenfoselin perkütan kateter drenajı sonrasında hastanın klinik durumu dramatik şekilde düzeldi. Bu olgu, dev lenfosele bağlı olarak ortaya çıkan bilateral hidronefrozun görülmesi, artmış kreatinin seviyesine rağmen asemptomatik seyretmesi ve transperitoneal cerrahi sonrası erken dönemde gelişmesi açısından literatürdeki ilk vaka olması nedeniyle önem taşımaktadır. Bununla birlikte, lenfoselin perkütan kateter drenajıyla bulgular dramatik bir şekilde düzelebilmektedir.

Anahtar kelimeler: Hidronefroz, Lenfosel, Prostat kanseri, Robotik cerrahi

Introduction

Prostate cancer is the 2nd most common cause of cancer-related deaths in the world, after lung cancer. Robotic prostatectomy is a minimally invasive surgery method in the treatment of prostate cancer (PCa) with its increasing popularity worldwide. As a part of the surgical practice, the most effective procedure for accurate staging of PCa and removal of the tumoral foci is pelvic lymph node dissection (PLND) [1].

Lymphocele is the most common complication of lymphadenectomy which develops due to lymphatic fluid leakage from transected afferent lymphatic channels during lymph node dissection. The clinical course of a lymphocele is mostly asymptomatic. The most common symptoms are feeling of a pelvic pressure, increased urinary frequency, deep vein thrombosis, ileus, infection, and edema. It usually occurs between the 2nd and 12th postoperative months [2,3].

In this report, we aimed to present a bilateral hydronephrosis case which developed due to an early-detected giant lymphocele following robot-assisted laparoscopic radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND).

How to cite / Atıf için: Koç E, Gök B, Kamacı D, Asil E, Atmaca AF. Bilateral hydronephrosis subsequent to a giant lymphocele after robotic radical prostatectomy. J Surg Med. 2019;3(12):900-902.

Case presentation

A 69-year-old male patient presented with an increased serum PSA level of 9 ng/ml. In a 12-quadrant prostate biopsy which was performed via transrectal ultrasonography (USG), Gleason 3+3 prostatic adenocarcinoma was detected in 5 foci. Preoperative multiparametric prostate magnetic resonance imaging (MRI) revealed a 6-mm lymphadenopathy in the right obturator region. The patient underwent RARP and ePLND. The first postoperative flatus was passed on the 1st day, and the abdominal drain was removed on the 3rd postoperative day. The patient was discharged on the postoperative 3rd day with recommendations. Cystography was planned on the 7th postoperative day, which revealed that the bladder was deviated to the left despite no obvious complaints (Figure 1).

Physical examination revealed mild tenderness in the right lower quadrant during deep palpation. A non-contrast abdominal computed tomography (CT) showed bilateral grade II renal pelvicaliectasis and a 14x13x12 cm-sized giant lymphocele in right pelvic region (Figure 2). In the serum biochemistry, creatinine level was 1.5 mg/dL. Hemoglobin level and WBC count were 13 g/dL and 11.400 K/uL, respectively. Percutaneous drainage catheter was placed under USG guidance by interventional radiologists. Drainage fluid biochemistry of lymphocele was compatible with blood serum biochemistry values. The patient was started on abundant protein-containing diet. In the 7th day of the drainage, the lymphocele and pelvicaliectasis could not be visualized by ultrasonography, and drainage catheter and transurethral drain were removed (Figure 3). Serum PSA, creatinine and WBC values had regressed to 0,029 ng/ml, 0.9 mg/dl, and 6.310 K/uL, respectively, at the end of the 1st postoperative month. The final pathology result was reported as Gleason score 3+4, with intact surgical margins, and 10 and 8 metastasis-free lymph nodes right and left, respectively. Written informed consent was obtained from the patient for this case report.

Figure 1: Image of the deviated bladder on cystogram

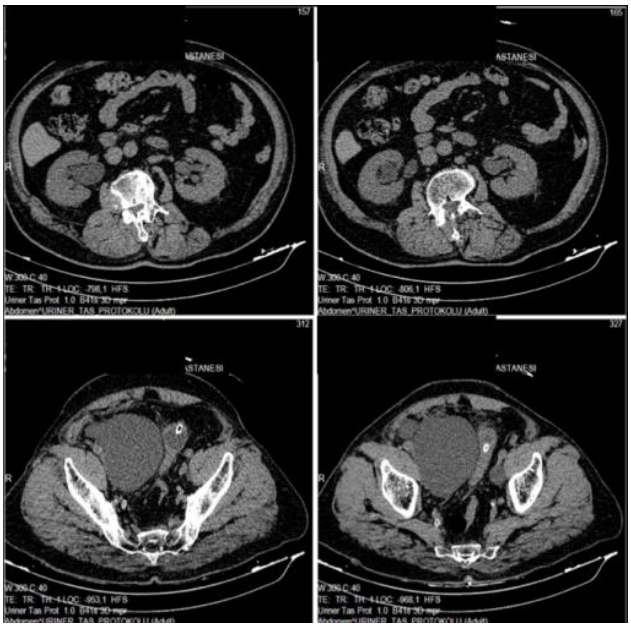

Figure 2: Bilateral grade II renal pelvicaliectasis and giant lymphocele in the non-contrast CT

Figure 3: Normal cystography findings at the 7th day of drainage

Discussion

Lymphocele is one of the most common complications following PLND, with a usually subclinical course. In a systematic review, lymphocele rate was reported as ranging from 0% to 8% [4]. Among all their patients who underwent CT imaging, Orvieto et al. [5] reported the incidence of asymptomatic and symptomatic lymphoceles as 51% and 7.8%, respectively.

Symptomatic lymphocele is frequently seen in between the 2nd and 12th postoperative months [4-6]. The giant lymphocele in our case was detected incidentally in the 1st postoperative week. However, findings obtained during the evaluation of the additional clinical and serum biochemistry parameters suggested that the clinically significant lymphocele may have developed during the early postoperative period. Although asymptomatic lymphoceles usually regress spontaneously, no study has been conducted on the correlation between the size of the lymphocele and its regression to this day.

Lymphocele is commonly seen after extraperitoneal RARP. Among symptomatic and asymptomatic patients who

underwent postoperative CT or MRI after extraperitoneal RARP, Lee et al. found that the incidence of lymphocele was 20.5% (41/200) [7]. Davis et al. [8] reported the symptomatic lymphocele rate as 19% after extraperitoneal RARP but observed no symptomatic lymphoceles after transperitoneal RARP. Keskin et al. [6] reported the lymphocele rate as 9% and the symptomatic lymphocele rate as 2.5% in a subgroup analysis of transperitoneal RARP series including 521 patients.

In general practice, surgeons believe that RARP may cause a lower incidence of lymphocele formation due to the peritoneum acting as a natural surface for lymphatic reabsorption. We performed transperitoneal ePLND in this case due to suspicious metastatic areas in multiparametric MRI, which may have contributed to the lymphocele formation. Briganti et al. [9] reported that the rate of lymphocele significantly increased (10.3%) after ePLND compared to limited PLND (4.6%). Naselli et al. [10] reported that the number of lymph nodes retrieved was an independent and statistically significant predictor of the symptomatic lymphocele development.

In this case, we emphasized that although bilateral pelvicaliectasis and related increase in creatinine level are presented as the result of compression to the surrounding organs, giant lymphoceles may be symptom-free in early periods of clinical course. However, cystography performed before the removal of the transurethral catheter invoked suspicion of a giant contralateral lymphocele.

Percutaneous drainage catheter application with or without sclerotherapy can be used in treatment of lymphocele drainage [11]. Surgical treatment options such as laparoscopy or open marsupialization may also be preferred [12]. In this case, percutaneous drainage catheter placement was curative for the giant lymphocele.

Previous studies showed that hydronephrosis may develop after lymphadenectomy, which was performed during open or laparoscopic approach in gynecologic oncology cases, and ureteral catheters were used in the treatment [13,14]. However, bilateral hydronephrosis due to lymphocele development after radical prostatectomy or radical cystectomy with ePLND has not been reported in the literature yet. To the best of our knowledge, our case is the first one in this respect. Without the need for ureteral catheters, lymphocele regressed and renal pelvicaliectasis dramatically improved after percutaneous catheter placement.

Conclusion

Lymphocele is one of the most common complications after PLND and its course is usually subclinical. In transperitoneal surgery, clinically significant asymptomatic lymphocele may rarely develop. Giant lymphoceles may cause bilateral hydronephrosis and increased levels of creatinine, and the findings can improve dramatically with percutaneous drainage.

References

1. Kölükçü E, Beyhan M, Atılgan D. Factors affecting complications of transrectal ultrasound-guided prostate biopsy: A cohort study with 403 patients in a single center. J Surg Med. 2018;3(2):183-6.
2. Williams SK, Rabbani F. Complications of lymphadenectomy in urologic surgery. Urol Clin North Am. 2011;38(4):507-18.
3. Carbone JM, Nadler RB, Bullock AD, Basler JW. Delayed infection of a pelvic lymphocele following pelvic lymphadenectomy. Urology. 1996;47(1):140-2.
4. Ploussard G, Briganti A, de la Taille A, Haese A, Heidenreich A, Menon M, et al. Pelvic lymph node dissection during robot-assisted radical prostatectomy: efficacy, limitations, and complications-a systematic review of the literature. Eur Urol. 2014;65(1):7-16.
5. Orvieto MA, Coelho RF, Chauhan S, Palmer KJ, Rocco B, Patel VR. Incidence of lymphoceles after robot-assisted pelvic lymph node dissection. BJU Int. 2011;108(7):1185-90.
6. Keskin MS, Argun ÖB, Öbek C, Tufek I, Tuna MB, Mourmouris P, et al. The incidence and sequela of lymphocele formation after robot-assisted extended pelvic lymph node dissection. BJU Int. 2016;118(1):127-31.
7. Lee JY, Diaz RR, Cho KS, Yu HS, Chung JS, Ham WS, et al. Lymphocele after extraperitoneal robot-assisted radical prostatectomy: a propensity score-matching study. Int J Urol. 2013;20(12):1169-76.
8. Davis JW, Shah JB, Achim M. Robot-assisted extended pelvic lymph node dissection at the time of radical prostatectomy: a video-based illustration of technique, results, and unmet patient selection needs. BJU Int. 2011;108(6 Pt 2):993-8.
9. Briganti A, Chun FK, Salonia A, Suardi N, Gallina A, Da Pozza LF, et al. Complications and other surgical outcomes associated with extended pelvic lymphadenectomy in men with localized prostate cancer. Eur Urol. 2006;50(5):1006-13.
10. Naselli A, Andreatta R, Introini C, Fontana V, Puppo P. Predictors of symptomatic lymphocele after lymph node excision and radical prostatectomy. Urology. 2010;75(3):630-5.
11. Karcaaltincaba M, Akhan O. Radiologic imaging and percutaneous treatment of pelvic lymphocele. Eur J Radiol. 2005;55(3):340-54.
12. WY Khoder, C Gratzke, N Haseke, Herlemann A, Stief CG, Becker AJ. Laparoscopic marsupialisation of pelvic lymphoceles in different anatomic locations following radical prostatectomy. Eur Urol. 2012;62(4):640-8.
13. Kim HY, Kim JW, Kim SH, Kim YT, Kim JH. An analysis of the risk factors and management of lymphocele after pelvic lymphadenectomy in patients with gynecologic malignancies. Cancer Res Treat. 2004;36(6):377-83.
14. Zikan M, Fischerova D, Pinkavova I, Slama J, Weinberger V, Dusek L, et al. A prospective study examining the incidence of asymptomatic and symptomatic lymphoceles following lymphadenectomy in patients with gynecological cancer. Gynecol Oncol. 2015;137(2):291-8.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine

J Surg Med. 2019;3(12):903-905.
DOI: 10.28982/josam.594025

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

An unusual catheter malposition following totally implantable venous access port insertion: The catheter tip is located into the right axillary vein

Venöz erişim portu yerleştirilmesi sonrası sıradışı bir kateter malpozisyonu: Kateter ucu sağ aksiller vende lokalize

Ahmet Yüksel [1], Yusuf Velioğlu [1], Mustafa Enes Demirel [2], Erhan Renan Uçaroğlu [1]

[1] Department of Cardiovascular Surgery, Bolu Abant Izzet Baysal University, Faculty of Medicine, Bolu, Turkey
[2] Department of Emergency Medicine, Düzce University, Faculty of Medicine, Düzce, Turkey

ORCID ID of the author(s)
AY: 0000-0003-0021-6509
YV: 0000-0003-4709-4705
MED: 0000-0001-5187-5737
ERU: 0000-0003-3655-1595

Corresponding author / Sorumlu yazar:
Ahmet Yüksel
Address / Adres: Bolu Abant İzzet Baysal Üniversitesi Tıp Fakültesi Kalp ve Damar Cerrahisi Anabilim Dalı, 14030, Gölköy, Bolu, Türkiye
e-Mail: ahmetyuksel1982@mynet.com

Informed Consent: The authors stated that the written consent was obtained from the patient presented with images in the study.
Hasta Onamı: Yazar çalışmada görüntüleri 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: 12/31/2019
Yayın Tarihi: 31.12.2019

Abstract
Totally implantable venous access port (TIVAP) devices have been used increasingly for repetitive chemotherapy administration, long-term parenteral nutrition, blood sampling and blood transfusion for last years. Several potential complications including catheter malposition can occur during the insertion of TIVAP devices. Catheter malposition is a less commonly reported and an important complication of TIVAP insertion. In this article, we presented an uncommon case report of catheter malposition following TIVAP insertion in a 47-year-old woman. To the best of our knowledge, this is the first reported case of mispositioned TIVAP where the tip of the catheter is in the right axillary vein.
Keywords: Totally implantable venous access port, Catheter malposition, Complication, Adverse event

Öz
Tamamen implante edilebilir venöz erişim port cihazları, tekrarlayan kemoterapi uygulamaları, kan örneklemesi, intravenöz hidrasyon ve parenteral nütrisyon için kanser hastalarında veya kronik hastalarda son yıllarda giderek daha fazla kullanılmaktadır. Tamamen implante edilebilir venöz erişim port cihazlarının yerleştirilmesi sırasında kateter malpozisyonu da dahil olmak üzere birçok potansiyel komplikasyon gelişebilir. Kateter malpozisyonu, tamamen implante edilebilir venöz erişim port yerleştirilmesinin daha az tarif edilmiş ancak önemli bir komplikasyonudur. Bu makalede, 47 yaşında bir kadın hastada tamamen implante edilebilir venöz erişim portu yerleştirilmesi sonrası gelişen sıradışı bir kateter malpozisyonu olgusu sunuldu. Bildiğimiz kadarıyla, bu olgu tamamen implante edilebilir venöz erişim portu yerleştirilmesi sonrası kateter ucunun sağ aksiller ven içinde konumlandığı literatürdeki ilk rapordur.
Anahtar kelimeler: Tamamen implante edilebilir venöz erişim portu, Kateter malpozisyonu, Komplikasyon, İstenmeyen olay

Introduction

Totally implantable venous access port (TIVAP) devices provide significant comfort for not only repeated administration of chemotherapeutic agents in cancer patients but also for long-term parenteral nutrition, blood sampling and blood transfusion. These devices ensure readily available, safe, easy, long-term central venous access that are placed under the skin; thus, their utilization has been gradually increased in the recent times [1]. However, the insertion of TIVAP devices has several potential complications such as pneumothorax, hemothorax, venous thrombosis, catheter infection, occlusion and malposition. Of these adverse events, a relatively lesser described yet a considerable complication of TIVAP insertion is the malposition of catheter tip into a vessel other than the superior vena cava (SVC) [2,3]. In this paper, we presented a case of an unusual catheter malposition following TIVAP insertion, in which the catheter tip is located in the right axillary vein, for the first time in the literature.

How to cite / Atıf için: Yüksel A, Velioğlu Y, Demirel ME, Uçaroğlu ER. An unusual catheter malposition following totally implantable venous access port insertion: The catheter tip is located into the right axillary vein. J Surg Med. 2019;3(12):903-905.

Case presentation

A 47 year-old woman with a diagnosis of cervix cancer was admitted to our department for TIVAP insertion. She was hospitalized and prepared for intervention. The right subclavian vein was accessed by the percutaneous Seldinger technique under local anesthesia in the operating room, without ultrasound guidance or fluoroscopy. A 7 Fr silicone catheter was inserted into the right subclavian vein along the guidewire. The port reservoir was placed into the previously created subcutaneous pouch at the deltopectoral area. A subcutaneous tunnel was created between the access area and deltopectoral pouch. The silicone venous catheter was connected to the port reservoir, and the function of the TIVAP device was checked by withdrawing venous blood and injecting a diluted heparin solution. The port reservoir was fixed on the subcutaneous tissue with a 3-0 vicryl suture, and skin was closed with a 2-0 polypropylene suture. Resistance and technical difficulty were encountered during both the progression of the guidewire in the vessel and the insertion of silicone catheter. After the intervention was completed, a postero-anterior chest radiography was obtained to check the position of tip of catheter. The chest radiography revealed that the catheter was kinked, and the tip of catheter was in the right axillary vein (Figure 1). The TIVAP was removed and re-implanted under ultrasound and fluoroscopy guidance. Afterwards, the patient was discharged uneventfully.

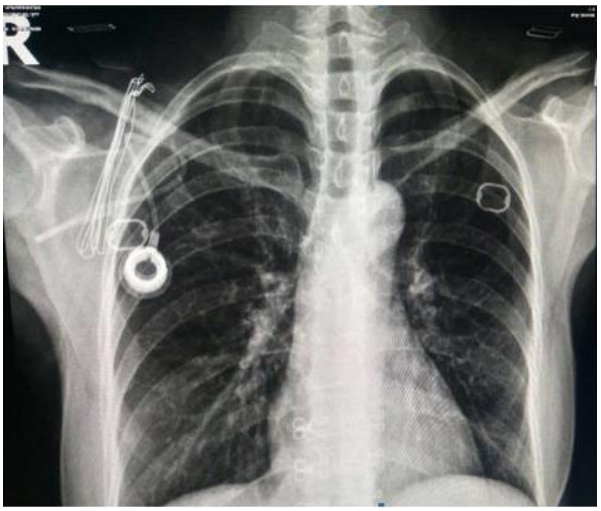

Figure 1: Catheter tip is in the right axillary vein

Discussion

In this article, we reported an unusual case of catheter mispositioning following TIVAP insertion. To the best of our knowledge, this is the first reported case of mispositioned TIVAP where the tip of the catheter is in the right axillary vein.

After the first report of TIVAP insertion by Niederhuber et al. [4] in 1982, TIVAP devices have been routinely used for safe and long-term central venous access in particular for cancer patients. The device increases the patient's quality of life, and decreases various adverse events including pain, phlebitis, frequent needle penetration, and cosmetic problems [1]. However, despite these advantages, the risks of TIVAP-related complications remain high. In a review study, overall procedure-related complication was reportedly between 16% and 28% [5].

One of these procedure-related complications is catheter mispositioning, which is defined as catheter tip placement into a vein other than the SVC or right atrium, kinking within the SVC (>40° with the lateral wall of SVC) and arterial cannulation [3]. If not taken into account, this complication can result in various serious events like catheter wedging and dysfunction, venous thrombosis, vascular erosion and even perforation [6]. Roldan et al.[3] does not consider mispositioning as a complication of central venous catheterization, while stating that missed diagnosis or delayed management of this adverse event may be related to the considerable morbidity and mortality.

According to the large case series, the rate of catheter mispositioning following TIVAP insertion varies between 0.2% and 3.1% [2,7-17] (Table 1).

Table 1: Catheter mispositioning and overall complication rates in the literature

Study	Publication year	Number of port catheters inserted	Catheter malposition rate	Overall complication rate
Kock et al. [2]	1998	1500	2.4%	12.8%
Guth [7]	2001	513	1.5%	3.1%
Yildizeli et al. [8]	2004	225	3.1%	12.4%
Araújo et al. [9]	2008	1231	1.2%	15.1%
Narducci et al. [10]	2011	815	0.9%	16.1%
Keum et al. [11]	2013	245	2.4%	9.4%
An et al. [12]	2015	397	0.8%	8.3%
Gurkan et al. [13]	2015	324	1.2%	33.9%
Ma et al. [14]	2016	2996	0.9%	6.2%
Feo et al. [15]	2017	527	1.3%	4.2%
Yanık et al. [16]	2018	3000	0.2%	9.6%
Kim et al. [17]	2019	843	0.3%	4%

Nowadays, both the surgeons and interventional radiologists all around the world frequently perform TIVAP insertion, but they use different techniques and prefer different venous access routes. In general, the interventional radiologists perform the procedure under ultrasonographic and fluoroscopic guidance and prefer the right internal jugular vein as the first choice for venous access. It has been indicated that TIVAP insertion under imaging guidance reduces the procedure-related complication rates [18-20]. On the other hand, surgeons use either cut-down or percutaneous landmark-based technique for implantation, with low complication rates [2,7-17]. Since we, the surgeons, are very familiar with blind-landmark technique as well as vascular anatomy of neck and chest regions, and also may recognize and treat the potential procedure-related complications quickly and properly, we applied the blind-landmark technique during TIVAP insertion but unfortunately observed this adverse event. In addition, we did not have adequate experience to routinely implement the radiologically guided method.

In conclusion, it should be noted that TIVAP insertion has a risk of significant catheter mispositioning even in experienced hands, and we suggest that radiological guidance should be routinely used during TIVAP insertion if possible.

References

1. Deser SB, Demirag MK. Analysis of totally implantable venous access of 70 cases with modified fast track technique. Turk J Vasc Surg. 2017;26:39-44.
2. Kock HJ, Pietsch M, Krause U, Wilke H, Eigler FW. Implantable vascular access systems: experience in 1500 patients with totally implanted central venous port systems. World J Surg. 1998;22:12-6.
3. Roldan CJ, Paniagua L. Central venous catheter intravascular malpositioning: causes, prevention, diagnosis, and correction. West J Emerg Med. 2015;16:658-64.
4. Niederhuber JE, Ensminger W, Gyves JW, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. Surgery. 1982;92:706-12.
5. Kurul S, Saip P, Aydin T. Totally implantable venous-access ports: local problems and extravasation injury. Lancet Oncol. 2002;3:684-92.
6. Walshe C, Phelan D, Bourke J, Buggy D. Vascular erosion by central venous catheters used for total parenteral nutrition. Intensive Care Med. 2007;33:534-7.
7. Guth AA. Routine chest X-rays after insertion of implantable long-term venous catheters: necessary or not? Am Surg. 2001;67:26-9.
8. Yildizeli B, Laçin T, Batirel HF, Yüksel M. Complications and management of long-term central venous access catheters and ports. J Vasc Access. 2004;5:174-8.

9. Araújo C, Silva JP, Antunes P, Fernandes JM, Dias C, Pereira H, et al. A comparative study between two central veins for the introduction of totally implantable venous access devices in 1201 cancer patients. Eur J Surg Oncol. 2008;34:222-6.
10. Narducci F, Jean-Laurent M, Boulanger L, El Bédoui S, Mallet Y, Houpeau JL, et al. Totally implantable venous access port systems and risk factors for complications: a one-year prospective study in a cancer centre. Eur J Surg Oncol. 2011;37:913-8.
11. Keum DY, Kim JB, Chae MC. Safety of a totally implantable central venous port system with percutaneous subclavian vein access. Korean J Thorac Cardiovasc Surg. 2013;46:202-7.
12. An H, Ryu CG, Jung EJ, Kang HJ, Paik JH, Yang JH, Hwang DY. Insertion of totally implantable central venous access devices by surgeons. Ann Coloproctol. 2015;31:63-7.
13. Gurkan S, Seber S, Gur O, Yetisyigit T, Okan Donbaloglu M, Ozkaramanli Gur D. Retrospective evaluation of totally implantable venous access port devices: early and late complications. J BUON. 2015;20:338-45.
14. Ma LI, Liu Y, Wang J, Chang Y, Yu L, Geng C. Totally implantable venous access port systems and associated complications: A single-institution retrospective analysis of 2,996 breast cancer patients. Mol Clin Oncol. 2016;4:456-60.
15. Feo CF, Ginesu GC, Bellini A, Cherchi G, Scanu AM, Cossu ML, et al. Cost and morbidity analysis of chest port insertion in adults: Outpatient clinic versus operating room placement. Ann Med Surg (Lond). 2017;21:81-4.
16. Yanık F, Karamustafaoğlu YA, Karataş A, Yörük Y. Experience in totally implantable venous port catheter: analysis of 3000 patients in 12 years. Turk Gogus Kalp Dama. 2018;26:422-8.
17. Kim DH, Ryu DY, Jung HJ, Lee SS. Evaluation of complications of totally implantable central venous port system insertion. Exp Ther Med. 2019;17:2013-8.
18. Teichgräber UK, Kausche S, Nagel SN, Gebauer B. Outcome analysis in 3,160 implantations of radiologically guided placements of totally implantable central venous port systems. Eur Radiol. 2011;21:1224-32.
19. Yoldaş H, Karagöz İ, Demirkol ME, Velioğlu Y, Yıldız İ. Widespread thrombus during central venous catheterization in ultrasonography: a case. Abant Med J. 2017;6:71-3.
20. Menteş O, Cırık MÖ, Ünver M, Avcı S, Doğanay G, Alagöz A. Ultrasonographically marked catheterization of internal jugular vein in intensive care patients: Retrospective cohort study. J Surg Med. 2019;3:553-6.

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.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine