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Volume: 5 - Issue: 9

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Research article

Research Article

1. Combination of the Simplified Modified Geneva and Wells Clinical Prediction Scoring promise a good performance in pulmonary embolism diagnosis

Gökhan ÇORAPLI Ayşe Füsun TOPÇU

Page: 828-831 PDF

Research Article

2. The rate and associated factors with antibody response in patients with COVID-19 infection

Semiha ÇELİK EKİNCİ Bengü ŞAYLAN

Page: 832-837 PDF

Research Article

3. Evaluation of macular perfusion in patients with treatment-naive overt hypothyroidism using optical coherence tomography angiography

Ayşegül MAVİ YILDIZ Gülçin ŞAHİNGÖZ ERDAL Hatice TARAKCİOGLU Ali Atakhan YILDIZ Sami YILMAZ

Page: 838-842 PDF

Research Article

4. Effects of antenatal magnesium sulfate use for neuroprotection on cardiorespiratory complications during the early neonatal period in preterm infants

Nuran ÜSTÜN Meryem HOCAOĞLU Abdulkadir TURGUT Fahri OVALI

Page: 843-847 PDF

Research Article

5. Early enteral nutrition with L-glutamine improves anastomotic healing in rats administered hyperthermic intraperitoneal chemotherapy with cisplatin and 5-FU

Hüseyin ALAKUŞ Mustafa GÖKSU Siraç ERTEN

Page: 848-852 PDF

Research Article

6. Where is it logical to break-up a ureter stone with endoscopic surgery?

Mehmet CANİKLİOĞLU Volkan SELMİ Sercan SARI Ünal ÖZTEKİN Emin GÜRTAN Levent IŞIKAY

Page: 853-856 PDF

Research Article

Download Cover Image

ISSUE FILES

Issue Full File

Archive

Volume: 5 Issue: 7

Volume: 5 Issue: 8

Volume: 5 Issue: 9

Volume: 5 Issue: 10

7. Likelihood of cancer in breast cancer imaging according to BI-RADS

Mahmut ÇORAPLI Hacı Taner BULUT Gökhan ÇORAPLI Burcin PEHLİVANOGLU Hüseyin ALAKUŞ Hasan SOYSALDI

Page: 857-861 PDF

Research Article

8. Preoperative effects of magnesium sulfate on hemodynamics and muscle relaxation

Funda ATAR Helin ŞAHİNTÜRK Murat ÜNSEL Cengiz YUMRU

Page: 862-866 PDF

Research Article

9. The effect of cardiac rehabilitation on anxiety and depression in percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) patients

Pınar DEMİR GÜNDOĞMUŞ İbrahim GÜNDOĞMUŞ

Page: 867-870 PDF

Research Article

10. Investigation of septum pellucidum and its variations with magnetic resonance imaging

Keziban KARACAN Alper KARACAN

Page: 871-874 PDF

Research Article

11. Arthroscopic microfracture alone or combined application of acellular scaffold: Which one is more effective in the treatment of osteochondral lesions of the talus?

Bertan CENGİZ Ramin MORADİ

Page: 875-879 PDF

Research Article

12. Evaluating the role of Smartpilot® view assisted target-controlled infusion anesthesia during intracranial mass surgery: A comparative retrospective study with bispectral index-guided standard anesthesia

Gözde İNAN Gökçen EMMEZ Kutluk PAMPAL Zerrin ÖZKÖSE ŞATIRLAR

Page: 884-888 PDF

Research Article

13. Is this coccyx fractured, or is it a normal variant? A cohort study

Serdar TOY Alperen ZEYNEL Kemal ZENCİRLİ

Page: 880-883 PDF

Research Article

14. Prognostic value of preoperative glucose to lymphocytes ratio in patients with resected gastric cancer

Murat Baki YILDIRIM Murat Bulut ÖZKAN

Page: 889-893 PDF

Fatih ADA Erkan GÜMÜŞ Ferit KASIMZADE

Page: 924-927 PDF

Research Article

23. The effect of online education during the pandemic on ocular surface symptoms

Abdullah BEYOĞLU Muhammed Mustafa BEYOĞLU

Page: 928-931 PDF

Research Article

24. The relationship between renal oxygen saturation and renal function in patients with and without diabetes following coronary artery bypass grafting surgery

Hazal ŞEREN Onat BERMEDE Süheyla KARADAĞ Çiğdem DENKER

Page: 932-936 PDF

Research Article

25. Long-term results of laparoscopic Heller myotomy with Dor-fundoplication in surgical treatment of achalasia: A single-center experience

Ali SÜRMELİOĞLU Doğukan AKKUŞ

Page: 937-940 PDF

Research Article

26. Which anti-TNF is most effective for my patient? Which one should I choose?

Melih PAMUKCU Rabia AYDOGAN BAYKARA

Page: 941-945 PDF

Research Article

27. Evaluation of sinonasal complaints in obstructive sleep apnea

Ceyhun CENGİZ

Page: 946-949 PDF

Research Article

28. A new parameter for the determination of normal right ventricular function in patients with acute pulmonary embolism

Murat KERKÜTLÜOĞLU Hakan GÜNEŞ Oguzhan YÜCEL Ömer DOĞAN Mehmet Birhan YILMAZ

Page: 950-953 PDF

Research Article

30. Histological investigation of the protective effect of metformin on testis and sperm parameters in obese rats with type 2 diabetes mellitus

Özcan BUDAK

Page: 954-959 PDF

Research Article

31. Two-year outcomes in patients undergoing rotational atherectomy and drug

coated balloon therapy for chronic total occluded peripheral arterial diseases: A retrospective cohort study

Mustafa Özer ULUKAN Atalay KARAKAYA Murat UĞURLUCAN Korhan ERKANLI

Page: 960-963 PDF

Research Article

32. The effect of recruitment maneuver on the development of expansion defect and atelectasis after lobectomy: A double-blind randomized controlled trial

Kadir İDİN

Page: 964-968 PDF

Research Article

33. The publication rate of presented abstracts at a congress and determining its publication factor

Sami AÇAR

Page: 969-973 PDF

Research Article

34. Investigation of the effect of anti-epileptic drugs on bone metabolism using osteoprotegerin and bone-specific alkaline phosphatase: The direct effects of antiepileptic drugs on bone metabolism

Buket TUĞAN YILDIZ Tuba Tülay KOCA Muhammed SEYİTHANOĞLU Duygun ALTINTAŞ AYKAN

Page: 974-977 PDF

Research Article

35. Increased mouse double minute X expression in human placental villous macrophages (Hofbauer cells) in gestational diabetes mellitus

Sefa ARLIER Sadik KÜKRER Cevdet ADIGÜZEL

Page: 978-981 PDF

Research Article

36. Does vitamin D replacement therapy cause a regression in fatty liver disease? A case control study of comparison of vitamin D and other common therapy modalities

Vusal ABDURAHMANOV Arzu GÜNTÜRK Fatma KARTUFAN Rahman NURMUHAMMEDOV Yaşar KÜÇÜKARDALI

Page: 982-987 PDF

Research Article

37. The effects of capsular repair on quality of life after hip arthroplasty with the anterolateral approach

Mehmet YETİŞ Emre YURDAKUL

Page: 988-991 PDF

Case report

Case Report

1. Topical mitomycin C treatment in corneal and conjunctival intraepithelial neoplasia: A case report

A case report

Asena KELEŞ ŞAHİN Aslıhan UZUN Havva ERDEM

Page: 992-994 PDF

Case Report

2. Giant retroperitoneal schwannoma removed with the laparoscopic approach: A case report

Emel ÖZVERİ Deniz Esin TEKCAN ŞANLI Metin ERTEM

Page: 995-997 PDF

Case Report

3. Anesthesia management in dystrophic epidermolysis bullosa: A case report

Sibel TETİKER Nilgün ALPAY

Page: 998-1001 PDF

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Combination of the Simplified Modified Geneva and Wells Clinical Prediction Scoring promise a good performance in pulmonary embolism diagnosis

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Ethics Committee Approval
Ethics committee approval was obtained from Dicle University Medical School (approval code: 18.05.2018/337).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Pulmonary thromboembolism (PTE) has high mortality and morbidity, is difficult to diagnose, and is generally preventable. Clinical scoring is used for early diagnosis. Two of these often-used scoring systems include the Wells and Simplified Modified Geneva scoring systems. We aimed to comparatively determine the values of the Wells and the Simplified Modified Geneva scoring systems in showing PTE.

Methods: This prospective cohort study included 195 patients who underwent computerized tomography pulmonary angiography (CTPA) with suspected PTE between May 2018 and November 2018. The Wells and Simplified Modified Geneva scores of the patients were calculated. Wells Clinical Scoring results were grouped as having a weak/strong probability of PTE, while those of the Modified Geneva clinical scoring were categorized as possible/unlikely PTE. The analyses were performed with the SPSS package 21.0 program.

Results: One hundred and nine (55.9%) patients presented to the emergency department and eighty-six (44.1%) patients visited the outpatient clinic for chest diseases. Of all cases, 83 (42.6%) were male and 112 (57.4%) were female. The mean age was 57.16 (18.62) years. Forty-one (21%) patients had PTE. The sensitivity and specificity of Wells Clinical Scoring for PTE were 87.8% and 83.8%, respectively, while those of the Simplified Modified Geneva Clinical Scoring were 82.9% and 53.3%, respectively. The chi-square analysis for two clinical scorings revealed a *p*-value of 0.001. The negative predictive values of Wells and Simplified Modified Geneva Scores were 96.2% and 92.1%, respectively. The positive predictive value was the highest in the emergency department (80% and 39.4%, respectively). When the two clinical scores were used together, the negative and positive predictive values were 95.6% and 61.1%, respectively.

Conclusion: We found that Wells Clinical Scoring is superior to the Simplified Modified Geneva Score in terms of sensitivity and specificity. The use of these two clinical scores in the outpatient clinic was more useful in excluding PT, while in the emergency department, their combination was more effective in diagnosing it.

Keywords: Pulmonary thromboembolism, Computed tomography pulmonary angiography, Wells Clinical Scoring, Simplified Modified Geneva Score

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Introduction

Pulmonary thromboembolism (PTE) has high mortality and morbidity, is challenging to diagnose, and is generally preventable [1]. PTE ranks third among the causes of cardiovascular death after myocardial infarction and cerebrovascular events [2]. Although clinical symptoms and findings vary according to the size and localization of the embolism, infarction development, the age of the patient, whether it is recurrent, comorbidities, and the patient's cardiopulmonary reserve also significantly affect mortality [3]. Whereas the mortality of PTE is approximately 25-30% in untreated cases, it decreases to 2-8% among treated patients [4]. The first stage in the diagnosis of PTE is clinical suspicion about the disease. The algorithm to be followed for diagnosis is determined, necessary examinations are requested and a decrease in mortality can be achieved by immediately starting the treatment.

Clinical findings and laboratory data are not sufficient to diagnose or exclude PTE. For this reason, clinical classifications are needed to help and guide in deciding the cases requiring further examination. Today, the most widely accepted clinical probability classifications are the Wells and Modified Geneva classifications [5], both of which also have simplified forms. Since the clinical probability classifications are determined by objective data, they are used more in emergency services [6]. Widespread use of clinical risk scorings in daily practice will provide great benefits in preventing unnecessary expensive, invasive, and time-consuming tests. The pulmonary embolism guide recommended using the clinical risk scorings by combining them with serum D-Dimer levels for excluding PTE.

In this study, we aimed to comparatively determine the diagnostic values of Wells and Simplified Modified Geneva scorings and their combination in patients with a PTE pre-diagnosis who visited the emergency department and chest diseases outpatient clinics.

Materials and methods

This prospective study was approved by Dicle University Non-Interventional Ethics Committee (approval code: 18.05.2018/337). All participants were informed about the study verbally and in writing and signed informed consent forms.

Patient selection

A total of 195 patients, who visited the emergency service and chest diseases outpatient clinic ambulatorily between May 2018 – November 2018, who were suspected of PTE and whose computed tomography pulmonary angiography (CTPA) scans were performed were included in this study. PTE was diagnosed by CTPA, which was reported as positive or negative for pulmonary embolism. These patients were prospectively evaluated with the Wells (Canadian) and the Simplified Modified Geneva pulmonary thromboembolic scorings.

Computerized tomography pulmonary angiography

Computed tomography pulmonary angiography examinations were performed with the CT device with 64 detectors (Brilliance CT device, Philips Medical Systems, Cleveland, Ohio). Before the scanning began, venous access was established in all patients through an 18-20 G catheter from the forearm. For pulmonary CTPA examination, 100 mL of non-ionic contrast agent was injected through the antecubital vein at 4 mL/sec with an automatic injector. From the moment the contrast agent density in pulmonary truncus reached the threshold value, sections were filmed with a delay of 18.5 seconds.

Clinical scorings

Patients' Wells (Canadian) and Simplified Modified Geneva scores were calculated for PTE. Wells Clinical Scoring results were grouped as weak/strong probability of PTE, while those of the Modified Geneva clinical scoring were categorized as possible/unlikely PTE [7, 8].

Statistical analysis

Analyses were performed with the SPSS 21 package program. If the data showed normal distribution, they were shown as mean (standard deviation). Descriptive data were presented as a ratio. Categorical data were compared by the Pearson's chi-square test. The sensitivity and specificity of the scoring systems were determined for PTE. Power analysis was performed for sample size estimation, based on a similar study. The sample size required for an effect size of 0.258, an alpha of 0.05, and a power of 0.95 at a 95% confidence interval was 195. Results were statistically significant when *P*-value ≤0.05.

Results

One hundred and ninety-five patients with CTPAs performed for suspicion of a pulmonary embolism were included in this study. CTPA results were interpreted as positive or negative for pulmonary embolism. All patients were prospectively evaluated with Wells (Canadian) and Simplified Modified Geneva pulmonary thromboembolic scoring.

Among all patients, 86 patients (44.1%) had visited the chest diseases department, and 109 (55.9%) had presented to the emergency service ambulatorily. There were 112 (57.4%) females and 83 (42.6%) males. The overall mean age was 57.16 (18.62) years (range: 17-91).

The CTPAs were negative and positive for a pulmonary embolism in 154 (79%) and 41 (21%) patients, respectively, yielding a PTE prevalence of 21%. The results of 10 (11.6 %) of 86 patients who visited the outpatient clinic, and 31 of 109 patients (28.4 %) who presented to the emergency service were positive for PTE.

According to Wells Clinical Scoring, 134 patients (68.7%) had a weak probability of PTE, among which 129 were CTPA-negative and 5 were CTPA-positive, and 61 (31.3%) had a strong probability of PTE (Table 1), of which 25 were CTPA-negative, and 36 were CTPA-positive. This test's sensitivity and specificity were 87.8% and 83.8%, respectively. The chi-square analysis revealed p=0.001, based on which the Wells Clinical Scoring system was considered significant for PTE (Table 1).

Table 1: The relationship between Clinical scorings and CTPA results

		Negative CTPA n (%)	Positive CTPA n (%)	*P*-value	Sensitivity	Specificity	PPV	NPV
Wells Clinical Scoring	Weak probability	129 (96.3%)	5 (3.7%)	0.001	87.8%	83.8%	59%	96.3%
	Strong probability	25 (41%)	36 (59%)					
Simplified Modified Geneva Clinical Scoring	Not probable	82 (92.1%)	7 (7.9%)	0.001	82.9%	53.3%	32%	92.1%
	Probable	72 (67.9%)	34(32.1%)					

CTPA: Computerized Tomography Pulmonary Angiography

The Simplified Modified Geneva Clinical Scoring results of 106 patients (54.4%) were interpreted as probable, of which 72 and 34 were CTPA-negative and -positive, respectively, and those of 89 (45.6%), as not probable in terms of PTE diagnosis, among which 82 were CTPA-negative, and 7, CTPA-positive (Table 1). This scoring system's sensitivity and specificity were 82.9% and 53.3%, respectively, with a p-value of 0.001 in the Chi-square test, making its results significant for PTE.

The negative predictive values of the Wells and Simplified Modified Geneva Scorings were at their highest in the outpatient clinic (96.7%, and 95.7%, respectively) (Table 2), while their positive predictive values were at their highest in the emergency service (80%, and 39.4%, respectively (Table 2).

Table 2: Effectiveness of Wells clinical score and Simplified Modified Geneva Scoring according to the place of use

		Negative CTPA n (%)	Positive CTPA n (%)
WCS evaluation in polyclinic	Weak probability	58 (96.7%)	2 (3.3%)
	Strong probability	18 (69.2%)	8 (30.8%)
WCS evaluation in emergency service	Weak probability	71 (95.9%)	3 (4.1%)
	Strong probability	7 (20.0%)	28 (80.0%)
SMGCS evaluation Scoring in polyclinic	Not probable	44 (95.7%)	2 (4.3%)
	Probable	32 (80.0%)	8 (20.0%)
SMGCS evaluation in emergency service	Not probable	38 (88.4%)	5 (11.6%)
	Probable	40 (60.6%)	26 (39.4%)

CTPA: Computerized Tomography Pulmonary Angiography, WCS: Wells Clinical Scoring, SMGCS: Simplified Modified Geneva Clinical Scoring

The two scores' combined use revealed a low probability in 82 patients, of which 78 (95.1%) were CTPA-negative, and a high probability in 54 patients, of which 33 (61.1%) were CTPA-positive. The negative and positive predictive values of the combined use of two scoring systems were 95.1% and 61.1%, respectively (Table 3).

Table 3: Effectiveness of Wells and Simplified Modified Geneva Scorings in combination

			Negative CTPA n (%)	Positive CTPA n (%)	Sensitivity	Specificity	PPV	NPV
Not Probable in SMGS	WCS	Weak probability	78 (95.1%)	4 (4.9%)	9.8%	50.6%	32.7%	95.1%
		Strong probability	4 (57.1%)	3 (42.9%)	7.3%	2.5%	42.8%	79.7%
Probable in SMGS	WCS	Weak probability	51 (98.1%)	1 (1.9%)	2.4%	33.2%	1.9%	72%
		Strong probability	21 (38.9%)	33 (61.1%)	80.5%	13.7%	61.1%	94.3%

CTPA: Computed tomography pulmonary angiography, WCS: Wells Clinical Scoring, SMGS: Simplified Modified Geneva Scoring

Discussion

The early diagnosis and treatment of PTE, which has a high mortality rate, is essential. The diagnosis of PTE starts with a suspicion. Difficulties are experienced in PTE diagnosis because PTE symptoms and findings are not specific, and not all centers have access to advanced diagnostic modalities. One of the most important steps of the diagnostic algorithm in PTE diagnosis is to determine the clinical probability and proceed to the next phase. Researchers tried developing clinical probability scoring systems with several parameters to be used in predicting PTE with many resulting clinical probability scores.

Our study aimed to comparatively assess the value of two clinical probability scoring methods used in PTE diagnosis, the Wells and Simplified Modified Geneva Clinical scoring. A prospective study conducted in the Netherlands between July 2008-November 2009 in 7 hospitals on 807 patients with suspicion of acute PTE examined four clinical scoring systems and reported that acute PTE prevalence was 23% [9]. Wells and Simplified Modified Geneva scores were previously compared in a study that revealed the PTE prevalence as 19% [10]. The clinical probability of PTE was prospectively evaluated by Wells Clinical Scoring and retrospectively evaluated with the revised Geneva Score on 300 consecutive patients, and PTE prevalence was 16% [11]. In a cross-sectional study, PTE was detected in 55 of the 598 patients (9%) who underwent CTPA due to PTE suspicion [12]. In our study, the PTE prevalence among patients with a clinical suspicion was 21%, comparable to other studies. Performing CTPA in all patients with PTE suspicion exposes many patients without PTE to radiation. This can be prevented by the combined use of clinical scoring and D-dimer levels.

In a prospective study conducted by Wells and his friends, PTE was detected only in 7.8% of the cases with a Wells clinical score of ≤4 (weak probability), and not detected in 92.2% [13].

In a prospective study performed on 3306 patients in 12 centers in the Netherlands between 2002-2004, Wells Clinical Scoring results were dichotomized and trichotomized. The sensitivity and specificity of the dichotomized Wells clinical scoring were 71%, and 41%, respectively. Accordingly, the dichotomized scoring was more effective than the trichotomized scoring in clinical practice [14].

In a prospective study conducted with 339 patients with clinical suspicion of PTE, the Wells and Simplified Modified Geneva Scores were compared. There were 104 patients with a strong probability of PTE according to Wells, of which 46 were diagnosed with PTE, and 235 patients with a weak probability of PTE, of which 19 were diagnosed with it. The sensitivity and specificity of Wells Clinical Scoring were 70% and 78%, respectively. The same patients were evaluated with the Simplified Modified Geneva Score, and of 115 patients with probable and 224 patients with not probable PTE, 43 and 22 patients, respectively, were diagnosed with PTE. The sensitivity and specificity of the dichotomized Simplified Modified Geneva Scoring system were 66% and 72%, respectively. Both clinical scores were significant, and Wells Clinical Scoring surpassed Simplified Modified Geneva Score in terms of sensitivity and specificity [10].

In a prospective study including 613 patients in Argentina, the sensitivity and specificity of the dichotomized Wells Clinical Scoring were 65% and 81%, respectively [15]. In a PTE study conducted with 922 patients, PTE was diagnosed in 95 of the 722 patients, who were considered to have a weak probability of PTE according to Wells Clinical Scoring; and it was diagnosed in 112 of the 200 patients with a strong probability. In this study, the sensitivity and specificity of Wells Clinical Scoring were 54% and 87%, respectively [16].

In a meta-analysis conducted on 7268 patients suspected of embolism, the sensitivity and specificity of Wells Clinical Scoring were 53% and 79%, respectively [17]. The effectiveness of the Simplified Modified Geneva Score was examined in research conducted on 1049 patients by combining two prospective studies. Its sensitivity and specificity were 61% and 71%, respectively, proving significant for PTE [11].

In our study, the sensitivity and specificity of Wells Clinical Scoring were 87.8% and 83.8%, respectively, while those of the Simplified Modified Geneva Clinical Scoring system were 82.9% and 53.3%, respectively. Both results were comparable to those in the literature, and both clinical scoring systems were significant. Wells clinical scoring was stronger than the simplified modified Geneva score in terms of both sensitivity and specificity. Using these two clinical scores separately was more useful in excluding embolism in the outpatient clinic, while it was better in making a pre-diagnosis in the emergency service. Their combinational use was more effective in excluding PTE. Since the Simplified Modified Geneva Scoring is easy to remember because the same points are given to each item, it can be an alternative to Wells clinical scoring.

Conclusion

Our results prove the effectiveness of Wells and Simplified Modified Geneva Scores in showing PTE, and the risk scoring systems should be well examined before performing invasive tests on patients for diagnostic purposes. The Wells Score is more effective than the Simplified Modified Geneva Score in the diagnosis of PTE.

References

1. Sandler DA, Martin JF. Autopsy proven pulmonary embolism in hospital patients: are we detecting enough deep vein thrombosis. J R Soc Med. 1989 Apr;82(4):203-5. doi: 10.1177/014107688908200407.
2. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008 Mar;28(3):370-2. doi: 10.1161/ATVBAHA.108.162545 .
3. Cohen AT, Dobromirski M, Gurwith MM. Managing pulmonary embolism from presentation to extended treatment. Thromb Res. 2014 Feb;133(2):139-48. doi: 10.1016/j.thromres.2013.09.040.
4. Nijkeuter M, Söhne M, Tick LW, Kamphuisen PW, Kramer MH, Laterveer L, et al. The natural course of hemodynamically stable pulmonary embolism: Clinical outcome and risk factors in a large prospective cohort study. Chest. 2007 Feb;131(2):517-23. doi: 10.1378/chest.05-2799.
5. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014 Nov 14;35(43):3033-69, 3069a-3069k. doi: 10.1093/eurheartj/ehu283.
6. Wicki J, Perneger TV, Junod AF, Bounameaux H, Perrier A. Assessing clinical probability of pulmonary embolism in the emergency ward: a simple score. Arch Intern Med. 2001 Jan 8;161(1):92-7. doi: 10.1001/archinte.161.1.92 .
7. Ceriani E, Combescure C, Le Gal G, Nendaz M, Perneger T, Bounameaux H, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. J Thromb Haemost. 2010 May;8(5):957-70. doi: 10.1111/j.1538-7836.2010.03801.x .
8. Le Gal G, Righini M, Roy PM, Sanchez O, Aujesky D, Bounameaux H, et al. Prediction of pulmonary embolism in the emergency department: the revised Geneva score. Ann Intern Med. 2006 Feb 7;144(3):165-71. doi: 10.7326/0003-4819-144-3-200602070-00004.
9. Douma RA, Mos IC, Erkens PM, Nizet TA, Durian MF, Hovens MM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med. 2011 Jun 7;154(11):709-18. doi: 10.7326/0003-4819-154-11-201106070-00002.
10. Penaloza A, Melot C, Motte S. Comparison of the Wells score with the simplified revised Geneva score for assessing pretest probability of pulmonary embolism. Thromb Res. 2011 Feb;127(2):81-4. doi: 10.1016/j.thromres.2010.10.026.
11. Klok FA, Mos IC, Nijkeuter M, Righini M, Perrier A, Le Gal G, et al. Simplification of the revised Geneva score for assessing clinical probability of pulmonary embolism. Arch Intern Med. 2008 Oct 27;168(19):2131-6. doi: 10.1001/archinte.168.19.2131.
12. Hall WB, Truitt SG, Scheunemann LP, Shah SA, Rivera MP, Parker LA, et al. The prevalence of clinically relevant incidental findings on chest computed tomographic angiograms ordered to diagnose pulmonary embolism. Arch Intern Med. 2009 Nov 23;169(21):1961-5. doi: 10.1001/archinternmed.2009.360.
13. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000 Mar;83(3):416-20.
14. van Belle A, Büller HR, Huisman MV, Huisman PM, Kaasjager K, Kamphuisen PW, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA. 2006 Jan 11;295(2):172-9. doi: 10.1001/jama.295.2.172.
15. Posadas-Martínez ML, Vázquez FJ, Giunta DH, Waisman GD, de Quirós FG, Gándara E. Performance of the Wells score in patients with suspected pulmonary embolism during hospitalization: a delayed-type cross sectional study in a community hospital. Thromb Res. 2014 Feb;133(2):177-81. doi: 10.1016/j.thromres.2013.11.018.
16. Righini M, LE Gal G, Perrier A, Bounameaux H. Clinical probability assessment of pulmonary embolism by the Wells' score: is the easiest the best. J Thromb Haemost. 2006 Mar;4(3):702-4. doi: 10.1111/j.1538-7836.2006.01797.x.
17. van Es N, Kraaijpoel N, Klok FA, Huisman MV, Den Exter PL, Mos IC, et al. The original and simplified Wells rules and age-adjusted D-dimer testing to rule out pulmonary embolism: an individual patient data meta-analysis. J Thromb Haemost. 2017 04;15(4):678-84. doi: 10.1111/jth.13630.

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The rate and associated factors with antibody response in patients with COVID-19 infection

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Ethics Committee Approval
The study was approved by the Clinical Research Ethics Committee of Ümraniye Training and Research Hospital, University of Health Sciences in June 12, 2020 with the number B.10.1.TKH.4.34.H.GP.0.01/177.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

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Abstract

Background/Aim: It remains unknown in what form and to what extent antibodies to SARS-CoV-2 confer immunity and whether these antibodies from previous infections could ensure protection from reinfection. This study aimed to investigate the rate of antibody positivity among patients who recovered from COVID-19 infection and the factors influencing antibody production among these patients.
Methods: This prospective case control study included 111 males (mean age: 34 years, range: 18-60 years) who recovered from PCR-confirmed COVID-19. The patients underwent antibody testing on the 28th day of recovery. Sixty-seven patients (60.4%) had antibodies against COVID-19 as well as positive IgM and IgG, and 39.6% of patients were negative for Ab production.
Results: The mean ages of the antibody-positive and negative groups were 43 and 29 years, respectively, the age of the positive group was significantly higher than the age of the negative group (P<0.001). The rate of antibody production in symptomatic patients was approximately 4.5 times higher than that in asymptomatic patients. The factors that were associated with antibody production were advanced age (OR=1.1), cough (OR=6.1), fever (OR=4.5), shortness of breath (OR=12.4), myalgia (OR=4.7), increased levels of CRP (OR=32.1), sedimentation rate (OR=17.3), LDH (OR=6.9), D-dimer (OR=10.6), ferritin (OR=29.4), and the presence of lymphopenia (OR=4.2) and thrombocytopenia (OR=7.1).
Conclusion: The finding that a substantial number of patients recovering from COVID-19 did not develop antibody response suggests that these patients are still at risk for reinfection. In addition, patients who have experienced symptomatic disease course, advanced age and developed higher inflammatory response may be better candidates for plasma donation.

Keywords: Reinfection, SARS-CoV-2, Antibody, Covid-19

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Introduction

Severe Acute Respiratory Syndrome *Coronavirus*-2 (SARS-CoV-2) has been the third new coronovirus resulting in outbreaks following SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) in the past two decades. The infection is called *Coronavirus* Disease 2019 (COVID-19) [1].

The presence of positive anti-SARS-CoV-2 antibodies indicates that the individual experienced SARS-CoV-2. IgG antibodies which are specific for SARS-CoV-2 develop later than SARS-CoV-2 IgM antibodies. Concurrent IgM and IgG antibody positivity cannot rule out recently infected patients who may still be contagious [3]. Antibody response to SARS-CoV-2 presumably provides immunity that protects the individual against reinfection of the virus, but it still remains unknown in what form and to what extent antibodies to SARS-CoV-2 confer immunity and whether these antibodies from previous infections could ensure protection from reinfection [4]. People recovering from an infection are known to develop antibodies against the pathogen. The use of plasma from recovered patients has been utilized for years for treatment of infected patients or to protect healthy people against infections. This is also the case for plasma from COVID-19 survivors, which was shown to provide clinical improvement, to decrease viral load and increase blood oxygen concentrations within 24 hours [5]. Due to the role of convalescent plasma in the treatment of COVID-19 patients, efforts to identify individuals with immunity that protects against the disease have increased over time [2].

This study aimed to investigate the rate of antibody positivity and the factors affecting antibody production among COVID-19 survivors who presented to our hospital for plasma donation.

Materials and methods

Study design and patients

This study was planned as a retrospective cross-sectional study at our hospital, a tertiary education and research hospital working as a reference center during the COVID-19 pandemic. The study was approved by the Clinical Research Ethics Committee of Ümraniye Training and Research Hospital, University of Health Sciences in June 12, 2020 with the number B.10.1.TKH.4.34.H.GP.0.01/177.

A potential plasma donor must receive a prior diagnosis of COVID-19 confirmed by a positive RT-PCR test on the oro-nasopharyngeal swab specimen. To become a plasma donor after recovery, molecular test results of two consecutive oro/nasopharyngeal swab samples obtained at least 24 hours apart must be negative, and at least 14 must pass after recovery. In case of the absence of a negative test result, at least 28 days must pass from the clinical recovery. Plasma donors are preferably selected among men, but women who are not pregnant, and persons who have not received a blood transfusion can also be candidates [6]

This study included 111 male COVID-19 survivors aged 18-60 years whose clinical recovery was confirmed by RT-PCR testing from oro/nasopharyngeal swabs and who presented to our hospital between April 15 and June 1, 2020, for plasma donation at the 28th day of recovery. In the antibody-positive group, all patients had positive antibody tests both for IgM and IgG.

Exclusion criteria were female gender (due to their small number), being younger than18 or older than 60 years old, lack of a positive PCR test result, a history of previous blood transfusion, a longer or shorter period of recovery than 28 days.

Identification of SARS-CoV-2 IgM and IgG antibodies

The lateral flow immunochromatographic assay (ICA) strip (Colloidal Gold-The Weimi Diagnostic Kit, China) was used. Venous blood samples of the patients were sent to the laboratory immediately after being taken into EDTA tubes and serum samples were studied after centrifugation.

Definition of clinical recovery

The date of clinical recovery was defined as the date of discharge of hospitalized patients, the completion of a 5-day-treatment of patients who received treatment at home without any indication for hospitalization and who did not develop any symptoms that required re-presentation to the hospital.

Data collection

Among patients who presented to the outpatient department of infectious diseases to donate plasma, those who underwent SARS-CoV-2 antibody testing on the 28th day of clinical recovery were included in the study. The baseline laboratory findings were examined. Data were recorded on the laboratory findings, the symptoms at presentation, ages and comorbidities as well as the time when symptoms developed, and thorax computerized tomography (CT) was performed. The treatments specific to COVID-19 that the patients received either at the hospital or at home were also noted.

Signs of pneumonia on CT imaging, laboratory results including white blood cell (WBC), neutrophil, lymphocyte, platelet counts, levels of CRP, lactate dehydrogenase (LDH), D-dimer, and ferritin and sedimentation rate were recorded. Patients' records were reviewed in terms of symptoms at presentation including fever, shortness of breath, cough, myalgia, and impaired smell and taste. Treatment protocols specific to COVID-19 with hydroxychloroquine and azithromycin were noted.

Statistical analysis

Continuous variables were expressed as mean (SD), median, minimum and maximum, and categorical variables, as frequencies and percentages. Due to their small number (n=2), female patients were excluded from the study. The Mann–Whitney U or the Pearson Chi-square (or Fisher's exact) tests were used for statistical analysis, as appropriate. Logistic regression analysis was performed to determine the factors affecting antibody response. Analyses were performed using SPSS Version 21.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY). *P*-values less than or equal to 5% were considered significant.

Results

The mean age of the 111 patients included in the analysis was 34 (13.11) years (median: 33 years, range:19-60 years). At the 28th day of recovery, 67 patients (60.4%) had antibodies against COVID-19. The patients received

hydroxychloroquine for an average of five days (min:5, max:10) and azithromycin for four days (min:3, max:9) (Table 1). The mean age of those who had antibody response was 43 years, compared with 29 years in the antibody-negative group (Table 2).

Symptoms at presentation

Of 111 patients, 77 (69.4%) had at least one symptom at presentation, while 34 (30.6%) were asymptomatic at the time of RT-PCR and during the treatment (Figure 1). Thirty-eight patients (34.2%) had high fever, 16 (14.4%) had shortness of breath, 50 (45%) had cough, and 46 (41.4%) had myalgia. Three patients (2.7%) had loss of taste and smell.

In the antibody-positive group, 6 patients (9%) were asymptomatic at the time of RT-PCR-confirmed diagnosis. The remaining 61 patients (91%) had at least one complaint, including fever in 31 (46.3%), shortness of breath in 15 (22.4%), cough in 41 (61.2%), and myalgia in 37 (55.2%). All three patients (4.5%) with complaints of inability to smell and taste developed antibody response. (Table 2) (Figure 1).

Of patients who did not produce antibody response, seven (15.9%) had high fever, one (2.3%) had shortness of breath, nine (20.5%) had cough, and nine (20.5%) had myalgia (Table 3).

Laboratory findings

Laboratory results of the study group are summarized in Table 1. At baseline, 14 patients (12.6%) had decreased and seven (6.3%) had increased WBC counts. Thirty-six patients (32.4%) had an increased neutrophil percentage. Sixty-one patients (55%) had decreased lymphocyte counts and 43 (38.7%) had a decreased lymphocyte percentage. Thrombocytopenia was detected in 26 patients (23.4%). Elevated levels of CRP, LDH, D-dimer, and ferritin and an increased sedimentation rate were found in 50 (45%), 36 (33.3%), 25 (25%), 28 (28.3%), and 34 patients (40.5%), respectively. No patient had an increased procalcitonin level (Table 1).

Figure 1: The rates of antibody positivity in symptomatic and asymptomatic groups

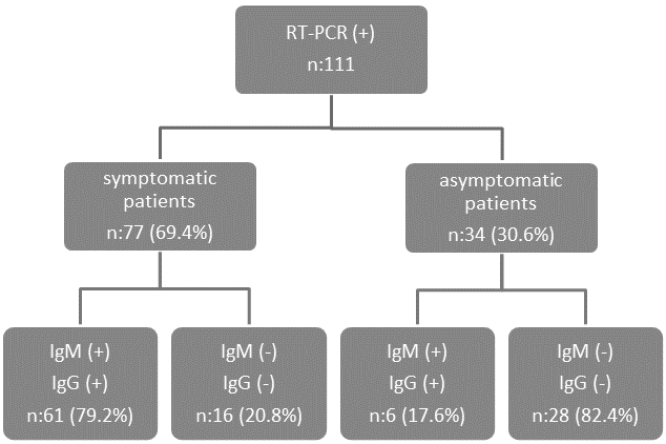

Table 1: Characteristics of the patients

Laboratory Findings		n	%
COVID-19 IgM & IgG	Positive	67	60.4
	Negative	44	39.6
	Total	111	100.0
Decreased WBC count	Present	14	12.6
	Absent	97	87.4
	Total	111	100.0
Increased WBC	Present	7	6.3
	Absent	104	93.7
	Total	111	100.0
Increased Neutrophil %	Present	36	32.4
	Absent	75	67.6
	Total	111	100.0
Decreased Lymphocyte Count	Present	61	55.0
	Absent	50	45.0
	Total	111	100.0
Decreased Lymphocyte %	Present	43	38.7
	Absent	68	61.3
	Total	111	100.0
Decreased platelet count	Present	26	23.4
	Absent	85	76.6
	Total	111	100.0
Increased CRP	Present	50	45.0
	Absent	61	55.0
	Total	111	100.0
Increased Sedimentation	Present	34	40.5
	Absent	50	59.5
	Total	84	100.0
Increased LDH	Present	36	33.3
	Absent	72	66.7
	Total	108	100.0
Increased D-dimer	Present	25	25.0
	Absent	75	75.0
	Total	100	100.0
Increased Ferritin	Present	28	28.3
	Absent	71	71.7
	Total	99	100.0
Increased Procalcitonin	Present	0	0.0
	Absent	110	100.0
	Total	110	100.0

Medical Background		n	%
Concomitant Disease	Present	13	11.7
	Absent	98	88.3
	Total	111	100.0
Hypertension	Present	7	6.3
	Absent	104	93.7
	Total	111	100.0
Diabetes Mellitus	Present	4	3.6
	Absent	107	96.4
	Total	111	100.0
Chronic heart disease	Present	4	3.6
	Absent	107	96.4
	Total	111	100.0
Psoriasis	Present	1	0.9
	Absent	110	99.1
	Total	111	100.0
HIV	Present	1	0.9
	Absent	110	99.1
	Total	111	100.0

Symptoms		n	%
Fever	Present	38	34.2
	Absent	73	65.8
	Total	111	100.0
Shortness of Breath	Present	16	14.4
	Absent	95	85.6
	Total	111	100.0
Cough	Present	50	45.0
	Absent	61	55.0
	Total	111	100.0
Myalgia	Present	46	41.4
	Absent	65	58.6
	Total	111	100.0
Loss of smell	Present	3	2.7
	Absent	108	97.3
	Total	111	100.0
Loss of taste	Present	3	2.7
	Absent	108	97.3
	Total	111	100.0.

Table 2: Treatments, regression of symptoms and involvement on CT of response-positive and negative patients

		COVID-19 IgM & IgG Positive	Negative	*P*-value
Symptom	Present	6 (9.0%)	28 (63.6%)	<0.001
	Absent	61 (91.0%)	16 (36.4%)	
Involvement on CT	Present	40 (59.7%)	19 (43.2%)	0.088
	Absent	27 (40.3%)	25 (56.8%)	
Age (Years)	Mean	43.0	29.0	<0.001
	Standard Deviation	12.387	9.103	
	Median	46.0	26.0	
	Minimum	20.0	19.0	
	Maximum	60.0	52.0	
Use of hydroxychloroquine (Days)	Mean	6.0	5.0	0.011
	Standard Deviation	1.812	1.257	
	Median	5.0	5.0	
	Minimum	2.0	2.0	
	Maximum	10.0	10.0	
Azithromycin use (Day)	Mean	4.0	3.0	0.275
	Standard Deviation	1.390	0.882	
	Median	3.0	3.0	
	Minimum	2.0	3.0	
	Maximum	9.0	5.0	

In the antibody-positive group, 12 patients (17.9%) had leukocytosis and four (6%) had leukopenia. Twenty-one patients (31.3%) had an increased neutrophil percentage, 46 (68.7%) had decreased lymphocyte counts and 30 (44.8%) had a decreased lymphocyte percentage. Twenty-three (34.3%) had thrombocytopenia. Elevated levels of CRP, LDH, D-dimer, and ferritin, and an increased sedimentation rate were detected in 47 (70.1%), 31 (47.7%), 23 (37.1%), 27 (44.3%), and 32 patients (57.1%), respectively, with none having an increased procalcitonin level (Table 3).

In the antibody-negative group, two patients (4.5%) had leukopenia and three (6.8%) had leukocytosis. Fifteen patients (34.1%) had an elevated neutrophil percentage. Decreased lymphocyte counts and decreased lymphocyte percentage were observed in 15 (34.1%) and 13 (29.5%) patients, respectively. Only three patients (6.8%) had thrombocytopenia. Increased levels of CRP, LDH, D-dimer, and ferritin and an increased sedimentation rate were found in three (6.8%), five (11.6%), two (5.3%), one (2.6%), and two (7.1%) patients, respectively. None had an increased procalcitonin level (Table 3).

Concomitant diseases

Overall, 13 patients (11.7%) had at least one accompanying disease, including hypertension in seven patients (6.3%), diabetes in four (3.6%), chronic heart disease in four (3.6%), psoriasis in one, and HIV in one (0.9%) (Table 1). In the antibody-positive group, 10 patients (14.9%) had at least one concomitant disease, including hypertension in five (7.5%), diabetes in four (6%), chronic heart disease in two (3%), and HIV in one patient (1.5%). The remaining three patients (6.8%) in the antibody-negative group had at least one concomitant disease, including hypertension in two (4.5%), chronic heart disease in two (4.5%) and psoriasis in one (2.3%) (Table 3).

CT findings

Chest CT showed pneumonia in 59 patients and no pulmonary involvement in 52 patients. The majority of patients with pulmonary involvement were in the antibody-positive group (n=40, 67.8%) (Table 2).

Logistic regression analysis

The factors associated with antibody production are summarized in Table 4. Only pneumonia on CT imaging did not have a significant effect on antibody production (P=0.09). All other factors were found to have significant effects on antibody positivity, including age (OR=1.1; %95 CI=1.0-1.2; P<0.001), decreased lymphocyte count (OR=4.2; 95% CI=1.9-9.5; P<0.001), thrombocytopenia (OR=7.1; 95% CI=2.0-25.6; P=0.003), elevated levels of CRP (OR=32.1; 95% CI=8.9-115.9; P<0.001), LDH (OR=6.9; 95% CI=2.4-19.8; P<0.001), D-dimer (OR=10.6; 95% CI=2.3-48.2; P=0.002), ferritin (OR=29.4; 95% CI=3.7-228.1; P=0.001), increased sedimentation rate (OR=17.3; 95% CI=3.7-80.2; P<0.001), high fever (OR=4.5; 95% CI=1.8-11.7; P=0.002), shortness of breath (OR=12.4; 95% CI=1.6-97.7; P=0.017), cough (OR=6.1; 95% CI=2.5-14.8; P<0.001) and myalgia (OR=4.7; 95% CI=2.0-11.5; P<0.001).

Table 3: Concomitant diseases and laboratory findings of response-positive and negative patients

		COVID-19 IgM & IgG Positive n (%)	Negative n (%)	*P*-value			COVID-19 IgM/IgG Positive n (%)	Negative n (%)	*P*-value
Concomitant Disease	Present	10 (14.9)	3 (6.8)	0.318	Decreased WBC	Present	12 (17.9)	2 (4.5)	0.075
	Absent	57 (85.1)	41 (93.2)			Absent	55 (82.1)	42 (95.5)	
Hypertension	Present	5 (7.5)	2 (4.5)	0.701	Increased WB	Present	4 (6.0)	3 (6.8)	1.000
	Absent	62 (92.5)	42 (95.5)			Absent	63 (94.0)	41 (93.2)	
Diabetes Mellitus	Present	4 (6.0)	0 (0.0)	0.151	Increased Neutrophil	Present	21 (31.3)	15 (34.1)	0.924
	Absent	63 (94.0)	44 (100.0)			Absent	46 (68.7)	29 (65.9)	
Chronic Heart Disease	Present	2 (3.0)	2 (4.5)	0.648	Decreased Lymphocyte count	Present	46 (68.7)	15 (34.1)	<0.001
	Absent	65 (97.0)	42 (95.5)			Absent	21 (31.3)	29 (65.9)	
Psoriasis	Present	0 (0.0)	1 (2.3)	0.396	Decreased Lymphocyte %	Present	30 (44.8)	13 (29.5)	0.107
	Absent	67 (100.0)	43 (97.7)			Absent	37 (55.2)	31 (70.5)	
HIV	Present	1 (1.5)	0 (0.0)	1.000	Decreased Thrombocyte count	Present	23 (34.3)	3 (6.8)	0.002
	Absent	66 (98.5)	44 (100.0)			Absent	44 (65.7)	41 (93.2)	
Fever	Present	31 (46.3)	7 (15.9)	0.001	Increased CRP	Present	47 (70.1)	3 (6.8)	<0.001
	Absent	36 (53.7)	37 (84.1)			Absent	20 (29.9)	41(93.2)	
Shortness of Breath	Present	15 (22.4)	1 (2.3)	0.007	Increased Sedimentation	Present	32 (57.1)	2 (7.1)	<0.001
	Absent	52 (77.6)	43 (97.7)			Absent	24 (42.9)	26 (92.9)	
Cough	Present	41 (61.2)	9 (20.5)	<0.001	Increased LDH	Present	31 (47.7)	5 (11.6)	<0.001
	Absent	26 (38.8)	35 (79.5)			Absent	34 (52.3)	38 (88.4)	
Myalgia	Present	37 (55.2)	9 (20.5)	<0.001	Increased D-dimer	Present	23 (37.1)	2 (5.3)	0.001
	Absent	30 (44.8)	35 (79.5)			Absent	39 (62.9)	36 (94.7)	
Loss of Smell	Present	3 (4.5)	0 (0.0)	0.276	Increased Ferritin	Present	27 (44.3)	1 (2.6)	<0.001
	Absent	64 (95.5)	44 (100.0)			Absent	34 (55.7)	37 (97.4)	
Loss of Taste	Present	3 (4.5)	0 (0.0)	0.276	Increased Procalcitonin	Present	0 (0.0)	0 (0.0)	NA
	Absent	64 (95.5)	44 (100.0)			Absent	66 (100.0)	44 (100.0)	

Table 4: Factors Affecting IgM/IgG Production in patients with COVID-19

Risk Factor	OR (95% Cl)	*P*-value
Age	1.1 (1.0-1.2)	<0.001
The Presence CT Involvement	1.9 (0.9-4.2)	0.090
Concomitant Disease	2.4 (0.6-9.3)	0.205
Hypertension	1.7 (0.3-9.1)	0.540
Diabetes Mellitus	NA	NA
Chronic Heart Disease	0.6 (0.1-4.8)	0.668
Psoriasis	NA	NA
Decreased WBC	4.6 (1.0-21.6)	0.054
Increased WBC	0.9 (0.2-4.1)	0.857
Increased NEU %	0.8 (0.4-2.0)	0.883
Decreased Lymphocyte count	4.2 (1.9-9.5)	<0.001
Decreased Lymphocyte %	1.9 (0.9-4.3)	0.109
Decreased Platelet count	7.1 (2.0-25.6)	0.003
Increased CRP	32.1 (8.9-115.9)	<0.001
Increased Sedimentation	17.3 (3.7-80.2)	<0.001
Increased LDH	6.9 (2.4-19.8)	<0.001
Increased D-Dimer	10.6 (2.3-48.2)	0.002
Increased Ferritin	29.4 (3.7-228.1)	0.001
Fever	4.5 (1.8-11.7)	0.002
Shortness of Breath	12.4 (1.6-97.7)	0.017
Cough	6.1 (2.5-14.8)	<0.001
Myalgia	4.7 (2.0-11.5)	<0.001
Loss of smell	NA*	NA*
Loss of taste	NA*	NA*

Variables specified as NA* were not evaluated because of impairing the significance of the model
[CI: Confidence Interval], [OR: Odds Ratio]. Dependent variable: IgM/IgG test result (positive or negative).

Discussion

Antibodies produced against SARS-CoV-2 can be detected at an average of 10 to 15 days after the onset of symptoms, and for IgG, it may take 20 days [7]. To detect seropositivity, we assessed only the results of antibody tests obtained on the 28th day of clinical recovery. Thus, time to detect antibodies was adequate and eliminated the effect of changes that may occur over time on antibody production.

COVID-19 specific antibodies can be detected by enzyme-linked immunosorbent assay (ELISA) and immunochromatographic assay (ICA). A study examined seven different ICA tests and compared them with ELISA. The sensitivity of ICA 14-25 days after the onset of the symptoms exceeded 92% for IgG as compared with 89.5% with ELISA. Specificity of ICA was between 91.3%-100% for IgM and 90.3%-99.0% for IgG, being between 97.1%-100% for both IgG and IgM. The sensitivity of ICA was as high as that of ELISA during the first 3 weeks from the onset of complaints [8]. In a study with the ICA antibody test, Imai et al. found that all COVID-19 patients with IgG positivity also had IgM positivity [9]. The utility and sensitivity of combined IgM-IgG analysis were higher than those of a single IgM or IgG test [10]. In our study, antibody tests were performed with the ICA and both IgM and IgG were positive in 67 patients.

Because the detection of antibodies is only possible after a considerably long time from the onset of infections, antibody tests are not a convenient method to detect acute infections. These tests may particularly be useful for isolation programs, examination of antibody responses related to protection against SARS-CoV-2, patient triage, identification of infection-related deaths, determining the exact rate of infection in an affected area, and identification of a potential plasma donor who has recovered from COVID-19 [11,12]. In the fight against the spread of COVID-19, considerable efforts have been made nationwide for the utilization of plasma treatment, screening for potential donors and encouraging plasma donation. Accordingly, we used antibody tests to analyze seroconversion of recovered patients who presented to our outpatient department to donate plasma.

This study included only men due to the small number (n=2) of female patients applying for plasma donation. Interestingly, there was a striking gap between the mean ages of antibody-positive and negative patients. Similar to our results, the incidence of antibody production was higher in individuals over 40 years of age than in the younger patients [7]. The low antibody response in young patients may be associated with the increased rate of asymptomatic disease among them.

Antibody positivity was linked to a poorer clinical course [7]. Long et al. found IgG positivity in 93.3% of asymptomatic patients and in 96.8% of symptomatic patients during the early recovery period. In the asymptomatic group, IgG became negative in the subsequent follow-up of 40% of seropositive patients. These findings suggest that asymptomatic individuals are likely to have a weaker immune response to SARS-CoV-2 infection [13]. In this study, the rate of antibody production in symptomatic patients was approximately 4.5 times higher than in asymptomatic patients. In addition, among the symptoms at presentation, dyspnea was the leading factor in antibody production with an OR of 12.4, followed by cough (OR 6.1), myalgia (OR 4.7), and fever (OR 4.5). Among the laboratory parameters, the leading factor was CRP (OR 32.1) followed by ferritin (OR 29.4) and sedimentation rate (OR 17.3).

Failure to develop anti-SARS-CoV-2 antibody response may result from several factors, including transient viral colonization, false-positive RT-PCR results, contamination of the specimens at the time of RT-PCR, failure of the host to produce an immune response to a specific genotype of the SARS-CoV-2 virus, decreased viral load of the SARS-CoV-2 RNA, and elimination of the virus with hydroxychloroquine treatment before inducing immune response [14]. Examining serial RT-PCR test results at the PCR laboratory, we found no evidence of contamination that could lead to false positivity. Although data were insufficient to assess the relationship between the underlying immunosuppression and antibody response, we found that four patients with diabetes and one patient with HIV had antibody response. Conversely, the antibody-negative group had neither drug use nor concomitant disease that could cause any immunosuppression. It has been reported that early use of hydroxychloroquine may also be associated with failure to produce antibody response by rapidly eliminating the virus before activating the immune system. The rate of antibody response was 60.4% among participants receiving hydroxychloroquine treatment.

Even though the patients might have produced antibody response following SARS-CoV-2 infection, false negative results may be obtained due to several causes, including low IgM and IgG antibody levels below the detection threshold, decreases in IgM antibody levels after 2 weeks and their disappearance over time, low IgM levels below the peak at the time of testing [10]. In our study, a negative test for IgM was never accompanied by a positive IgG test.

Limitations

Due to lack of RT-PCR kits at our hospital to detect the viral load of SARS-CoV-2, we could not assess the effect of viral load on patients' antibody response. In addition, as we only included male patients, the results cannot be generalized for females.

Conclusions

Since the antibody response rate is significantly higher in symptomatic patients, older patients and patients with higher inflammatory parameters, these patients appear to be more suitable candidates for plasma donation. Clinical observations from this study can be used for a controlled prospective study with a larger group of patients, including a more clinically diverse population and other laboratory parameters that may affect antibody response.

References

1. Lv H, Wu NC, Tsang OT, Yuan M, Perera RAPM, Leung WS, et al. Cross-reactive Antibody Response between SARS-CoV-2 and SARS-CoV Infections. Cell Rep. 2020 Jun 2;31(9):107725. doi: 10.1016/j.celrep.2020.107725. Epub 2020 May 18. PMID: 32426212; PMCID: PMC7231734.
2. Huang AT, Garcia-Carreras B, Hitchings MDT, Yang B, Katzelnick LC, Rattigan SM, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun. 2020 Sep 17;11(1):4704. doi: 10.1038/s41467-020-18450-4. PMID: 32943637; PMCID: PMC7499300.
3. Mathur G, Mathur S. Antibody Testing for COVID-19. Am J Clin Pathol. 2020 Jun 8;154(1):1-3. doi: 10.1093/ajcp/aqaa082. PMID: 32412044; PMCID: PMC7239247.
4. Lipsitch M, Kahn R, Mina MJ. Antibody testing will enhance the power and accuracy of COVID-19-prevention trials. Nat Med. 2020 Jun;26(6):818-9. doi: 10.1038/s41591-020-0887-3. PMID: 32341581.
5. Yi Y, Lagniton PNP, Ye S, Li E, Xu RH. COVID-19: what has been learned and to be learned about the novel coronavirus disease. Int J Biol Sci. 2020 Mar 15;16(10):1753-66. doi: 10.7150/ijbs.45134. PMID: 32226295; PMCID: PMC7098028.
6. T. C. Ministry of Health, General Directorate of Health Services, Department of Blood and Blood Products / COVID-19 Immun (Convelesan) Plasma Supply and Clinical Use Guide, Available at: https://dosyamerkez.saglik.gov.tr/Eklenti/37341,COVID-19-immun-konvalesan-plazma-tedarik-ve-klinik-kullanim-rehberi-guncel--r1-v1pdf.pdf?0 (Accessed, July 4, 2020)
7. Tong PB, Lin LY, Tran TH. Coronaviruses pandemics: Can neutralizing antibodies help? Life Sci. 2020 Aug 15;255:117836. doi: 10.1016/j.lfs.2020.117836. Epub 2020 May 22. PMID: 32450171; PMCID: PMC7243778.
8. Van Elslande J, Houben E, Depypere M, Brackenier A, Desmet S, André E, et al. Diagnostic performance of seven rapid IgG/IgM antibody tests and the Euroimmun IgA/IgG ELISA in COVID-19 patients. Clin Microbiol Infect. 2020 Aug;26(8):1082-7. doi: 10.1016/j.cmi.2020.05.023. Epub 2020 May 28. PMID: 32473953; PMCID: PMC7255746.
9. Imai K, Tabata S, Ikeda M, Noguchi S, Kitagawa Y, Matuoka M, et al. Clinical evaluation of an immunochromatographic IgM/IgG antibody assay and chest computed tomography for the diagnosis of COVID-19. J Clin Virol. 2020 Jul;128:104393. doi: 10.1016/j.jcv.2020.104393. Epub 2020 Apr 30. PMID: 32387968; PMCID: PMC7191278.
10. Li Z, Yi Y, Luo X, Xiong N, Liu Y, Li S, et al. Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. J Med Virol. 2020 Sep;92(9):1518-24. doi: 10.1002/jmv.25727. Epub 2020 Apr 13. PMID: 32104917; PMCID: PMC7228300.
11. Beeching NJ, Fletcher TE, Beadsworth MBJ. COVID-19: testing times. BMJ. 2020 Apr 8;369:m1403. doi: 10.1136/bmj.m1403. PMID: 32269032.
12. Amanat F, Stadlbauer D, Strohmeier S, Nguyen THO, Chromikova V, McMahon M, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans.medRxiv [Preprint]. 2020 Apr 16:2020.03.17.20037713. doi: 10.1101/2020.03.17.20037713. Update in: Nat Med. 2020 May 12: PMID: 32511441; PMCID: PMC7239062.
13. Long QX, Tang XJ, Shi QL, Li Q, Deng HJ, Yuan J, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med. 2020 Aug;26(8):1200-4. doi: 10.1038/s41591-020-0965-6. Epub 2020 Jun 18. PMID: 32555424.
14. Lin YC, Cheng CY, Chen CP, Cheng SH, Chang SY, Hsueh PR. A case of transient existence of SARS-CoV-2 RNA in the respiratory tract with the absence of anti-SARS-CoV-2 antibody response. Int J Infect Dis. 2020 Jul;96:464-6. doi: 10.1016/j.ijid.2020.05.070. Epub 2020 May 26. PMID: 32470604; PMCID: PMC7250069.

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Evaluation of macular perfusion in patients with treatment-naive overt hypothyroidism using optical coherence tomography angiography

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Ethics approval for this study was obtained from Uludag University, Faculty of Medicine, Ethics Committee (2021-4/6, 24.02.2021).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Thyroid hormones play an essential role in retinal development and physiological functions. Although the effects of hyperthyroidism on ocular circulation are well-defined, no studies report the effects of clinical hypothyroidism on retinal and choroidal circulation. We aimed to compare the macular vessel density and flow indexes of patients with treatment-naive hypothyroidism and healthy controls using optical coherence tomography angiography (OCTA).

Methods: This case-control study included 104 eyes of 52 participants. Group 1 (n=24) consisted of patients with treatment-naive overt hypothyroidism, while Group 2 (n=28) consisted of age and sex-matched healthy controls. Images were obtained using AngioVue software 2.0 of the OCTA device in a 6 × 6 mm area centered on the macula. Foveal avascular zone (FAZ) area, macular retinal thickness, FAZ perimeter (PERIM), choroidal flow index (CF), outer retinal flow index (ORF) and macular vessel density (VD) in the superficial (SCP) and deep retinal capillary plexus (DCP) were recorded for all patients.

Results: The whole [Group 1: 49.9 (7.0)%; Group 2: 54.6 (5.9)%], parafoveal [Group 1: 54.7 (4.8)%; Group 2: 58.6 (3.9)%] and perifoveal [Group 1: 51.5 (7.2)%; Group 2: 55.9 (6.8)%] VD in DCP were significantly lower in Group 1 compared to Group 2 (P=0.012; P=0.002 and P=0.028 respectively). However, parafoveal VD in SCP was significantly higher in Group 1 [52.4 (2.26)] than in Group 2 [49.9 (6.87)] (P=0.032). The mean VD in DCP was significantly positively correlated with the choroidal (P=0.021) and outer retinal flow indexes (P=0.033). The mean foveal VD in DCP was significantly positively correlated with the mean foveal (P<0.001), parafoveal (P=0.001) and perifoveal retinal thicknesses (P<0.001).

Conclusion: Our study has provided, for the first time, a quantitative assessment of macular perfusion in patients with overt hypothyroidism using OCTA. The reduction in VD in the DCP might be attributed to the lack of angiogenic effects of T4 or neural hypometabolism secondary to hypothyroidism.

Keywords: Choroidal flow, Hypothyroidism, Macular perfusion, Optic coherence tomography angiography, Vessel density

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Introduction

Hypothyroidism, which is most often caused by autoimmune thyroiditis (Hashimoto), is a relatively common disorder affecting approximately 5% of the population [1]. Females are eight times more likely to be affected than males and the incidence increases with age in both sexes [2]. Overt hypothyroidism is characterized by an increased thyroid-stimulating hormone (TSH) and a reduced thyroxine (T4) level, while subclinical hypothyroidism refers to slightly increased serum TSH level in the presence of normal serum T4 level [3].

Symptoms of hypothyroidism include fatigue, weight gain with poor appetite, constipation, poor memory and concentration, shortness of breath, hair loss, dry skin, and menstrual irregularities [4, 5]. Typical findings on physical examination include dry, coarse skin, bradycardia, increases in the level of cholesterol and triglycerides, sleep apnea, cognitive impairment, periorbital and pedal edema. Common ocular manifestations including periorbital edema and blepharoptosis' are generally attributed to the deposition of glycosaminoglycans in the dermis, which results in swelling of the affected area [6].

Thyroid hormones are essential for the development and proper functioning of the central nervous system through their role in gene expression, myelin production, axonal transportation, and neurotransmission [7]. Although less investigated, hypothyroidism may also cause a reduction in flow and vessel density of the central nervous system [8, 9]. Since the retina and optic nerves represent an extension of the central nervous system, one can suggest that hypothyroidism may cause alterations in retinal microstructure and perfusion. Accordingly, changes in peripapillary and macular vessel density values were recently shown in patients with established thyroid eye disease [10].

In the present study, we aimed to assess alterations in microvascular structure and perfusion of the macula in patients with treatment-naive, overt hypothyroidism using optic coherence tomography angiography (OCTA). There are many reports on retinal and choroidal changes related to Graves' Ophthalmopathy in the literature [11, 12]. However, to the best of our knowledge, this is the first study assessing the macular perfusion changes in patients with hypothyroidism using OCTA.

Materials and methods

This retrospective study included 48 eyes of 24 patients with treatment-naive overt hypothyroidism (Group 1) and 56 eyes of 28 age-matched euthyroid, healthy individuals (Group 2) examined between March 2017 and November 2019. A post hoc power analysis revealed that based on the mean, an n of approximately 34 would be needed to obtain statistical power of the recommended 0.80 level. The alpha was set at 0.05. The patients with hypothyroidism were referred to the ophthalmology clinic for suspected glaucoma, dry eye or thyroid-associated ophthalmopathy by an internist. The data recorded included clinical and endocrinologic analysis in addition to ocular examination. Informed consent was obtained from all participants included in the study. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices and was approved by the Ethics Committee of Uludağ University Faculty of Medicine, Bursa, Turkey (2021-4/6).

Patient eligibility

Included were cases aged 20-60 years with spherical or cylindrical refractive error < 6.0 diopters, visual acuity ≥ 20/20, and no systemic diseases in Group 2, and no systemic disease other than hypothyroidism in Group 1. Excluded were patients with diabetic retinopathy or any other choroidal/retinal pathologies, history of any intraocular surgery or laser treatment, history of regular smoking or medication use, including levothyroxine and OCTA images with motion artifacts or signal strength index < 60.

All participants were tested for thyroid function, including free T3, free T4 and thyroid-stimulating hormone (TSH). Overt hypothyroidism was diagnosed in the presence of serum TSH > 4.5 mIU/L and low serum free T4 concentration by an internist. All patients underwent comprehensive ophthalmologic examination, including visual acuity, biomicroscopic anterior and posterior examination, intraocular pressure (IOP, mmHg) assessment and OCTA.

Prior to OCTA measurements, the patients were asked to rest in the sitting position at least for 10 minutes and systemic blood pressure and pulse rate were measured. OCTA measurements were obtained at 3 p.m to avoid normal diurnal variations in flow density [13].

OCTA measurement system

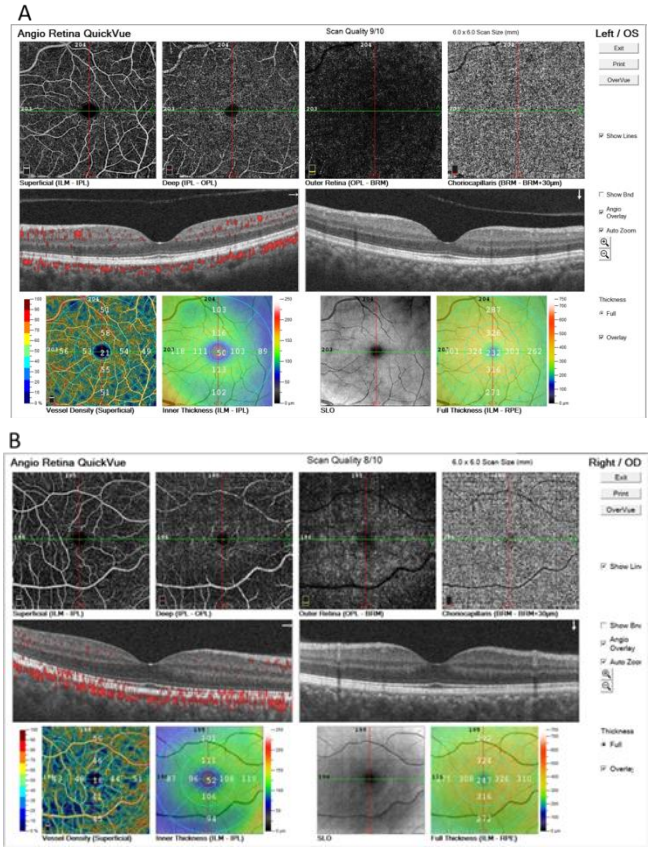
OCTA images were obtained using AngioVue OCTA device (v. 2015.0.1.7, Optovue, Inc., Freemont, CA, USA). This system used a split-spectrum amplitude-decorrelation angiography (SSADA) software algorithm and acquired 70,000 A-scans per second to compose OCTA volumes consisting of 304 × 304 A-scans [14]. The macula was imaged using a 6 mm × 6 mm scan. Quantitative analysis was performed on the OCTA using the AngioAnalytics Phase 7 software. Pupils of all the participants were dilated with 2.5% phenylephrine and 1.0% tropicamide prior to OCTA assessment. The OCTA images of the superficial and deep capillary networks were generated separately using the Optovue software. Based on these default settings, the superficial network comprised between 3 μm below the internal limiting membrane to 15 μm below the inner plexiform layer (IPL), while deep capillary plexus comprised between 15 to 70 μm below the IPL.

The measurements of foveal avascular zone (FAZ) area, FAZ perimeter (PERIM), choroidal flow index (CF) and outer retinal flow index (ORF), whole superficial capillary vessel density (wsVD), foveal superficial vessel density (fsVD), parafoveal superficial vessel density (pasVD), perifoveal superficial vessel density (pesVD), whole deep vessel density (wdVD), foveal deep vessel density (fdVD), parafoveal deep vessel density (padVD), perifoveal deep vessel density (pedVD) in addition to whole, foveal (FT), parafoveal (PaT) and perifoveal (PeT) retinal thicknesses were recorded for Group 1 (Figure 1 A) and Group 2 (Figure 1 B).

The automated FAZ boundary detection, provided by AngioVue, was used. Foveal thickness was expressed as the mean retinal thickness within the center of 1 mm diameter ring, whereas parafovea and perifovea were defined as rings centered on the fovea with inner and outer diameters of 1-3 mm and 3-6

mm, respectively. Vessel density is defined as the percentage area occupied by the blood vessels, while flow index is calculated as the average flow signal in the area of interest, providing information on both vessel area and blood velocity.

Figure 1: The quantitative analysis of macula on the OCTA in a patient with overt-hypothyroidism (A) and control subject (B) using a 6 mm × 6 mm scan



Statistical analysis

All statistical analyses were performed using SPSS 21.0 (Statistical Package for Social Science 21.0). The Kolmogorov–Smirnov test was used to analyze the normality of the data and an independent t test was used to compare the numerical variables between groups. The Chi-square test was used to compare categorical data. Pearson correlation coefficient was used to measure the linear correlation between two variables. A *P*-value less than 0.05 was considered statistically significant.

Results

The mean age of Groups 1 and 2 were 42.83 (11.07) (26-58) years and 41.0 (9.57) (28-57) years, respectively (P=0.53). Sixteen patients (66.6%) in Group 1 were female and the remaining 8 (33.3%) were male. Eighteen patients (64.2%) were female and 10 (35.8%) were male in Group 2 (P=0.89). All patients in Group 1 were newly diagnosed with overt hypothroidism and no thyroid replacement therapy was initiated yet. The mean free T4 and TSH concentrations were 0.430 (0.43) ng/dl and 60.96 (16.68) mIU/L, respectively, in Group 1 and 1.030 (0.347) ng/dl and 2.68 (0.32) mIU/, respectively, in Group 2 (P=0.004, P=0.001). The body mass index (BMI) in Group 1 [28.87 (1.79) kg/m^2] was significantly higher compared with Group 2 [21.83 (1.87) kg/m^2] (P<0.001). The IOP measurements were similar between the groups [Group 1:18.8 (2.24) mmHg, Group 2: 18.2 (1.84) mmHg] (P=0.46).

The mean OCTA features of two groups are shown and compared in Table 1. The parafoveal superficial vessel density was significantly higher in Group 1 compared to Group 2 (P=0.032); whole (P=0.012), parafoveal (P=0.002) and perifoveal (P=0.028) deep vessel density values were significantly lower in Group 1 than Group 2. No statistically significant difference was detected in terms of age, gender, fT4, TSH concentrations, BMI and OCTA parameters (P>0.05 for all).

Table 1: Comparison of the mean OCTA values of the eyes in Group 1(n=48 eyes) and Group 2 (n=56 eyes)

Measurements	Group 1 n=48 eyes	Group 2 n=56 eyes	*P*-value**
FAZ area (mm^2)	0.263 (0.09)	0.269 (0.77)	0.805
PERIM (mm)	1.96 (0.42)	1.98 (0.29)	0.857
CF (mm^2)	2.08 (0.14)	2.13 (0.15)	0.251
ORF (mm^2)	0.60 (0.47)	1.19 (0.60)	0.660
wsVD (%)	49.2 (3.52)	50.3 (2.90)	0.199
fsVD (%)	19.9 (5.08)	24.07 (9.36)	0.714
pasVD (%)	52.4 (2.26)	49.9 (6.87)	0.032*
pesVD (%)	49.9 (3.59)	50.9 (2.97)	0.283
wdVD (%)	49.9 (7.05)	54.6 (5.96)	0.012*
fdVD (%)	37.9 (8.31)	40.4 (6.78)	0.228
padVD (%)	54.7 (4.83)	58.6 (3.99)	0.002*
pedVD (%)	51.5 (7.29)	55.9 (6.81)	0.028*
Whole rT (µm)	285.6 (12.40)	286.5 (15.47)	0.833
FT (µm)	250.2 (25.34)	250.7 (16.13)	0.944
PaT (µm)	315.6 (12.15)	328.0 (16.50)	0.898
PeT (µm)	284.5 (11.17)	283.8 (17.04)	0.866

** Statistical analysis was performed by independent samples t-test, * statistically significant. Bold values represent the variables which show statistical significance, FAZ area: foveal avascular zone area, PERIM: FAZ perimeter, CF: choroidal flow index, ORF: outer retinal flow index, wsVD: whole superficial capillary vessel density, fsVD: foveal superficial vessel density, pasVD: parafoveal superficial vessel density, pesVD: perifoveal superficial vessel density, wdVD: whole deep vessel density, fdVD: foveal deep vessel density, padVD: parafoveal deep vessel density, pedVD: perifoveal deep vessel density, rT: retinal thickness, FT: foveal thickness, paT: parafoveal thickness and peT: perifoveal thickness, SCP: superficial capillary plexus, DCP: deep capillary plexus

The mean wdVD was significantly positively correlated with the mean outer flow and choroid flow (P=0.033, r=0.62; P=0.021, r=0.66, respectively). However, the relationship between the wsVD and outer retinal flow, choroidal flow did not reach statistical significance (P=0.205, P=0.081 respectively). The mean fdVD was significantly positively correlated with mean FT (P<0.001), PaT (P=0.001) and PeT (P<0.001). No significant correlation was observed between any other parameters (P>0.05 for all).

Discussion

The prevalence of overt hypothyroidism in relatively iodine-sufficient populations ranges between 0.3–0.5%, increases in incidence with age and is more common in females than in males at a ratio of 10:1 [15]. The clinical manifestations of hypothyroidism include a wide variety of symptoms that result from hypometabolism of different systems or over-accumulation of glucosaminoglycans in the connective tissues [16, 17]. Ocular findings of hypothyroidism include glaucoma, chemosis, periorbital edema and blepharoptosis due to the accumulation of mucopolysaccharides in the extracellular matrix [6, 18].

Significant associations between hypothyroidism and primary open-angle glaucoma have been reported in the literature [19, 20]. The possible mechanisms that could result in susceptibility to glaucoma include the accumulation of glycosaminoglycans in the meshwork pores, leading to an increase in outflow resistance and reduction in optic nerve head perfusion [21, 22].

The OCTA is a new imaging modality, which allows non-invasive qualitative and quantitative assessment of the retinal and choroidal microvasculature [23-25]. It relies on repeated B-scan OCT images from the same location of the

retina, which provides flow maps of retinal circulation. In addition, cross-sectional images of different retinal layers provide multi-depth assessment of retinal microvasculature. OCTA can measure retinal vessel density, which is defined as the percentage of vessel area with blood flow over the total area measured. Various studies investigated the applicability of OCTA for patients with glaucoma [26], diabetes [27], age-related macular degeneration [28], and Graves' ophthalmopathy [11]. However, no previous research investigated the macular microvascular alterations in hypothyroid patients. This is the first study investigating macular perfusion in hypothyroid patients using swept-source OCTA technology.

In the current study, superficial and deep foveal, parafoveal and perifoveal vessel density, FAZ area and choroidal, outer retinal flow indexes of the patients with treatment-naive overt hypothyroidism were evaluated using OCTA. We found that the whole, parafoveal and perifoveal VD values in DCP were significantly lower in the hypothyroidism group compared with the healthy subjects. The VD is a proportional measurement defining the percentage of the vessel area to the total measurement area. Therefore, the reduction in VD might be attributed to reduced vessel volume or increased total retinal extracellular volume. The glial cell over-stimulation by TSH results in increased production of glycosaminoglycan and connective tissue matrix in hypothyroidism. Accordingly, the mean choroidal thickness is higher in patients with hypothyroidism than in healthy subjects [29].

There are also studies that emphasize the vasomotor effects of thyroid hormones on microcirculation [30-32]. Hypothyroidism is characterized by a reduction in cardiac output and heart rate, and an increase in peripheral vascular resistance [33]. As a result, hypoperfusion of all the major organ systems of the body occurs. Tang et al. [34] reported a significant reduction in the myocardial blood flow and arteriolar vessel density in the drug-induced hypothyroidism animal model. Accordingly, Savinova et al. [35] reported a study investigating the capillary remodeling effect of T3 treatment in hypothyroid rats. The study demonstrated that T3 replacement therapy provides restoration of the arteriolar density to control levels as early as 72 hours. Furthermore, T3 treatment resulted in the simultaneous upregulation of Angiopoietin 1 and 2 expressions, consistent with vessel density improvement.

Another well-known mediator associated with angiogenesis is vascular endothelial growth factor (VEGF). Dedecjus et al. [36] detected significantly reduced plasma VEGF levels in hypothyroid patients. They also noted that the plasma VEGF level returned to a normal value following treatment with T4. Schlenker et al. [37] reported that the forebrain vessel density was reduced in adult thyroidectomized rats compared with healthy controls. They also observed a significant improvement in forebrain VD following 3.5-diiothyroprionic acid (DITPA) or T4 treatments comparable with levels noted in euthyroid rats.

In the current study we found a significant reduction in deep vessel density, which was correlated with outer retinal and choroidal flow indexes, and an increase in superficial parafoveal vessel density in the hypothyroid group. These results can be attributed to the unique circulatory system of the posterior segment. The outer retinal layers are perfused by choroidal vessels via diffusion [38]. However, the inner two thirds of the retina is perfused by the central retinal artery, which is the first branch of the ophthalmic artery. While inner retinal perfusion is mostly regulated by local angiogenic factors, deep retinal perfusion is associated with the systemic perfusion pressure reflecting the cardiac output [39]. Therefore, the cardiac output and, accordingly the outer retinal perfusion decreases in hypothyroidism [33].

This hypoperfusion could induce a compensatory vasodilator mechanism in the inner retina resulting in an increase in superficial retinal perfusion. On the other hand, thyroid hormones play an important role in embryonic development and physiology of the central nervous system throughout life. T3 is essential for myelination, and synaptogenesis, neuronal migration and differentiation [40]. In our study, the mean foveal deep vessel density was positively correlated with macular thickness, indicating a parallelism between macular perfusion and neurosensory retina vitality.

Limitations

There were some limitations to this study, such as the lack of post-treatment microvascular assessment, retrospective study design and a limited number of patients. Further longitudinal studies with a large population, including the comparison of pre-treatment and post-levothyroxine treatment values, are needed to determine whether hormone replacement would provide improvement in macular perfusion.

Conclusions

To the best of our knowledge, this is the first study that provides a quantitative assessment of macular perfusion in patients with treatment-naive overt hypothyroidism. The results of our study demonstrated a significantly reduced whole, parafoveal and perifoveal deep vessel density in the treatment-naive overt hypothyroid patients. Furthermore, the vessel density in the deep capillary plexus is correlated with the choroidal and outer retinal flow indexes and, accordingly, central retinal thickness. We postulate that these changes could reflect early microvascular disruption that precedes permanent thinning of the neurosensory retina.

References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med. 2000 Feb 28;160(4):526-34. doi: 10.1001/archinte.160.4.526.
2. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39-51. doi: 10.1093/bmb/ldr030. PMID: 21893493.
3. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev. 2008 Feb;29(1):76-131. doi: 10.1210/er.2006-0043. Epub 2007 Nov 8.
4. Wartofsky L, Van Nostrand D, Burman KD. Overt and 'subclinical' hypothyroidism in women. Obstet Gynecol Surv. 2006 Aug;61(8):535-42. doi: 10.1097/01.ogx.0000228778.95752.66.
5. Dias AC, Módulo CM, Jorge AG, Braz AM, Jordão AA Jr, Filho RB, et al. Influence of thyroid hormone on thyroid hormone receptor beta-1 expression and lacrimal gland and ocular surface morphology. Invest Ophthalmol Vis Sci. 2007 Jul;48(7):3038-42. doi: 10.1167/iovs.06-1309.
6. Wartofsky L. Diseases of the thyroid. Harrison's Principles of Internal Medicine Volume Chapter 331. 14th edition. Edited by: Fauci SA, Braunwald E. Philadelphia: The McGraw Hill Companies; 1998. pp. 2012-35.
7. Zhang M, Zhan XL, Ma ZY, Chen XS, Cai QY, Yao ZX. Thyroid hormone alleviates demyelination induced by cuprizone through its role in remyelination during the remission period. Exp Biol Med (Maywood). 2015 Sep;240(9):1183-96. doi: 10.1177/1535370214565975. Epub 2015 Jan 10.
8. David S, Nathaniel EJ. Development of brain capillaries in euthyroid and hypothyroid rats. Exp Neurol. 1981 Jul;73(1):243-53. doi: 10.1016/0014-4886(81)90059-5.
9. Gabrichidze GO, Lazrishvili NI, Metreveli DS, Bekaya GL, Mitagvariya NP. Local blood flow in the dorsal hippocampus and cerebellar cortex in the offspring of iodine-deficient rats. Neurosci Behav Physiol. 2007 Jun;37(5):495-8. doi: 10.1007/s11055-007-0041-4.
10. Jamshidian Tehrani M, Mahdizad Z, Kasaei A, Fard MA. Early macular and peripapillary vasculature dropout in active thyroid eye disease. Graefes Arch Clin Exp Ophthalmol. 2019 Nov;257(11):2533-2540. doi: 10.1007/s00417-019-04442-8. Epub 2019 Aug 23.
11. Mihailovic N, Lahme L, Rosenberger F, Hirscheider M, Termühlen J, Heiduschka P, et al. ALTERED RETINAL PERFUSION IN PATIENTS WITH INACTIVE GRAVES OPHTHALMOPATHY USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY. Endocr Pract. 2020 Mar;26(3):312-317. doi: 10.4158/EP-2019-0328. Epub 2019 Dec 20.

12. Zhang T, Xiao W, Ye H, Chen R, Mao Y, Yang H. Peripapillary and Macular Vessel Density in Dysthyroid Optic Neuropathy: An Optical Coherence Tomography Angiography Study. Invest Ophthalmol Vis Sci. 2019 May 1;60(6):1863-1869. doi: 10.1167/iovs.18-25941.
13. Sarwar S, Hassan M, Soliman MK, Halim MS, Sadiq MA, Afridi R, et al. Diurnal variation of choriocapillaris vessel flow density in normal subjects measured using optical coherence tomography angiography. Int J Retina Vitreous. 2018 Oct 10;4:37. doi: 10.1186/s40942-018-0140-0.
14. Huang D, Jia Y, Gao SS, Lumbroso B, Rispoli M. Optical Coherence Tomography Angiography Using the Optovue Device. Dev Ophthalmol. 2016;56:6-12. doi: 10.1159/000442770. Epub 2016 Mar 15.
15. De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Aug;97(8):2543-65. doi: 10.1210/jc.2011-2803. Erratum in: J Clin Endocrinol Metab. 2021 May 13;106(6):e2461.
16. Braverman LE, Utiger RD. Introduction to hypothyroidism. In: Braverman LE, Utiger RD, editors. Werner and Ingabar's the thyroid: a fundamental and clinical text. Philadelphia (PA): Lippincott Williams & Wilkins 2005. pp. 697-9.
17. Khandelwal D, Tandon N. Overt and subclinical hypothyroidism: who to treat and how. Drugs. 2012 Jan 1;72(1):17-33. doi: 10.2165/11598070-000000000-00000.
18. Smith KD, Arthurs BP, Saheb N. An association between hypothyroidism and primary open-angle glaucoma. Ophthalmology. 1993 Oct;100(10):1580-4. doi: 10.1016/s0161-6420(93)31441-7.
19. Kim M, Kim TW, Park KH, Kim JM. Risk factors for primary open-angle glaucoma in South Korea: the Namil study. Jpn J Ophthalmol. 2012 Jul;56(4):324-9. doi: 10.1007/s10384-012-0153-4. Epub 2012 Jun 5.
20. Girkin CA, McGwin G Jr, McNeal SF, Lee PP, Owsley C. Hypothyroidism and the development of open-angle glaucoma in a male population. Ophthalmology. 2004 Sep;111(9):1649-52. doi: 10.1016/j.ophtha.2004.05.026.
21. Wang X, Jiang C, Ko T, Kong X, Yu X, Min W, Shi G, Sun X. Correlation between optic disc perfusion and glaucomatous severity in patients with open-angle glaucoma: an optical coherence tomography angiography study. Graefes Arch Clin Exp Ophthalmol. 2015 Sep;253(9):1557-64. doi: 10.1007/s00417-015-3095-y. Epub 2015 Aug 11.
22. Stein R, Romano A, Treister G, Bartov E. Effect of subconjunctival injection of hyaluronidase on outflow resistance in normal and in open-angle glaucomatous patients. Metab Pediatr Syst Ophthalmol. 1982;6(3-4):169-74.
23. Nagiel A, Sadda SR, Sarraf D. A Promising Future for Optical Coherence Tomography Angiography. JAMA Ophthalmol. 2015 Jun;133(6):629-30. doi: 10.1001/jamaophthalmol.2015.0668.
24. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. Prog Retin Eye Res. 2018 May;64:1-55. doi: 10.1016/j.preteyeres.2017.11.003. Epub 2017 Dec 8.
25. Munk MR, Giannakaki-Zimmermann H, Berger L, Huf W, Ebneter A, Wolf S, et al. OCT-angiography: A qualitative and quantitative comparison of 4 OCT-A devices. PLoS One. 2017 May 10;12(5):e0177059. doi: 10.1371/journal.pone.0177059.
26. Rao HL, Pradhan ZS, Suh MH, Moghimi S, Mansouri K, Weinreb RN. Optical Coherence Tomography Angiography in Glaucoma. J Glaucoma. 2020 Apr;29(4):312-321. doi: 10.1097/IJG.0000000000001463.
27. Sousa DC, Leal I, Moreira S, do Vale S, Silva-Herdade AR, Dionísio P, et al. Optical coherence tomography angiography study of the retinal vascular plexuses in type 1 diabetes without retinopathy. Eye (Lond). 2020 Feb;34(2):307-311. doi: 10.1038/s41433-019-0513-0. Epub 2019 Jul 4.
28. Schneider EW, Fowler SC. Optical coherence tomography angiography in the management of age-related macular degeneration. Curr Opin Ophthalmol. 2018 May;29(3):217-225. doi: 10.1097/ICU.0000000000000469.
29. Ulas F, Dogan Ü, Dikbas O, Celebi S, Keles A. Investigation of the choroidal thickness in patients with hypothyroidism. Indian J Ophthalmol. 2015 Mar;63(3):244-9. doi: 10.4103/0301-4738.156976.
30. Wang X, Zheng W, Christensen LP, Tomanek RJ. DITPA stimulates bFGF, VEGF, angiopoietin, and Tie-2 and facilitates coronary arteriolar growth. Am J Physiol Heart Circ Physiol. 2003 Feb;284(2):H613-8. doi: 10.1152/ajpheart.00449.2002. Epub 2002 Oct 31.
31. Zheng W, Weiss RM, Wang X, Zhou R, Arlen AM, Lei L, et al. DITPA stimulates arteriolar growth and modifies myocardial postinfarction remodeling. Am J Physiol Heart Circ Physiol. 2004 May;286(5):H1994-2000. doi: 10.1152/ajpheart.00991.2003.
32. Tomanek RJ, Doty MK, Sandra A. Early coronary angiogenesis in response to thyroxine: growth characteristics and upregulation of basic fibroblast growth factor. Circ Res. 1998 Mar 23;82(5):587-93. doi: 10.1161/01.res.82.5.587.
33. Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A. Hypothyroidism and the Heart. Methodist Debakey Cardiovasc J. 2017 Apr-Jun;13(2):55-59. doi: 10.14797/mdcj-13-2-55.
34. Tang YD, Kuzman JA, Said S, Anderson BE, Wang X, Gerdes AM. Low thyroid function leads to cardiac atrophy with chamber dilatation, impaired myocardial blood flow, loss of arterioles, and severe systolic dysfunction. Circulation. 2005 Nov 15;112(20):3122-30. doi: 10.1161/CIRCULATIONAHA.105.572883. Epub 2005 Nov 7.
35. Savinova OV, Liu Y, Aasen GA, Mao K, Weltman NY, Nedich BL, et al. Thyroid hormone promotes remodeling of coronary resistance vessels. PLoS One. 2011;6(9):e25054. doi: 10.1371/journal.pone.0025054. Epub 2011 Sep 22.
36. Dedecjus M, Kołomecki K, Brzeziński J, Adamczewski Z, Tazbir J, Lewiński A. Influence of L-thyroxine administration on poor-platelet plasma VEGF concentrations in patients with induced short-term hypothyroidism, monitored for thyroid carcinoma. Endocr J. 2007 Feb;54(1):63-9. doi: 10.1507/endocrj.k05-112. Epub 2006 Nov 8.
37. Schlenker EH, Hora M, Liu Y, Redetzke RA, Morkin E, Gerdes AM. Effects of thyroidectomy, T4, and DITPA replacement on brain blood vessel density in adult rats. Am J Physiol Regul Integr Comp Physiol. 2008 May;294(5):R1504-9. doi: 10.1152/ajpregu.00027.2008. Epub 2008 Mar 19.
38. Campbell JP, Zhang M, Hwang TS, Bailey ST, Wilson DJ, Jia Y, Huang D. Detailed Vascular Anatomy of the Human Retina by Projection-Resolved Optical Coherence Tomography Angiography. Sci Rep. 2017 Feb 10;7:42201. doi: 10.1038/srep42201.
39. Delaey C, Van De Voorde J. Regulatory mechanisms in the retinal and choroidal circulation. Ophthalmic Res. 2000 Nov-Dec;32(6):249-56. doi: 10.1159/000055622.
40. Bernal J. Thyroid Hormones in Brain Development and Function. 2015 Sep 2. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, de Herder WW, Dhatariya K, et al. editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000–. PMID: 25905404.

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Effects of antenatal magnesium sulfate use for neuroprotection on cardiorespiratory complications during the early neonatal period in preterm infants

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Ethics Committee Approval
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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Antenatal magnesium sulfate ($MgSO_4$) treatment is widely used for fetal neuroprotection in women at risk of preterm delivery. Possible adverse effects of $MgSO_4$ include respiratory depression and delay in closure of ductus arteriosus by antagonism of calcium channels. The aim of this study was to investigate the effects of antenatal $MgSO_4$ exposure on cardiorespiratory complications during the early neonatal period in premature infants.

Methods: A retrospective cohort study was performed on 340 preterm infants born between 23 and 32 weeks of gestational age. Patients were divided into two groups according to antenatal $MgSO_4$ exposure: The $MgSO_4$ group (n=186) and the no-$MgSO_4$ group (n=154). Outcomes were acute cardiorespiratory events (intubation at birth, respiratory support, and hypotension in first day of life), and hemodynamically significant patent ductus arteriosus (HsPDA).

Results: Mothers in the $MgSO_4$ group were more likely to have preeclampsia and antenatal steroid treatment, while their infants were younger in gestation and weighed less (P<0.05). Multivariate regression analysis showed that antenatal $MgSO_4$ exposure was significantly associated with decreased mechanical ventilation (odds ratio [OR] 0.45 95% confidence interval [CI] 0.25-0.81, P=0.008), hypotension (OR 0.47, 95% CI 0.24-0.90, P=0.023) and HsPDA (OR 0.52, 95% CI 0.28-0.97, P=0.039). There was no significant association between antenatal $MgSO_4$ exposure and intubation at birth (OR 1.06 95% CI 0.62-1.82, P=0.828).

Conclusion: Among the preterm infants ≤32 weeks, antenatal $MgSO_4$ was not associated with increased risk for acute cardiorespiratory events during the early neonatal period. It might have a protective role in helping with ductal closure.

Keywords: Antenatal magnesium sulfate, Neonatal resuscitation, Patent ductus arteriosus, Preterm infants, Neuroprotection

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Introduction

Recent advances in perinatal medicine have markedly increased the survival rates of premature infants. However, long-term neurodevelopmental outcomes, particularly cerebral palsy, and cognitive deficits, remain important health challenges [1, 2].

Magnesium sulfate ($MgSO_4$) therapy has long been widely used for tocolysis in preterm labor and seizure prevention in preeclampsia [3]. Large randomized controlled trials and systematic reviews have reported that antenatal $MgSO_4$ exposure reduces the risk of gross motor dysfunction and cerebral palsy in surviving infants [4-7]. Based on the available evidence, some national guidelines have recommended antenatal $MgSO_4$ for fetal neuroprotection [8].

However, several studies raised concerns about the possible adverse effects of antenatal $MgSO_4$ in terms of neonatal morbidities [9]. In the Magnesium and Neurological Endpoints Trial [10], antenatal $MgSO_4$ was associated with a higher risk for adverse neonatal outcomes. Previous studies reported that antenatal $MgSO_4$-exposed infants had an increased risk for hypotonia, delivery room intubation, and significant patent ductus arteriosus (PDA) compared with infants not exposed to antenatal $MgSO_4$ [11-13]. However, the cardiorespiratory effect of antenatal $MgSO_4$ in preterm infants is still controversial [14, 15].

In our unit, $MgSO_4$ is administered for fetal neuroprotection in preterm deliveries. This study aimed to investigate the effects of antenatal $MgSO_4$ exposure on cardiorespiratory complications during the early neonatal period in premature infants.

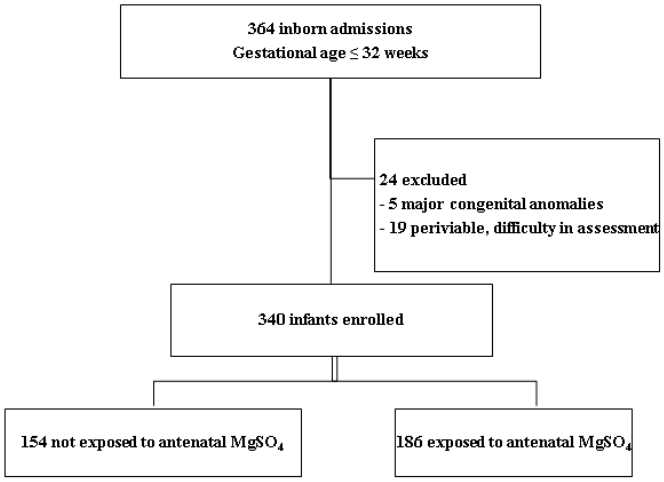
Materials and methods

This retrospective study was performed in the neonatal intensive care unit (NICU) of a university hospital. It was approved by Istanbul Medeniyet University, Goztepe Training and Research Hospital Ethics Committee (Number: 2021/0287, date: 21.06.2021) and conducted per the principles of the 2008 Declaration of Helsinki. Informed consent was obtained from the families of the patients included in the study for all interventional procedures during admission to the NICU. The STROBE checklist was used in the study design and drafting of the manuscript [16].

All inborn infants with a gestational age of 32 weeks or less admitted to our NICU during the study period were evaluated. Data were obtained from the electronic records and patients' files. Infants with major congenital anomalies were excluded from the study. We also excluded the periviable infants who died within the first day of life due to the difficulty in determining the effects of $MgSO_4$ on neonatal outcomes.

A total of 364 preterm infants were assessed for eligibility for the study. Of these, 24 infants were excluded based on our criteria, leaving 340 infants in the cohort for analysis. Patients were divided into two groups according to antenatal $MgSO_4$ exposure as the $MgSO_4$ group and no-$MgSO_4$ group. Of the 340 infants in the study, 186 (54.7%) were exposed to antenatal $MgSO_4$ (Figure 1).

Figure 1: Flow diagram of the study



In our center, antenatal $MgSO_4$ therapy for neuroprotection is standard practice for preterm deliveries ≤ 32 weeks since 2014 and consists of a loading dose of 4 g, followed by a 2 g per hour continuous infusion. It is discontinued if the delivery has not occurred in 12 hours. Antenatal care and delivery of patients were carried out according to the unit protocols.

We reviewed hospital electronic records and patients' files and collected the following data: Maternal age, complications during pregnancy (preeclampsia, preterm prolonged rupture of membrane, and chorioamnionitis), whether mothers received antenatal steroid (ANS) and $MgSO_4$ therapy, delivery mode, gestational age, birth weight, gender, 1- and 5-minute APGAR scores and neonatal outcomes. Antenatal steroid treatment was defined as the completion of 2 doses of 12 mg betamethasone before delivery. Gestational age determination was based on the last menstrual period confirmed by ultrasonography during the first half of pregnancy or Ballard score.

Primary outcomes were acute cardiorespiratory events such as intubation at birth, respiratory support, and hypotension (treated with volume resuscitation, pressors, or steroids) within the first day of life, and hemodynamically significant PDA (HsPDA) (non-restrictive left-to-right shunt identified by echocardiography that was medically or surgically treated). Intubation for surfactant administration followed by immediate removal was not considered as intubation at birth. Types of respiratory support included invasive mechanical ventilation, nasal intermittent positive pressure ventilation or continuous positive airway pressure (CPAP). Data on intraventricular hemorrhage (IVH), duration of invasive ventilation, age at full enteral feeds, necrotizing enterocolitis (NEC) (stage ≥2) [17], moderate to severe bronchopulmonary dysplasia (BPD) [18], retinopathy of prematurity (ROP) [19], length of NICU stay and mortality were also collected.

All infants were evaluated by echocardiography performed by a pediatric cardiologist within the first 3 days of life, as per our unit protocol. The management of PDA was based on the Turkish Neonatal Society PDA guidelines [20]. These infants were also screened for IVH at least weekly by a neonatologist.

Statistical analysis

SPSS 23.0 for Windows program was used for data analysis. The distribution of continuous variables was checked

by the Shapiro-Wilk test. Non-normally distributed numerical variables were presented as median and interquartile range (IQR) and compared with the Mann-Whitney U test. Chi-square and Fisher's exact tests were used for the comparison of categorical variables. Baseline characteristics with $P<0.1$ (gestational age, ANS treatment, preeclampsia, and 5-minute Apgar score) were selected and included in the multivariate model. Stepwise binary logistic regression was used to identify the association between antenatal $MgSO_4$ exposure and primary outcomes. Results were presented as odds ratio (OR) and 95% confidence interval (CI). *P*-values <0.05 were considered statistically significant.

Results

The mean gestational age and birth weight of the infants in the study were 28.9 (2.6) (range: 23-32) weeks and 1228.9 (441.5) (range: 400-2290) g, respectively. The female to male ratio was 0.9.

Baseline characteristics of the groups are presented in Table 1. Women in the $MgSO_4$ group were more likely to have preeclampsia (37.6% vs. 13.6%, $P<0.001$) and received ANS treatment (83.9% vs. 70.1%, $P=0.002$). Infants in the $MgSO_4$ group had lower gestational age and birth weight ($P<0.001$ for both).

Table 1: Comparison of baseline characteristics among the study groups

	$MgSO_4$ (n=186) Median (IQR)	No-$MgSO_4$ (n=154) Median (IQR)	*P*-value
Maternal age (y)	29 (26-32)	29 (25-31)	0.218
Gestational age (wk)	29 (26-30)	30 (28-32)	<0.001
Birth weight (g)	1096 (788-1400)	1348 (998-1655)	<0.001
Apgar score at 1 min	5 (4-6)	5 (4-6)	0.227
Apgar score at 5 min	7 (7-8)	7 (6-8)	0.096
	n (%)	n (%)	
Preeclampsia	70 (37.6)	21 (13.6)	<0.001
Prolonged rupture of membrane	32 (17.2)	34 (22.1)	0.258
Chorioamnionitis	11 (5.9)	13 (8.4)	0.361
Antenatal steroid	157 (84.4)	105 (68.2)	<0.001
Cesarean delivery	149 (80.1)	113 (78.6)	0.142
Male sex	94 (50.5)	81 (52.6)	0.705
Multiple gestation	19 (10.2)	17 (11)	0.806
Small for gestational age	29 (15.6)	16 (10.4)	0.159

IQR, interquartile range

There were no significant differences in the rates of intubation at birth, respiratory support, hypotension treatment in the first day of life, and HsPDA between the groups (Table 2). Other morbidities, and the length of mechanical ventilation or hospital stay, and age at full enteral feeds were also similar (Table 3).

Table 2: Comparison of primary outcomes among the study groups

	MgSO4 (n=186) n (%)	No MgSO4 (n=154) n (%)	*P*-value
Intubation at birth	75 (40.3)	47 (30.5)	0.061
Respiratory support [a]	138 (74.2)	110 (71.4)	0.568
Mechanical ventilation	100 (53.8)	82 (53.2)	0.924
Hypotension	42 (22.6)	36 (23.4)	0.862
HsPDA	50 (26.9)	37 (24.0)	0.548

a: Respiratory support included invasive mechanical ventilation and nasal intermittent positive pressure ventilation or continuous positive airway pressure (CPAP). HsPDA: hemodynamically significant patent ductus arteriosus

After adjustment for covariates including gestational age, preeclampsia, ANS status, and 5-minute Apgar score, antenatal $MgSO_4$ was significantly associated with reduced risk for mechanical ventilation (OR 0.45 95% CI 0.25-0.81, $P=0.008$), hypotension treatment (OR 0.47 95% CI 0.24-0.90, $P=0.023$) and HsPDA (OR 0.52 95% CI 0.28-0.97, $P=0.039$). There was no significant association between antenatal $MgSO_4$ exposure and the need for intubation at birth (OR 1.06 95% CI 0.62-1.82, $P=0.828$) (Table 4).

Table 3: Comparison of neonatal mortality and morbidity among the study groups

	MgSO4 (n=186) n (%)	No MgSO4 (n=154) n (%)	*P*-value
IVH	46 (24.7)	33 (21.4)	0.473
IVH (Grade ≥3)	8 (4.3)	7 (4.5)	0.913
PVL	2 (1.3)	2 (1.1)	0.849
NEC (Stage ≥2)	13 (7)	7 (4.6)	0.340
Sepsis (culture proven)	42 (22.6)	24 (15.8)	0.117
Moderate to severe BPD	47 (25.3)	28 (18.2)	0.117
ROP	16 (8.6)	10 (6.5)	0.466
Mortality	30 (16.1)	19 (12.3)	0.322
	Median (IQR)	Median (IQR)	
Length of mechanical ventilation (d)	5 (0-18)	4 (0-13)	0.512
Time to full enteral feed (d)	24 (17-35)	21.5 (15-32)	0.243
Length of hospitalization (d)	66 (35-89)	58.5 (34-84)	0.408

IVH: intraventricular hemorrhage, PVL: periventricular leukomalacia, NEC: necrotizing enterocolitis, BPD: bronchopulmonary dysplasia, ROP: retinopathy of prematurity; IQR: interquartile range

Table 4: Multivariate logistic regression analysis estimating effects of antenatal magnesium exposure and risk of cardiorespiratory complications

Outcomes	OR	95% CI	*P*-value
Intubation at birth	1.06	0.62 – 1.82	0.828
Respiratory support	0.61	0.34 – 1.11	0.108
Mechanical ventilation	0.45	0.25 – 0.81	0.008
Hypotension	0.47	0.24-0.90	0.023
HsPDA	0.52	0.28 – 0.97	0.039

Covariates: gestational age, antenatal steroids, preeclampsia. 5 min Apgar score, OR: odds ratio, CI: confidence interval, HsPDA: hemodynamically significant patent ductus arteriosus

Discussion

In this retrospective analysis of very premature infants, we demonstrated that antenatal $MgSO_4$ exposure was not associated with increased risk for resuscitation at the delivery room, neonatal morbidities, delayed feeding, mortality, or longer hospital stay. Moreover, the rates of invasive mechanical ventilation, hypotension and HsPDA of infants exposed to antenatal $MgSO_4$ were significantly less compared to non-exposed infants.

There are limited data on the effect of antenatal $MgSO_4$ exposure on neonatal cardiorespiratory complications. Magnesium given to the mother was associated with hypotonia, hyporeflexia, and respiratory depression in neonates [21, 22]. Abbassi-Ghanavati et al. [11] reported hypotonia, lower APGAR scores, increased intubation at the delivery room with antenatal MgSO4 exposure. However, in a clinical trial, Johnson et al. [23] did not find any correlation between antenatal magnesium exposure and the need for resuscitation among preterm infants exposed to antenatal $MgSO_4$ for neuroprotection. In the current study, there was no association between antenatal $MgSO_4$ and risk for intubation at birth.

A study from Turkey reported a significantly lower rate of respiratory distress among antenatal $MgSO_4$ exposed infants than antenatal $MgSO_4$ unexposed infants, though mechanical ventilation rates were similar [24]. In our study, antenatal $MgSO_4$ was significantly associated with a reduced need for invasive mechanical ventilation, but there was no significant association between antenatal $MgSO_4$ exposure and total respiratory support. In preterm infants, invasive mechanical ventilation can lead to lung injury resulting in chronic lung disease. Therefore, ventilation strategies were changed to use more non-invasive modes to prevent lung injury [25, 26]. The change in ventilation practices can explain the differences in the rates of invasive ventilation between studies. In our study, more infants in the $MgSO_4$ group received ANS treatment, which reduces the severity of RDS and need for mechanical ventilation

[27], which again might result in a lower need for mechanical ventilation among infants in the $MgSO_4$ group.

Reports on the association of antenatal $MgSO_4$ with hypotension are limited. Two clinical trials reported no significant relationship between antenatal $MgSO_4$ exposure and the risk of hypotension [4, 5]. In our study, infants exposed to antenatal $MgSO_4$ had significantly less hypotension treatment, consistent with the study by De Jesus et al. [14]. They evaluated 1544 infants <29 weeks' gestational age and reported a significant decrease in hypotension treatment related to antenatal $MgSO_4$ exposure. Magnesium ions regulate vascular tone and contribute to the stabilization of blood pressure and improvement of cardiac function in the first days of life [28]. Hypotension in preterm infants is associated with lower gestational age, and higher mean airway pressure. Also, ANS treatment improves systemic blood pressure in preterm infants [29]. In our study, more ANS exposure and less invasive MV in these infants may explain our finding of less hypotension in infants exposed to antenatal $MgSO_4$.

Magnesium ions antagonize the effects of intracellular calcium and modulate prostacyclin synthesis in the vascular smooth muscle cell. Both mechanisms lead to vasodilatation and can cause a delay in ductus arteriosus closure in preterm infants [30]. Previous studies reported an increased risk for symptomatic PDA in extremely preterm infants who were exposed to antenatal $MgSO_4$ [12, 13]. However, in a study on cardiovascular effects of antenatal $MgSO_4$, Paradisis et al. [31] reported an incidental finding of significantly smaller PDA in the exposed group. Qasım et al. [15] recently showed a decreasing trend of HsPDA with antenatal $MgSO_4$ exposure. In our study, antenatal $MgSO_4$ was associated with significantly decreased HsPDA. Although there were more infants treated with ANS in the antenatal $MgSO_4$ exposed group, ANS treatment did not show an association with HsPDA in multivariate analysis. The variations in the study results can be explained by the differences in PDA management. Most previous studies evaluated PDA after clinical symptoms were encountered. In our study, all infants were routinely screened by echocardiography for evaluation of PDA. Our finding of reduced risk for HsPDA with antenatal $MgSO_4$ exposure indicates that magnesium might affect ductal closure by different complex intracellular actions rather than antagonizing the calcium channels responsible for mediating ductal constriction. Further studies are needed to explore the effects of antenatal $MgSO_4$ on PDA.

In our center, antenatal $MgSO_4$ therapy consisted of a 4 g loading dose followed by an infusion of 2 g per hour and stopped if delivery did not occur in 24 hours. However, there is no consensus on an effective and safe dose of antenatal $MgSO_4$. Studies using higher doses of $MgSO_4$ have shown a trend towards increased perinatal mortality [5, 9]. McPherson et al. [32] reported similar effectivity on neuroprotection between higher and lower doses of antenatal $MgSO_4$. In addition to dose, gestational age, birth weight, maternal characteristics are related to the effects of antenatal $MgSO_4$. Ohhashi et al [33] found that antenatal $MgSO_4$ was more effective in infants born at 28-32 weeks of gestation with a low dose regimen (<50 g). In this study, we could not perform subgroup analysis due to the small sample size. In addition, we were unable to investigate the association between total magnesium dose received and change in neonatal outcomes.

Another limitation of this study includes the lack of data on neonatal serum magnesium concentration. In preterm infants, higher neonatal serum magnesium concentrations were associated with an increased risk for mortality [9, 10]. As this was a retrospective study, possible confounding factors might be missed. However, being a single center study in which all patients were managed using the same standard protocols regarding maternal and newborn follow-up can be considered a strength. In our center, antenatal $MgSO_4$ for neuroprotection is a standard practice in all women at risk of preterm birth before 33 weeks of gestation. However, 45.3% of eligible women did not receive antenatal MgSO4 and the rate of receiving ANS treatment was also low. These women probably do not have enough time between admission to the hospital and delivery. To account for the effects of ANS and maternal factors, we performed a multivariate analysis and found that antenatal MgSO4 has significant reducing effects on mechanical ventilation, hypotension, and HsPDA independent of ANS and other confounders.

Conclusions

The use of antenatal $MgSO_4$ for neuroprotection was not associated with an increase in cardiorespiratory complications in preterm infants born ≤ 32 weeks of gestation. Moreover, infants exposed to antenatal $MgSO_4$ had significantly less invasive mechanical ventilation, and hypotension treatment in the first day of life. Antenatal Mg appears to have a protective role in helping with ductal closure. Further studies with a larger population are needed to clarify the effect of antenatal MgSO4 on acute cardiorespiratory events and HsPDA.

References

1. Kruse M, Michelsen S, Flachs EM, Brønnum-Hansen H, Madsen M, Uldall P. Lifetime costs of cerebral palsy. Dev Med Child Neurol. 2009;51(8):622–8. doi: 10.1111/j.1469-8749.2008.03190.x.
2. Paneth N, Hong T, Korzeniewski S. The descriptive epidemiology of cerebral palsy. Clin Perinatol. 2006;33(2):251–67. doi: 10.1016/j.clp.2006.03.011.
3. Duley L, Gulmezoglu AM, Chou D. Magnesium sulphate versus lytic cocktail for eclampsia. Cochrane Database Syst Rev 2010;2010(9):CD002960. doi: 10.1002/14651858.CD002960.pub2.
4. Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before pretermbirth: a randomized controlled trial. JAMA 2003; 290(20):2669–76. doi: 10.1001/jama.290.20.2669
5. Rouse DJ, Hirtz DG, Thom E, Varner MW, Spong CY, Mercer BM, et al; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. N Engl J Med 2008;359 (9):895–905. doi: 10.1056/NEJMoa0801187.
6. Marret S,Marpeau L, Follet-Bouhamed C, Cambonie G, Astruc D, Delaporte B, et al; le groupe PREMAG. Effect of magnesium sulphate on mortality and neurologic morbidity of the very-preterm newborn (of less than 33 weeks) with two-year neurological outcome: results of the prospective PREMAG trial. Gynecol Obstet Fertil 2008;36(3):278–288. doi: 10.1016/j.gyobfe.2008.01.012.
7. Shepherd E, Salam RA, Middleton P, Makrides M, McIntyre S, Badawi N, et al. Antenatal and intrapartum interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews. Cochrane Database Syst Rev 2017;8(8):CD012077. doi: 10.1002/14651858.CD012077.pub2
8. Committee Opinion No. 455: Magnesium sulfate before anticipated preterm birth for neuroprotection. Obstet Gynecol. 2010;115(3):669-671. doi: 10.1097/AOG.0b013e3181d4ffa5.
9. Narasimhulu D, Brown A, Egbert NM, Rojas M, Haberman S, Bhutada A, et al. Maternal magnesium therapy, neonatal serum magnesium concentration and immediate neonatal outcomes. J Perinatol. 2017;37(12):1297-1303. doi: 10.1038/jp.2017.132
10. Mittendorf R, Dambrosia J, Pryde PG, Lee KS, Gianopoulos JG, Besinger RE, et al. Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants. Am J Obstet Gynecol. 2002;186 (6):1111-8. doi: 10.1067/mob.2002.123544.
11. Abbassi-Ghanavati M, Alexander JM, McIntire DD, Savani RC, Leveno KJ. Neonatal effects of magnesium sulfate given to the mother. Am J Perinatol 2012;29(10):795-9. doi: 10.1055/s-0032-1316440.
12. del Moral T, Gonzalez-Quintero VH, Claure N, Vanbuskirk S, Bancalari E. Antenatal exposure to magnesium sulfate and the incidence of patent ductus arteriosus in extremely low birth weight infants. J Perinatol 2007;27(3):154-7. doi: 10.1038/sj.jp.7211663.
13. Katayama Y, Minami H, Enomoto M, Takano T, Hayashi S, Lee YK. Antenatal magnesium sulfate and the postnatal response of the ductus arteriosus to indomethacin in extremely preterm neonates. J Perinatol. 2011;31(1):21-4. doi: 10.1038/jp.2010.62.
14. De Jesus LC, Sood BG, Shankaran S, Kendrick D, Das A, Bell EF, et al. ; Eunice Kennedy Shriver National Institute of Health and Human Development Neonatal Research Network. Antenatal magnesium sulfate exposure and acute cardiorespiratory events in preterm infants. Am J Obstet Gynecol. 2015;212(1):94.e1-7. doi: 10.1016/j.ajog.2014.07.023

15.Qasim A, Jain SK, Aly AM. Antenatal Magnesium Sulfate Exposure and Hemodynamically Significant Patent Ductus Arteriosus in Premature Infants. AJP Rep. 2019;9(4):e353-e356. doi: 10.1055/s-0039-3400316.
16.Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Epidemiology 2007;18(6):805-35
17.Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: pathogenesis, classification, and spectrum of disease. Curr Probl Pediatr Adolesc Health Care 1987;7(4):213-88. doi: 10.1016/0045-9380(87)90031-4.
18.Walsh MC, Wilson-Costello D, Zadell A, Newman N, Fanaroff A. Safety, reliability, and validity of a physiologic definition of bronchopulmonary dysplasia. J Perinatol 2003;23(6):451-6. doi: 10.1038/sj.jp.7210963.
19.Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005;123(7):991-9. doi: 10.1001/archopht.123.7.991.
20.Köksal N, Aygün C, Uras N. Türk Neonatoloji Derneği. Prematüre Bebekte Patent Duktus Arteriosus'a Yaklaşım Rehberi 2016.
21.Lipsitz PJ, English IC. Hypermagnesemia in the newborn infant.Pediatrics 1967;40(5):856–862
22.Rasch DK, Huber PA, Richardson CJ, L'Hommedieu CS, Nelson TE, Reddi R. Neurobehavioral effects of neonatal hypermagnesemia. J Pediatr 1982;100(2):272-6. doi: 10.1016/s0022-3476(82)80654-9.
23.Johnson LH, Mapp DC, Rouse DJ, Spong CY, Mercer BM, Leveno KJ, et al. Association of cord blood magnesium concentration and neonatal resuscitation. J Pediatr 2012;160(4):573-577.e1. doi: 10.1016/j.jpeds.2011.09.016.
24.Özlü F, Hacıoğlu C, Büyükkurt S, Yapıcıoğlu H, Satar, M . Changes on preterm morbidities with antenatal magnesium. Cukurova Medical Journal 2019;44:502-508
25.Bancalari E, Claure N. Strategies to accelerate weaning from respiratory support. Early Hum Dev 2013;89 Suppl 1:S4-6. doi: 10.1016/S0378-3782(13)70002-1
26.Vendettuoli V, Bellu R, Zanini R, Mosca F, Gagliardi L; for the Italian Neonatal Network. Changes in ventilator strategies and outcomes in preterm infants. Arch Dis Child Fetal Neonatal Ed 2014;99(4):F321-4. doi: 10.1136/archdischild-2013-305165
27.Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017;3(3):CD004454. doi: 10.1002/14651858.CD004454.pub3.
28.Osborn DA, Evans N, Kluckow M. Hemodynamic and antecedent risk factors of early and late periventricular/intraventricular hemorrhage in premature infants. Pediatrics 2003;112(1 Pt 1):33-9. doi: 10.1542/peds.112.1.33
29.Demarini S, Dollberg S, Hoath SB, Ho M, Donovan EF. Effects of antenatal corticosteroids on blood pressure in very low birth weight infants during the first 24 hours of life. J Perinatol 1999;19(6 Pt 1):419-25. doi: 10.1038/sj.jp.7200245.
30.Satake K, Lee JD, Shimizu H, Uzui H, Mitsuke Y, Yue H, et al. Effects of magnesium on prostacyclin synthesis and intracellular free calcium concentration in vascular cells. Magnes Res 2004;17(1):20-27
31.Paradisis M, Osborn DA, Evans N, Kluckow M. Randomized controlled trial of magnesium sulfate in women at risk of preterm delivery-neonatal cardiovascular effects. J Perinatol 2012;32(9):665-70. doi: 10.1038/jp.2011.168.
32.McPherson JA, Rouse DJ, Grobman WA, Palatnik A, Stamilio DM. Association of duration of neuroprotective magnesium sulfate infusion with neonatal and maternal outcomes. Obstet Gynecol. 2014;124(4):749-755. doi: 10.1097/AOG.0000000000000467
33.Ohhashi M, Yoshitomi T, Sumiyoshi K, Kawagoe Y, Satoh S, Sameshima H, et al. Magnesium sulphate and perinatal mortality and morbidity in very-low birth weight infants born between 24 and 32 weeks of gestation in Japan. Eur J Obstet Gynecol Reprod Biol 2016;201:140-5. doi: 10.1016/j.ejogrb.2016.03.048.

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Early enteral nutrition with L-glutamine improves anastomotic healing in rats administered hyperthermic intraperitoneal chemotherapy with cisplatin and 5-FU

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Ethics Committee Approval
This study was conducted at Adiyaman University Experimental Animal Application and Research Center (Adiyaman, Turkey) after obtaining the approval of the Experimental Animals Local Ethics Committee of the university (Referance No: 2019/019).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: One of the most significant aspects of intestinal surgery is anastomotic wound healing. After intestinal surgery, the most serious complication is gastrointestinal leakage, which is associated with a high rate of morbidity and mortality. The rate of morbidity and mortality can be reduced by increasing the mechanical resistance of the anastomosis. Glutamine improves impaired wound healing through effects on the healing process. This study investigated the effects of early enteral glutamine supplementation on colonic anastomosis healing in rats treated with hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin and fluorouracil (5-FU).

Methods: Twenty-four rats were divided into three groups. Group 1 underwent colonic anastomosis and intraabdominal hyperthermic saline administration, Group 2 underwent colonic anastomosis and HIPEC, and Group 3 underwent colonic anastomosis and HIPEC and postoperative administration of glutamine solution via an orogastric tube for 7 days. On day 7, all rats were sacrificed and anastomotic bursting pressure (ABP) was evaluated. Tissue specimens were taken to examine tissue hydroxyproline levels and histopathological changes in the anastomotic line.

Results: The ABP was significantly greater in Group 2 than in Groups 1 and 3 (P=0.001 and P=0.046, respectively). The tissue hydroxyproline level was higher in Group 1 and Group 3 than in Group 2 (P=0.001 and P=0.043, respectively). The histopathological findings in Group 3 were better than those in Group 2. The histopathological findings were observed to improve in the early enteral nutrition with Glutamine group.

Conclusions: The findings of this study indicate that early enteral glutamine supplementation facilitates colonic anastomosis healing following HIPEC with cisplatin and 5-FU, by increasing the ABP and tissue concentrations of hydroxyproline and decreasing the inflammatory response.

Keywords: Glutamine, Colonic anastomosis, Bursting pressure, Wound Healing, Hyperthermic Intraperitoneal Chemotherapy

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Introduction

Peritoneal carcinomatosis (PC) is a clinical condition caused by the dissemination of cancer cells originating from the peritoneal surface or often internal organs to the abdominal cavity and is associated with poor prognosis and reduced survival. The cancer spreads to the intestines, peritoneum, mesentery, and other visceral organs, leading to malnutrition, ileus and death [1, 2]. In selected patients with PC, the combination of cytoreductive surgery (CRS) with hyperthermic chemotherapy (HIPEC) administered to the peritoneal cavity is an effective approach for clinically managing this disease [3]. Gastrointestinal leakage occurs in approximately 5–34% of patients treated with CRS and HIPEC and is also a cause of severe morbidity and mortality [4-6]. Previous studies demonstrated the adverse effects of HIPEC treatment on anastomosis by impairing wound healing [7, 8].

Glutamine is the most abundant free amino acid in plasma and is stored mainly in the lungs and skeletal muscles [9]. Oral glutamine administration improves wound healing through its role in wound healing processes such as collagen synthesis, wound contraction, and epithelization, and increases the anastomotic bursting pressure (ABP) of colorectal anastomoses [10, 11].

To the best of our knowledge, no studies evaluated the effects of early enteral nutritional support with glutamine on anastomosis in HIPEC patients. Therefore, we investigated the effects of early enteral glutamine supplementation on colonic anastomosis recovery in rats treated with HIPEC with cisplatin combined with fluorouracil (5-FU).

Materials and methods

This study was conducted at Adiyaman University Experimental Animal Application and Research Center (Adiyaman, Turkey) after obtaining the approval of the Experimental Animals Local Ethics Committee of the university (Referance No: 2019/019). All animal experiments were performed according to the World Medical Association Code of Ethics (Helsinki Declaration). The study used Twenty-four Wistar-Albino rats weighing 360–401 g. The rats were kept in groups of eight in controllable, specifically designed cages with free access to food and water under appropriate temperature and light and dark conditions. None of the animals were administered antibiotics.

Study groups and procedure

For the number of laboratory animals to be used in the study, a power analysis was carried out using G * Power 3.1.94 package program. When the effect size used in the program and expressed by Cohen was 0.69, a total of 24 rats (8 in each group) were included in the study [12]. The statistical power of the test was set at 80% with a significance level of $P<0.05$. The animals were divided into three groups, as follows: Group 1, control: Transection of the left colon followed by end-to-end anastomosis and hyperthermic administration (41°C) of saline. Group 2, cisplatin + 5-FU: Left colon transection followed by end-to-end anastomosis and hyperthermic administration of 2 mg/kg cisplatin and 5 mg/kg 5-FU for 45 min. Group 3, cisplatin + 5-FU and early enteral nutrition with glutamine: Left colon transection followed by end-to-end anastomosis and hyperthermic administration of 2 mg/kg cisplatin and 5 mg/kg 5-FU for 45 min. Following surgery, 0.4 g/kg/day L-glutamine dissolved in 5 mL water was administered via an orogastric tube for 7 days. The rats were administered intramuscular anesthetic agents of 5 mg/kg Rompun (xylazine, Bayer, İstanbul, Turkey) and 50 mg/kg Ketalar (ketamine hydrochloride, Park Devis, İstanbul, Turkey). The abdominal surface of the rat was cleaned, and 10% povidone-iodine was used to ensure antisepsis of the surgical site. A 4 cm midline laparotomy incision was made. At ~3 cm above the peritoneal reflection, the left colon was defined and transected. Then, an end-to-end anastomosis was performed with eight sutures using 6-0 propylene (Prolene; Ethicon, NJ, USA) in a single-layer interrupted fashion. In Groups 2 and 3, HIPEC was implemented using an open method with 40 mL saline solution (5 mg/kg) heated to 41°C, and the abdomen was closed. The temperature of the solution was measured with a thermometer probe in the abdomen. When the intra-abdominal temperature fell below 40°C, the HIPEC fluid was aspirated and 41°C HIPEC solution was added again. An intermittent massage was conducted to distribute the chemotherapy agent. After 45 min, the abdomen was opened, and the washing solution was removed. Then the abdomen was sutured and closed. All operations were carried out using sterile surgical methods by the same surgeon. In Group 3, following surgery, 0.4 g/kg/day L-glutamine dissolved in 5 mL water was administered via an orogastric tube for 7 days. A combination of cisplatin and 5-FU as chemotherapeutic agents was used for the HIPEC procedure, as cisplatin exerts cytotoxic effects with increased temperature independently of the cell proliferation stage and 5-FU exerts its effect independently of the cell proliferation stage. Such a combination is frequently used in clinical practice. The rats were placed in their cages following surgery and subcutaneously administered 5 mL saline. All groups started feeding at the 6th postoperative hour. Groups 1 and 2 were fed standard food and water, while Group 3 was also fed glutamine daily via an orogastric tube for enteral nutrition.

ABP

All rats underwent a re-laparotomy on postoperative day 7. ABP was measured using a pressure transmitter (Transpac IV; Abbott Laboratories, Rockville, MD, USA) and a monitor (BM5; Bionet Patient Monitor, Seoul, Korea). A 2F feeding catheter was placed in the rectum. The colon was tied with 2-0 silk in a manner that included the catheter 3 cm below the anastomosis. The proximal section of the anastomosis was blocked using a clamp to establish a closed loop. Saline was delivered to the colon via the catheter inserted in the rectum at a rate of 2 mL/min using an infusion pump, and the pressure was monitored. The last measured value on the ABP monitor was registered as the ABP [13]. Upon the recording of ABP values, the colonic segment was resected and separated into two equal pieces: One was placed in a 10% formalin solution for histopathological analysis and the other was kept at -70°C for hydroxyproline (HYP) analysis. The rats were sacrificed by high doses of anesthetic drugs.

Histopathological analysis

The histopathological parameters of anastomotic healing were assessed using the Phillips scoring system [14]. The

colonic material that was placed in 10% formalin solution was embedded in paraffin after a 24-hour fixation. The paraffin-embedded tissues were stained with hematoxylin and eosin (H&E) and Masson's trichrome stain. The specimens were evaluated for fibroblasts, neovascularization, collagen, and inflammation, with each parameter rated on a scale from 0 to 3: 0: None; 1: Slight increase; 2: Moderate infiltration; and 3: Dense infiltration.

HYP determination

The levels of HYP were determined using the biotin double-antibody sandwich technology enzyme-linked immunosorbent assay (ELISA). From the 24 rat colonic tissue samples, 50 µg specimens were cut at equal weight and placed in phosphate-buffered saline (PBS, pH 7.4). The tissues in PBS were mixed manually for homogenization and centrifuged at 3000 rpm for 20 min. The supernatants were filtered and analyzed. The specimens and kits (Rat Hydroxyproline ELISA Kit, Rel Assay Diagnostic; MEGA TIP group, Gaziantep, Turkey) were stored outside until they reached room temperature. For each specimen to be studied, two wells were prepared (one for the standard and one as an empty well for the study). Chromogen solutions and stop solution were added to the empty wells, and 50 µL biotin antibody-integrated standard and 50 µL streptavidin horseradish peroxidase (HRP) were added to the standard wells. Then 40 µL sample was added to the sample wells, followed by the addition of 10 µL anti-HYP antibody and 50 µL streptavidin-HRP. Subsequently, the microplate was kept in an incubator (Nüve incubator; Nüve, Ankara, Turkey) at 37°C for 60 min. Then, 50 µL chromogen solution was added to each well. The plate was incubated in the dark for 15 min to allow color development followed by the addition of 50 µL stop solution. The plates were evaluated in an automated ELISA analyzer (Rel Reader, Rel Assay Diagnostic; MEGA TIP group) at a wavelength of 450 nm.

Statistical analysis

The statistical analyses were performed using the SPSS (version 25.0; SPSS, Chicago, IL, USA) software package. Statistical data were evaluated using average parameter values (ABP, tissue concentrations of HYP, and histopathological scores). Between-group variables were assessed with one-way analysis of variance (ANOVA) and X^2, and between-group differences were analyzed using Tukey's honest significant test and Tamhane's post-hoc test. $P<0.05$ was considered statistically significant.

Results

There were no mortalities throughout the study. No complications such as surgical site infection or wound dehiscence were observed.

ABP

The mean ABPs were 145.25 (25.18), 113.25 (8.12), and 133.00 (3.81) mmHg in Groups 1, 2 and 3, respectively. One-way ANOVA revealed statistical significance in the ABP values (P=0.002). The post-hoc analysis showed statistically significant differences in ABP between Group 1 and Group 2 (P=0.001), and between Group 2 and Group 3 (P=0.046). The difference between Group 1 and Group 3, was insignificant (P=0.213). These findings indicate that early enteral nutrition with glutamine improved colonic anastomosis wound healing by improving ABP in the group undergoing HIPEC with cisplatin + 5-FU (Table 1).

Concentrations of HYP

Average concentrations of HYP in the intestinal wall were 247.10 (4.76), 237.15 (5.32), and 242.90 (2.78) µg/g in Groups 1, 2, and 3, respectively. One-way ANOVA revealed a significant difference in HYP tissue concentrations among the groups (P=0.001). Post-hoc analysis revealed a statistically significant difference in tissue concentrations of HYP between Groups 1 and 2 (P=0.001), and between Groups 2 and 3 (P=0.043). The difference between Group 1 and Group 3, in turn, was nonsignificant (P=0.164) (Table 1). These findings indicate that the HIPEC procedure is likely to repair reduced concentrations of HYP in the wound of colonic anastomosis by increasing tissue HYP concentrations through enteral nutrition with glutamine.

Table 1: Mean and standard deviation values for ABP and tissue HYP levels of groups

Groups	Group 1	Group 2	Group 3	*P*-value
Anastomotic Bursting Pressure (mmHg)	145.25(25.18)	113.25(8.12)	133.00(3.81)	0.002*
Tissue hydroxyproline (µg/g)	247.10(4.76)	237.15(5.32)	242.90(2.78)	0.001**

*The differences between Groups 1 and 2 and Groups 2 and 3 were significant (P=0.001 and P=0.046, respectively). The difference between Groups 1 and 3 was not significant (P=0.273). ** The differences between Groups 1 and 2 and Groups 2 and 3 were significant (P=0.001 and P=0.043, respectively). The difference between Groups 1 and 3 was not significant (P=0.164).

Histopathological findings

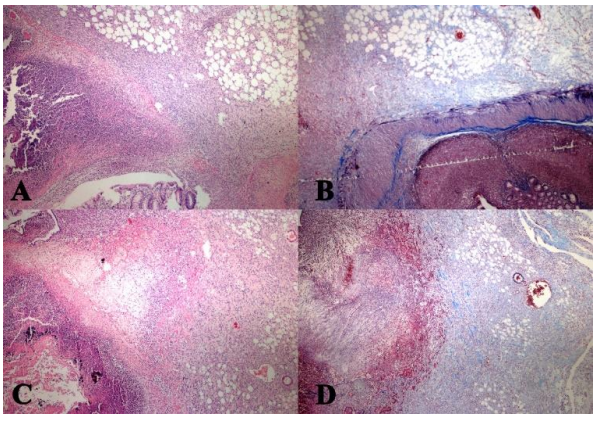
The histopathological results of the groups were defined according to the Phillips scale. One-way ANOVA indicated a significant difference in fibroblast and collagen values among the groups (P=0.041 and P=0.017, respectively) (Table 2). In terms of fibroblast values, post hoc analysis revealed a significant difference between Groups 1 and 2 (P=0.032). The collagen levels were significantly different between Groups 1 and 2, and between Groups 2 and 3 (P=0.001 and P=0.043, respectively). These findings suggest that enteral nutrition with glutamine had beneficial effects on colonic anastomosis recovery performed using HIPEC with cisplatin and 5-FU by increasing collagen levels (Figure 1).

Table 2: Histopathological findings of groups by Phillip's scale

Groups	Group 1	Group 2	Group 3	*P*-value
Fibroblast	2.75(0.46)	2.13(0.35)	2.50(0.53)	0.041*
Neovascularization	2.50(0.53)	2.13(0.35)	2.38(0.51)	0.296(NS)
Collagen	2.75(0.46)	1.75(0.46)	2.38(0.51)	0.017**
Inflammation	2.63(0.51)	2.13(0.35)	2.38(0.51)	0.128(NS)

* The difference between Groups 1 and 2 was significant (P=0.032). The difference between Groups 2 and 3 was significant (P=0.250). The difference between Groups 1 and 3 was not significant (P=0.537). ** The difference between Groups 1 and 2 was significant (P=0.001). The difference between Groups 2 and 3 was significant (P=0.043). The difference between Groups 1 and 3 was not significant (P=0.286).

Figure 1: Histopathologic appearance of the anastomotic line in the groups. A. H&E-stained anastomotic line of cisplatin+5-FU-delivered subject at 40x magnification, B. Masson's trichrome-stained anastomotic line of cisplatin+5-FU-delivered subject at 40x magnification, C. H&E-stained anastomotic line of cisplatin+5-FU-delivered and early enteral nutrition with glutamine-administered subject at 40x magnification, D. Masson's trichrome-stained anastomotic line of cisplatin+5-FU-delivered and early enteral nutrition with glutamine-administered subject at 40x magnification



Discussion

CRS is an aggressive local treatment carried out ahead of perioperative HIPEC [15]. Despite the increased survival in patients with PC, a prominent increase is seen in morbidity and mortality with mortality resulting mainly from sepsis and respiratory complications [16-18]. The most reported (5–34%) complications are intraabdominal sepsis, anastomotic leakage and intestinal fistulas, the latter of which is the most common and requires CRC and HIPEC treatment [18-21]. Intestinal fistulas occur as a result of anastomotic leakage or intestinal perforations. In a previous study examining complications of CRS and HIPEC, a fistula was identified in the anastomotic and suture lines in 17 of 203 patients [6]. Verwaal et al. observed intestinal fistulas and intraabdominal sepsis at a rate of 17.6% and 15.6%, respectively [18]. It is worth noting that more anastomoses are required following CRS and HIPEC compared to other gastrointestinal surgeries. Thus, to minimize postoperative fistula rates, some surgeons perform a diverting ostomy proximal to the colonic and rectal anastomoses [6]. After the treatment of patients is completed, another issue is ostomy closure. A previous study reported that 71% of colostomies could be closed, and a re-colostomy was performed in 14% of the closed colostomies due to emerging complications [16]. Makrin et al. investigated the effects of chemotherapy and hyperthermia on colorectal anastomosis, and found that the ABP fell in the hyperthermia groups compared to the control group on day 10 [22]. The authors observed that the ABP dropped the most in the cisplatin group. HIPEC had particularly adverse effects on colon ABP during the early postoperative period (up to day 10). The negative effects of HIPEC may cause anastomotic leakage and postoperative morbidity. Therefore, they suggest that avoiding unnecessary anastomosis is essential for patient and procedure selection. Pelz et al. demonstrated the detrimental effects of a chemotherapeutic (Mitomycin) on anastomotic healing [23]. In a study by Aarts et al., anastomosis of the ileum and colon was performed, followed by HIPEC with mitomycin C . The authors observed a decrease in wound strength of colonic anastomosis in the HIPEC group after cytoreduction [24].

Glutamine is the body's most available free amino acid and plays a critical role in nitrogen transport and acid-base equilibrium. Therefore, glutamine is one of the most studied nutrients and the starting point of metabolic support studies [25]. It is necessary for the rapid division of enterocytes, lymphocytes, and fibroblasts, and is also involved in antioxidant defense mechanisms by affecting glutathione synthesis [26]. Under physiological conditions, enough glutamine is produced to maintain the body's glutamine storage requirements (especially of the skeletal muscles) and to meet the demands of glutamine-consuming tissues [27]. In case of stress such as injury, sepsis and inflammation, glutamine consumption is increased in the gastrointestinal system, immunological cells, inflammatory tissue, and kidneys. Under severe stress, the intracellular and plasma glutamine levels decrease by 50% and 30%, respectively [9]. In this case, nitrogen balance and immunosuppression can be improved with glutamine supplementation [28]. Oral glutamine administration is reportedly effective in relieving oxidative stress and the proinflammatory responses induced by endotoxemia [29]. Goswami et al. [10] studied the impact of oral glutamine on wound healing in rats and found that glutamine had a positive effect on wound healing by affecting various wound healing stages such as collagen synthesis, wound contraction, and epithelialization. Sapidis et al. [11] studied the preoperative administration of glutamine and symbiosis, which increased the mechanical strength of the anastomosis. Thus, they claimed that it decreases the rupture of anastomotic line and bacterial translocation. Da Costa et al. reported that perioperative orally glutamine supplementation increased both the mechanical strength of the anastomosis and the percentage of mature collagen in the anastomosis line on postoperative days 3 and 8 [30]. Gökpınar et al. [31] investigated the effects of early and late enteral nutrition with glutamine on anastomotic healing, and found that in the postoperative period, early administration of total enteral nutrition significantly increased anastomotic resistance and collagen synthesis. In this study, enteral nutrition with glutamine led to an improvement in ABP and tissue concentrations of HYP following HIPEC treatment with cisplatin and 5-FU. These findings are consistent with the previous publications in literature.

Earlier experimental studies used one chemotherapeutic agent (e.g., 5-FU, cisplatin, paclitaxel, mitomycin-c); however, two chemotherapeutic agents are currently included in the HIPEC regimen after CRS in clinical practice. These agents include drugs that exert increased effects with hyperthermia, independently of cell proliferation (e.g., cisplatin, mitomycin-c, doxorubicin); and those that are not associated with hyperthermia, independently of cell proliferation (e.g., 5-FU and paclitaxel). This the first study to investigate the effects of early enteral glutamine supplementation on colonic anastomotic healing in patients treated with HIPEC with cisplatin and 5-FU.

This study had some limitations. First, experiments were performed on laboratory animals, so future studies of a similar nature are needed prior to the study findings being included in clinical practice. Second, although this procedure is performed on a selected patient group with good performance in clinical practice, most patients are malnourished and the duration of surgery is long for cytoreduction, necessitating one or several anastomoses thereafter. The rats used in our study had no malnutrition or peritoneal disease. Third, colonic anastomosis was performed after transection without colonic resection. When assessing complications due to surgery, 30 postoperative days should be taken into account. We completed this study on day 7. Finally, in clinical practice, HIPEC treatment is combined with early postoperative intraperitoneal chemotherapy (EPIC), which generally begins on the first postoperative day and continues for 5 days. EPIC was not used in this study. We believe that such limitations should be taken into consideration in prospective experimental studies.

Conclusion

Enteral nutrition with glutamine after HIPEC positively affected anastomotic wound healing by increasing the number of fibroblasts, collagen deposits, tissue HYP levels in the anastomosis area, and the anastomosis's mechanical resistance. Thus, we believe that early enteral glutamine supplementation after HIPEC can reduce postoperative morbidity and mortality by preventing anastomotic leaks.

References

1. Carmignani CP, Sugarbaker TA, Bromley CM, Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. Cancer Metastasis Rev. 2003;22(4):465-72. doi: 10.1023/a:1023791229361. PubMed PMID: 12884919.
2. Chua TC, Yan TD, Saxena A, Morris DL. Should the treatment of peritoneal carcinomatosis by cytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure?: a systematic review of morbidity and mortality. Ann Surg. 2009;249(6):900-7. doi: 10.1097/SLA.0b013e3181a45d86. PubMed PMID: 19474692.
3. Sugarbaker PH, Jablonski KA. Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg. 1995;221(2):124-32. doi: 10.1097/00000658-199502000-00002. PubMed PMID: 7857141; PubMed Central PMCID: PMCPMC1234945.
4. Elias D, Gilly F, Boutitie F, Quenet F, Bereder JM, Mansvelt B, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28(1):63-8. doi: 10.1200/JCO.2009.23.9285. PubMed PMID: 19917863.
5. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from nonovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. Cancer. 2010;116(24):5608-18. doi: 10.1002/cncr.25356. PubMed PMID: 20737573.
6. Younan R, Kusamura S, Baratti D, Oliva GD, Costanzo P, Favaro M, et al. Bowel complications in 203 cases of peritoneal surface malignancies treated with peritonectomy and closed-technique intraperitoneal hyperthermic perfusion. Ann Surg Oncol. 2005;12(11):910-8. doi: 10.1245/ASO.2005.11.030. PubMed PMID: 16177862.
7. Aghayeva A, Benlice C, Bilgin IA, Atukeren P, Dogusoy G, Demir F, et al. The effects of hyperthermic intraperitoneal chemoperfusion on colonic anastomosis: an experimental study in a rat model. Tumori. 2017;103(3):307-13. doi: 10.5301/tj.5000610. PubMed PMID: 28291907.
8. Lopez-Lopez V, Lynn PB, Gil J, Garcia-Salom M, Gil E, Gonzalez A, et al. Effect of Paclitaxel-based Hyperthermic Intraperitoneal Chemotherapy (HIPEC) on colonic anastomosis in a rat model. Clin Transl Oncol. 2019;21(4):505-11. doi: 10.1007/s12094-018-1948-7. PubMed PMID: 30229392.
9. Kovacevic Z, McGivan JD. Mitochondrial metabolism of glutamine and glutamate and its physiological significance. Physiol Rev. 1983;63(2):547-605. doi: 10.1152/physrev.1983.63.2.547. PubMed PMID: 6132422.
10. Goswami S, Kandhare A, Zanwar AA, Hegde MV, Bodhankar SL, Shinde S, et al. Oral L-glutamine administration attenuated cutaneous wound healing in Wistar rats. Int Wound J. 2016;13(1):116-24. doi: 10.1111/iwj.12246. PubMed PMID: 24690128.
11. Sapidis N, Tziouvaras C, Ioannidis O, Kalaitsidou I, Botsios D. The effect of glutamine and synbiotics on the healing of colonic anastomosis. Rev Esp Enferm Dig. 2014;106(4):255-62. PubMed PMID: 25075656.
12. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9. doi: 10.1037//0033-2909.112.1.155. PubMed PMID: 19565683.
13. Erdem E, Dinc S, Erdem D, Ustun H, Caydere M, Alagol H. Effects of intraperitoneal chemotherapy and GM-CSF on anastomotic healing: an experimental study in rats. J Surg Res. 2002;108(1):1-6. doi: 10.1006/jsre.2002.6425. PubMed PMID: 12443708.
14. Phillips JD, Kim CS, Fonkalsrud EW, Zeng H, Dindar H. Effects of chronic corticosteroids and vitamin A on the healing of intestinal anastomoses. Am J Surg. 1992;163(1):71-7. doi: 10.1016/0002-9610(92)90255-p. PubMed PMID: 1733376.
15. Jahne J. Cytoreduction including total gastrectomy for pseudomyxoma peritonei (Br J Surg 2002; 89: 208-12). Br J Surg. 2002;89(7):938-9; discusssion 9. doi: 10.1046/j.1365-2168.2002.02161_4.x. PubMed PMID: 12081750.
16. Glehen O, Osinsky D, Cotte E, Kwiatkowski F, Freyer G, Isaac S, et al. Intraperitoneal chemohyperthermia using a closed abdominal procedure and cytoreductive surgery for the treatment of peritoneal carcinomatosis: morbidity and mortality analysis of 216 consecutive procedures. Ann Surg Oncol. 2003;10(8):863-9. doi: 10.1245/aso.2003.01.018. PubMed PMID: 14527903.
17. Jafari MD, Halabi WJ, Stamos MJ, Nguyen VQ, Carmichael JC, Mills SD, et al. Surgical outcomes of hyperthermic intraperitoneal chemotherapy: analysis of the american college of surgeons national surgical quality improvement program. JAMA Surg. 2014;149(2):170-5. doi: 10.1001/jamasurg.2013.3640. PubMed PMID: 24352601.
18. Verwaal VJ, van Ruth S, de Bree E, van Sloothen GW, van Tinteren H, Boot H, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21(20):3737-43. doi: 10.1200/JCO.2003.04.187. PubMed PMID: 14551293.
19. Blaj S, Nedelcut S, Mayr M, Leebmann H, Leucuta D, Glockzin G, et al. Re-operations for early postoperative complications after CRS and HIPEC: indication, timing, procedure, and outcome. Langenbecks Arch Surg. 2019;404(5):541-6. doi: 10.1007/s00423-019-01808-8. PubMed PMID: 31352505.
20. Jaehne J. Cytoreductive procedures-strategies to reduce postoperative morbidity and management of surgical complications with special emphasis on anastomotic leaks. J Surg Oncol. 2009;100(4):302-5. doi: 10.1002/jso.21328. PubMed PMID: 19697435.
21. Yamaguchi R, Terashima H, Yoneyama S, Tadano S, Ohkohchi N. Effects of platelet-rich plasma on intestinal anastomotic healing in rats: PRP concentration is a key factor. J Surg Res. 2012;173(2):258-66. doi: 10.1016/j.jss.2010.10.001. PubMed PMID: 21074782.
22. Makrin V, Lev-Chelouche D, Even Sapir E, Paran H, Rabau M, Gutman M. Intraperitoneal heated chemotherapy affects healing of experimental colonic anastomosis: an animal study. J Surg Oncol. 2005;89(1):18-22. doi: 10.1002/jso.20161. PubMed PMID: 15612012.
23. Pelz JO, Doerfer J, Decker M, Dimmler A, Hohenberger W, Meyer T. Hyperthermic intraperitoneal chemoperfusion (HIPEC) decrease wound strength of colonic anastomosis in a rat model. Int J Colorectal Dis. 2007;22(8):941-7. doi: 10.1007/s00384-006-0246-y. PubMed PMID: 17245567.
24. Aarts F, Bleichrodt RP, de Man B, Lomme R, Boerman OC, Hendriks T. The effects of adjuvant experimental radioimmunotherapy and hyperthermic intraperitoneal chemotherapy on intestinal and abdominal healing after cytoreductive surgery for peritoneal carcinomatosis in the rat. Ann Surg Oncol. 2008;15(11):3299-307. doi: 10.1245/s10434-008-0070-4. PubMed PMID: 18712445.
25. Ziegler TR, Bazargan N, Leader LM, Martindale RG. Glutamine and the gastrointestinal tract. Curr Opin Clin Nutr Metab Care. 2000;3(5):355-62. doi: 10.1097/00075197-200009000-00005. PubMed PMID: 11151079.
26. Mertes N, Schulzki C, Goeters C, Winde G, Benzing S, Kuhn KS, et al. Cost containment through L-alanyl-L-glutamine supplemented total parenteral nutrition after major abdominal surgery: a prospective randomized double-blind controlled study. Clin Nutr. 2000;19(6):395-401. doi: 10.1054/clnu.2000.0142. PubMed PMID: 11104589.
27. Kuhn KS, Schuhmann K, Stehle P, Darmaun D, Furst P. Determination of glutamine in muscle protein facilitates accurate assessment of proteolysis and de novo synthesis-derived endogenous glutamine production. Am J Clin Nutr. 1999;70(4):484-9. doi: 10.1093/ajcn/70.4.484. PubMed PMID: 10500016.
28. Miller AL. Therapeutic considerations of L-glutamine: a review of the literature. Altern Med Rev. 1999;4(4):239-48. PubMed PMID: 10468648.
29. Cruzat VF, Bittencourt A, Scomazzon SP, Leite JS, de Bittencourt PI, Jr., Tirapegui J. Oral free and dipeptide forms of glutamine supplementation attenuate oxidative stress and inflammation induced by endotoxemia. Nutrition. 2014;30(5):602-11. doi: 10.1016/j.nut.2013.10.019. PubMed PMID: 24698353.
30. Da Costa MA, Campos AC, Coelho JC, de Barros AM, Matsumoto HM. Oral glutamine and the healing of colonic anastomoses in rats. JPEN J Parenter Enteral Nutr. 2003;27(3):182-5; discussion 5-6. doi: 10.1177/014860710302700318 2. PubMed PMID: 12757111.
31. Gökpinar I, Gürleyik E, Pehlivan M, Özcan Ö, Özaydın İ, Aslaner A, et al. Early enteral and glutamine enriched enteral feeding ameliorates healing of colonic anastomosis. Turkish Journal of Trauma and Emergency Surgery. 2006;12(1):17-21. PubMed PMID: 16456746.

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Where is it logical to break-up a ureter stone with endoscopic surgery?

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This study was approved by Ethics Committee of Yozgat Bozok University (protocol number: 2017-KAEK-189_2020.11.11_02).
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Abstract

Background/Aim: Today, we have the technology to break up a ureter stone in the ureter, as well as in the renal pelvis, with ureterorenoscopic procedures. In the past, when this option was not available, the surgeons improved several techniques and antiretropulsion devices to let the stone migrate through the renal pelvis. This study was conducted to clarify whether it is more advantageous to dust a stone in the ureter where it is impacted or in a wider area such as the renal pelvis.
Methods: The data of 134 patients who underwent semirigid ureterorenoscopy (srURS) due to single and primary upper ureteral stones were included and analyzed in this retrospective cohort study. The patients were divided into two groups according to the development of spontaneous push-up during surgery (Group 1: The non-push-up group, Group 2: The push-up group).
Results: While hemoglobin levels lowered significantly in both groups after the surgery, creatinine levels increased ($P<0.05$). However, there was no significant difference between the groups regarding preoperative or postoperative laboratory findings ($P>0.05$). Operation times were similar in both groups, in contrast with the literature. Stone-free rates were significantly higher in srURS than in intrarenal surgery (RIRS) ($P=0.03$). Complication rates were also similar in this study.
Conclusion: The application of srURS after fixing an upper ureter stone at its location using a Stone Cone® results in higher stone-free rates than pushing it back to dust it in renal pelvis. We recommend srURS supported by an antiretropulsion method as a treatment for upper ureteral stones.

Keywords: Ureter Stone, Push-up, Stone migration, Antiretropulsion, Flexible ureterorenoscopy, Rigid ureteroscopy

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Introduction

Urinary stones occupy the agenda of the medical world with both their frequency and high recurrence rates [1]. Over the last 60 years, great strides have been made in urinary stone treatment, and in the previous two decades, endoscopic surgeries have taken the lead in treatment [2, 3].

Ureterorenoscopy (URS) and flexible ureterorenoscopy/retrograde intrarenal surgery (RIRS) are commonly used surgical methods in ureter stone treatment. Although it is not possible to cure kidney stones with URS, since the introduction of RIRS, even kidney stones can be treated endoscopically when accessed through the urethral meatus [2]. One of the most important advantages of RIRS in ureter stone treatment is that the unintended spontaneous stone push-up that could cause the termination of URS in the past does not any longer. Nowadays, if a stone is pushed up, surgeons can stop performing URS and begin using RIRS to treat stones in the kidney, allowing surgeries to be completed successfully [4, 5].

Different techniques and devices have been used to mitigate the push-up problem [6, 7]. However, it is not clear whether these methods are truly necessary with today's technology. To go a step further and dust the stone after pushing it into the kidney instead of dusting it in a narrow area in the ureter might be more advantageous. In this study, our aim is to compare the clinical parameters of semirigid URS (srURS) in the upper ureter with RIRS for upper ureteral stones which are pushed-up during srURS perioperatively.

Materials and methods

The data of 134 patients who underwent srURS due to single and primary upper ureteral stones between January 2018-October 2020 were included and analyzed in this retrospective cohort study. The necessary permissions were obtained from Yozgat Bozok University Clinical Research Ethics Committee (protocol number: 2017-KAEK-189_2020.11.11_02) for the use and analysis of this data. Seventy-three patients who were treated with srURS successfully were included in Group 1. Sixty-one patients in whom srURS failed due to spontaneous unintended push-up and the surgical technique was changed to RIRS, were included in Group 2 (alpha=0.05; power: 0.89). Surgeries were performed by four surgeons experienced in endourological procedures. Preoperative complete blood count, routine biochemical analysis (glucose, creatinine, electrolytes), complete urinalysis, and urine culture were obtained from all patients. Patients with signs of infection and pyuria were operated on after receiving appropriate oral therapy and obtaining a sterile urinalysis result. Furthermore, the data of patients with stones reported to be enclaved during surgery, a history of a urinary anomaly, nephrectomy, chronic renal failure, and a JJ stent in the preoperative period were excluded.

Surgical procedures

Before srURS, cystourethroscopy was performed on the patients. A Stone Cone® was placed in the ipsilateral ureter under fluoroscopy during cystoscopy. Ureteral access was gained with a 9.5F semi-rigid ureterorenoscope (Karl Storz, Tuttlingen, Germany) with a guidewire. After the stone was reached by the ureterorenoscope, it was dusted with a 272 µm holmium: YAG laser (Ho YAG Laser; Dornier MedTech; Munich, Germany/Dornier Med-Tech GmbH, Medilas H20 and HSolvo, Wessling, Germany) at a frequency of 8-12 Hz and an energy level of 0.8-1.5 J. When a spontaneous unintended push-up occurred during ureteral access or Stone Cone® placement before starting to dust the stone, the surgeon altered the instruments and continued to RIRS. A ureteral accessory sheath (UAS) (Elite Flex, Ankara, Turkey) was placed over the guidewire into the ureter. Following this, the stones were reached by advancing the flexible ureteroscope (Flex-X2, Karl Storz, Tuttlingen, Germany/Karl Storz, Flex X2, GmbH, Tuttlingen, Germany). The stones were dusted with a 272 µm laser. In both procedures, no stone fragment was extracted, and a JJ stent was placed in the ureter. The time from the entrance to the urethral meatus to the end of JJ stent placement after starting to RIRS was recorded as the operative time.

Patient follow-up

On the first postoperative day, patients received a direct urinary system radiography to check for the presence of opaque stones and ultrasonography to check for the presence of non-opaque stones. JJ stents were removed at the third postoperative week in all patients. All patients underwent non-contrast computed tomography in the first month postoperatively to evaluate residual fragments and stone free status. The procedure was considered successful for patients with a residual stone fragment of 2 mm or less. Follow-up or medical expulsive therapy was administered to patients with residual stone fragments larger than 2mm. A summary of Clavien-Dindo classification for complications is given in Table 2 [8].

Statistical analysis

All statistical analyses were performed with the IBM® SPSS® Statistics version 25 data analysis program (IBM Corp. Released 2017. IBM® SPSS® Statistics version 25.0. Armonk, NY: IBM Corp). The distributions were determined according to the skewness and kurtosis values. Normally distributed data were given as mean (standard deviation), while median (minimum-maximum) values were presented when no normal distribution was observed. Student t-test and Mann-Whitney U test were used for numerical data to compare the two groups. A chi-squared test was used for categorical data. The significance level for the *P*-value was 0.05.

Results

The demographic and clinical data of the cases are summarized in Table 1. We observed no statistically significant differences between the two groups in terms of age, gender, body mass index (BMI), laboratory data, presence of hydronephrosis, stone size, stone density, operation time, and complication rates ($P>0.05$ for all). However, stone-free rates were significantly higher in srURS compared to intrarenal surgery (RIRS) ($P=0.03$).

The hemoglobin (Hb) and creatinine (Cre) levels of the patients before and after surgery were compared separately, and a significant change was observed (Table 1). The Hb values before and after surgery were 14.50 g/dL and 13.05 g/dL, respectively, in Group 1, and 14.30 g/dL and 13.30 g/dL, respectively, in Group 2. In group 1, the mean creatinine value was 0.94 mg/dL preoperatively and 0.87 mg/dL afterwards. The

mean creatinine levels in Group 2 were 0.89 mg/dL and 0.83 mg/dL before and after the surgery, respectively. The rate of the patients with grade 3 and higher hydronephrosis were below 7% in both groups.

Complication rates were similar in both groups (P=0.87) (Table 1). After the operation, 1 patient from group 1 and 3 patients from group 2 developed renal colic. The patient in Group 1 had steinstrasse. Additional interventions were performed in these 4 patients in the second session (Stage 3). Urosepsis developed secondary to ureteral perforation in one patient from Group 1 (Stage 4). The patient recovered following appropriate parenteral antibiotherapy and intensive care support. Urinary infection developed in one patient in Group 2 (stage 2) which improved following oral antibiotherapy given in accordance with the urine culture results. One patient had a fever of >38.5°C, which recurred with antipyretic therapy. Macroscopic hematuria was observed in one patient. He improved with bed rest and standard hydration practices (Table 2).

Table 1: Demographic and clinical parameters of two groups

Parameters		Group 1 (n=73)	Group 2 (n=61)	*P*-value
Age		46.25 (12.87)	45.51 (14.36)	0.75
Gender (n, %)	Female	18 (24.7)	20 (32.8)	0.39
	Male	55 (75.3)	41 (67.2)	
BMI		28.38 (21.51-37.89)	27.34 (20.20-47.56)	0.36
Preoperative Hb (g/dL)		14.50 (9.1-17.9)	14.30 (10.6-17)	0.72
Postoperative Hb (g/dL)		13.05 (7.9-17.0)	13.05 (7.9-17.0)	0.98
Preoperative Cre (mg/dL)		0.94 (0.6-2.63)	0.89 (0.47-2.24)	0.22
Postoperative Cre (mg/dL)		0.87 (0.51-1.75)	0.87 (0.51-1.75)	0.33
Preop vs Postop Hb**		-6.6	-5.7	<0.001
Preop vs Postop Cre**		-3.2	-3.7	<0.001
Hydronephrosis	Absent	14 (19.2)	15 (24.6)	0.67
(n, %)	Grade 1	21 (28.8)	21 (34.4)	
	Grade 2	33 (45.2)	22 (36.1)	
	Grade 3	4 (5.5)	3 (4.9)	
	Grade 4	1 (1.4)	0 (0)	
Stone size (mm)		9 (5-16)	10 (5-24)	0.54
Stone density (HU)		986 (480-1428)	900 (254-1632)	0.06
Operation time (dk)		46.97 (20.51)	48.54 (27.98)	0.70
Stone-free	Residual +	3 (4.2)	9 (15.0)	0.03
(n, %)	Residual -	69 (95.8)	51 (85.0)	
Complication	Absent	56 (77.8)	46 (76.7)	0.87
(n, %)	Present	16 (22.2)	14 (23.3)	

Data were given as mean (SD) in cases with normal distribution, and as median (min-max) in data that did not show normal distribution. For categorical data, it was shown as n (%). BMI: Body mass index; HU: Hounsfield unit; mm: millimeters. * P<0.05 ** It is shown as "Z value" for Wilcoxon test.

Table 2: The numerical distributions of complications between the groups due to Clavian-Dindo classification

Complication Grade	Group 1 (n=16)	Group 2 (n=14)
Grade 1	14	9
Grade 2	0	1
Grade 3	1	3
Grade 4	1	0

Data were given as frequency (n) in all cases.

Discussion

The development of stone push-up during URS was a significant problem that resulted in the termination of urinary stone surgeries in the past. Sun et al. reported this rate as 10% for all ureteral stones [9], while Knispel et al. [10] reported it as 40% for upper ureteral stones. To address this problem, various manipulations and antiretropulsion devices or techniques were developed. In an experimental study, Patel et al. [11] showed that the inclination of the patient on the operating table can preclude the development of push-ups during ureteroscopy. Zehri et al. [12] reported that gel instillation to the proximal part of the stone increased stone-free rates. Dretler [13] demonstrated that a ureteral balloon advanced over a guidewire to the proximal part of the stone is useful in averting a push-up. A year later, Dretler [14] reported the successful results of a device called a Stone Cone®. Wang et al. [15] reported that an N-trap occlusion device is effective in preventing stone migration. Heat-sensitive polymers, Lithovac, Lithocatch, Parachute and PercSys devices were developed and put into use [16–18]. As can be seen, stone push-up directly affected the stone-free rates and unsuccessful surgery. However, with the introduction of laser lithotripsy and RIRS, stone push-up is no longer such an impediment to successful surgical completion. Even if a ureter stone migrates retrograde to the kidney during URS, the surgeon can continue the surgery by altering the surgical instrument and successfully complete the operation.

It is known that intrarenal pressure increases during both URS and RIRS. The use of UAS during RIRS significantly reduces intrarenal pressure [19, 20]. This can be considered an advantage of RIRS over URS. However, whether this creates a clinical result in terms of renal functions is controversial. In a study conducted on patients who underwent RIRS, Yang et al. did not detect a significant increase in creatinine on the first postoperative day and in the 1st month postoperatively in stones smaller than 3 cm, while they reported that there was a significant increase in creatinine on the first postoperative day in stones larger than 3 cm and that this regressed in the first postoperative month [21]. Based on these findings, a temporary deterioration of renal function can be expected, especially in cases where surgery time is prolonged. Öztekin et al. reported that they did not detect a significant creatinine change either preoperatively or postoperatively between the two groups who underwent RIRS and URS [22]. In this study, although our operative times were not long in both groups, we did not observe a significant difference between pre-and postoperative creatinine levels.

Considering the larger number of manipulations of RIRS, operation time is expected to be longer in RIRS than srURS. In a study where they compared RIRS with srURS in the treatment of upper ureteral stones, Kartal et al. [4] reported that operation times where RIRS was performed were significantly longer. Similar findings were also reported by Karadag et al [23]. Although Özkaya et al. [24] reported that the use of UAS in patients who underwent RIRS shortened the operative time compared to those in whom UAS was not used, Galal's study [5] comparing RIRS with URS showed that operation times where srURS was carried out were significantly shorter. In our study, although the average length of operations using srURS were shorter than those using RIRS, these differences were not statistically significant.

It is evident that the development of push-up in ureter stones during surgery will make a significant difference between RIRS and srURS in terms of stone-free rates and surgery success. Researchers developed antiretropulsion devices to prevent stone push-up [18, 25]. In addition, methods such as putting patients in the Trendelenburg position or applying gel to the proximal part of the stone were employed to increase stone-free rates [6, 12, 26]. As the surgical technology and technique of RIRS improves, it seems likely that push-up developing during srURS will be treated more easily, and there will no longer be a need for antiretropulsion techniques or devices. However, there are scarcely any studies in the literature comparing the stone-free rates of srURS with antiretropulsion and RIRS. In their study, in

which they did not use an antiretropulsion device, Karadag et al. [23] reported that stone-free rates were superior when RIRS was used compared to srURS both directly after the surgery and in the following months. Similarly, Kartal et al. [4] reported a significant stone-free rate in RIRS procedures compared to srURS without antiretropulsion. Galal et al. [5] found RIRS superior in terms of stone-free rates as a result of their studies comparing rigid URS and RIRS, which they performed without using an antiretropulsion device. However, they added the comment that if they had used a Stone Cone® or N-Trap basket, a higher rate would probably have been achieved using rigid URS. In our study, stone-free rates were significantly higher when srURS was performed compared to RIRS. This may be because we used a Stone Cone® as a standard part of the srURS procedure. In addition, leaving the stone fragments and dust particles in the natural flow path of urine may have given this result. During URS, the surgeon works in a narrow space and may cause iatrogenic damage to the fragile tissue of the ureter, especially in impacted stones. Furthermore, complication rates are lower when RIRS is used [5, 27]. Özkaya et al. [24] reported that complications such as fever, infection, and unsuccessful surgery are less common when using UAS in RIRS. Therefore, RIRS seems to be a more advantageous method. However, not all the data in the literature supports this point of view. Kartal et al. [4] reported that they could not find a significant difference in intraoperative complication rates between RIRS and srURS in upper ureteral stones. Karadag et al. [23] also reported that there was no difference in intraoperative complications. Finally, Galal et al. [5] reported no significant difference between both intraoperative and postoperative complications. In our study, the complication rates were similar between the two groups.

In the light of all this information, it seems that preferring RIRS over srURS in an upper ureteral stone will not make a difference in terms of renal functions; indeed, the possibility of using UAS during RIRS may even provide other benefits [24]. Although the shorter operation time of srURS in the literature suggests that dusting such stones at the location of impaction in the ureter will give faster results, no significant difference was shown in terms of operation times in this study. While it has been reported in the literature that srURS without using antiretropulsion will obtain a lower score than RIRS in terms of stone-free rates, we showed that srURS using antiretropulsion can be superior to RIRS in terms of stone-free rates. Moreover, there is no significant difference between these two surgical options regarding complication rates in upper ureteral stones.

Limitations

The limitations of our study include its retrospective design, a small sample size, and a short follow-up period. Prospective studies should be conducted with larger patient groups. The advantage of our study is that there are few studies comparing URS or srURS with RIRS in upper ureteral stones. In addition, it is a unique study in the literature comparing stone dusting after stone push-up with stone dusting performed in the ureter.

Conclusion

While choosing between RIRS or srURS in patients with an upper ureteral stone, the idea of pushing a stone that can easily be treated with srURS to the kidney and, instead, treating it with RIRS is not supported by the findings of this study. The application of srURS after fixing an upper ureter stone at its location using a Stone Cone® results in higher stone-free rates. For these stones, RIRS and srURS yield similar results in terms of laboratory values, complication rates and operation time. Surgeons should use antiretropulsion devices and break the stone in the proximal ureter rather than breaking it in the kidney. Further prospective randomized controlled studies are needed.

References

1. Shah TT, Gao C, Peters M, Manning T, Cashman S, Nambiar A, et al. Factors associated with spontaneous stone passage in a contemporary cohort of patients presenting with acute ureteric colic: results from the Multi-centre cohort study evaluating the role of Inflammatory Markers In patients presenting with acute ureteric Colic (MIMIC) study. BJU Int. 2019;124:504–13.
2. Akkoç A, Uçar M. Can rigid ureteroscopic lithotripsy be an alternative to flexible ureteroscopic lithotripsy in the treatment of isolated renal pelvis stones smaller than 2 cm? J Surg Med. 2020;4:305–8. doi: 10.28982/JOSAM.722331.
3. Yencilek F, Sarica K, Erturhan S, Yagci F, Erbagci A. Treatment of ureteral calculi with semirigid ureteroscopy: Where should we stop? Urol Int. 2010;84:260–4. doi: 10.1159/000288225.
4. Kartal I, Yalçınkaya F, Baylan B, Cakıcı MC, Sarı S, Selmi V, et al. Comparison of semirigid ureteroscopy, flexible ureteroscopy, and shock wave lithotripsy for initial treatment of 11-20 mm proximal ureteral stones. Arch Ital di Urol e Androl. 2020;92:39–44. doi: 10.4081/aiua.2020.1.39.
5. Galal EM, Anwar AZ, Fath El-Bab TK, Abdelhamid AM. Retrospective comparative study of rigid and flexible ureteroscopy for treatment of proximal ureteral stones. Int Braz J Urol. 2016;42:967–72. doi: 10.1590/S1677-5538.IBJU.2015.0644.
6. Zhou R, Han C, Hao L, Chen B, Zang G, Fan T, et al. Ureteroscopic lithotripsy in the Trendelenburg position for extracting obstructive upper ureteral obstruction stones: a prospective, randomized, comparative trial. Scand J Urol. 2018;52:291–5. doi: 10.1080/21681805.2018.1492966.
7. Saussine C, Andonian S, Pacík D, Popiolek M, Celia A, Buchholz N, et al. Worldwide Use of Antiretropulsive Techniques: Observations from the Clinical Research Office of the Endourological Society Ureteroscopy Global Study. J Endourol. 2018;32:297–303. doi: 10.1089/end.2017.0629.
8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery. 2004;240:205–13.
9. Sun Y, Wang L, Liao G, Xu C, Gao X, Yang Q, et al. Pneumatic lithotripsy versus laser lithotripsy in the endoscopic treatment of ureteral calculi. In: Journal of Endourology. Mary Ann Liebert Inc.; 2001. p. 587–90. doi: 10.1089/089277901750426346.
10. Knispel HH, Klän R, Heicappell R, Miller K. Pneumatic lithotripsy applied through deflected working channel of miniureteroscope: Results in 143 patients. J Endourol. 1998;12:513–5. doi: 10.1089/end.1998.12.513.
11. Patel RM, Walia AS, Grohs E, Okhunov Z, Landman J, Clayman R V. Effect of positioning on ureteric stone retropulsion: 'gravity works.' BJU Int. 2019;123:113–7. doi: 10.1111/bju.14510.
12. Zehri AA, Ather MH, Siddiqui KM, Sulaiman MN. A Randomized Clinical Trial of Lidocaine Jelly for Prevention of Inadvertent Retrograde Stone Migration During Pneumatic Lithotripsy of Ureteral Stone. J Urol. 2008;180:966–8. doi: 10.1016/j.juro.2008.05.008.
13. Dretler SP. Ureteroscopy for proximal ureteral calculi: Prevention of stone migration. J Endourol. 2000;14:565–7. doi: 10.1089/08927790050152159.
14. Dretler SP. The stone cone: A new generation of basketry. J Urol. 2001;165 5 I:1593–6.
15. Wang CJ, Huang SW, Chang CH. Randomized trial of NTrap for proximal ureteral stones. Urology. 2011;77:553–7. doi: 10.1016/j.urology.2010.07.497.
16. Mirabile G, Phillips CK, Edelstein A, Romano A, Okhunov ZN, Hruby GW, et al. Evaluation of a novel temperature-sensitive polymer for temporary ureteral occlusion. In: Journal of Endourology. J Endourol; 2008. p. 2357–9. doi: 10.1089/end.2008.0029.
17. Gonen M, Cenker A, Istanbulluoglu O, Ozkardes H. Efficacy of Dretler Stone Cone in the treatment of ureteral stones with pneumatic lithotripsy. Urol Int. 2006;76:159–62.
18. Sen H, Bayrak O, Erturhan S, Urgun G, Kul S, Erbagci A, et al. Comparing of different methods for prevention stone migration during ureteroscopic lithotripsy. Urol Int. 2014;92:334–8. doi: 10.1159/000351002.
19. Rehman J, Monga M, Landman J, Lee DI, Felfela T, Conradie MC, et al. Characterization of intrapelvic pressure during ureteropyeloscopy with ureteral access sheaths. Urology. 2003;61:713–8. doi: 10.1016/S0090-4295(02)02440-8.
20. Auge BK, Pietrow PK, Lallas CD, Raj G V., Santa-Cruz RW, Preminger GM. Ureteral Access Sheath Provides Protection against Elevated Renal Pressures during Routine Flexible Ureteroscopic Stone Manipulation. J Endourol. 2004;18:33–6. doi: 10.1089/089277904322836631.
21. Yang B, Ning H, Liu Z, Zhang Y, Yu C, Zhang X, et al. Safety and efficacy of flexible ureteroscopy in combination with holmium laser lithotripsy for the treatment of bilateral upper urinary tract calculi. Urol Int. 2017;98:418–24. doi: 10.1159/000464141.
22. Öztekin Ü, Erkoç F, Sarı S, Selmi V, Gürel A, Ataç F. The effect of ureterorenoscopy and retrograde intrarenal surgery procedures on renovascular hemodynamics. Ann Clin Anal Med. 2020;11:272–6. doi: 10.4328/acam.20066.
23. Karadag MA, Demir A, Cecen K, Bagcioglu M, Kocaaslan R, Sofikerim M, et al. Flexible ureterorenoscopy versus semirigid ureteroscopy for the treatment of proximal ureteral Stones: A retrospective comparative analysis of 124 patients. Urol J. 2013;11:1867–72.
24. Özkaya F, Sertkaya Z, Karabulut I, Aksoy Y. The effect of using ureteral access sheath for treatment of impacted ureteral stones at mid-upper part with flexible ureterorenoscopy: A randomized prospective study. Minerva Urol e Nefrol. 2019;71:413–20. doi: 10.23736/S0393-2249.19.03356-3.
25. Cabrera FJ, Preminger GM, Lipkin ME. Antiretropulsion devices. Current Opinion in Urology. 2014;24:173–8. doi: 10.1097/MOU.0000000000000032.
26. Pan J, Xue W, Xia L, Zhong H, Zhu Y, Du Z, et al. Ureteroscopic lithotripsy in Trendelenburg position for proximal ureteral calculi: A prospective, randomized, comparative study. Int Urol Nephrol. 2014;46:1895–901. doi: 10.1007/s11255-014-0732-z.
27. Xu C, Song RJ, Jiang MJ, Qin C, Wang XL, Zhang W. Flexible ureteroscopy with holmium laser lithotripsy: A new choice for intrarenal stone patients. Urol Int. 2015;94:93–8. doi: 10.1159/000365578.

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Likelihood of cancer in breast cancer imaging according to BI-RADS

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Abstract

Background/Aim: Breast cancer is the most common type of cancer among women and one of the most common causes of cancer-related death. Breast Imaging-Reporting and Data System (BI-RADS) is widely used in breast imaging and aims to provide effective communication between physicians. This study aimed to investigate the positive predictive values (PPVs) of BI-RADS categories as assessed by different imaging modalities in reference to Tru-Cut biopsy results.

Methods: This retrospective cross-sectional observational study included 415 lesions obtained by Tru-Cut biopsy between March 2018 and December 2020. The lesions were examined by ultrasound (US), mammography, and magnetic resonance imaging (MRI) and categorized as BI-RADS 3, 4, or 5. In this system, every category has its own likelihood of cancer ratio.

Results: The most common malign and benign lesions were invasive ductal carcinoma and fibroepithelial lesion, respectively. The PPVs of US BI-RADS category 3, 4, and 5 lesions were 2.15%, 47.44%, and 95.19%, respectively, those of mammographic BI-RADS 3, 4, and 5 lesions were 3.79%, 53.45%, and 94.2%, respectively, and those of MRI BI-RADS 3, 4, and 5 lesions were 0%, 57.89%, and 88.1%, respectively.

Conclusion: Predicting the probability of cancer in breast imaging is of significance for patient management and effective communication between the radiologist and other physicians. We demonstrated the compatibility of our experience with the literature with this study, in which we demonstrated the possibility of imaging modalities to predict cancer according to BIRADS categories.

Keywords: Breast, Ultrasonography, Mammography, Magnetic resonance imaging, BI-RADS

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Introduction

Breast cancer, the most common cancer among women, constitutes 35% of female cancers in Turkey and 23% of all cancers affecting women worldwide [1, 2]. It is also one of the most common causes of cancer-related deaths [3]. Widespread screening programs and advances in imaging technologies allowed the early diagnosis of breast cancer and drastically reduced breast cancer-related deaths [4, 5]. The most common and easy-to-use breast imaging method is ultrasonography (US). Mammography is another frequently used imaging method, particularly for detecting early breast cancer and as a screening tool. Magnetic resonance imaging (MRI) is an advanced imaging method used particularly as a problem-solving tool and for the screening of high-risk patient groups, albeit less commonly. The American College of Radiology (ACR) developed a lexicon named the Breast Imaging-Reporting and Data System (BI-RADS) to standardize reporting between radiologists and facilitate communication with other clinicians in 1992 [6]. Most recently, the ACR published the revised and modified 5th edition of BI-RADS in 2013 [7]. Breast lesions are assigned BI-RADS categories based on US, mammography, and MRI findings.

The diagnosis of breast lesions often includes a multidisciplinary approach involving radiology, pathology, and general surgery specialists. After categorization, imaging-guided Tru-Cut biopsy is routinely used to confirm the diagnosis. Tru-Cut biopsy has been used to diagnose solid lesions since 1930 [8]. With this study, we aimed to evaluate the agreement between Tru-Cut biopsy results and BI-RADS classifications and compare our results with the literature.

Materials and methods

This retrospective cross-sectional observational study was approved by Adıyaman University Non-Interventional Ethics Committee (approval code: 2021/05-15).

Patient selection

We analyzed 415 lesions obtained by Tru-Cut biopsy in our interventional radiology clinic between March 2018 and December 2020. To prevent potential bias, Tru-Cut biopsies performed by defining BIRADS in our center were included in the study. Fine-needle biopsies and BIRADS definitions performed in an external center were excluded from the study. All participants were informed about the study verbally and in writing and signed informed consent forms.

Radiologic assessment

Patients' US, mammography, and MRI findings were evaluated. Breast lesions were assigned BI-RADS categories based on US, mammography, and MRI findings according to the last (5th) edition of the ACR BI-RADS lexicon [9] (Figure 1, 2, 3). Patients who were assessed only by US were assigned US BI-RADS categories. In patients who underwent US and mammography, the lesions were classified using only mammography findings. MRI BI-RADS was separately evaluated in patients who underwent MRI. Biopsy specimens were obtained from all patients with BI-RADS 4 or 5 lesions, and from patients with BI-RADS 3 lesions who were at high risk for breast cancer, whose lesions had grown in size on follow-up, or at the request of the physician and/or the patient. Lesion sizes and locations were recorded. Mammography was performed for all patients over 40 years of age and for patients under 40 years of age if recommended by a radiologist. Breast MRI was decided by a radiologist according to the indications specified by the Turkish Society of Radiology [10].

Figure 1: The patient was diagnosed with intraductal papilloma by Tru-Cut biopsy. A) Mammography screen, evaluated as mammography-BIRADS 3, shows the increase in periareolar density (white circle). B) US image shows that tru-cut biopsy needle and US-BIRADS 3 lesion (white arrow). C) Contrast-enhanced MR image shows MR-BIRADS 3 lesion (white circle).

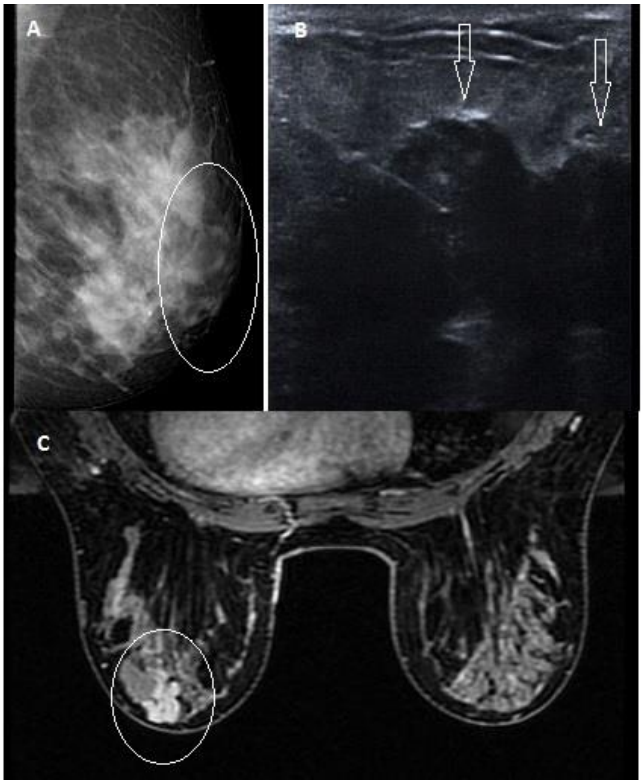


Figure 2: The patient was diagnosed with granulomatous mastitis by Tru-Cut biopsy. A) Mammography screen shows mammography-BIRADS 4 lesion (white circle). B) US image shows US-BIRADS 4 lesion (white circle). C) Contrast-enhanced MR image shows BIRADS 4 lesion (white circle).

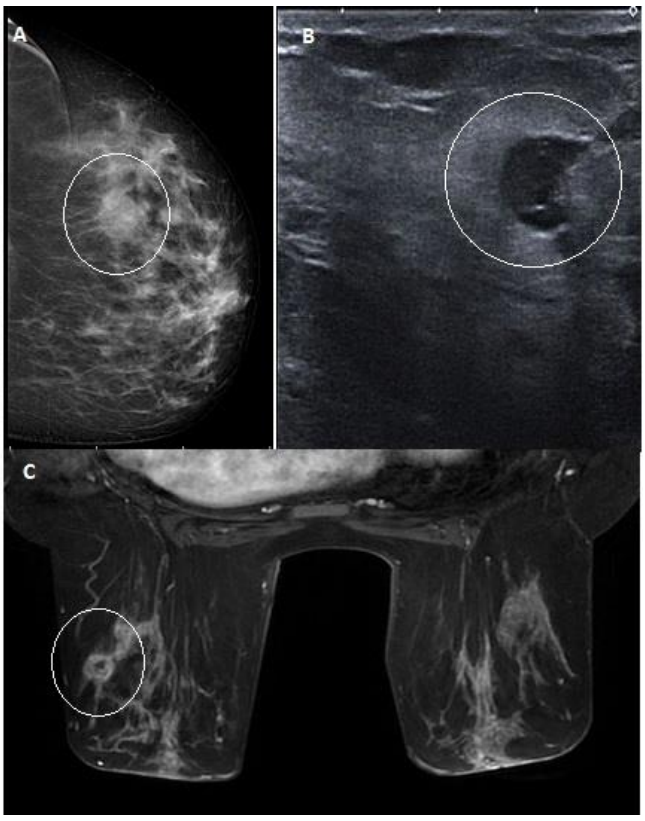
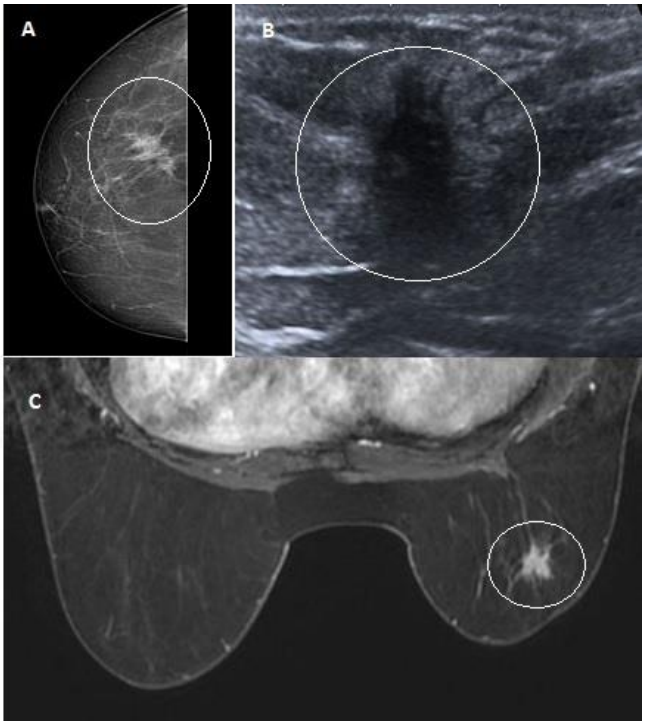


Figure 3: The patient was diagnosed with invasive ductal carcinoma by Tru-Cut biopsy. A) Mammography screen shows mammography-BIRADS 5 lesion (white circle). B) US image shows US-BIRADS 5 lesion (white circle). C) Contrast-enhanced MR image shows MR-BIRADS 5 lesion (white circle).



Biopsy procedure

All biopsy procedures were performed under ultrasound guidance using a Toshiba Aplio 300 ultrasound device (Toshiba Medical System, Tokyo, Japan) and a 7-MHz linear-array transducer. After the patient was positioned, the biopsy site was wiped with an antiseptic. Local anesthesia was administered (Citanest %2, 2-3 mL; AstraZeneca, Kırklareli, Turkey). A small incision was made with a scalpel, allowing the biopsy needle to pass through the skin. Targeted biopsy was performed with a 16-gauge coaxial semi-automatic biopsy needle (Geotek Healthcare Products, Ankara, Turkey). Samples were obtained from different sites of the lesions. Sampling was repeated at least three times until a sufficient amount of specimen was obtained from each lesion. The specimens were placed in formaldehyde and sent for pathological examination. The patients were kept under observation for 30 minutes for possible complications. They were not given antibiotic prophylaxis before the procedure. Coagulation tests and complete blood count were not assessed for patients without known coagulopathies and who were not on any medication.

Statistical analysis

The subjects were divided into two groups: Those aged ≤40 and >40 years. Statistical analysis was performed with SPSS 25.0 (IBM Corp., Armonk, NY, USA). The chi-square (χ^2) test was used to compare radiological classification and histopathological results. Pearson's correlation analysis was used to test the correlation between age and malignancy. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 579 patients were included in the evaluation. Forty-one patients who underwent fine-needle biopsy, 91 patients who visited our center for biopsy after the definition of BIRADS in another center, and 32 patients who underwent a biopsy without using BIRADS lexicon were excluded from the study, leaving 415 patients to be included (Figure 4). The mean age was 44.13 (12.60) years (range: 13-82). All participants were female. The biopsy results indicated that 274 lesions (66%) were benign, and 141 lesions (34%) were malignant. While 156 biopsies (115 benign, 41 malignant) were obtained from women younger than 40 years of age, 259 biopsies (159 benign, 100 malignant) were from women older than 40 years. The incidence of malignancy significantly differed according to age (*P*=0.01) (Table 1). The most common malignant and benign lesions were invasive ductal carcinoma and fibroepithelial lesions, respectively (Table 2). There were no complications associated with the biopsy procedure.

Figure 4: Flow-diagram of patient selection

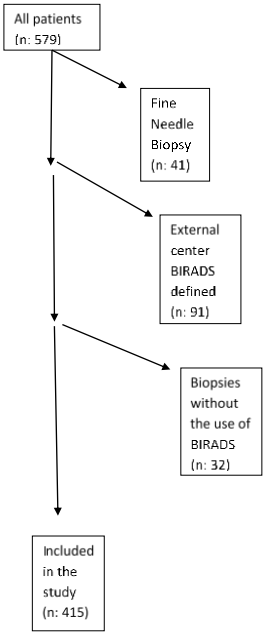


Table 1: The relationship between demographic characteristics and biopsy results *

	<40 (n=156)	≥40 (n=259)	All Patients (n=415)	*P*-value
Age(years)	32.07 (6.65) (13-39)	53.50 (13.35) (40-82)	44.13 (12.60) (13-82)	
Pathology				0.01
Benign, n(%)	115(73.7%)	159(61.3%)	274(66%)	
Malignant, n(%)	41(26.2%)	100(38.6%)	141(34%)	

* Expressed as mean (SD) or n (%)

Table 2: Distribution of pathologies *

Benign, n(%)	274 (100%)	Malignant, n(%)	141(100%)
Fibroepithelial Lesion	144(52.5%)	Invasive Ductal Carcinoma	127(90%)
Fibrocystic Change	12(4.3%)	Invasive Lobular Carcinoma	11(7.8%)
Adenosis	17(6.2%)	Neuroendocrine Carcinoma	1(0.7%)
Mastitis	69(25.1%)	Papillary Carcinoma	1(0.7%)
Ductal Hyperplasia	8(2.9%)	Chondroid Carcinoma	1(0.7%)
Fat Necrosis	7(2.5%)		
Intraductal Papilloma	5(1.8%)		
Stromal Fibrosis	5(1.8%)		
Radial Scar	4(1.4%)		
Breast Tissue	3(1%)		

* Expressed as n (%)

All patients (100%) underwent US, 259 patients (62.4%) underwent mammography, and 64 (15.4%) underwent MRI. US examinations were most commonly (n=305, 73.4%) performed due to pain and swelling in the breast, mammography was mostly (n=203, 78.3%) performed for breast cancer screening, and MRI examinations, mostly (n=51, 79.6%) at the recommendation of the radiologist.

Among patients who underwent US, 233 cases were classified as BI-RADS 3, 78 as BI-RADS 4, and 104 as BI-RADS 5. Among these, 5 (2.1%) BI-RADS 3, 37 (47.4%) BI-RADS 4, and 99 (95.1%) BI-RADS 5 lesions were malignant. A higher US BI-RADS category was associated with malignancy

(P<0.01). The positive predictive values (PPVs) of US BI-RADS category 3, 4, and 5 lesions were 2.15%, 47.44%, and 95.19%, respectively (Table 3).

Table 3: Radiologic assessment and pathology results *

	Benign (n)	Malignant (n)	&Sensitivity (%)	&Specificity (%)	&PPV (%)	&NPV (%)
US BI-RADS 3	228	5	3.5	16.7	2.1	25.2
US BI-RADS 4	41	37	26.2	85	47.4	69.1
US BI-RADS 5	5	99	70.2	98.1	95.1	86.5
Mammographic BI-RADS 3	127	5	4.9	19.6	3.7	24.4
Mammographic BI-RADS 4	27	31	30.6	82.9	53.4	65.1
Mammographic BI-RADS 5	4	65	64.3	97.4	94.2	81
MRI BI-RADS 3	3	0	0	81.2	0	21.3
MRI BI-RADS 4	8	11	22.9	50	57.8	17.7
MRI BI-RADS 5	5	37	77	68	88.1	50

* Expressed as n and %, &To detect malignancy

Among the patients who underwent mammography, 132 cases were classified as BI-RADS 3, 58 as BI-RADS 4, and 69 as BI-RADS 5. Among these, 5 (3.7%) BI-RADS 3, 31 (53.4%) BI-RADS 4, and 65 (94.2%) BI-RADS 5 lesions were malignant. A higher mammographic BI-RADS category was associated with malignancy (P < 0.01). The PPVs of mammographic BI-RADS category 3, 4, and 5 lesions were 3.79%, 53.45%, and 94.2% respectively (Table 3).

Among those who underwent MRI, 3 cases were classified as BI-RADS 3, 19 as BI-RADS 4, and 42 as BI-RADS 5. Among these, 0 (0%) BI-RADS 3, 11 (57.8%) BI-RADS 4, and 37 (88%) BI-RADS 5 lesions were malignant. A higher MRI BI-RADS category was associated with malignancy (P=0.015). The PPVs of MRI BI-RADS category 3, 4, and 5 lesions were 0%, 57.89%, and 88.1%, respectively (Table 3).

Discussion

We designed this study to correlate breast lesion biopsy results with BI-RADS assessment categories as determined by US, mammography, and MRI, the mostly used breast imaging modalities in daily practice. We then calculated the PPV of BI-RADS categories 3, 4, and 5 for each imaging modality. Due to the lack of similar studies and the relatively large sample size of the present work, we believe that our study contributes valuable information to the literature.

Our study revealed that benign pathologies were more common in patients under 40 years of age, whereas malignant pathologies were more common in those aged >40 years. This finding is consistent with the literature and data from Turkey [2, 11]. We showed that the diagnostic accuracy of Tru-Cut biopsies was 100%, in line with the literature [12]. Due to its low complication rates, high diagnostic accuracy, and easy application, Tru-Cut biopsy should be used for breast lesions.

The PPVs of US BI-RADS category 3, 4, and 5 lesions were 2.15%, 47.44%, and 95.19%, respectively. İmamoğlu et al. reported the PPVs of US BI-RADS category 3, 4, and 5 lesions as 0%, 29.8%, and 100%, respectively [13]. In our study, there were several malignant cases classified as BI-RADS category 3, as well as benign lesions classified as BI-RADS category 5. In this regard, our study conflicts with the data presented by İmamoğlu et al., who highlighted the lack of malignant BI-RADS 3 and benign BI-RADS 5 lesions as a limitation of their study. We also found a higher PPV for BI-RADS 4 lesions.

In our clinic, mammography examinations are mostly performed for women aged over 40 years for screening purposes. Our study included patients who were diagnosed with breast lesions by mammography who subsequently underwent biopsy. In our clinic, mammography is routinely performed in combination with US. However, since our study aimed to establish the PPV of mammographic BI-RADS, to prevent bias, we did not include US findings while determining mammographic BI-RADS categories. The PPVs of mammographic BI-RADS category 3, 4, and 5 lesions were 3.79%, 53.45%, and 94.2%, respectively. Ağaçlı et al. correlated mammographic and sonographic BI-RADS categories with pathology results and calculated the PPVs of BI-RADS categories 3, 4, and 5 as 3.8%, 40.6%, and 100% for malignancy, respectively [14]. The literature reports similar PPVs for mammography findings [15-18].

In our study, 64 (15.4%) breast lesions were assessed by MRI. All MRIs were obtained at the request of a radiologist and, to prevent bias, US and mammography findings were not utilized while determining MRI BI-RADS categories. MRI BI-RADS categories were determined by evaluating morphological characteristics and enhancement patterns. MRI enhancement kinetics were not considered. The PPVs of MRI BI-RADS category 3, 4, and 5 lesions were 0%, 57.89%, and 88.1%, respectively. In their study, Mahoney et al. investigated the positive predictive value of BI-RADS MRI and reported PPVs for BI-RADS categories 3, 4, and 5 as 0.9%, 20.5%, and 71.4%, respectively [19]. There is a prominent difference between the PPVs of BI-RADS category 4 as reported by Mahoney et al. and our results. This difference may be ascribed to differences in methodology, as Mahoney et al. evaluated lesion morphology as well as lesion kinetics and included more benign lesions in BI-RADS category 4 [19]. Breast MRI is increasingly used in recent years and it is quite sensitive in detecting breast cancer. Sensitivity rates ranging from 94% to 100% have been reported in the literature [20, 21]. That said, breast MRI has a relatively low specificity due to overlapping of malignant and benign lesions [22, 23].

The ACR states that the likelihood of malignancy is < 2% for BI-RADS3, ≥ 2% and ≤ 95% for BI-RADS 4, and >95% for BI-RADS 5 [24]. Our PPVs for malignancy for BI-RADS categories 3, 4, and 5 as assessed by US, mammography, and MRI are consistent with those reported by the ACR, demonstrating our success in evaluating breast lesions.

Limitations

Its retrospective and single-centered design are some of the major limitations of our study. All biopsies were obtained under US guidance; mammography-guided biopsy and MRI-guided biopsy were not considered as they were not available at the time. Moreover, we did not evaluate the subcategories of BI-RADS category 4. Premalignant lesions such as lobular and ductal carcinoma in situ were excluded from the study; therefore, they were not assessed according to BI-RADS. Finally, our study did not include elastography, a more recent imaging modality.

Conclusion

We conclude that BI-RADS categories as assessed by US, mammography, and MRI are highly correlated with pathology results. Our study showed that the BI-RADS lexicon can yield successful results that are consistent with the literature when used correctly. Predicting the probability of cancer in breast imaging is of great importance for patient management

and effective communication between the radiologist and other physicians. We recommend that all physicians dealing with breast diseases have knowledge of the BIRADS classification.

References

1. Sha Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005 Mar-Apr;55(2):74-108. doi: 10.3322/canjclin.55.2.74.
2. T.C. Sağlık Bakanlığı Türkiye Halk Sağlığı Kurumu, Türkiye Kanser İstatistikleri, Ankara 2017.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15;127(12):2893-917. doi: 10.1002/ijc.25516.
4. Hortobagyi GN, de la Garza Salazar J, Pritchard K, Amadori D, Haidinger R, Hudis CA, et al. The global breast cancer burden: variations in epidemiology and survival. Clin Breast Cancer. 2005 Dec;6(5):391-401. doi: 10.3816/cbc.2005.n.043.
5. Kopans DB. The positive predictive value of mammography. AJR Am J Roentgenol. 1992 Mar;158(3):521-6. doi: 10.2214/ajr.158.3.1310825.
6. Burnside ES, Sickles EA, Bassett LW, Rubin DL, Lee CH, Ikeda DM, et al. The ACR BI-RADS experience: learning from history. J Am Coll Radiol. 2009 Dec;6(12):851-60. doi: 10.1016/j.jacr.2009.07.023.
7. D'Orsi, C., Bassett, L., & Feig, S. (2018). Breast imaging reporting and data system (BI-RADS). Breast imaging atlas.
8. Martin HE, Ellis EB. Biopsy By Needle Puncture And Aspiration. Ann Surg. 1930 Aug;92(2):169-81. doi: 10.1097/00000658-193008000-00002.
9. Spak DA, Plaxco JS, Santiago L, Dryden MJ, Dogan BE. BI-RADS® fifth edition: A summary of changes. Diagn Interv Imaging. 2017 Mar;98(3):179-90. doi: 10.1016/j.diii.2017.01.001 .
10. Turkish Society of Radiology TRD MRG ve BT inceleme standartları 2018. (https://www.turkrad.org.tr/assets/2018/standartlar2018.pdf. June 19, 2021).
11. Cameron JL. Current surgical therapy. 9nd edition. Mosby Ine, Philadelphia, PA, USA, 2008.
12. Wu YC, Chen DR, Kuo SJ. Personal experience of ultrasound-guided 14-gauge core biopsy of breast tumor. Eur J Surg Oncol. 2006 Sep;32(7):715-8. doi: 10.1016/j.ejso.2006.04.012.
13. İmamoğlu Ç, İmamoğlu Fg, Adibelli Zh, Bayrak A, Aribaş Bk, Erdil Hf. Meme kitlelerinde ultrasonografi eşliğinde koaksiyel tru-cut biyopsi: Klinik tecrübemiz. Acta Oncologica Turcica. 2018;51(2):145-50.
14. Ağaçlı MO, Kılıçoğlu ZG, Şimşek MM, Meriç K, Kış N, Aker FV, et al. Pathologic Correlation Of Mammographic-Sonographic Bi-Rads Scores. Haydarpasa Numune Med J. 2013;53(1):20-8.
15. Orel SG, Kay N, Reynolds C, Sullivan DC. BI-RADS categorization as a predictor of malignancy. Radiology. 1999 Jun;211(3):845-50. doi: 10.1148/radiology.211.3.r99jn31845 .
16. Siegmann KC, Wersebe A, Fischmann A, Fersis N, Vogel U, Claussen CD, et al. [Stereotactic vacuum-assisted breast biopsy--success, histologic accuracy, patient acceptance and optimizing the BI-RADSTM-correlated indication]. Rofo. 2003 Jan;175(1):99-104. doi: 10.1055/s-2003-36600.
17. Tan YY, Wee SB, Tan MP, Chong BK. Positive predictive value of BI-RADS categorization in an Asian population. Asian J Surg. 2004 Jul;27(3):186-91. doi: 10.1016/S1015-9584(09)60030-0.
18. Zonderland HM, Pope TL, Nieborg AJ. The positive predictive value of the breast imaging reporting and data system (BI-RADS) as a method of quality assessment in breast imaging in a hospital population. Eur Radiol. 2004 Oct;14(10):1743-50. doi: 10.1007/s00330-004-2373-6.
19. Mahoney MC, Gatsonis C, Hanna L, DeMartini WB, Lehman C. Positive predictive value of BI-RADS MR imaging. Radiology. 2012 Jul;264(1):51-8. doi: 10.1148/radiol.12110619.
20. Harms SE, Flamig DP, Hesley KL, Meiches MD, Jensen RA, Evans WP, et al. MR imaging of the breast with rotating delivery of excitation off resonance: clinical experience with pathologic correlation. Radiology. 1993 May;187(2):493-501. doi: 10.1148/radiology.187.2.8475297.
21. Orel SG, Schnall MD, LiVolsi VA, Troupin RH. Suspicious breast lesions: MR imaging with radiologic-pathologic correlation. Radiology. 1994 Feb;190(2):485-93. doi: 10.1148/radiology.190.2.8284404.
22. Bluemke DA, Gatsonis CA, Chen MH, DeAngelis GA, DeBruhl N, Harms S, et al. Magnetic resonance imaging of the breast prior to biopsy. JAMA. 2004 Dec 8;292(22):2735-42. doi: 10.1001/jama.292.22.2735.
23. Kuhl CK, Mielcareck P, Klaschik S, Leutner C, Wardelmann E, Gieseke J, et al. Dynamic breast MR imaging: are signal intensity time course data useful for differential diagnosis of enhancing lesions. Radiology. 1999 Apr;211(1):101-10. doi: 10.1148/radiology.211.1.r99ap38101.
24. Mercado CL. BI-RADS update. Radiol Clin North Am. 2014 May;52(3):481-7. doi: 10.1016/j.rcl.2014.02.008.

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Preoperative effects of magnesium sulfate on hemodynamics and muscle relaxation

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Although there are many studies on the effects of magnesium sulfate in the literature, there is no publication on the effects of low doses of magnesium sulfate, as we administered in our study. This prospective randomized study aimed to reveal that the use of low-dose magnesium sulfate ($MgSO_4$) shortens the onset time and prolongs the block duration of neuromuscular blockers (NMBs) without changing the hemodynamics in patients monitored using the train-of-four (TOF) ratio.
Methods: This is a prospective randomized study. A total of 60 cases aged between 18–65 years with American Society of Anesthesiologists classifications I–II who were scheduled for elective open cholecystectomy were randomly divided into 3 groups. Notably, 15 minutes before the anesthesia induction, 25 mg/kg $MgSO_4$ in intravenous 0.9% saline (total volume, 100 mL) was administered to the MgSO4 group (MS group), 0.03 mg/kg midazolam was administered to the midazolam group (MD group), and the same volume of 0.9% saline solution was administered to the control group (PSS group). Nerve-muscle conduction monitoring was performed using TOF-Watch® SX (Organon, Ireland) and anesthesia depth was monitored with a BIS® monitor (A-2000; Aspect Medical Systems, USA).
Results: NMB onset times were 83.95 (26.8), 111.15 (28.12), and 163.7 (34.16) seconds (P=0.001) in the MS, MD, and PSS groups, respectively. The times until additional rocuronium requirement after the intubation dose were 60.1 (4.19), 50.8 (4.99), and 38.25 (7.27) minutes in the MS, MD, and PSS groups, respectively, which was significantly longer in the MS group compared to the other groups (P<0.001). The recovery time to TOF of 0.9 and time to T1 height of >95% was longer in the MS group than in the other groups. No difference was found between the groups in terms of hemodynamic data.
Conclusion: Low-dose $MgSO_4$ administration before rocuronium injection significantly reduces neuromuscular agent consumption without altering hemodynamics and causing a residual neuromuscular block.

Keywords: Magnesium sulfate, Muscle relaxant, Bispectral index

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Introduction

Magnesium sulfate ($MgSO_4$) is prominently used as an adjuvant drug in multimodal anesthesia. It inhibits norepinephrine release by blocking N-type and partially L-type calcium channels, increases prostacyclin synthesis, and acts as a vasodilator by inhibiting angiotensin-converting enzyme activity, which make its use a promising strategy to induce controlled hypotension [1, 2]. $MgSO_4$ reduces the amount of acetylcholine released at the motor nerve terminals by inhibition of voltage-dependent P-/Q-type calcium channels, suppresses the endplate depolarizing effect of acetylcholine, and finally inhibits muscle fiber membrane excitability [2, 3]. Although MgSO4 only causes significant neuromuscular block at high plasma concentrations (6–10 mM) [4], its use along with nondepolarizing neuromuscular blockers (NMBs) causes the faster onset of nerve block [5, 6], longer duration [3, 7], and strengthening of the block effect [8-10]. In addition, $MgSO_4$ is a central nervous system depressant that antagonizes the N-methyl-D-aspartate receptor and inhibits the release of catecholamines [2, 11, 12].

This study aimed to reveal that the use of $MgSO_4$ before administering NMBs in patients monitored with the train-of-four (TOF) ratio shortens the onset time of the block and prolongs its duration. As a secondary outcome, we aimed to evaluate the hemodynamic changes in patients who received $MgSO_4$ infusion.

Materials and methods

The American Society of Anesthesiologists classifications I–II (age of 18–65 years; body mass index [BMI], 18.5–24.9 kg/m^2) and Mallampati I–II patients scheduled for elective open cholecystectomy were included in the study. All patients were informed verbally and in writing about the study, and written informed consent was obtained. Comprehensive preoperative clinical evaluation was performed immediately after hospitalization. Patients with rocuronium allergy, history of drug use affecting the neuromuscular function (e.g., aminoglycosides or phenytoin), neuromuscular diseases, hepatic, or renal failure, or expected difficult airway and pregnant patients were excluded from the study. All patients fasted for at least 6 hours before anesthesia induction, and no premedication was administered.

Before starting anesthesia induction, standard monitoring was performed with electrocardiography, noninvasive blood pressure (BP), end-tidal carbon dioxide pressure, and peripheral oxygen saturation (SpO_2). In addition, the TOF-Watch® SX monitor (Organon, Ireland) was used for nerve-muscle conduction monitoring, and the BIS® monitor (A-2000; Aspect Medical Systems, USA) was used for anesthesia depth monitoring. Before bispectral index [13] monitoring, after wiping the forehead area with an alcohol swab, BIS electrodes were placed and measured every 10 minutes during the operation.

The patients were randomly divided into the following 3 groups: PSS group (saline group, n = 20), MD group (midazolam group, n = 20), and MS group ($MgSO_4$ group, n = 20). Patients who met the inclusion criteria were included in the groups determined by simple randomization methods (coin toss). While determining the number of patients in this study, we used the number of patients in similar studies. Fifteen minutes before the anesthesia induction, 25 mg/kg MgSO4 in intravenous (IV) 0.9% saline (total volume, 100 mL) was administered to the MS group, 0.03 mg/kg midazolam was administered to the MD group, and the same volume of 0.9% saline solution was administered to the PSS group. At the end of the infusions, the IV line was cleared and anesthesia induction was initiated.

Neuromuscular monitoring

Neuromuscular monitoring was performed using TOF-Watch® SX (Organon, Oss, the Netherlands), provided that the blood pressure muff (BP) or intravenous (IV) cannula was on the other side. Neuromuscular functions were monitored using the transcutaneous electrodes (Red Dots 3M Health Care®; Neuss, Germany) placed on the cleansed skin over the ulnar nerve on the volar side of the wrist. The position of the transducer is fixed by placing the thumb in a hand adapter (Hand Adapters®; Organon). To minimize motion-induced changes in the twitch response during electromyography and prevent electrode displacement, the arm was fixed with a special board (cardboard TOF-Guards®; Organon) and kept in the same position throughout the study procedure. A temperature sensor was placed at the distal end of the forearm. Heating blankets covering the body and arm were positioned to keep the arm temperature at >32°C (Bair Huggers®; Arizant Healthcare Inc., Eden Prairie, MN). Propofol 2 mg/kg and fentanyl 1 μg/kg were used for anesthesia induction. After induction, TOF-Watch SX acceleromyography was calibrated and stimulation was initiated (supramaximal square wave, 4 stimuli of 2 Hz of 200 ms duration with 15-second intervals). After stable baseline measurements were obtained, a bolus dose of rocuronium 0.6 mg/kg was administered intravenously for 5 seconds. The time elapsed after rocuronium injection, depression of up to 95% of a single twitch (onset time), and TOF rate during neuromuscular block were measured. Continuous TOF stimulation began at a frequency of 2 Hz and 12 seconds. Intervals with a predetermined supramaximal stimulation and orotracheal intubation of the patient were performed when TOF was 0. Neuromuscular block was measured every 20 seconds from anesthesia induction until the end of skin closure.

In all groups, anesthesia was maintained with 50% (2 L/min) oxygen-air mixture and 60% (2 L/min) N_2O to keep the end-tidal carbon dioxide pressure between 4.6-6.0 kPa and 2% sevoflurane ventilation to keep the BIS values between 40 and 60. The time from the start of rocuronium injection until the TOF count reached 0 (onset of rocuronium), and the time from 95% depression of the first twitch of TOF (T1) (rocuronium time) were measured. Hemodynamic parameters, SpO_2, $EtCO_2$, BIS, and TOF values of the patients were monitored and measured regularly. Values were recorded every 10 minutes and finally when TOF was 1. When the T4-to-T1 ratio was 90% and BIS was ≥70 during skin closure, neuromuscular block was antagonized with 10 mg/kg atropine and 20 mg/kg neostigmine, and tracheal extubation was performed.

Statistical analysis

The Number Cruncher Statistical Systems 2007 software package program (Utah, USA) was used for all statistical analyses in this study. In addition to descriptive statistical methods (mean and standard deviation), one-way paired variance analysis was used in repeated measurements of

multiple groups, Newman-Keuls multiple comparison tests were utilized for subgroup comparisons, paired *t-test*, for paired comparisons of repetitive variables, one-way analysis of variance for intergroup comparisons, Tukey multiple comparison test for comparisons of subgroups, and chi-square and Fisher reality tests for comparisons of qualitative data. *P*-value <0.05 was considered statistically significant.

Results

The mean age of 60 patients (30 females and 30 males) enrolled in the study was 47.7 (11.5) years. The patients were divided into three groups of 20 each. Saline was administered to the first group (PSS group), midazolam to the second group (MD group), and MgSO4 to the last group (MS group). Patient demographics, such as age, gender, weight, height, BMI, and ASA distributions did not differ between the groups (*P*>0.05) (Table 1). Basal and postinduction BIS, $ETCO_2$, and SpO_2 values measured during anesthesia maintenance were also similar in all 3 groups.

Table 1: Patients' demographic features and BIS values at different time-points

	PSS Group (n=20)	MD Group (n=20)	MS Group (n=20)	*P*-value
Age (years)	44.15(11.95)	47.7(16.65)	44.65(11.54)	0.672
Sex (M/F)	11/9	10/10	9/11	0.819
Weight (kg)	73(21.16)	75.5(12.22)	73.95(9.94)	0.872
Height (cm)	165.6(10.05)	164.8(10.61)	166.8(10.09)	0.825
BMI ($kg.m^2$)	27.21(9.79)	28.2(6.09)	26.66(3.67)	0.780
ASA (I/II)	12 (60%) / 8 (40%)	14 (70%) / 6 (30%)	13 (65%) / 7 (35%)	0.803
BIS at baseline	98.05(0.95)	94.75(8.85)	97.15(0.88)	0.122
BIS at injection of rocuronium	37.8(6.63)	36.2(7.63)	37.5(7.52)	0.762

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate, BMI: Body Mass Index, BIS: Bispectral Index, ASA: American Society of Anesthesiologists, M/F: Male/Female

Intra- or postoperative hemodynamic instability was not observed in any patient, and the mean baseline values of hemodynamic parameters were similar between the groups. After anesthesia induction in all groups, systolic, diastolic, and mean arterial BPs and heart rate were lower than the baseline values (p > 0.05 for each group). These values increased after laryngoscopy and tracheal intubation. The comparison of hemodynamic parameters between the groups is summarized in Tables 2 and 3. The onset time of neuromuscular block was longest in the PSS group, followed by the MD group, and the shortest time was observed in the MS group (163.7 (34.16), 111.15 (28.12), and 83.95 (26.8) seconds, respectively) (*P*=0.001) (Table 4). After the intubation dose, the time until additional rocuronium requirement for maintenance was shortest in the PSS group, followed by the MD and MS groups (38.25 (7.27), 50.8 (4.99), and 60.1 (4.19) minutes, respectively) (*P*<0.001) (Table 5).

Table 2: Heart Rate (HR) Values of Groups

	HR (bpm)			
	PSS Group	MD Group	MS Group	*P*-value
Basal	80.75(11.36)	77.55(15.24)	78.45(16.95)	0.778
Post- infusion	80.55(12.68)	80.1(25.26)	78.55(15.96)	0.939
Post- induction	79.8(14.31)	73.2(15.42)	74.1(10.53)	0.258
Post-intubation	82.7(14.5)	79.8(17.93)	80.5(15.3)	0.836
5th min	75.9(12.09)	68.1(14.9)	74.1(11.56)	0.145
10th min	78.8(14.6)	77.25(11.85)	73.8(8.89)	0.409
20th min	73.5(10.38)	74.65(11.21)	71.45(12.28)	0.665
30th min	75.35(14.25)	71.35(11.63)	72.1(11.43)	0.564
40th min	77.05(12.34)	69.8(14.18)	71.35(8.92)	0.142

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate

Table 3: Mean Arterial Pressure (MAP) Values by Groups

	MAP (mmHg)			
	PSS Group	MD Group	MS Group	*P*-value
Basal	97(12.65)	93.15(20.16)	91.6(13.06)	0.537
Post- infusion	93.75(9.85)	94.55(14.6)	98.05(18.67)	0.623
Post- induction	88.9(16.08)	82.6(12.65)	83.75(14.41)	0.347
Post- intubation	89.15(13.35)	94.05(16.01)	93.5(23.58)	0.648
5th min	99.25(13.1)	91.5(15.96)	94.9(19.07)	0.325
10th min	90.4(16.21)	88.5(17.68)	87.15(12.77)	0.806
20th min	95.2(14.49)	90.2(20.23)	93.65(20.89)	0.691
30th min	97.95(17.09)	96.7(18.33)	94.15(16.62)	0.780
40th min	99.4(14.26)	96.15(17.92)	96(18.18)	0.773

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate

Table 4: Time until onset and duration of neuromuscular blockade after administration of rocuronium (total dose 0.6 $mg.kg^{-1}$) in patients randomly allocated to rocuronium alone (Control), midazolam pretreatment with rocuronium and magnesium pretreatment with rocuronium.

	PSS Group (n=23)	MD Group (n=23)	MS Group (n=23)	*P*-value
Onset; s	163.7(34.16)	111.15(28.12)	83.95(26.8)	<0.001
Duration; min	38.25(7.27)	50.8(4.99)	60.1(4.19)	<0.001

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate

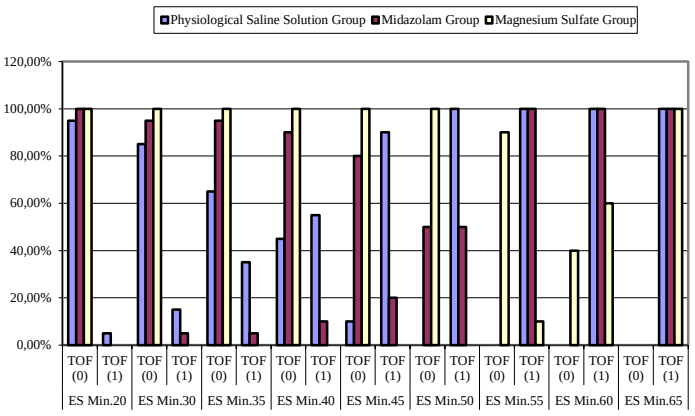
Table 5: Post-induction TOF values of groups

TOF	PSS Group	MD Group	MS Group	*P*-value
Post- induction	119.3(13.21)	121.05(22.42)	107.9(12.49)	0.038

PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate, TOF: Train-of-Four

After the first 25 minutes of stabilization of the TOF ratio and T1 height (*P*=0.362 and *P*=0.153, respectively), T1 height started to increase in the SF and MD groups. In the MS group, T1 increase was seen 15 minutes after the MD group and 25 minutes after the PSS group. The TOF ratio first reached 0.9 at the 45^{th} minute in the SF group, 55^{th} minute in the MD group, and at the 65^{th} minute in the MS group (Figure 1).

Figure 1: TOF distribution of groups



PSS: Physiological Saline Solution, MD: Midazolam, MS: Magnesium Sulfate, TOF: Train-of-Four

Discussion

In this study in which we investigated the effects of IV $MgSO_4$ infusion administered before rocuronium injection, the NMB onset time was shorter in the MS group than the PSS group. We used acceleromyography for neuromuscular monitoring and determined the time until the start of T1 to be longer in the MS group compared to the PSS group. The TOF ratio reached 0.9 in a much shorter time in the PSS group than in the MS group. Thus, the duration of the clinical effect of rocuronium 0.6 mg/kg intubation dose was significantly prolonged after premedication with $MgSO_4$. BIS scores, mean arterial pressure, and heart rate were similar in all groups. In our study, we used the lowest dose of $MgSO_4$ according to the studies performed using $MgSO_4$ so far. Thus, while increasing the duration and effect of neuromuscular block by creating a safer dose interval, the hemodynamics were not affected. As a secondary gain, we did not observe residual neuromuscular block or negative respiratory distress among the groups.

In this study, we observed that the group treated with $MgSO_4$ had an earlier onset time of rocuronium-induced neuromuscular block and a longer clinical block duration than the PSS group. We determined the NMB onset time to be approximately 2 times longer in the PSS group than in the MS group. We attribute this to the fact that $MgSO_4$ is similar to "muscle relaxants." The primary mechanism of action of $MgSO_4$ is inhibiting the calcium-mediated acetylcholine release from the presynaptic terminal of the neuromuscular junction [2, 3]; its secondary mechanism is reducing synaptic sensitivity to acetylcholine and myocyte excitability [2]. These effects concretize the effect of nondepolarizing NMBs[12]. Accordingly, many clinical studies are reporting that MgSO4 shortens the onset time, prolongs the clinical duration, and increases the potency of nondepolarizing NMBAs [3, 5, 7, 12, 14-21]. In all these studies, the infusion time of $MgSO_4$, the rocuronium dose, and the time between $MgSO_4$ administration and NMB injection are similar to our study. However, although Kussman et al. [22] used a higher dose of $MgSO_4$ than our study, they administered it as an IV bolus injection within 1 minute just before rocuronium administration and suggested that MgSO4 did not affect the onset time; however, it prolonged the duration of rocuronium-induced neuromuscular block. The effect of $MgSO_4$ on the neuromuscular junction depends on concentration and time. Therefore, there may not be enough time left for magnesium ions to pass to the neuromuscular endplate at a measurable level. In our study, we administered $MgSO_4$ 15 minutes before anesthesia induction and as an IV infusion. However, owing to the different MgSO4 regimens, anesthesia techniques (propofol and inhaled anesthetics), high pharmacodynamic variability of rocuronium, and the lack of standards for neuromuscular measurement methods, it is difficult to compare our findings with similar previous studies.

Acceleromyography is an approved method for use in neuromuscular research studies [23]. Although some studies have observed that patients treated with $MgSO_4$ do not have a significant increase in recovery parameters when monitored through TOF [24, 25], we used TOF-Watch® for neuromuscular monitoring in this study. Therefore, we closely monitored the onset time and duration of action of NMBs. Neuromuscular monitoring is mandatory to assess a TOF rate of >0.9 at which extubation is considered safe [26]. In this study, we used the TOF-Watch that has a special algorithm to calculate the TOF ratio and found that the neuromuscular block time was significantly longer in the MS group. Therefore, in line with previous studies, we also observed a significantly lesser need for NMBs in the MS group [16, 21, 23, 24]. However, the fact that $MgSO_4$ decreases the height of all twitches of the TOF response may reduce its effect on TOF fading. Therefore, in addition to the fading of the TOF ratio, we also analyzed the time course of changes in the height of the initial twitch of the TOF complex (T1) and studied the T1 value and the TOF ratio in the intraoperative neuromuscular block monitoring. When the T2 value is higher than the T1 value, the TOF value is calculated by the T4-to-T2 ratio, and if this ratio is >1.0, a 100% value can be assigned [27]. Even though the importance of this is questioned, we evaluated the period until when T1 first started to form to eliminate this risk in this study [28]. The time that T1 first started to form was determined as 35 minutes in the PSS group and 55 minutes in the MS group. Thus, it was observed that T1 height in the MS group occurred 20 minutes after the PSS group. Similar results were reported by Czarnetzki et al. [3] and by Germano Filho et al. [29]. The duration of clinical effect of 0.6 mg/kg rocuronium (intubation dose) was significantly prolonged after premedication with $MgSO_4$. Our results indicate that IV $MgSO_4$ infusion significantly reduces the consumption of neuromuscular agents.

BIS monitoring is considered a valuable method in demonstrating adequate general anesthesia formation and intraoperative awareness [13, 30-34]. To objectively evaluate the effects of magnesium sulfate on the need for anesthesia, we kept the BIS scores in the 40-60 range and did not find any difference between the groups in terms of BIS scores. Ryu et al. also suggested that magnesium has no effect on propofol requirements in parallel with our study [24]. In the literature, investigators [25] compared different $MgSO_4$ doses in study groups with a control group and found that the BIS values of the study groups were significantly lower when $MgSO_4$ was administered by infusion. Manaa and Alhabib also found similar results in their studies and advocated that $MgSO_4$ was a safe and cost-effective additional agent in the general anesthesia regimen because it reduced total anesthesia requirements, including propofol, fentanyl, and rocuronium [34]. We believe that different inhaled anesthetic agents given and inhaled at different end-tidal concentration levels may have caused different BIS values, which is the reason for the differences between the studies [35]. In addition, when stable and reasonable MAC values and hemodynamic parameters increased by 20% from baseline, fentanyl administration may have prevented any possible awareness experience in our study.

In our study, no significant difference was found in the mean arterial pressures and heart rates of the two groups. In the literature, publications are reporting that the calcium inhibitory effect of $MgSO_4$ causes central arteriolar vasodilation and reduces the need for anesthetic agents (fentanyl, vecuronium, and sevoflurane), which decreases the BP and cardiac index [11, 34, 36, 37]. However, in parallel with our study, there are also publications reporting that there is no change in heart rate [22]. We believe that this difference is caused by the differences in analgesic drug dosage and technique, $MgSO_4$ dosage and route of administration, patient category, and surgical operations. Our results indicate that low-dose $MgSO_4$ administration significantly reduced neuromuscular agent consumption without significantly affecting mean arterial pressure and heart rate.

$MgSO_4$ concentrations of 1.8–3.1 mM were used to treat eclamptic convulsions. Higher concentrations can cause residual neuromuscular block and consequent fatal complications such as respiratory and cardiac arrest [38, 39]. However, $MgSO_4$ doses were considered safe in our study, as magnesium toxicity started at a serum concentration of 2.5–5 mmol/L [16], which was much higher than the highest level in the MS group. No events that would require discontinuation or treatment in any patient were reported. In addition, no residual neuromuscular block or negative respiratory distress was observed between the groups at the time of admission to the post-anesthesia care unit and until 1 hour postoperatively.

Limitations

Our study has some limitations. Although $MgSO_4$ was infused for only 15 minutes in the current study design, it increased peripheral blood flow, and consequently, transport of rocuronium molecules to the motor nerve terminals may have been accelerated compared with control patients. Ephedrine pretreatment accelerates the neuromuscular block of rocuronium [40].

We did not measure serum and cerebrospinal fluid $MgSO_4$ concentrations for 2 main reasons. The intracellular and extracellular $MgSO_4$ concentration has no clinical significance because they do not accurately predict $MgSO_4$ levels in other body tissues. Furthermore, because renal excretion depends on plasma $MgSO_4$ concentration, it is difficult to assume that doubling the infusion rate doubles the plasma $MgSO_4$ concentration. Therefore, we cannot determine how much higher the plasma $MgSO_4$ levels were.

Although the neuromuscular block was antagonized before, initiating the evaluation of healing indices in all cases and projecting the ongoing effects of the inversion may lead to longer recovery times. We assumed that the overlap potential is true for the entire population and leads to proportional increases in recovery. However, it is difficult to predict whether such a delay in reversing the accuracy of the $MgSO_4$ recovery assessment in the group using MgSO4 infusion was indeed intense. If we had shown complete restoration of neuromuscular conduction before recovery, the reliability of the available data would be increased.

Conclusion

Our study showed that IV $MgSO_4$ infusion administered before rocuronium injection increases the standard intubation initiation rate of rocuronium and decreases the duration. We also observed that it increased the block duration of NMBs in the MS group. In addition, we found no difference between the groups in terms of mean arterial pressure and heart rate. Therefore, our results indicate that low-dose $MgSO_4$ administration significantly reduces neuromuscular agent consumption without altering the hemodynamics and causing a residual neuromuscular block. However, the optimal timing and duration of $MgSO_4$ remain uncertain. In this context, further research is required.

References

1. Jee D, Lee D, Yun S, Lee C. Magnesium sulphate attenuates arterial pressure increase during laparoscopic cholecystectomy. British journal of anaesthesia. 2009;103(4):484-9.
2. Herroeder S, Schoenherr ME, De Hert SG, Hollmann MW, Warner DS. Magnesium—essentials for anesthesiologists. The Journal of the American Society of Anesthesiologists. 2011;114(4):971-93.
3. Czarnetzki C, Lysakowski C, Elia N, Tramer M. Time course of rocuronium-induced neuromuscular block after pre-treatment with magnesium sulphate: a randomised study. Acta anaesthesiologica scandinavica. 2010;54(3):299-306.
4. Bom A, Hope F, Rutherford S, Thomson K. Preclinical pharmacology of sugammadex. Journal of critical care. 2009;24(1):29-35.
5. Kim M, Oh AY, Jeon YT, Hwang J-W, Do S. A randomised controlled trial comparing rocuronium priming, magnesium pre-treatment and a combination of the two methods. Anaesthesia. 2012;67(7):748-54.
6. Kim M-H, Oh A-Y, Han S-H, Kim J-H, Hwang J-W, Jeon Y-T. The effect of magnesium sulphate on intubating condition for rapid-sequence intubation: a randomized controlled trial. Journal of clinical anesthesia. 2015;27(7):595-601.
7. Rotava P, Cavalcanti IL, Barrucand L, Vane LA, Verçosa N. Effects of magnesium sulphate on the pharmacodynamics of rocuronium in patients aged 60 years and older: A randomised trial. European Journal of Anaesthesiology (EJA). 2013;30(10):599-604.
8. Yoshida A, Itoh Y, Nagaya K, Takino K, Sugawara J-i, Murakami T, et al. Prolonged relaxant effects of vecuronium in patients with deliberate hypermagnesemia: time for caution in cesarean section. Journal of anesthesia. 2006;20(1):33-5.
9. Aissaoui Y, Qamous Y, Serghini I, Zoubir M, Salim JL, Boughalem M. Magnesium sulphate: an adjuvant to tracheal intubation without muscle relaxation–a randomised study. European Journal of Anaesthesiology (EJA). 2012;29(8):391-7.
10. Singh S, Malviya D, Rai S, Yadav B, Kumar S, Sharma A. Pre-treatment with magnesium sulphate before non depolarizing muscle relaxants: effect on speed on onset, induction and recovery. Int J Med Sci Public Health. 2014;3:1238.
11. Elsharnouby N, Elsharnouby M. Magnesium sulphate as a technique of hypotensive anaesthesia. BJA: British Journal of Anaesthesia. 2006;96(6):727-31.
12. Hans GA, Bosenge B, Bonhomme VL, Brichant JF, Venneman IM, Hans PC. Intravenous magnesium re-establishes neuromuscular block after spontaneous recovery from an intubating dose of rocuronium: a randomised controlled trial. European Journal of Anaesthesiology (EJA). 2012;29(2):95-9.
13. Sadhasivam S, Ganesh A, Robison A, Kaye R, Watcha MF. Validation of the bispectral index monitor for measuring the depth of sedation in children. Anesthesia & Analgesia. 2006;102(2):383-8.
14. Dong J, Gao L, Lu W, Xu Z, Zheng J. Pharmacological interventions for acceleration of the onset time of rocuronium: a meta-analysis. PloS one. 2014;9(12):e114231.
15. Altan A, Turgut N, Yıldız F, Türkmen A, Üstün H. Effects of magnesium sulphate and clonidine on propofol consumption, haemodynamics and postoperative recovery. British journal of anaesthesia. 2005;94(4):438-41.
16. Seyhan T, Tugrul M, Sungur M, Kayacan S, Telci L, Pembeci K, et al. Effects of three different dose regimens of magnesium on propofol requirements, haemodynamic variables and postoperative pain relief in gynaecological surgery. British journal of anaesthesia. 2006;96(2):247-52.
17. Czarnetzki C, Tassonyi E, Lysakowski C, Elia N, Tramèr MR. Efficacy of Sugammadex for the Reversal of Moderate and Deep Rocuronium-induced Neuromuscular Block in Patients Pretreated with Intravenous MagnesiumA Randomized Controlled Trial. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2014;121(1):59-67.
18. Abdulatif M, Ahmed A, Mukhtar A, Badawy S. The effect of magnesium sulphate infusion on the incidence and severity of emergence agitation in children undergoing adenotonsillectomy using sevoflurane anaesthesia. Anaesthesia. 2013;68(10):1045-52.
19. Bondok RS, Ali RM. Magnesium sulfate reduces sevoflurane-induced emergence agitation in pediatric patients. Ain-Shams Journal of Anaesthesiology. 2014;7(3):282.
20. Abu-Sinna R, Talat SM. The effect of a pre-induction bolus dose of magnesium sulphate on emergence agitation after sevoflurane anesthesia in children undergoing adenotonsillectomy. Ain shams J Anaesthesiol. 2011;4(1):75-83.
21. Na H-S, Lee J-H, Hwang J-Y, Ryu J-H, Han S-H, Jeon Y-T, et al. Effects of magnesium sulphate on intraoperative neuromuscular blocking agent requirements and postoperative analgesia in children with cerebral palsy. British journal of anaesthesia. 2010;104(3):344-50.
22. Kussman B, Shorten G, Uppington J, Comunale M. Administration of magnesium sulphate before rocuronium: effects on speed of onset and duration of neuromuscular block. British journal of anaesthesia. 1997;79(1):122-4.
23. Claudius C, Skovgaard L, Viby-Mogensen J. Acceleromyography and mechanomyography for establishing potency of neuromuscular blocking agents: a randomized-controlled trial. Acta anaesthesiologica scandinavica. 2009;53(4):449-54.
24. Ryu J-H, Kang M-H, Park K-S, Do S-H. Effects of magnesium sulphate on intraoperative anaesthetic requirements and postoperative analgesia in gynaecology patients receiving total intravenous anaesthesia. British Journal of Anaesthesia. 2008;100(3):397-403.
25. Lee D, Kwon I. Magnesium sulphate has beneficial effects as an adjuvant during general anaesthesia for Caesarean section. British journal of anaesthesia. 2009;103(6):861-6.
26. Kotake Y, Ochiai R, Suzuki T, Ogawa S, Takagi S, Ozaki M, et al. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. Anesthesia & Analgesia. 2013;117(2):345-51.
27. Fuchs-Buder T, Claudius C, Skovgaard L, Eriksson L, Mirakhur R, Viby-Mogensen J. 8th International Neuromuscular Meeting. Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision. Acta Anaesthesiol Scand. 2007;51(7):789-808.
28. Kopman A, Kopman D. An analysis of the TOF-watch algorithm for modifying the displayed train-of-four ratio. Acta anaesthesiologica scandinavica. 2006;50(10):1313.
29. Germano Filho P, Cavalcanti I, Barrucand L, Verçosa N. Effect of magnesium sulphate on sugammadex reversal time for neuromuscular blockade: a randomised controlled study. Anaesthesia. 2015;70(8):956-61.
30. Orliaguet GA, Lambert FB, Chazot T, Glasman P, Fischler M, Liu N. Feasibility of closed-loop titration of propofol and remifentanil guided by the bispectral monitor in pediatric and adolescent patientsa prospective randomized study. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2015;122(4):759-67.
31. Malviya S, Voepel-Lewis T, Tait AR, Watcha MF, Sadhasivam S, Friesen RH. Effect of age and sedative agent on the accuracy of bispectral index in detecting depth of sedation in children. Pediatrics. 2007;120(3):e461-e70.
32. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, et al. Anesthesia awareness and the bispectral index. New England Journal of Medicine. 2008;358(11):1097-108.
33. Bruhn J, Myles PS, Sneyd R, Struys MM. Depth of anaesthesia monitoring: what's available, what's validated and what's next? BJA: British Journal of Anaesthesia. 2006;97(1):85-94.
34. Manaa EM, Alhabib AF. Effect of magnesium sulfate on the total anesthetic and analgesic requirements in neurosurgery. Journal of Neurology & Neurophysiology. 2013:1-6.
35. Samarkandi A-H. The bispectral index system in pediatrics—Is it related to the end-tidal concentration of inhalation anesthetics. Middle East J Anesthesiol. 2006;18(4):769-78.
36. Vickovic S, Pap D, Pjevic M, Uvelin A. Magnesium sulphate as an adjuvant to anaesthesia in patients with arterial hypertension: 1AP7-4. European Journal of Anaesthesiology (EJA). 2013;30:25-.
37. Do S-H. Magnesium: a versatile drug for anesthesiologists. Korean journal of anesthesiology. 2013;65(1):4.
38. Albrecht E, Kirkham K, Liu S, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013;68(1):79-90.
39. De Oliveira GS, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative Systemic Magnesium to Minimize Postoperative Pain: A Meta-analysis of Randomized Controlled Trials. Anesthesiology: The Journal of the American Society of Anesthesiologists. 2013;119(1):178-90.
40. Han D, Chun DH, Kweon T, Shin YS. Significance of the injection timing of ephedrine to reduce the onset time of rocuronium. Anaesthesia. 2008;63(8):856-60.

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The effect of cardiac rehabilitation on anxiety and depression in percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) patients

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Abstract

Background/Aim: It is well-known that Cardiac Rehabilitation (CR) brings about a marked improvement in depression and anxiety. As far as we know, there are no studies that research the effect of CR, Percutaneous Coronary Intervention (PCI), and Coronary Artery Bypass Grafting (CABG) on anxiety and depression. This study aimed to investigate the effects of the CR program on anxiety and depression and the change of anxiety and depression symptoms in patients who underwent PCI and CABG.
Methods: This cross-sectional study included 27 patients with PCI and 16 patients who had undergone CABG admitted to the CR program. The Beck Depression Inventory (BDI) was used to determine the severity of depression symptoms, and the Situational and Trait Anxiety Inventory (STAI I-II) were used.
Results: After CR, the BDI, STAI-1, and STAI-2 significantly decreased in both the PCI (P<0.001, P=0.002, and P=0.006, respectively) and CABG groups (P<0.001, P=0.001, and P=0.015, respectively) compared to before CR. The change in BDI was higher in the CABG group (P=0.033), while there were no significant differences between the changes in STAI-1 and STAI-2 scores (P=0.378 and P=0.361).
Conclusion: The results of this study demonstrate the CR benefits for depression and anxiety in patients undergoing CABG and PCI. On the other hand, CABG patients show relatively more benefit in terms of depressive symptoms. Prospective and controlled studies with larger sample sizes are needed to support our findings.

Keywords: Anxiety, Depression, Cardiac rehabilitation, Coronary artery bypass grafting, Percutaneous coronary intervention

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Introduction

Coronary Artery Disease (CAD) increases morbidity and mortality and decreases the quality of life [1, 2]. Coronary artery bypass grafting (CABG) and Percutaneous Coronary Intervention (PCI) are commonly used in the treatment of CAD, which requires myocardial revascularization [3, 4]. Despite their successful results, those procedures are stressful life events for many patients and can cause anxiety and depression before and after treatment [5]. This can negatively affect the treatment processes and the quality of life of the patients [6].

Depression and anxiety are two significant and common debilitating mental disorders [7]. Studies are reporting an association between these diseases and poor prognosis and mortality, especially among cardiac disease patients [8]. Cardiac Rehabilitation (CR) is a multidisciplinary program that includes the increase of physical exercise capacity, nutrition counseling, biopsychosocial management, and identification of metabolic cardiac risk factors [9]. Various practices, such as training the family members, support in lifestyle change, group training, and stress management, are also included in CR [10]. It is a well-known approach that CR not only increases the exercise capacities in cardiac patients but also brings about a marked improvement in depression and anxiety [11-13]. However, it is still not an easy-to-come-by treatment method due to the lack of specialized centers.

After the cardiac rehabilitation program was seen to improve anxiety and depression, the researchers investigated whether these effects changed with the cardiac diagnosis [11, 12, 14]. Solak et al. [12] compared the CAD and CABG patients and reported that CR improved the depressive symptoms among the CAD patients, but not among the CABG patients. This is mostly due to the limited number of CABG patients. On the other hand, Sharif et al., who researched the effect of CR on anxiety and depression in CABG patients, indicated its effectiveness [14]. As far as we know, no studies are examining the change in the anxiety and depression severity of patients who received CR after PCI. Similarly, we did not encounter any studies which research the effect of CR, PCI, and CABG on anxiety and depression.

In the light of such information, the present study aims first to research the effect of CR on anxiety and depression in patients who underwent PCI and CABG. The second aim is to compare the changes in the anxiety and depression symptoms of the PCI and CABG patients.

Materials and methods

The files of the patients, who joined and finished the Phase II CR program at Sultan Abdulhamid Han Training and Research Hospital between February 2017 and September 2018 were examined retrospectively. Twenty-seven patients who received Percutaneous Coronary Intervention (PCI) (removing the obstructive lesion in a coronary artery with balloon angioplasty and/or coronary stent implantation), and 16 patients who underwent Coronary Artery Bypass Grafting (CABG) were included in the study. The inclusion criteria were as follows: a) Having undergone PCI or CABG, b) Not having any physical or metabolic diseases preventing the patient from joining the CR program, c) Having finished the CR program, d) Not having any psychiatric disorders and/or history of psychiatric drug use before and during CR. After the protocol of the study was approved by the Ethics Committee of Zeynep Kamil Training and Research Hospital (IRB: 2018/128), the data were collected, and all the rights of the patients were protected following the Helsinki Declaration.

The CR program consisted of 36 exercise sessions performed over 12 weeks, 3 times a week. The vital signs of the patients, including pulse, arterial blood pressure, cardiac rhythm, and oxygen saturation, were monitored during the program. Each session consisted of a 10-minute warm-up, a 30-minute continuous aerobic exercise and the use of light hand weights, and then a 10-minute cooling period. In addition to an exercise program, the patients were trained in terms of diet, cardiac risk factors, stress management, diabetes management, hypertension, and smoking cessation.

The patients were asked to fill in the scales before the CR started. The depression symptoms of the patients were measured with the Beck Depression Inventory (BDI); their anxiety statuses were measured with STAI I-II. The vital signs of the patients, measured by the ergometer, were recorded before and after the program.

Beck Depression Inventory (BDI), one of the most used self-report scales to determine depressive symptoms in the general population, consists of 21 items scored between 0 and 3. The score interval is 0-63 and the recommended cutoff score is 17. Its validity and reliability studies were carried out in Turkish [15].

State and Trait Anxiety Inventory (STAI I-II) was used to determine the trait and situational anxiety levels of the patients. It is a self-report scale that consists of two scales with twenty items each. The situational part is used to determine how the individual feels and what his/her feelings are at a certain time and under certain conditions. The trait part is used to determine how the individual generally feels. The scores of each part range between 20-80. Elevated scores indicate a high anxiety level [16].

Statistical analysis

Power analysis was conducted with the G*Power software. Twenty-eight patients were needed for an 80% power, a 5% margin of error, and a 0.5 effect size. A total of 43 patients were included in the study; we predicted that the total patient population loss would be around 20%. The data were analyzed with SPSS (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) 20.0 version. Descriptive statistics were used to identify the properties of the data. Separation norms of continuous variables were evaluated with the Kolmogorov-Smirnov test. The paired t-test was used to compare results obtained before and after CR. The student t-Test and the Mann Whitney U test were utilized to compare two independent groups, when suitable. The chi-square test was used for the comparison of categorical data. *P*-value of <0.05 was considered statistically significant.

Results

Socio-demographic features of the patients were presented in Table 1. The mean age of the patients was 61.30

(12.53) years and 37.2% were female. The mean body mass index was 27.44 (4.31) kg/m^2. Among all, 88.4% of the participants were married and 37.2% were smokers. The demographic data of the PCI and CABG patients were similar (P>0.05 for all).

A comparison of the participants' BDI and STAI I-II scores before and after CR based on the diagnosis was shown in Table 2. After CR, the BDI, STAI-1, and STAI-2 significantly decreased in both the PCI (P<0.001, P=0.002, and P=0.006, respectively) and CABG groups (P<0.001, P=0.001, and P=0.015, respectively) compared to before CR. The change in BDI was higher in the CABG group (P=0.033), while there were no significant differences between the changes in STAI-1 and STAI-2 scores (P=0.378 and P=0.361).

Table 1: Socio-demographic features of the percutaneous coronary intervention and coronary artery bypass grafting patients who underwent cardiac rehabilitation

Variable	Total	Percutaneous coronary intervention patients	Coronary artery bypass grafting patients	t/U Value	*P*-value
N	43	27 (62.8)	16 (37.2)		
Age; Mean (SD)	61.30 (12.53)	62.37 (13.43)	59.50 (11.03)	0.722	[a]0.475
Gender n (%)					
Female	16 (37.2)	11 (40.7)	5 (31.2)	0.387	[c]0.534
Male	27 (62.8)	16 (59.3)	11 (68.8)		
BMI; Mean (SD)	27.44 (4.31)	27.53 (4.54)	27.30 (4.07)	-0.124	[b]0.901
Marital Status; n (%)					
Married	38 (88.4)	23 (85.2)	15 (93.8)	0.045	[c]0.831
Single	5 (11.6)	4 (14.8)	1 (6.2)		
Smoking; n (%)					
Yes	16 (37.2)	9 (33.3)	7 (43.8)	0.467	[c]0.495
No	27 (62.8)	18 (66.7)	9 (56.2)		

a: Sutudnet t test, b: Mann Withney U test, c: Chi square test

Table 2: Comparison of depression and anxiety scores of the patients before and after cardiac rehabilitation

Variable	Diagnosis	Before Cardiac Rehabilitation	After Cardiac Rehabilitation	t Value	*P*-value	Difference	T/U Value	*P*-value
BDI; Mean(SD)	PCI	12.55 (8.50)	6.74 (4.67)	5.113	[a]<0.001**	-5.81 (5.90)	2.212	[b]0.033*
	CABG	19.0 (9.91)	8.31 (3.53)	4.926	[a]<0.001**	-10.75 (8.75)		
STAI-1 Mean(SD)	PCI	36.85 (9.90)	32.48 (6.94)	3.388	[a]0.002**	-4.37 (6.70)	0.891	[b]0.378
	CABG	39.00 (8.42)	32.81 (8.42)	4.108	[a]0.001**	-6.18 (6.02)		
STAI-2 Mean(SD)	PCI	39.48 (9.01)	37.25 (8.92)	2.994	[a]0.006**	-2.22 (3.85)	-0.913	[c]0.361
	CABG	41.62 (11.30)	37.43 (10.03)	2.731	[a]0.015*	-4.18 (6.13)		

BDI: Beck Depression Inventory, [a] Paired T-test, [b] Student T Test, [c] Mann Whitney U Test, * P<0.05, ** P<0.001, PCI: Percutaneous Coronary Intervention, CABG: Coronary Artery Bypass Grafting

Discussion

We found that the CR program was associated with significant improvement in the anxiety and depression levels of the outpatients who underwent PCI and CABG. The improvement in the depression levels of the CABG patients was significantly higher than that of the PCI patients. The changes in the anxiety levels of the CABG and PCI patients were similar.

Anxiety and depression are among the frequent problems in patients with coronary artery disease and according to many studies, they can lead to negative outcomes [1, 6]. Previous studies revealed that the CABG patients had more severe depression and anxiety than the PCI patients [17]. In our study, the BDI and STAI I-II scores of the CABG patients were higher, which may be due to the high-risk surgical operation performed, follow-up in the intensive care unit, longer hospital stays, and more frequent outpatient follow-up visits.

The CR program improved anxiety and depression, as expected [18-20]. Although not exactly clear, the exercise program implemented during CR is the most probable mechanism for this improvement [21]. Also, we think that stress management and behavioral change training provided to the patients contributed greatly. Socialization with the other patients going through the same process may have also played a role [22]. The studies revealed that sympathetic activity, hypothalamic-pituitary axis stimulation, and inflammatory process may be of significance in the effects of depressive symptoms on the cardiovascular system [23-25]. More extensive studies are needed to clarify this mechanism.

The depressive findings of the CABG patients improved significantly more compared to the PCI patients, a finding that is first reported by our study. This is mostly because the CABG patients have relatively more severe depressive symptoms. Furthermore, the fact that CABG is performed on relatively more severe CAD patients causes an increase in the depression severity of the patients. On the other hand, the improvement in anxiety scores was similar between the two groups.

Our study had some limitations, including the small sample size and the retrospective design. Also, the anxiety and depression scores of the patients were measured with self-report scales. It should be noted that such scales may be easily manipulated by the patients. Further studies should focus on multidisciplinary interventions to increase the quality of life of cardiac patients to improve both physical and mental health. Prospective and controlled studies with bigger sample sizes are necessary to support our results.

Conclusion

Our results shed light on the beneficial effect of CR on the depression and anxiety of the CABG and PCI patients. The CABG patients' depressive symptoms improved more compared to those of PCI patients. Even though the changes seen in our study seem limited, we believe that its cumulative effect shall be high. We recommend increasing rehabilitation programs to prevent depression and anxiety among these patients, which may decrease health expenses and increase the quality of life.

References

1. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosomatic medicine. 2004;66:802-13.
2. Kubzansky LD, Kawachi I. Going to the heart of the matter: do negative emotions cause coronary heart disease? Journal of psychosomatic research. 2000;48:323-37.
3. Taggart DP. Coronary artery bypass grafting is still the best treatment for multivessel and left main disease, but patients need to know. The Annals of thoracic surgery. 2006;82:1966-75.
4. Soran O, Manchanda A, Schueler S. Percutaneous coronary intervention versus coronary artery bypass surgery in multivessel disease: a current perspective. Interactive cardiovascular and thoracic surgery. 2009;8:666-71.
5. Sullivan MD, LaCroix AZ, Spertus JA, Hecht J. Five-year prospective study of the effects of anxiety and depression in patients with coronary artery disease. The American journal of cardiology. 2000;86:1135-8, A6, A9.
6. Frasure-Smith N, Lespérance F. Reflections on depression as a cardiac risk factor. Psychosomatic medicine. 2005;67:S19-S25.
7. Gündüz A, Gündoğmuş İ. Üniversite öğrencilerinde çocukluk çağı olumsuz yaşantıları ile otomatik düşünceler, ara inançlar, uyumsuz şemalar, anksiyete ve depresif belirti şiddeti ve yaşam kalitesi arasındaki ilişki. Klinik Psikiyatri Dergisi. 2019;22:424-35.
8. Van Dijk MR, Utens EM, Dulfer K, Al-Qezweny MN, van Geuns R-J, Daemen J, van Domburg RT. Depression and anxiety symptoms as predictors of mortality in PCI patients at 10 years of follow-up. European journal of preventive cardiology. 2016;23:552-8.
9. Balady GJ, Williams MA, Ades PA, Bittner V, Comoss P, Foody JM, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: A scientific statement from the american heart association exercise, cardiac rehabilitation, and prevention committee, the council on clinical cardiology; the councils on cardiovascular nursing, epidemiology and prevention, and nutrition, physical activity, and metabolism; and the american association of cardiovascular and pulmonary rehabilitation. Circulation. 2007;115:2675-82.
10. Jolliffe J, Rees K, Taylor R, Thompson D, Oldridge N, Ebrahim S. Exercise-based rehabilitation for coronary heart disease. Cochrane Database Syst Rev. 2001:CD001800.
11. Kulcu D, Kurtais Y, Tur B, Gulec S, Seckin B. The effect of cardiac rehabilitation on quality of life, anxiety and depression in patients with congestive heart failure. A randomized controlled trial, short-term results. Europa Medicophysica. 2007;43:489-97.
12. Solak Ö, Yaman F, Ulaşlı M, Eroğlu S, Akçi Ö, Özkeçeci G, et al. Improvement in quality of life, functional capacity, and depression level after cardiac rehabilitation. Turk J Phys Med Rehab. 2015;61:130-5.
13. Demir Gündoğmuş P, Topçu Özcan B, Hayıroğlu M, Gündoğmuş İ, Ölçü EB, Uzun M, et al. The effect of age on outcomes in a cardiac rehabilitation center from Turkey. Archives of the Turkish Society of Cardiology. 2020;48:270-7.

14. Sharif F, Shoul A, Janati M, Kojuri J, Zare N. The effect of cardiac rehabilitation on anxiety and depression in patients undergoing cardiac bypass graft surgery in Iran. BMC cardiovascular disorders. 2012;12:40.
15. Hisli N. Beck depresyon envanterinin universite ogrencileri icin gecerliligi, guvenilirligi.(A reliability and validity study of Beck Depression Inventory in a university student sample). J Psychol. 1989;7:3-13.
16. Öner N, Le Compte A. Durumluk Sürekli Anksiyete Envanteri el kitabı. İstanbul: Boğaziçi Üniversitesi Yayınları. 1985.
17. Moradian ST, Msc FF. Comparison of hospital anxiety and depression among patients with coronary artery disease based on proposed treatment. Iranian journal of critical care nursing. 2011;4:97-102.
18. Glazer KM, Emery CF, Frid DJ, Banyasz RE. Psychological predictors of adherence and outcomes among patients in cardiac rehabilitation. Journal of Cardiopulmonary Rehabilitation and Prevention. 2002;22:40-6.
19. Rutledge T, Redwine LS, Linke SE, Mills PJ. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. Psychosomatic medicine. 2013;75:335-49.
20. Gundogmus PD. The effect of gender on anxiety and depressive symptoms in Turkish cardiac rehabilitation patients. Annals of Medical Research. 2019;26:670-5.
21. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. Journal of psychosomatic research. 2002;53:897-902.
22. Kulik JA, Mahler HI. Social support and recovery from surgery. Health Psychology. 1989;8:221.
23. Ehlert U, Gaab J, Heinrichs M. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: the role of the hypothalamus–pituitary–adrenal axis. Biological psychology. 2001;57:141-52.
24. Lett HS, Blumenthal JA, Babyak MA, Sherwood A, Strauman T, Robins C, Newman MF. Depression as a risk factor for coronary artery disease: evidence, mechanisms, and treatment. Psychosomatic medicine. 2004;66:305-15.
25. Gundogmus İ, Algul A, Karagöz A, Kıyançiçek M. PDW and RDW are new parameters for bipolar episodes and unipolar depression. Psychiatry and Clinical Psychopharmacology. 2018;29:1-7.

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Investigation of septum pellucidum and its variations with magnetic resonance imaging

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Ethics Committee Approval
The study protocol was approved by the local ethics committee of Sakarya University, Faculty of Medicine (71522473/050.01.04/113). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The septum pellucidum (SP) is the thin layer formed by the two laminas that form the medial wall of the lateral ventricle. When the laminas do not fuse, a cavity called cavum septum pellucidum (CSP) or Cavum Vergae (CV) forms. CSP is a developmental anomaly with unclear pathological significance and is common in people with neuropsychiatric diseases, especially schizophrenia, as well as post-traumatic stress disorder, Tourette's disease, and patients who suffer from recurrent and severe head trauma. However, few studies in the literature examine the CSP morphology among healthy individuals. Therefore, we aimed to evaluate the morphology and variations of septum pellucidum in healthy individuals.

Methods: In this retrospective cohort study, the septum pellucidum was morphologically evaluated in 509 patients who underwent brain Magnetic Resonance Imaging (MRI) at Sakarya University Faculty of Medicine, Sakarya Training and Research Hospital. We classified the anatomical variations of the septum pellucidum as CSP, CV, CVI and evaluated their dimensions.

Results: CSP was detected in 11.98% of the cases, and CV, in 1.38%. While 55.74% of individuals with CSP were male, 44.26 % were female. The mean CSP length and height were 7.71 (2.95) mm (P=0.103), and 2.80 (1.12) mm (P=0.649), respectively, and the mean length and height of the SP were 30.98 (7.36) mm (P=0.001), and 11.89 (3.32) mm (P=0.042), respectively.

Conclusion: Knowledge of CSP, one of the septum pellucidum variations, is of great importance in the differential diagnosis of midline cystic mass lesions. Its volumetric changes may be related to the development of psychiatric disorders in childhood and adulthood.

Keywords: Septum pellucidum, Cavum septum pellucidum, Cavum vergae, Magnetic resonance imaging

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Introduction

Septum pellucidum (SP), considered a part of the limbic system, is a vertically extending closed cavity between the lateral ventricles, covered with ependyma on both sides, consisting of a thin pia layer with white matter and gray matter [1]. It is attached cranially to the corpus callosum and caudally to the columna of fornix on the front between the rostrum and truncus corporis callosi [2, 3]. The thickness of this partition is usually 1-3 mm, and it is formed by the union of two separate leaves during fetal life [4, 5]. There may be a potential gap between the two leaves, sometimes detected at autopsy or radiological imaging [6, 8]. If the cavity extends rostrally, it is called Cavum Septum Pellucidum (CSP), and is in front of the foramen interventriculare. When the cavity extends caudally and is behind the foramen interventriculare, it is called Cavum Vergae (CV). The cavum veli interpositi (CVI) is in front of the quadrigeminal (superior) cistern above the roof of the third ventricle. Cisterna interventricularis, ventriculi tertii, transverse fissure and sub-trigonal fissure are also used instead of CVI. It develops because of the abnormal separation of the limbs of the fornix and is independent from the septum pellucidum [9].

The defect in the SP structure may indicate a disruption in the development of the hippocampus or corpus callosum during the embryological period because the development of CP is synchronous with the hippocampus, corpus callosum or nucleus septalis, all limbic system structures. During the embryological period, the growth of the hippocampus and corpus callosum pushes the SP leaves and allows the leaves to adhere from the back to the front. Therefore, it is thought that dysgenesis occurring in neighboring structures will also affect SP and may cause CSP, CV or CVI by disrupting the adhesion process of leaves [10]. It is clearly emphasized in the literature that the presence of CSP or CV may be an indicator of a disruption in limbic system embryology and may be associated with schizophrenia, obsessive-compulsive disorder or other psychotic disorders [11-13]. Based on this information, we aimed to evaluate SP and its variations in our study.

Materials and methods

Participants

The present retrospective study included 640 patients who were admitted to Sakarya University Faculty of Medicine Training and Research Hospital between 2013 and 2016. The study protocol was approved by the local ethics committee of Sakarya University, Faculty of Medicine (71522473/050.01.04/113). The patients presented with headache, dizziness, tinnitus, hearing disturbance, hemisensory disturbance, and seizures. Initial neurological examination and interviews confirmed that none of the 509 patients had a history of previous intracranial hemorrhage, cerebral infarction, meningitis, ventriculitis, neurodegenerative disease, traumatic brain injury, intracerebral and intraventricular cysts, hydrocephalus, brain tumor, or psychotic disorders. One hundred and thirty-one patients were excluded due to operation history, structural anomaly and the presence of space-occupying lesions. Brain MRI scans of 509 (189 males, 320 females) cases aged 1-89 years were reviewed. The mean age of the patients was 44.99 (18.945) years among females and 49.98 (20.46) years among males.

Magnetic Resonance Imaging

Examinations were performed using a 1.5 T MRI unit (Signa Voyager; GE Healthcare, Milwaukee, WI) with spine coil, in supine position. The cranial MRI protocol included coronal T2-weighted TSE images (TR/TE, 5102/102 ms; slice thickness/interslice gap, 5/1.5 mm and NEX, 2), sagittal T2-weighted TSE images (TR/TE, 4410/102 ms; slice thickness/interslice gap, 5/1.5 mm and NEX, 2), and axial T2-weighted Propeller images (TR/TE,6335/125 ms; slice thickness/interslice gap, 5/1.5 mm and NEX, 1).The T2WIs at the level of the foramen of Monro and that at the lowest level of the body of the lateral ventricles were used as references for identifying the CSP, CV, and CVI.

Measurements

The presence of CSP, CV and CVI investigation with length and height measurements were made for these variations when detected. The shape and extent of the CSP, CV and CVI were assessed on the coronal and sagittal images. In addition, the study group was divided into four age groups as 0-20, 21-40, 41-60 and 60+ years to better reveal the development of CP. The present study was performed per our institution's guidelines for human research. Ethics committee approval (71522473/050.01.04/113) was obtained before starting the measurements. All authors declare that the study was conducted in accordance with the World Medical Association Helsinki Declaration, "Ethical Principles for Medical Research on Human Subjects".

Statistical analysis

Data management and statistical analysis were performed with the statistical package for social sciences (SPSS) version 18 for Microsoft Windows. After descriptive statistical analyses (frequency, percentage distribution, mean (standard deviation)) were performed, normal distribution of continuous variables was assessed by Shapiro-Wilk and Kolmogorov Smirnov Tests. Chi-square test was conducted to evaluate the group difference in terms of discrete variables. Independent t-tests were used for continuous variables meeting parametric assumptions. The data were compared by gender. Statistical significance was indicated by a *P*-value of less than 0.05.

Results

Among all, 84.64% of the cases had normal CP anatomy. The CSP and CV incidences were 11.98% (n=61) (Figure 1), and 1.38% (n=7) (Figure 2), respectively; however, no CVI was not found in these cases. The incidence, length, and height of CSP were insignificantly higher in males, while those of CV were higher among females (71.43% vs. 28.57%) (Table 1). In the comparison of the length and height of SP, the values of men were significantly higher than that of women (Table 1) (Figure 3).

CP length was similar between individuals aged 0-20 years and 21-40 years (P=0.277). However, significant differences existed between individuals aged 0-20 years and those aged 41-60 years and 61+ years (P=0.001). Those in the 21-40-year age group significantly differed from those aged 41-60 years and 61+ years (P=0.001). The CP length of individuals

aged 41-60 years significantly differed from all other groups (P=0.001). Similarly, there was a significant difference between the CP lengths of those over the age of 61 and all other age groups (P=0.001) (Table 2).

Figure 1: Presence of cavum septum pellucidum (CSP) on coronal MR image

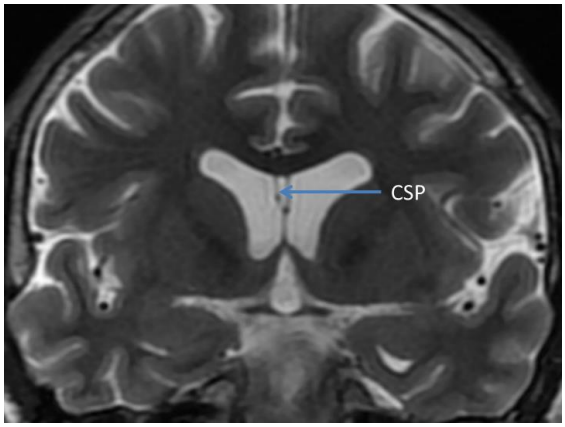

Figure 2: Presence of cavum vergae (CV) on axial MR image

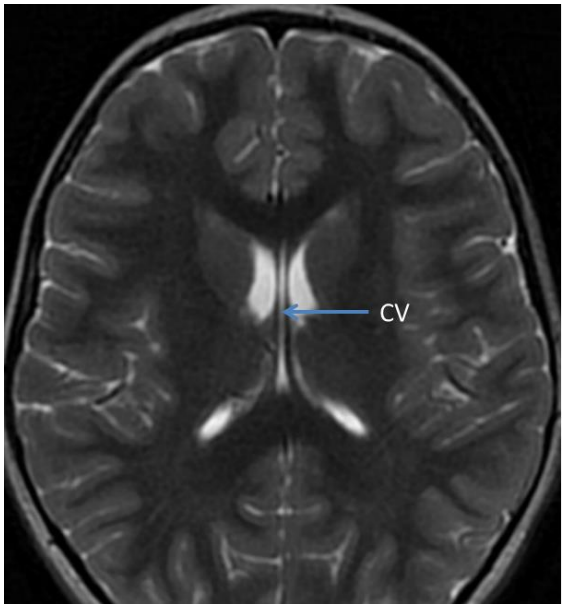

Figure 3: Presence of septum pellucidum (SP) on coronal MR image

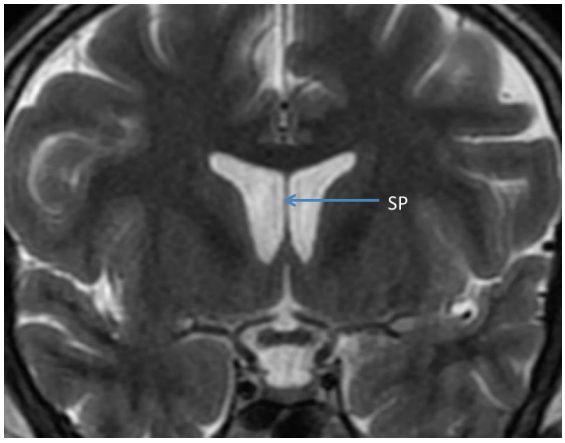

Table 1: Evaluation of cavum septum pellucidum (CSP), cavum vergae (CV) and septum pellucidum in terms of length, height, and width according to gender

		Male	Female	Total	*P*-value
CSP	n (%)	34(55.74)	27(44.26)	61(11.98)	
	Length Mean(SD)	8.26(3.29)	7.02(2.34)	7.71(2.95)	0.103
	Height Mean(SD)	2.86(1.37)	2.73(0.72)	2.80(1.12)	0.649
CV	n (%)	2(28.57)	5(71.43)	7(1.38)	
	Length Mean(SD)	12.04(3.06)	14.80(2.34)	14.01(1.43)	0.456
	Height Mean(SD)	51.13(1.98)	47.50(0.72)	48.54(5.78)	0.505
	Width Mean(SD)	5.43(1.43)	8.77(5.17)	7.82(4.56)	0.432
SP	n (%)	153(34.7)	288(65.3)	441(100)	
	Length Mean(SD)	32.59(7.36)	30.13(7.23)	30.98(7.36)	0.001*
	Height Mean(SD)	12.33(3.55)	11.66(3.17)	11.89(3.32)	0.042*

SD: Standard deviation, *P<0.01 statistically significant

Table 2: Evaluation of septum pellucidum (SP) in terms of length and height according to age groups

Age Groups	n(%)	SP length	height
0-20	47(10.7)	25.49(6.42)	10.14(2.74)
21-40	131(29.7)	27.40(5.63)	10.60(2.26)
41-60	144(32.6)	31.43(6.57)	11.78(2.93)
61+	119(27.0)	36.54(6.42)	14.15(3.73)
Total	441(100)		

CP height was similar between individuals aged 0-20 years and 21-40 years (P=0.811). There were significant differences between individuals aged 0-20 years and those aged 41-60 years (P=0.007) and 61+ years (P=0.001). The CP length of individuals aged 41-60 years significantly differed from all other groups. Similarly, there was a significant difference between the CP heights of those over the age of 61 and all other age groups (Table 2).

Both CP length and height were insignificantly lower in females (P>0.05) (Table 3).

Table 3: Evaluation of septum pellucidum (SP) in terms of length and height according to gender

Age Groups	Gender	SP				
		n(%)	length	*P*-value	height	*P*-value
0-20	Male	14(29.8)	28.24(6.87)	0.055	11.01(2.92)	0.164
	Female	33(70.2)	24.33(5.94)		9.78(2.62)	
21-40	Male	36(27.5)	28.17(6.43)	0.341	10.61(2.46)	0.952
	Female	95(72.5)	27.11(5.30)		10.59(2.19)	
41-60	Male	52(36.1)	32.25(6.91)	0.263	11.87(3.28)	0.764
	Female	92(63.9)	30.97(6.36)		11.72(2.73)	
61+	Male	51(42.9)	37.24(5.77)	0.304	14.37(3.71)	0.568
	Female	68(57.1)	36.01(6.87)		3.98(3.76)	
Total		441	p>0.05			

Discussion

The development of the septum pellucidum is synchronized with the development of the corpus callosum, hippocampus, amygdala, and septal nuclei, all of which are limbic system structures. Therefore, possible variations of septum pellucidum can be accompanied by the variations of these structures [8].

CSP, an indication of the abnormal development of the brain's midline structures, is a closed space that is generally not connected to the ventricular system and cisterna. Septum pellucidum agenesis is seen at a frequency of 2-3/100,000 and associated with some congenital brain anomalies, especially holoprosencephaly, septo-optic dysplasia and schizencephaly [14-16]. There were no individuals with septum pellucidum agenesis in our study. The rate of CVI variation, which was also not found among our patients, was reported as 5.54% by Alessandro et al. [17]. Meanwhile, Satoshi et al. [18] reported an unusually high and controversial rate of 50%. CSP volume increases until the 32nd week of gestation and then decreases [19]. D Addriove et al. [20] found the average size of midline cysts to be 12.4 mm prenatally. Behnaz et al. [21] reported the cut-off value of CSP width as 7.1 mm for indicating a probability of brain anomaly during the prenatal period. However, the generally accepted view is that if the CSP width is 10 mm in any period of pregnancy, it should be called a cyst instead of an anatomical variation [18]. Dremmen et al. [22] found the incidence of CSP to be 4.6% in their study on school-age children. Studies on the prevalence of CSP in healthy adults have revealed vastly different numerical results (0.1-85%). This difference was attributed to the sensitivity of the imaging method in many articles. Studies with a low incidence of CSP are generally performed with CT, and those reporting higher incidences of CSP are performed with MRI. In the study of

Oktem et al. investigating the MRIs of 3128 patients, the incidence of CSP was reported as 3.7% [8]. In our study, the incidence of CSP is 12%. Some studies indicate that the association of neurological diseases with CV is much more common than CSP. Oktem et al. reported the incidence of CV as 3.1% (8). In our study, this rate was 1.2%. Raine et al. showed that adult patients with large CSP had significantly more antisocial activities than patients with normal CSP [23]. Filipovic and Teofilovski-Parapid [24] found a CSP rate of 68.63% in the autopsy series of cases with neuropsychiatric disorders. In the same study, the incidence of CSP in asymptomatic cases was 10.61%, and 22.96% in total. In addition, CSP length and width are significantly higher in the symptomatic group. Cystic lesions in the midline such as arachnoid cysts can be confused with CSP, CV, and CVI variations due to their localization. In these cases, distinction can be made by evaluating their relationship with the surrounding anatomical structures, especially the third ventricle-lateral ventricle and cisterns. Arachnoid cysts and other cystic lesions are not related to these structures and usually present with compression findings [25]. Most CSPs are asymptomatic and considered anatomical variations [26]. Symptomatic CSP is rare; its diagnosis is both difficult and controversial [27]. In symptomatic cases, the cause is increased intracranial pressure and the most common symptom is headache [28]. Endoscopic fenestration is used in the safe and effective treatment of CSP [29].

Limitations

Our study contains some limitations, one being its retrospective nature, including results from a single center, and the relatively small sample size.

Conclusions

SP variations which are indetectable in CT may be detected by MRI. We wanted to share the frequency of CP variation and detailed morphometric evaluation in the Turkish population in this study we conducted on healthy individuals using MRI. We think that the age-grouped data we shared for CSP, and CV will contribute to the literature. Patients with SP variations should be evaluated in detail in terms of other accompanying anomalies. Due to the superiority of showing anatomical details in the anatomy of the septum pellucidum region, the preferred imaging method should be MRI.

References

1. Standring S. Gray's Anatomy: the anatomical basis of clinical practice: 40th Edition, Churchill Livingstone Elsevier 2008; pp.241-243.
2. Arıncı K, Alaittin E. Anatomi. 5.Baskı. Cilt 2. 2014;314.
3. Sarwar M. The septum pellucidum: normal and abnormal. American Journal of Neuroradiology. 1989;10.5:989-1005.
4. Harding BN. Malformations of the nervous system. In:Hume Adams J, Duchen LW (eds) Greenfield's neuropathology, 5th ed. Edward Arnold, London, 1992;521–638.
5. Aldur MM, Berker M, Celik HM, Sargon MF, Ugur Y, Dagdeviren A. The ultrastructure and immunohistochemistry of the septum pellucidum in a case of thalamic low-grade astrocytoma with review of literature. Neuroanatomy. 2002;1:7–11.
6. Malinger G, Lev D, Kidron D, Heredia F, Hershkovitz R, Lerman-Sagie T. Differential diagnosis in fetuses with absent septum pellucidum. Ultrasound in Obstetrics and Gynecology: The Official Journal of the International Society of Ultrasound in Obstetrics and Gynecology. 2005;25(1):42-9.
7. Degreef G, Lantos G Bogerts B Ashtari M J Lieberman. Abnormalities of the septum pellucidum on MR scans in first-episode schizophrenic patients. American Journal of Neuroradiology. 1992;13(3):835-40.
8. Oktem H, Dilli A, Kurkcuoğlu A, Pelin C. Prevalence of Septum Pellucidum Variations: A Retrospective Study. Open Access Library Journal. 2018;5(11):1. doi: 10.4236/oalib.1105017.
9. Born CM, Meisenzahl EM, Frodl T, Pfluger T, Reiser M, Möller HJ, Leinsinger GL. The septum pellucidum and its variants. European Archives of Psychiatry and Clinical Neuroscience. 2004;254(5):295-302.
10. Sarnat HB, Curatolo P. Malformations of the Nervous System. Amsterdam: Elsevier B.V. 2008;533-56.
11. Onur E, Alkın T, Ada E. The Relationship of Cavum Septum Pellucidum with Obsessive Compulsive Disorder and Tourette Disorder: A Case Report. Klinik Psikiyatri Dergisi. 2007;10(1):53-7.
12. Sagır B, Binbay T, Ceylan D, Yalın N, Özerdem A, Alptekin K. Cavum Vergae and Schizophrenia: Brain Imaging Findings and Treatment Outcome of a Case with 25 Years of Untreated Psychosis. Turk Psikiyatri Dergisi. 2015;26:295-8.
13. Yıldırım YE, Sert E, Aydın PÇ, Berkol TD, Kunt S. Two Cases of Schizophrenia; The Relationship Between Cavum Septum Pellucidum And Clinical Course. The Journal of Neurobehavioral. 2019;6(1):131-3.
14. Falco P, Gabrielli S, Visentin A, Perolo A, Pil G, Bovicelli,L. Transabdominal Sonography of the Cavum Septum Pellucidum in Normal Fetuses in the Second and Third Trimesters of Pregnancy. Ultrasound in Obstetrics & Gynecology. 2000;16:549-53. doi: 10.1046/j.1469-0705.2000.00244
15. Sundarakumar DK, Farley SA, Smith CM, Maravilla KR, Dighe MK. Nixon JN. Absent Cavum Septum Pellucidum: A Review with Emphasis on Associated Commissural Abnormalities. Pediatric Radiology. 2015;45:950-64. doi: 10.1007/s00247-015-3318-8
16. Supprian T, Sian J, Heils A, Hofmann E, Warmuth-Metz M, Solymosi L. Isolated Absence of the Septum Pellucidum. Neuroradiology. 1999;41:563-6. doi: 10.1007/s002340050805
17. De leucıo A, Dossanı, RH. Cavum Veli Interposit. In: StatPearls [Internet]. StatPearls Publishing, 2020. https://www.ncbi.nlm.nih.gov/books/NBK559000/
18. Tsutsumı S, Ishii H, Ono H, Yasumoto Y. Visualization of the cavum septi pellucidi, cavum Vergae, and cavum veli interpositi using magnetic resonance imaging. Surgical and Radiologic Anatomy. 2018;40(2):159-64. doi: 10.1007/s00276-017-1935-7
19. Deborah J, Paul DG. Normal appearances and dimensions of the foetal cavum septi pellucidi and vergae on in utero MR imaging. Neuroradiology. 2020;62:617–27. doi: 10.1007/s00234-020-02364-5
20. Addario V, Pinto V, Rossi AC, Pintucci A, Di Cagno L. Cavum veli interpositi cyst:prenatal diagnosis and postnatal outcome. Ultrasound Obstet Gynecol e Off J Int Soc Ultrasound Obstet Gynecol. 2009;34(1):52-4.
21. Behnaz M, Maryam R, Kolsoom K, Mohammad AK, Ahmad-Reza T. Cavum velum interpositum cysts in normal and anomalous fetuses in second trimester of pregnancy: Comparison of its size and prevalence. Taiwanese Journal of Obstetrics & Gynecology. 2019;58:814-9. doi: 10.1016/j.tjog.2019.09.016 1028-4559
22. Dremmen MHG, Bouhuis RH, Blanken LME, Muetzel RL, Vernooij MW, Marroun H.E, Jaddoe VWV and et al. Cavum Septum Pellucidum in the General Pediatric Population and Its Relation to Surrounding Brain Structure Volumes, Cognitive Function, and Emotional or Behavioral Problems. American Journal of Neuroradiology. 2019;40(2):340-6. doi: 10.3174/ajnr.A593
23. Raine A, Lee L, Yang Y, Colletti P. Neurodevelopmental marker for limbic maldevelopment in antisocial personality disorder and psychopathy. Br J Psychiatry. 2010;197(3):186–92.
24. Filipović B, Teofilovski-Parapid G. Linear Parameters of Normal and Abnormal Cava Septi Pellucidi: A Post-Mortem Study. Clinical Anatomy. 2004;17:626-30. doi: 10.1002/ca.20014
25. Funaki T, Makino Y, Arakawa Y, Hojo M, Kunieda T, Takagi Y, Takahashi JC, Miyamoto S. Arachnoid Cyst of the Velum Interpositum Originating from Tela Choroidea. Surgical Neurology International. 2012;3:120. doi: 10.4103/2152-7806.102334
26. Dandy WE. Congenital cerebral cysts of the cavum septi pellucidi (fifth ventricle) and cavum vergae (sixth ventricle). Diagnosis and treatment. Arch Neurol Psychiatry. 1931; 25(1):44–66.
27. Inaji T, Akimoto H, Hashiomoto T, Yamanaka S, Wada J, Miki T, Ito H. Neuroendoscopic fenestration of expanding cavum septi pellucidum: a case report. Jpn J Neurosurg. 2002;11:283–8.
28. Amin BH. Symptomatic cyst of the septum pellucidum. Childs Nerv Syst. 1986;2(6):320–2.
29. Gangemi M, Donati P, Maiuri F, Sigona L. Cyst of the velum interpositum treated by endoscopic fenestration, Surg. Neurol. 1997;47:134–7.

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Arthroscopic microfracture alone or combined application of acellular scaffold: Which one is more effective in the treatment of osteochondral lesions of the talus?

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Ethics Committee Approval
The study was approved by the Ethics Committee of Acibadem University (Date 17.09.2020 /No. 2020-20/07)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: The optimal treatment method of the talar osteochondral lesions (TOLs) is still controversial. Although the success of arthroscopic microfracture treatment (AMFx) in smaller lesions is known, different treatment methods are tried in larger-sized TOLs. This study aimed to compare the clinical and radiological outcomes of the single-step AMFx repair procedure and the combined application of AMFx and cell-free scaffold (CFS) in the treatment of TOLs.
Methods: This retrospective cohort study included patients presenting with a TOL larger than 1.5 cm^2 and smaller than 3 cm^2 between March 2015 and June 2018 who received arthroscopic treatment and attended follow-up for at least 24 months. Eighteen patients (group 1) were treated with the AMFx method, and 16 patients (group 2) with AMFx + CFS. American Orthopedic Foot and Ankle Society (AOFAS), Visual Analog Scale (VAS), and Tegner Activity Scores were used for clinical evaluation, and MOCART (magnetic resonance observation of cartilage repair tissue) score was used to assess cartilage repair tissue.
Results: The mean patient age was 33.47 (8.67) years and the mean follow-up time was 32.24 (9.33) months. There was no significant difference between the two groups in terms of age (P=0.984), body mass index (P=0.450), defect size (P=0.081) and follow-up time (P=0.484). The median AOFAS score increased from preoperative assessment until follow-up assessment at 12 months in groups 1 (P<0.001) and group 2 (P<0.001). There was no significant difference between the two groups in terms of clinical scores, or the components of the MOCART score.
Conclusion: Comparisons revealed that outcomes at the end of 24-month follow-up were similar between two groups. Therefore, TOLs appear to benefit similarly from the AMFx and AMFx + CFS techniques.

Keywords: Talus, Osteochondral Lesion, Microfracture, Scaffold

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Introduction

Although the etiology of the talar osteochondral lesions (TOLs) is still uncertain, these lesions are well-defined to be cartilage injuries involving both the chondral and subchondral layers that are thought to occur secondary to ankle trauma [1] or ischemic causes [2]. The clinical findings of TOLs may vary from asymptomatic disease to the presence of severe pain and significantly worsened quality of daily life [3]. While TOL secondary to trauma generally manifests in the anterolateral area, ischemic lesions are usually located posteromedially [4]. Planning of treatment approach has become more important due to the increasing incidence of TOLs [5]. The main factors affecting treatment are the size, depth, and localization of the TOL and the degree of subchondral bone involvement [5]. Several treatment options are available, including conservative treatment, arthroscopic debridement and microfracture, mosaicplasty, allograft applications, and autologous chondrocyte implantation [6,7]; however, it has been shown that inappropriate treatment may lead to cartilage degeneration and osteoarthritis in the long-term [8].

The arthroscopic microfracture (AMFx) technique is an easily performed single-step procedure that is the most frequently employed cartilage repair method. Today, arthroscopic techniques are usually based on the stimulation of bone marrow and the gathering of mesenchymal stem cells (MSCs) in order to ensure healing [9-11]. Despite being reported to have inadequate effectiveness in long-term follow-up due to the high failure rate and formation of biomechanically poor fibrocartilage in lesions larger than 1.5 cm^2, the AMFx procedure remains popular, especially for the treatment of smaller lesions [9,10,12].

Cell-free scaffolds (CFS) are cost-effective and can be applied as a single-step arthroscopic procedure. The application of CFS in combination with AMFx provides a basis for the maturation of mesenchymal stem cells from the subchondral bone [13,14]. In addition, these biomaterials also ensure the mechanical stability of mesenchymal stem cells by providing 3-dimensional support [15]. Current evidence shows that, compared to 2-dimensional support, a 3-dimensional support environment preserves chondrocyte structure, enables relatively better chondrocyte transformation, and procures a tissue structure that mimics native tissue characteristics, thereby enhancing repair [15-17].

In this study, it was aimed to comparatively present the short-term clinical and radiological outcomes of the stand-alone AMFx procedure and the combined AMFx + CFS application, which are utilized in the single-step treatment of TOLs.

Materials and methods

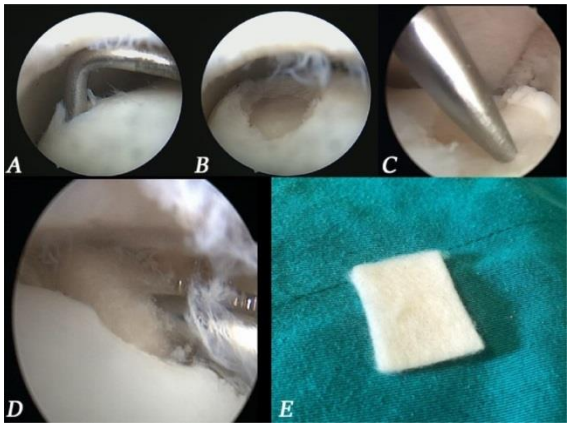
The study was approved by the Ethics Committee of Acibadem University (Date 17.09.2020 /No. 2020-20/07), and written informed consent –for the procedures and also the use of data as part of a scientific study– was obtained from all patients. This study was performed in line with the principles of the Declaration of Helsinki. In this retrospective cohort study, patients who were screened for talus focal osteochondral lesions between March 2015 and June 2018 were evaluated. Inclusion criteria were as follows: Being aged between 20 and 50 years, having received surgical treatment for Outerbridge grade 3–4 lesions larger than 1.5 cm^2 and smaller than 3 cm^2 affecting the talar dome, having a body mass index (BMI) of <30 kg/m2, and attending follow-up visits for at least 24 months. Patients who were lost to follow-up, those who had a history of ankle surgery, patients who needed revision surgery, and those who had ankle instability or a kissing lesion were excluded from the study. The sample size was reached by including thirty-four patients who met the inclusion/exclusion criteria, out of a total of one-hundred-eighteen patients who were operated for TOLs between the dates mentioned above.

Thirty-four patients who fulfilled the inclusion/exclusion criteria were included in the study. All patients were operated on by one of two surgeons (A and B). Eighteen patients (10 females, 8 males) who were operated by surgeon A using the AMFx procedure (stand-alone) comprised Group 1, and 16 patients (10 males, 6 females) who were operated by Surgeon B using the combined procedure (AMFx + CFS) (SupraFelt^{TM}, BMT Calsis, Ankara, Turkey) comprised Group 2.

The data of the two groups were reviewed, and age, body mass index (BMI), follow-up time, and TOL size were recorded. The American Orthopedic Foot and Ankle Society (AOFAS) Ankle-Hindfoot Scale, Visual Analog Scale (VAS), and Tegner Activity Scale were determined preoperatively. They were consistently used to evaluate clinical results during the postoperative period. Magnetic resonance observation of cartilage repair tissue (MOCART) score was used to evaluate cartilage quality from magnetic resonance (MR) images [18]. The groups were compared in terms of demographics and the size of cartilage defects, in addition to scores obtained from the AOFAS, VAS, Tegner Activity Scale, and MOCART analysis.

In both groups, debridement was performed on cartilage defects, and subchondral bone was reached via standard ankle arthroscopy. A probe was used to measure the depth and size of the lesions in millimeters. In Group 1, AMFx was performed using a 30-degree awl on the TOL site, and the procedure was terminated following joint debridement. In Group 2, AMFx was also performed via the use of a 30-degree awl on the TOL site, followed by arthroscopic application of CFS (SupraFelt^{TM}) in order to fill the defect completely. A fixation method was not used for scaffold stabilization, and the procedure was terminated (Figure 1).

Figure 1: Arthroscopic images of ankle arthroscopy (A) Osteochondral lesion (OCL) of the medial talar dome of talus (B) After debridetment of the OCL to stable margins (C) Microfracture (AMFx) application (D) Application of the cell- free scaffold (CFS) after AMFx (E) Image of CFS



Statistical analysis

All analyses were performed with SPSS v21 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to check normality. Data were expressed with mean (standard deviation-SD) or median (minimum-maximum) values for continuous variables according to the normality of distribution and frequency (percentage) values for categorical variables. Normally distributed variables were analyzed with the independent samples t-test, and non-normally distributed variables, with the Mann–Whitney U test. Categorical variable distributions were assessed with the Pearson Chi-square test or the Fisher's exact test. Repeated measurements were evaluated with Friedman's analysis of variance by ranks depending on the normality of distribution. Pairwise comparisons were performed with the Bonferroni correction method. Comparisons of the changes in these variables between the groups were performed by analyzing the differences between measurements via the Mann-Whitney U test. *P*-values of <0.05 were considered to demonstrate statistical significance.

Results

Among 34 patients included in the study, 55.5% of the patients in Group 1 (stand-alone AMFx) and 37.5% of the patients in Group 2 (combined procedure) were female. The mean ages were 28.8 (6.2) and 30.4 (7.6) years in Group 1 and Group 2, respectively. The mean BMI values were 24.2 (4.3) and 25.3 (3.6) kg/m^2 in Groups 1 and 2, respectively. In terms of defect size, the mean value was 1.9 (0.3) cm^2 in Group 1 and 2.1 (0.4) cm^2 in Group 2. Follow-up durations were 42.2 (9.2) months and 40.1 (11.6) months, in groups 1 and 2, respectively. There was no significant difference between the two groups in terms of demographic features and lesion size (*P*>0.05 for all, Table 1).

Table 1: Summary of the patient characteristics and scale scores with regard to the surgical method

	Surgical method		
	Microfracture(n=18)	Microfracture + Scaffold (n=16)	*P*-value
Age	33.50 (8.26)	33.44 (9.39)	0.984
Gender			
Female	10 (55.56%)	6 (37.50%)	0.479
Male	8 (44.44%)	10 (62.50%)	
Body mass index	26.13 (3.31)	25.28 (3.16)	0.450
Follow-up time	29 (24 - 52)	27.5 (12 - 49)	0.484
Size of the lesion	2.1 (1.6 - 4)	2.5 (1.8 - 3.2)	0.081
AOFAS Ankle-Hindfoot Scale score			
Baseline	60 (50 - 66) [a]	56 (52 - 66) [a]	0.198
1st assessment	89 (84 - 96) [b]	92 (86 - 96) [b]	
2nd assessment	92 (88 - 96) [b]	94 (92 - 96) [b]	
P (within variables)	<0.001	<0.001	
Visual Analog Scale score			
Baseline	6.5 (5 - 7) [a]	7 (6 - 7) [a]	0.281
1st assessment	2 (1 - 2) [b]	1 (1 - 2) [b]	
2nd assessment	1 (1 - 2) [b]	1 (1 - 2) [b]	
P (within variables)	<0.001	<0.001	
Tegner Activity Scale score			
Baseline	3 (1 - 7) [a]	3 (1 - 4) [a]	0.403
1st assessment	4 (2 - 7) [ab]	4 (2 - 7) [b]	
2nd assessment	4 (3 - 7) [b]	4 (2 - 7) [b]	
P (within variables)	<0.001	<0.001	
Complication	2 (11.11%)	1 (6.25%)	1.000

Data are given as mean (SD) or median (minimum - maximum) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables
Same letters denote the lack of statistically significant difference between repeated measurements

When compared to preoperative findings, both groups exhibited a significant change in AOFAS, VAS, and Tegner Activity scores at the 12th month (the first postoperative evaluation included in the study) (*P*<0.001 for all, Table 1). However, the comparison of the amount of change in scores showed no statistically significant differences in the AOFAS, VAS, and Tegner Activity scores (*P*>0.05 for all, Table 1) (Figure 2, Figure 3). Furthermore, in terms of AOFAS, VAS, and Tegner scores reported at baseline (preoperative) and postoperative 12th and 24th months, there were no significant differences between the two groups (*P*=0.198, *P*=0.281, *P*=0.403, respectively; Table 1).

Figure 2: AOFAS Ankle-Hindfoot Scale scores with regard to groups

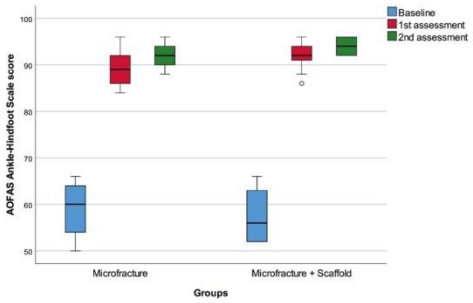
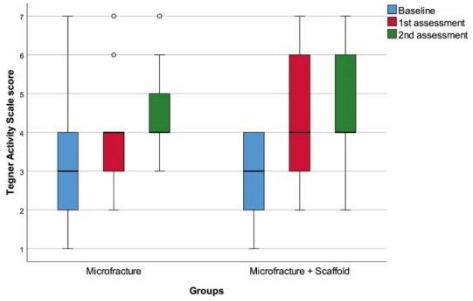


Figure 3: Tegner Activity Scale scores with regard to groups



There was again no significant difference in MOCART scores between the two groups (*P*>0.05, Table 2). Nevertheless, we observed that Group 2 had higher scores in the surface integration and effusion subgroups of the MOCART analysis compared to Group 1. Subchondral bone was intact in >60% of subjects in both groups. Effusion was identified in 22.22% and 18.75% of the patients in Group 1 and Group 2, respectively (Table 2).

Table 2: Summary of the MOCART scoring system with regards to the surgical method

	Surgical method		
	Microfracture (n=18)	Microfracture + Scaffold (n=16)	*P*-value
Degree of defect repair and filling of the defect			
Complete	8 (44.44%)	9 (56.25%)	0.305
Hypertrophy	0 (0.00%)	2 (12.50%)	
Incomplete			
> 50% of the adjacent cartilage	6 (33.33%)	3 (18.75%)	
< 50% of the adjacent cartilage	4 (22.22%)	2 (12.5%)	
Subchondral bone exposed	0 (0.00%)	0 (0.00%)	
Integration to border zone			
Complete	4 (22.22%)	6 (37.50%)	0.685
Incomplete			
Demarcating border visible (split like)	6 (33.33%)	5 (31.25%)	
Defect visible			
< 50% of the length of the repair tissue	5 (27.78%)	4 (25.00%)	
> 50% of the length of the repair tissue	3 (16.67%)	1 (6.25%)	
Surface of the repair tissue			
Surface intact	4 (22.22%)	6 (37.50%)	0.475
Surface damaged			
< 50% of repair tissue depth	11 (61.11%)	9 (56.25%)	
> 50% of repair tissue depth or total degeneration	3 (16.67%)	1 (6.25%)	
Structure of the repair tissue			
Homogenous	6 (33.33%)	6 (37.50%)	1.000
Inhomogeneous or cleft formation	12 (66.67%)	10 (62.50%)	
Signal intensity of the repair tissue			
T2-FSE			
Isointense	4 (22.22%)	5 (31.25%)	0.821
Moderately hyperintense	11 (61.11%)	9 (56.25%)	
Markedly hyperintense	3 (16.67%)	2 (12.50%)	
Subchondral Lamina			
Intact	6 (33.33%)	7 (43.75%)	0.787
Non-intact	12 (66.67%)	9 (56.25%)	
Subchondral bone			
Intact	11 (61.11%)	11 (68.75%)	0.849
Non-intact			
Edema	5 (27.78%)	4 (25.00%)	
Cyst formation or degeneration	2 (11.11%)	1 (6.25%)	
Adhesions			
No	18 (100.00%)	16 (100.00%)	N/A
Yes	0 (0.00%)	0 (0.00%)	
Effusion			
No	14 (77.78%)	13 (81.25%)	1.000
Yes	4 (22.22%)	3 (18.75%)	

There were no major complications in the patients. In Group 1, transient Sudeck's atrophy and paresthesia were observed, and both resolved within 6 months. In Group 2, one patient developed a superficial infection which was successfully treated with oral antibiotic therapy.

Discussion

The most important finding of this study was that both the stand-alone AMFx and the combined AMFx + CFS procedures provided decreased pain levels and yielded considerably good clinical outcomes within the follow-up period among patients treated for TOL. Additionally, although results were similar in the majority of evaluations, we noted that hyaline-like chondral tissue was better organized, and MOCART scores were relatively higher with the AMFx + CFS technique.

Treatment for cartilage problems is still controversial, and the options vary depending on lesion size. While AMFx provides good clinical outcomes with the advantage of bone marrow stimulation in the treatment of small osteochondral lesions, it cannot achieve the desired success in large lesions since structural support to mesenchymal stem cells is insufficient when lesion size and depth are greater [7,19,20]. According to the literature, AMFx is the first-line treatment for TOLs, particularly those measuring around 1.5 cm^2 [9,21]. In a study by Choi et al., 32 patients with TOLs larger than 1.5 cm^2 were treated with the AMFx method, and it was reported that a successful outcome could only be achieved in 1 patient [21]. Therefore, a size of 1.5 cm^2 has been described as a critical threshold for AMFx treatment of TOLs [21,22]. Treatment options for TOLs larger than 1.5 cm^2 include methods that promote the formation of fibrous cartilage with cell-containing or cell-free scaffolds in addition to restoration techniques such as mosaicplasty and autologous chondrocyte implantation. At the same time, allograft use is suggested in much larger lesions [23]. However, it would be more effective to consider such restoration techniques in revision surgeries rather than in the first-line treatment of TOLs, since these techniques are more expensive and complex (compared to stand-alone AMFx) and may result in morbidity. From this standpoint, we comparatively evaluated the effectiveness of AMFx and AMFx + CFS treatments in lesions larger than 1.5 cm^2 (up to a maximum of 3 cm^2) and found that both treatment methods provided a significant improvement in terms of clinical scores during short-term follow-up.

The interest in CFS treatment has been increasing due to several advantages, including low cost, wide availability, and the fact that there is no need for cell culture or a donor site [24-27]. Recent animal studies suggest that CFS is also effective in cartilage regeneration. It can provide a well-structured subchondral trabecular bone and enables the generation of repair tissue rich in proteoglycans and type II collagen, which are important histological characteristics of the hyaline cartilage [28,29]. In addition to the ease of using CFS as a single-step arthroscopic procedure without the need for arthrotomy for the treatment of TOL, CFS application was also shown to induce chondrogenesis due to its hyaluronic acid (HA)-based scaffold structure [30]. In a study by Kanatli et al., cell-free polyglycolic acid (PGA) - HA scaffolds were reported to provide successful clinical outcomes in the treatment of TOLs sized 2.5 cm^2 and greater [31]. In the present study, we also obtained successful clinical outcomes after cell-free PGA-HA scaffold application in the treatment of TOLs measuring 1.5 cm^2 - 3 cm^2, which is consistent with the literature. Considered together, these results indicate that PGA-HA-based CFSs are effective and successful in the treatment of TOLs sized up to 3 cm^2.

The AMFx + CFS group had marginally better MOCART results; however, statistical significance was not present in any of the comparisons –possibly due to the low number of patients. Nonetheless, we believe it should be emphasized that the AMFx + CFS group had better border integration in the current study, similar to the results obtained by Valderrabano et al. and Wiewiorski et al. [32,33]. Two studies in the literature showed that PGA-HA-based CFS use led to a high rate of hypertrophic healing in TOLs [31,34]; whereas, in contrast to the literature, “none of the patients in the current study suffered from this complication”. This was attributed to the fact that the CFSs used in this study had a different scaffold-matrix structure as compared to their counterparts employed in other studies.

This study had some limitations. First of all, it had a retrospective design and follow-up was short, which might have prevented the identification of procedure-based differences that could develop with time. Second, although the procedures were carried out in a similar fashion by both surgeons, the fact that the groups had undergone treatment by different surgeons may be a cause of bias. Third, various important factors (age, gender, trauma characteristics etc.) that could have had an impact on treatment results could not be investigated separately with subgroup analyses, since sample size was not large enough. Finally, the lack of histological evaluation could put the current outcome analysis in question; however, we used the MOCART scoring system, which is accepted as an objective method that enables the quantitative analysis of repair tissue.

Conclusion

Significant improvements in clinical scores were observed in the short-term follow-up of patients who underwent stand-alone AMFx and combined AMFx + CFS application for the treatment of TOLs measuring up to 3 cm^2. The outcomes were similar in both groups when compared at postoperative 12 and 24 months, and the changes in scores were also similar with the two methods. Therefore, with respect to short-term follow-up, both the single-step AMFx and the combined AMFx + CFS techniques are effective in the treatment of TOLs.

References

1. Badekas T, Takvorian M, Souras N. Treatment principles for osteochondral lesions in foot and ankle. Int Orthop. 2013 Sep;37(9):1697-706. doi: 10.1007/s00264-013-2076-1. Epub 2013 Aug 28. PMID: 23982639; PMCID: PMC3764304.
2. Albano D, Martinelli N, Bianchi A, Messina C, Malerba F, Sconfienza LM. Clinical and imaging outcome of osteochondral lesions of the talus treated using autologous matrix-induced chondrogenesis technique with a biomimetic scaffold. BMC Musculoskelet Disord. 2017 Jul 18;18(1):306. doi: 10.1186/s12891-017-1679-x. PMID: 28720091; PMCID: PMC5516391.
3. van Dijk CN, Reilingh ML, Zengerink M, van Bergen CJ. Osteochondral defects in the ankle: why painful? Knee Surg Sports Traumatol Arthrosc. 2010 May;18(5):570-80. doi: 10.1007/s00167-010-1064-x. Epub 2010 Feb 12. PMID: 20151110; PMCID: PMC2855020.
4. Navid DO, Myerson MS. Approach alternatives for treatment of osteochondral lesions of the talus. Foot Ankle Clin. 2002 Sep;7(3):635-49. doi: 10.1016/s1083-7515(02)00037-2. PMID: 12512414.
5. Leontaritis N, Hinojosa L, Panchbhavi VK. Arthroscopically detected intra-articular lesions associated with acute ankle fractures. J Bone Joint Surg Am. 2009 Feb;91(2):333-9. doi: 10.2106/JBJS.H.00584. PMID: 19181977.
6. Gobbi A, Francisco RA, Lubowitz JH, Allegra F, Canata G. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. Arthroscopy. 2006 Oct;22(10):1085-92. doi: 10.1016/j.arthro.2006.05.016. Erratum in: Arthroscopy. 2008 Feb;24(2):A16. PMID: 17027406.

7. Gobbi A, Scotti C, Peretti GM. Scaffolding as treatment for osteochondral defects in the ankle. In: Randelli P, Dejour D, van Dijk CN, Denti M, Seil R, eds. Arthroscopy. Basic to Advanced. Berlin, Heidelberg: Springer-Verlag; 2016: 1003e1012. https://doi.org/10.1007/978-3-662-49376-2_83.
8. Schachter AK, Chen AL, Reddy PD, Tejwani NC. Osteochondral lesions of the talus. J Am Acad Orthop Surg. 2005 May-Jun;13(3):152-8. doi: 10.5435/00124635-200505000-00002. PMID: 15938604.
9. Chuckpaiwong B, Berkson EM, Theodore GH. Microfracture for osteochondral lesions of the ankle: outcome analysis and outcome predictors of 105 cases. Arthroscopy. 2008 Jan;24(1):106-12. doi: 10.1016/j.arthro.2007.07.022. Epub 2007 Nov 19. PMID: 18182210.
10. Gudas R, Kalesinskas RJ, Kimtys V, Stankevicius E, Toliusis V, Bernotavicius G, et al. A. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. Arthroscopy. 2005 Sep;21(9):1066-75. doi: 10.1016/j.arthro.2005.06.018. PMID: 16171631.
11. Khan WS, Johnson DS, Hardingham TE. The potential of stem cells in the treatment of knee cartilage defects. Knee. 2010 Dec;17(6):369-74. doi: 10.1016/j.knee.2009.12.003. Epub 2010 Jan 3. PMID: 20051319.
12. Polat G, Erşen A, Erdil ME, Kızılkurt T, Kılıçoğlu Ö, Aşık M. Long-term results of microfracture in the treatment of talus osteochondral lesions. Knee Surg Sports Traumatol Arthrosc. 2016 Apr;24(4):1299-303. doi: 10.1007/s00167-016-3990-8. Epub 2016 Feb 1. PMID: 26831855.
13. Cortese F, McNicholas M, Janes G, Gillogly S, Abelow SP, Gigante A, Coletti N. Arthroscopic Delivery of Matrix-Induced Autologous Chondrocyte Implant: International Experience and Technique Recommendations. Cartilage. 2012 Apr;3(2):156-64. doi: 10.1177/1947603511435271. PMID: 26069628; PMCID: PMC4297127.
14. Patrascu JM, Freymann U, Kaps C, Poenaru DV. Repair of a post-traumatic cartilage defect with a cell-free polymer-based cartilage implant: a follow-up at two years by MRI and histological review. J Bone Joint Surg Br. 2010 Aug;92(8):1160-3. doi: 10.1302/0301-620X.92B8.24341. PMID: 20675765.
15. Zhang L, Hu J, Athanasiou KA. The role of tissue engineering in articular cartilage repair and regeneration. Crit Rev Biomed Eng. 2009;37(1-2):1-57. doi: 10.1615/critrevbiomedeng.v37.i1-2.10. PMID: 20201770; PMCID: PMC3146065.
16. Georgiannos D, Bisbinas I, Badekas A. Osteochondral transplantation of autologous graft for the treatment of osteochondral lesions of talus: 5- to 7-year follow-up. Knee Surg Sports Traumatol Arthrosc. 2016 Dec;24(12):3722-3729. doi: 10.1007/s00167-014-3389-3. Epub 2014 Oct 19. PMID: 25326766.
17. Fennema E, Rivron N, Rouwkema J, van Blitterswijk C, de Boer J. Spheroid culture as a tool for creating 3D complex tissues. Trends Biotechnol. 2013 Feb;31(2):108-15. doi: 10.1016/j.tibtech.2012.12.003. Epub 2013 Jan 18. PMID: 23336996.
18. Marlovits S, Singer P, Zeller P, Mandl I, Haller J, Trattnig S. Magnetic resonance observation of cartilage repair tissue (MOCART) for the evaluation of autologous chondrocyte transplantation: determination of interobserver variability and correlation to clinical outcome after 2 years. Eur J Radiol. 2006 Jan;57(1):16-23. doi: 10.1016/j.ejrad.2005.08.007. Epub 2005 Oct 3. PMID: 16203119.
19. van Dijk CN. Ankle arthroscopy. Techniques Developed by the Amsterdam Foot and Ankle School. Cham, Switzerland: Springer; 2014.
20. Yasui Y, Wollstein A, Murawski CD, Kennedy JG. Operative Treatment for Osteochondral Lesions of the Talus: Biologics and Scaffold-Based Therapy. Cartilage. 2017 Jan;8(1):42-49. doi: 10.1177/1947603516644298. Epub 2016 May 9. PMID: 27994719; PMCID: PMC5154422.
21. Choi WJ, Park KK, Kim BS, Lee JW. Osteochondral lesion of the talus: is there a critical defect size for poor outcome? Am J Sports Med. 2009 Oct;37(10):1974-80. doi: 10.1177/0363546509335765. Epub 2009 Aug 4. PMID: 19654429.
22. Murawski CD, Foo LF, Kennedy JG. A Review of Arthroscopic Bone Marrow Stimulation Techniques of the Talus: The Good, the Bad, and the Causes for Concern. Cartilage. 2010 Apr;1(2):137-44. doi: 10.1177/1947603510364403. PMID: 26069545; PMCID: PMC4297045.
23. Ferkel RD, Zanotti RM, Komenda GA, Sgaglione NA, Cheng MS, Applegate GR, Dopirak RM. Arthroscopic treatment of chronic osteochondral lesions of the talus: long-term results. Am J Sports Med. 2008 Sep;36(9):1750-62. doi: 10.1177/0363546508316773. PMID: 18753679.
24. Brouwer KM, van Rensch P, Harbers VE, Geutjes PJ, Koens MJ, Wijnen RM, Daamen WF, van Kuppevelt TH. Evaluation of methods for the construction of collagenous scaffolds with a radial pore structure for tissue engineering. J Tissue Eng Regen Med. 2011 Jun;5(6):501-4. doi: 10.1002/term.397. Epub 2011 Feb 8. PMID: 21604385.
25. Efe T, Theisen C, Fuchs-Winkelmann S, Stein T, Getgood A, Rominger MB, Paletta JR, Schofer MD. Cell-free collagen type I matrix for repair of cartilage defects-clinical and magnetic resonance imaging results. Knee Surg Sports Traumatol Arthrosc. 2012 Oct;20(10):1915-22. doi: 10.1007/s00167-011-1777-5. Epub 2011 Nov 18. PMID: 22095486.
26. Kon E, Roffi A, Filardo G, Tesei G, Marcacci M. Scaffold-based cartilage treatments: with or without cells? A systematic review of preclinical and clinical evidence. Arthroscopy. 2015 Apr;31(4):767-75. doi: 10.1016/j.arthro.2014.11.017. Epub 2015 Jan 27. PMID: 25633817.
27. Pot MW, Gonzales VK, Buma P, IntHout J, van Kuppevelt TH, de Vries RBM, et al. Improved cartilage regeneration by implantation of acellular biomaterials after bone marrow stimulation: a systematic review and meta-analysis of animal studies. PeerJ. 2016 Sep 8;4:e2243. doi: 10.7717/peerj.2243. PMID: 27651981; PMCID: PMC5018675.
28. Erggelet C, Endres M, Neumann K, Morawietz L, Ringe J, Haberstroh K, Sittinger M, Kaps C. Formation of cartilage repair tissue in articular cartilage defects pretreated with microfracture and covered with cell-free polymer-based implants. J Orthop Res. 2009 Oct;27(10):1353-60. doi: 10.1002/jor.20879. PMID: 19382184.
29. Siclari A, Mascaro G, Gentili C, Cancedda R, Boux E. A cell-free scaffold-based cartilage repair provides improved function hyaline-like repair at one year. Clin Orthop Relat Res. 2012 Mar;470(3):910-9. doi: 10.1007/s11999-011-2107-4. Epub 2011 Oct 1. PMID: 21965060; PMCID: PMC3270167.
30. Hegewald AA, Ringe J, Bartel J, Krüger I, Notter M, Barnewitz D, Kaps C, Sittinger M. Hyaluronic acid and autologous synovial fluid induce chondrogenic differentiation of equine mesenchymal stem cells: a preliminary study. Tissue Cell. 2004 Dec;36(6):431-8. doi: 10.1016/j.tice.2004.07.003. PMID: 15533458.
31. Kanatlı U, Eren A, Eren TK, Vural A, Geylan DE, Öner AY. Single-Step Arthroscopic Repair With Cell-Free Polymer-Based Scaffold in Osteochondral Lesions of the Talus: Clinical and Radiological Results. Arthroscopy. 2017 Sep;33(9):1718-1726. doi: 10.1016/j.arthro.2017.06.011. PMID: 28865575.
32. Valderrabano V, Miska M, Leumann A, Wiewiorski M. Reconstruction of osteochondral lesions of the talus with autologous spongiosa grafts and autologous matrix-induced chondrogenesis. Am J Sports Med. 2013 Mar;41(3):519-27. doi: 10.1177/0363546513476671. Epub 2013 Feb 7. PMID: 23393079.
33. Wiewiorski M, Miska M, Kretzschmar M, Studler U, Bieri O, Valderrabano V. Delayed gadolinium-enhanced MRI of cartilage of the ankle joint: results after autologous matrix-induced chondrogenesis (AMIC)-aided reconstruction of osteochondral lesions of the talus. Clin Radiol. 2013 Oct;68(10):1031-8. doi: 10.1016/j.crad.2013.04.016. Epub 2013 Jun 25. PMID: 23809267.
34. Eren TK, Ataoğlu MB, Eren A, Geylan DE, Öner AY, Kanatlı U. Comparison of arthroscopic microfracture and cell-free scaffold implantation techniques in the treatment of talar osteochondral lesions. Eklem Hastalik Cerrahisi. 2019 Aug;30(2):97-105. doi: 10.5606/ehc.2019.64401. PMID: 31291856.

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Is this coccyx fractured, or is it a normal variant? A cohort study

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Ethics Committee Approval
Ethics approval was received from Atatürk University Faculty of Medicine Clinical Research Ethics Committee (meeting number: 08, decision no: 07, date: 26.12.2019).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: The coccyx has several variants which could sometimes be confused with fractures. Our study aimed to alert physicians about the types of coccyges that can be easily confused with coccyx fractures in daily practice.
Methods: Mid-sagittal and mid-coronal computerized images of 75 patients were analyzed to determine the types of coccygeal fracture, the coccyx types, number of segments, joint fusion, coccygeal bony spicules, subluxation, sacrococcygeal angle (SCA), intercoccygeal angle (ICA), and lateral deviation of the coccyx.
Results: The mean age of the patients was 43.5 (13.6) years. There were 33 (44%) males, and 42 (56%) females. While 57 (76%) patients were thought to have a coccygeal fracture, only 18 patients (24%) actually had them. There was a significant difference between the coccyx types mistaken for fractures and actual coccygeal fractures (P<0.001).
Conclusion: It is essential to know the coccyx types and distinguish normal variants from fractures. If the difference between coccyx fractures and coccyx types is known and the patients are informed accordingly, both the loss of workforce decreases, and the necessary treatment can be started early.

Keywords: Back injuries, Coccyx, Spinal injuries, Spinal fractures

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Introduction

The coccyx is derived from the Greek word "kokkιs" because it resembles the inclined beak of a cuckoo. The coccyx is a triangular-shaped bone consisting of 3 to 5 fused vertebral segments at the terminal part of the vertebra [1]. It is a vital structure because it forms a leg of the tripod together with the two ischia and is an adhesion site for numerous pelvic muscles and in the pelvic region [2].

Local pain on the coccyx, "coccydynia" [3], was first described by Simpson in history [2]. The etiology is multifactorial, and the most common cause is trauma. Structurally, the most common causes of coccydynia are instabilities and bone spicules. Coccydynia can be seen after an external trauma, such as a fall, an internal trauma caused by birth, or because of microtrauma due to prolonged sitting on hard and uneven surfaces. Female gender and obesity are predisposing factors that increase the risk of coccydynia. It should also be remembered that non-organic causes may present as somatization [4].

Coccyx fractures are the most critical cause of coccydynia which occur after external and internal (obstetrical fractures) trauma. After external traumas, flexion (type 1) and compression (type 2) fractures are seen. Extension (type 3) fractures occur after internal traumas. All three types of fractures affect different areas. Flexion (type 1) fractures affect the sacrococcygeal area consisting of the lower sacrum (S5) or upper coccyx (Co1). Compression (type 2) fractures affect the Co1 and Co2 vertebrae. Compression (type 2) fractures are vertical, and the fracture line extends from the upper to the lower endplate. The lower coccyx is affected in extension (type 3) fractures [5].

In clinical examination, the sacrococcygeal area should be inspected for the presence of pilonidal sinuses or cysts. Masses and muscle spasms in the surrounding tissues are also evaluated. Localized tenderness and swelling may often be revealed by palpation of the sacrococcygeal region. In most cases of coccydynia, a rectal examination with a thumb and an index finger is essential. The coccyx is grasped and evaluated for pain, tenderness, crepitation, and sacrococcygeal hypo-hypermobility. Pain can be elicited by rectal manipulation of the coccygeal segments or sacrococcygeal joint in patients with coccydynia.

Fracture, mass, and degenerative changes can be evaluated in more detail. A dynamic X-ray is obtained while the patient is sitting and standing. Typically, the coccyx moves between 5-25 degrees on the anterior or posterior axis in the sitting position and returns to its normal position when the patient stands up. The presence of >25 degrees or <5 degrees movement is considered abnormal [6]. This imaging reveals abnormalities such as luxation and subluxation in 70% of patients with coccydynia. In the recent years, MRI was used as a second-line diagnostic method to investigate the coccyx. It can reveal edema and inflammation in the tissue. Hyperintense signal increases are noteworthy, especially in T2-weighted STIR images, and indicate local inflammatory lesions. MRI is also used to exclude mass diagnosis in persistent pain [3].

In coccydynia treatment, it is possible to achieve up to 90% success with conservative methods [2]. Initially, seat cushions, NSAIDs, hot-cold applications, and manipulations are recommended, and lifestyle changes are implemented. Treatment methods such as steroid injection [7] and blockade [8] are also available for long-term pain. In case of persistent pain, coccygectomy [9] is the last option.

The coccyx morphology of the patients was evaluated from the computed tomography images obtained to exclude vertebral injury. This study aimed to raise awareness about coccyx structures and typical variants that can easily be confused with coccyx fractures in daily practice.

Materials and methods

The ethics approval for this retrospective study was received from Atatürk University Faculty of Medicine, Clinical Research Ethics Committee (meeting number: 08, decision no: 07, date: 26.12.2019). This study was conducted in accordance with the STROBE guidelines.

The files of patients presenting to the emergency service between December 2018 and December 2019 were retrospectively scanned. One hundred and thirty-six patients were consulted for coccyx fractures by doctors working in the emergency department. Inclusion criteria were complete bone development and patients with no additional fractures. Exclusion criteria from the study were incomplete bone development, presence of iliac bone fracture, sacroiliac joint luxation, and presence of femoral head or neck fracture.

After the implementation of the inclusion and exclusion criteria, 75 patients were included in this study. Seventy-five patients who underwent vertebral tomography in the emergency department due to simple trauma were evaluated. Computed tomography images of the patients were evaluated by a single orthopedic surgeon (AZ).

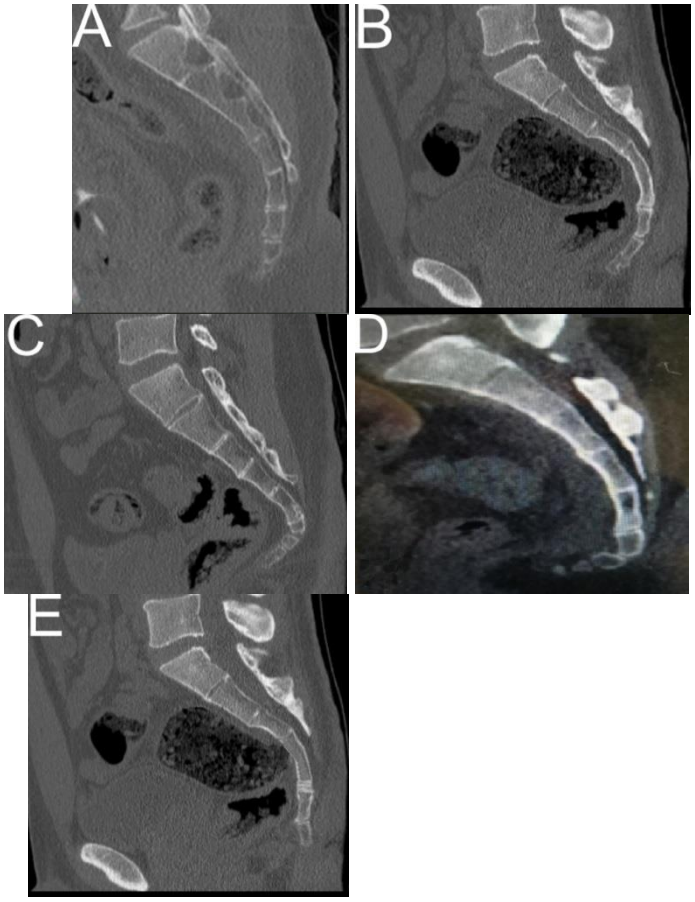
Mid-sagittal and mid-coronal images were obtained from the computed tomography images of the patients. From these images, the type of coccyx (Figure 1), number of segments, joint fusion, coccygeal bony spicules, subluxation, sacrococcygeal angle (SCA), intercoccygeal angle (ICA), and lateral deviation of the coccyx were evaluated (Table 1).

Table 1: Definitions of terms

	Definition [10]
Joint fusion	Bony continuity between adjacent vertebrae on all sagittal slices (at sacrococcygeal and/or intercoccygeal joints)
Coccygeal types	Type 1 is a slightly curved coccyx pointing downwards; type 2 is more curved and points forwards; type 3 is sharply angulated at the first or second intercoccygeal joint; type 4 is a coccyx with an anterior subluxation at the sacrococcygeal or first intercoccygeal joint; and type 5 is a coccyx with a retroverted tip.
Bony spicule	A bone spicule projecting from the terminal coccygeal segment
Joint subluxation	Abnormal translation between two adjacent vertebrae at the intervertebral disc.
Lateral deviation of the tip of the coccyx	Determined by measuring the angle between the tip of the coccyx and a line passing through the middle of the sacrum
Sacrococcygeal angle	Formed by the intersection of a line between the midpoint of the upper borders of S1 and Co1 and a line between the latter and the tip of the coccyx
Intercoccygeal angle	The intercoccygeal angle formed between the lines intersecting the middle of the first and last coccygeal segments in the median plane. Sacrococcygeal joint angle (S5–Co1) and the first and second intercoccygeal joint angles (Co1–Co2 and Co2–Co3) were also measured.

S: Sacrum, Co: Coccyx

Figure 1: Type 1 is a slightly curved coccyx pointing downwards (A). Type 2 is more curved and points forwards (B). Type 3 is sharply angulated at the first or second intercoccygeal joint (C). Type 4 is a coccyx with an anterior subluxation at the sacrococcygeal or first intercoccygeal joint (D). Type 5 is a coccyx with a retroverted tip (E).



Statistical analysis

IBM SPSS Statistics 22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software was used to evaluate the findings obtained in this study. The normality of parameter distributions was assessed with the Shapiro Wilk test. Descriptive statistics (mean, standard deviation, frequency) and Student's t-tests were used to compare the parameters of the patients. Fisher's Exact tests, Fisher Freeman Halton tests, and Yates Correction for Continuity were used to compare qualitative data. Independent samples t-test was used to compare quantitative data. A *P*-value of <0.05 indicated statistical significance.

Results

There were 33 (44%) males, and 42 (56%) females. The mean age of 75 patients was 43.5 (13.6) (range: 19-70) years. Coccyx types, segmentation numbers, the presence of fusion, spicule, subluxation, lateralization, and types of coccyx fractures were shown in Table 2 according to the number and rates of patients.

The mean sacrococcygeal and intercoccygeal angles obtained in the computed tomography images of the patients with normal coccygeal variants was 110.2 (11.4) (range: 87-135) degrees, and 41.6 (11.8) (range: 20-70) degrees, respectively.

Seven (38.9%), eight (44.4%) and three (16.7%) patients had type 1, type 2, and type 3 fractures, respectively. A significant difference was found between patients with coccyx fractures and those with typical coccyx variants (*P*<0.001).

Table 2: The results of the patients

		Patients (n)	Percentage %	Total Patients (%)
Coccygeal types	1	25	43.9%	57 (76.0%)
	2	16	28.1%	
	3	10	17.5%	
	4	4	7.0%	
	5	2	3.5%	
Segmentation	2	10	17.5%	
Numbers	3	25	43.9%	
	4	20	35.1%	
	5	2	3.5%	
Fusion	No	44	77.2%	
	Yes	13	22.8%	
Spicule of coccyx	No	51	89.5%	
	Yes	6	10.5%	
Subluxation	No	49	86.0%	
	Yes	8	14.0%	
Lateralization	No	46	80.7%	
	Yes	11	19.3%	
Fracture	Type 1	7	38.9%	18 (24.0%)
	Type 2	8	44.4%	
	Type 3	3	16.7%	
P-value				<0.001

n: number

Discussion

Being the attachment point of many ligaments, muscles, and tendons, and changing angles in the standing and sitting positions, the coccyx has essential and dynamic functions in the human body. It consists of 3-5 fused vertebral segments. In 2013, Woon et al. found that the most common number of segments was 4, but ranged from 3-5, in a healthy adult coccyx when examined by CT [10]. Marwan et al. examined the coccyx morphology in the Arab community in 2014 [11] and reported that it most contained 3 fused segments (68%). In a study by Przybylski et al., 50.8% of coccyges had three fused segments [12]. In our study, the number of patients with three fused segments were 43.9%. The number of segments may vary between ethnic groups and from person to person. In daily practice, these morphological changes of coccyx should not be perceived as fractures or dislocations.

Different types of coccyges were described in the literature. The first classification was made radiologically by Postacchini in 1983 [13]. In his study, type 1 was the most common, with a rate of 68%. In 2004, Dennell et al. reported a retroverted coccyx [14]. In 2007, Kerimoglu et al. suggested that retroverted coccyx types be referred to as "type 0" [15]. In 2013, Woon et al. added the retroverted coccyx to the literature as "type 5" in tomographic image examination [10]. In our study, type 1 was the most common with a rate of 43.9%. The retroverted coccyx (type 5) was detected in only two patients.

In 2012, Woon et al. [1] performed sacrococcygeal and intercoccygeal measurements in 112 adult CT scans. The SCA and ICA were 166 and 143 degrees, respectively. No significant differences existed between the two genders in terms of both angles. SCA and ICA measurements of 202 patients in CT scans examined by Marwan [11] in the Arab population were 110.9 and 132.5 degrees, respectively. A significant difference was found between males and females. In our study, the SCA and ICA were 110 and 138 degrees, respectively. The two genders were similar in terms of SCA and ICA.

The presence of subluxation, bone spicule, fusion, and lateralization may differ between ethnic groups. In Woon's study in 2012, subluxation was rarely found in the New Zealand population, bone spicule rate was 23%, and 57% of patients had fusion [1]. In the studies of Marwan [11] and Shalaby [16], subluxation was found in 31.7%, bone spicule, in 54%, fusion, in

38.6%, and lateralization, in 38.6% among the Arab population. In our study, the rates of subluxation, bone spicule, fusion, and lateralization were 14%, 10.5%, 22.8%, and 19.3%, respectively.

Coccyx types are often confused with coccyx fractures in daily practice. Flexion (type 1) fractures occur after a fall or impact that affects the sacrococcygeal joint. This fracture affects the S5 and Co1 vertebrae and forces the sacrococcygeal joint to flexion (Figure 2). Flexion fractures can be confused with type 2, type 3, and type 4 coccyges. Compression (type 2) fractures also occur after external trauma by the compression of the first independent coccygeal vertebra. These fractures which involve the Co1 or Co2 vertebrae are also named "nutcracker fractures" [5]. A compression fracture makes a vertical fracture line. These type 2 fractures are unstable. Furthermore, the fracture line could hardly be visible on standard radiographs. Dynamic radiographs or CT scans should be ordered to establish the diagnosis. Compression (type 2) fractures may be mixed with type 1 coccyges (Figure 3). Extension (type 3) fractures occur in obstetrical fractures and affect the lower coccygeal vertebra (Figure 4). These fractures are mostly confused with coccyges type 4 or type 5.

Figure 2: Flexion (type 1) fracture causes a forced flexion of the lower sacrum or upper coccyx. The arrow shows the fracture line.

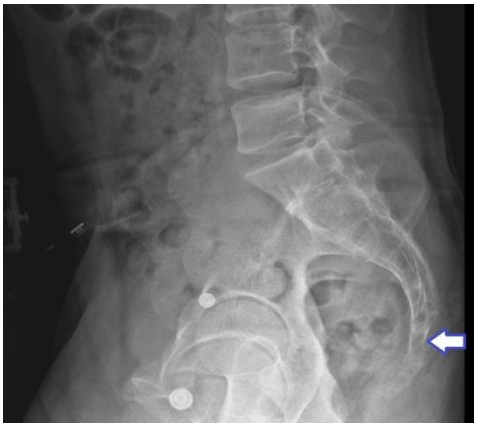


Figure 3: Compression (type 2) fracture affects the first independent coccygeal vertebra. The arrow shows the fracture area.

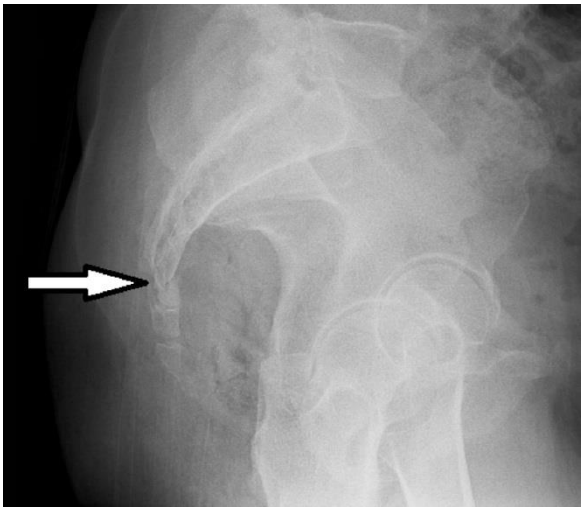
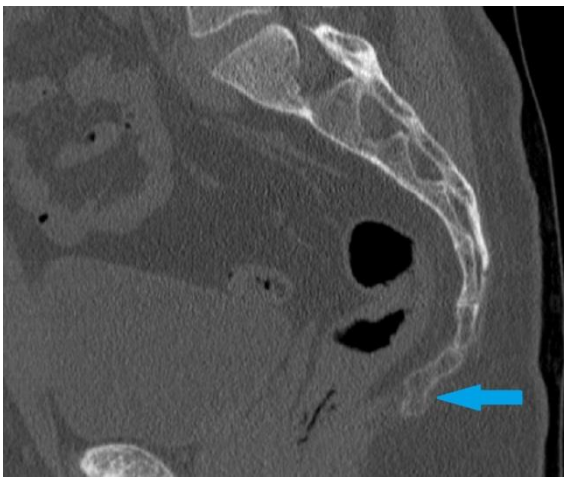


Figure 4: Extension (type 3) fracture occurs in obstetrical fractures and affects the lower coccygeal vertebra. The arrow shows the fracture line.



Limitations

The limitations of our study include the small number of patients, and its single centered design. Also, the patients were evaluated with CT imaging only. Simultaneous studies with multiple patients and CT and MR imaging results from many centers can provide more detailed information.

Conclusion

Some coccyx types could be confused with coccygeal fractures. To avoid this confusion, patients should be evaluated with computed tomography.

References

1. Woon JT, Stringer MD. Clinical anatomy of the coccyx: a systematic review. Clin Anat. 2012;25(2):158-67.
2. Lirette LS, Chaiban G, Tolba R, Eissa H. Coccydynia: an overview of the anatomy, etiology, and treatment of coccyx pain. Ochsner J. 2014;14(1):84-7.
3. Protzer L, Seligson D, Doursounian L. The coccyx in clinical medicine. Curr Orthop Pract. 2017;28(3):314-7.
4. Nathan S, Fisher B, Roberts C. Coccydynia: a review of pathoanatomy, aetiology, treatment and outcome. J Bone Joint Surg Br. 2010;92(12):1622-7.
5. Maigne J-Y, Doursounian L, Jacquot F. Classification of fractures of the coccyx from a series of 104 patients. Eur Spine J. 2019:1-9.
6. Grassi R, Lombardi G, Reginelli A, Capasso F, Romano F, Floriani I, et al. Coccygeal movement: assessment with dynamic MRI. Eur J Radiol. 2007;61(3):473-9.
7. Mitra R, Cheung L, Perry P. Efficacy of fluoroscopically guided steroid injections in the management of coccydynia. Pain Physician. 2007;10(6):775.
8. Gunduz OH, Sencan S, Kenis-Coskun O. Pain relief due to transsacrococcygeal ganglion impar block in chronic coccygodynia: a pilot study. Pain Med. 2015;16(7):1278-81.
9. Trollegaard A, Aarby N, Hellberg S. Coccygectomy: an effective treatment option for chronic coccydynia: retrospective results in 41 consecutive patients. J Bone Joint Surg Br. 2010;92(2):242-5.
10. Woon JT, Perumal V, Maigne J-Y, Stringer MD. CT morphology and morphometry of the normal adult coccyx. Eur Spine J 2013;22(4):863-70.
11. Marwan YA, Al-Saeed OM, Esmaeel AA, Kombar ORA, Bendary AM, Azeem MEA. Computed tomography–based morphologic and morphometric features of the coccyx among Arab adults. Spine. 2014;39(20):E1210-E9.
12. Przybylski P, Pankowicz M, Boćkowska A, Czekajska-Chehab E, Staśkiewicz G, Korzec M, et al. Evaluation of coccygeal bone variability, intercoccygeal and lumbo-sacral angles in asymptomatic patients in multislice computed tomography. Anat Sci Int. 2013;88(4):204-11.
13. Postacchini F, Massobrio M. Idiopathic coccygodynia. Analysis of fifty-one operative cases and a radiographic study of the normal coccyx. J Bone Joint Surg Am. 1983;65(8):1116-24.
14. Dennell LV, Nathan S. Coccygeal retroversion. Spine. 2004;29(12):E256-E7.
15. Kerimoglu U, Dagoglu MG, Ergen FB. Intercoccygeal angle and type of coccyx in asymptomatic patients. Surg Radiol Anat. 2007;29(8):683-7.
16. Shalaby SA, Eid EM, Allam O, Ali AM, Gebba MA. Morphometric study of the normal Egyptian coccyx from (age 1-40 year). Int J Clin Dev Anat. 2015;1(1):32-41.

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Evaluating the role of Smartpilot® view assisted target-controlled infusion anesthesia during intracranial mass surgery: A comparative retrospective study with bispectral index-guided standard anesthesia

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Ethics Committee Approval
Ethics committee approval was obtained from Ethics Committee of Gazi University School of Medicine (Date: 08/01/2018 - Decision No: 02) All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Neuroanesthesia necessitates the control of both systemic and cerebral hemodynamics, the prevention of intracranial pressure increase, knowledge of anesthetics' cerebral effects, and early neurological recovery. The titration of anesthetics becomes crucial to optimize the appropriate level of anesthesia required for surgery while reducing postoperative neurological consequences. Smartpilot® View (SPV) is a new decision support system that uses pharmacologic models to optimize anesthetic depth and improve patient outcomes. The goal of this study was to compare the effectiveness of SPV with standard BIS-guided anesthesia administration in terms of intraoperative hemodynamic stabilization, anesthetic consumption, and postoperative recovery times during intracranial mass surgery.

Methods: Following ethics committee approval, the records of the patients who underwent elective supratentorial craniotomy between November 15, 2017 and March 15, 2018 were reviewed retrospectively. The demographics of the patients, anesthesia and surgery times, eye opening and extubation times, time to reach an Aldrete score of 9 and anesthetic consumptions were compared between those who were monitored with SPV in addition to BIS (SPV Group) and those who were monitored with solely BIS for standard anesthetic follow-up (BIS Group).

Results: A total of 139 subjects were analyzed (SPV (n=71), BIS (n=68)). Hemodynamic responses to induction and intubation were more pronounced in the BIS group (P<0.05). Time until eye opening and extubation were 3.6 (2.4) versus 6.06 (1.63) minutes and 5.76 (1.3) versus 9.16 (1.0) minutes in the SPV and BIS groups (P<0.001). In the SPV Group, it took much less time to achieve an Aldrete score of 9 or above (P<0.001). Total consumed amount of both propofol and remifentanil were significantly lower in the SPV group (P<0.001).

Conclusion: Use of SPV compared to BIS-guided routine anesthesia follow-up improved titration and consumption of anesthetic drugs, thereby facilitating the early recovery process in patients who underwent intracranial mass surgery.

Keywords: Intravenous anesthetics, Propofol, Remifentanil, Anesthesia recovery period, Bispectral index, Neurosurgery

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Introduction

Neuroanesthesia necessitates the regulation of both systemic and cerebral hemodynamics, avoidance of intracranial pressure changes, knowledge of anesthetics' cerebral effects, and prompt recovery for early neurological assessment [1]. To achieve all these, it's crucial to optimize the anesthetic agents and provide the appropriate depth of anesthesia intraoperatively.

Opioids and hypnotics are routinely combined in the clinical practice of anesthesiology. Maintaining an optimal combination for adequate anesthetic conditions while limiting adverse effects like hemodynamic alterations or prolonged recovery remains a challenge especially during craniotomies [2]. The manner anesthetics are adjusted intraoperatively is likely to have a greater impact on anesthesia quality than a specific drug utilized. As a result, anesthetic titration becomes critical to maintain the adequate level of anesthesia required for surgery while minimizing postoperative neurological consequences. Previous research revealed that the electroencephalographically (EEG) derived Bispectral Index (BIS) can help with titration of both intravenous and volatile anesthetics [3, 4]. The Bispectral Index, on the other hand, can only anticipate the hypnotic effect of anesthetic drugs and cannot assess the balance of nociception and antinociception [5].

In recent years, new and high-tech monitors that assess general anesthesia components including hypnosis, immobility were developed, and anti-nociception and drug advisory display systems that use pharmacological models to guide the administration of anesthetic agents were commercialized [2, 6-9]. The working principle of SmartPilot® View (SPV, Dräger, Lübeck, Germany) is based on these promising pharmacological models.

The SmartPilot® View is a drug advisory system that displays real-time information on actual and expected levels of anesthesia and demonstrates the effects of combined hypnotic-analgesic drugs. The SmartPilot® View monitor is connected to an anesthetic workstation. As a result, all monitoring data, patient information, ventilation, and syringe pump settings included in the station are automatically displayed on the SPV screen. Complex pharmacological models can be depicted in clinical practice using this innovative technology. SmartPilot® View allows for more precise anesthetic titration for the specified therapeutic goals, making intraoperative decision-making easier [8, 10]. Even though there is few research on SPV in the literature, current studies demonstrate that SPV-guided anesthesia enhances anesthetic management and is related with improved anesthesia quality [8, 10].

The goal of this retrospective study was to demonstrate that SPV would offer clinical usefulness in patients undergoing craniotomy for supratentorial lesions. It was designed to see if SPV-guided administration of intravenous anesthetics and analgesics would improve titration of anesthetics and, as a result, provide more efficient general anesthesia that meets neuroanesthesia standards. The effect of SPV-guided anesthesia on hemodynamics, anesthetic and analgesic requirements and recovery profile in patients who had supratentorial craniotomy was investigated in this study by comparing it with conventional BIS-guided anesthesia administration.

Materials and methods

This retrospective study was conducted with the approval of the Ethics Committee of Gazi University School of Medicine (Date: 08/01/2018 - Decision No: 02) and in compliance with the Declaration of Helsinki's ethical principles. Adult patients who underwent an elective supratentorial craniotomy in the neurosurgery operating theatre between November 15, 2017, and March 15, 2018, were reviewed retrospectively. Preoperative anesthesia registration forms, intraoperative anesthetic sheets, patient files, the medical information system, and data recorded by the SPV monitor were all used to collect data. Investigators who were not involved in the anesthetic administration conducted the research.

The study included patients who ranged in age from 18 to 65 years, had an ASA physical classification of I to III, had no kidney or liver illness and underwent total intravenous anesthesia. Patients with an ASA physical classification of IV, a Glasgow coma grade of 8, those whose records could not be reached and who were not extubated after surgery, as well as those who had emergency surgery, awake craniotomy or surgery requiring neuromonitoring were excluded from the study.

After data scanning, the patients were divided into two groups: Those who were monitored with SPV in addition to BIS (SPV Group) and those who were monitored with BIS for standard anesthetic follow-up (BIS Group). Patient demographics, peroperative hemodynamic parameters, anesthesia and surgery times, eye opening times (time from discontinuation of anesthetic drugs until the patient opens his/her eyes), extubation times (time from discontinuation of anesthetic drugs to extubation), the time to achieve an Aldrete score of at least 9 after tracheal extubation and the total amount of anesthetic (propofol) and analgesic (remifentanil) consumed were compared between the two groups. To reduce bias, patient data were collected and compared by a researcher who were blinded to the patient groups.

Statistical analysis

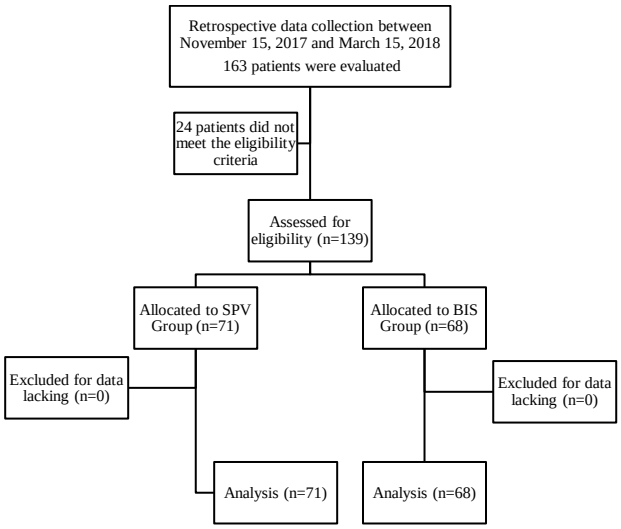
Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows 19 (Chicago IL, USA) program. Continuous data were expressed as mean (standard deviation) or as the number of cases (n) for categorical variables. Changes between the two categorical variables were examined with the Pearson Chi-square test or the Fisher Exact test. Continuous variables were compared with the unpaired two-tailed Student's t -test. A *P*-value of less than 0.05 was considered statistically significant.

Results

The data of 163 adult patients who underwent elective supratentorial mass surgery in the neurosurgery operating theater between November 15, 2017, and March 15, 2018 were analyzed. Twenty-four patients were dropped from the research because they did not meet the eligibility requirements. Figure 1 shows the study's flow chart. In total, 139 patients were evaluated, with 71 patients (SPV Group) monitored with BIS + SPV and 68 patients (BIS Group) who underwent conventional anesthetic follow-up with BIS. Electrocardiography (ECG), blood pressure, pulse oximetry (SpO_2), end-tidal carbon dioxide ($EtCO_2$) (Infinity Delta XL, SPV, Dräger, Lübeck, Germany),

and Bispectral Index (BIS) (Infinity Delta XL, SPV, Dräger, Lübeck, Germany) were used to monitor the patients.

Figure 1: The study flow chart



SPV: Smartpilot® View, BIS: Bispectral index

Target Controlled Infusion (TCI) of propofol, Schnider effect-site concentration (Ce) model and remifentanil, Minto effect-site concentration (Ce) model were used for the induction and maintenance of anesthesia (Braun Space Station for infusion pumps; Perfusor Space, Braun Medical, Germany). Scalp block was performed in all patients.

SmartPilot® View (software version 3.00.12, Dräger, Lübeck, Germany) monitor was connected to the anesthesia workstation. In the SPV Group, anesthesia maintenance was decided according to Noxious Stimulation Response Index (NSRI) values shown on the SPV screen (Figure 2). The Noxious Stimulation Response Index was maintained between 0 and 20 for intubation, Mayfield pin placement, skin incision, craniotomy, and dural opening, and between 20 and 50 for the rest of the procedure in the SPV Group. For patients in the BIS Group, a BIS of 40 to 60 was targeted to achieve routine anesthetic follow-up.

Figure 2: SmartPilot® View (SPV) screen and Noxious Stimulation Response Index (NSRI)

Blue arrow: Noxious Stimulation Response Index (NSRI)
The Noxious Stimulation Response Index indicates the probability of tolerating and predicting the intraoperative response to a noxious stimulus. NSRI 100 means 100% probability of response and if the response decreases the NSRI approaches 0.

Table 1 shows the demographic information and tumor sites of the patients. Both groups had similar demographics and tumor sites.

Hemodynamic variables at significant time points during the surgery are shown in Table 2. Mean baseline heart rate (HR) and mean arterial blood pressure (MAP) were similar among the groups with a significantly greater decrease in HR and MAP following induction and a significantly greater increase in HR and MAP at intubation among patients in BIS Group (P<0.05). Hemodynamic changes in both groups were comparable during other painful stimulations, maintenance of surgery and following extubation.

Table 1: Patients' demographic data and localization of tumor

	SPV Group (n=71)	BIS Group (n=68)
Age (years)	62 (16)	58 (13)
Gender (Female/Male)	34/37	36/32
ASA physical status (I/II/III) (n)	34/29/8	26/33/9
Weight (kg)	79 (16)	83 (18)
Height (cm)	162.0 (11.7)	161.0 (17.3)
Localization of tumor (n)		
Frontoparietal	23	21
Temporoparietal	30	32
Occipital	18	15

Values are expressed as mean (standard deviation) or number. No significant differences between groups. ASA: American Society of Anesthesiologists

Table 2: Hemodynamic data: Heart rate and mean arterial blood pressure values at various time points

	HR (bpm)		MAP (mmHg)	
	SPV Group	BIS Group	SPV Group	BIS Group
Baseline	79 (19)	77 (16)	92 (12)	94 (11)
Induction	75 (12)	63 (15)*Ŧ	88 (14)	74 (14)*Ŧ
Intubation	80 (13)	89 (16)*Ŧ	91 (16)	105 (18)*Ŧ
Scalp block	83 (11)	85 (14)*	93 (14)	95 (16)
Mayfield placement	78 (17)	81 (13)	89 (13)	91 (15)
Skin incision	75 (16)	77 (11)	86 (16)	87 (13)
Craniotomy	71 (14)	72 (16)	84 (17)*	84 (16)*
Dural incision	71 (14)	73 (17)	85 (16)*	83 (15)*
Maintenance	68 (11)*	69 (15)*	81 (17)*	84 (14)*
Skin closure	67 (15)*	63 (17)*	81 (16)*	83 (16)*
Extubation	80 (14)	83 (12)	94 (18)	96 (12)

Values are expressed as mean (standard deviation). SPV: Smartpilot® View, HR: Heart rate, MAP: Mean arterial pressure, *P<0.05 vs. baseline values, Ŧ P<0.05 vs. SPV Group

The durations of anesthesia and surgery, as well as the patients' recovery times, are shown in Table 3. Both groups had comparable anesthesia and surgery durations. The mean time until eye opening was 3.6 (2.4) minutes in the SPV Group versus 6.06 (1.63) minutes in the BIS Group (P<0.001) and extubation time, 5.76 (1.3) minutes in the SPV Group versus 9.16 (1.0) minutes in the BIS Group (P<0.001) (Table 3). The time it took for the patients in the SPV Group to reach an Aldrete score of 9 or above was also shorter (P<0.001).

The SPV group had considerably reduced total consumed doses of propofol and remifentanil (P<0.001) (Table 3).

Table 3: Anesthesia and surgery times, recovery times, anesthetics consumed

	SPV Group	BIS Group	P-value
Duration of surgery (min)	199 (39)	187 (49)	0.454
Duration of anesthesia (min)	237 (40)	220 (37)	0.328
Time to eye opening (min)	3.6 (2.4)	6.06 (1.63)	<0.001
Time to extubation (min)	5.76 (1.3)	9.16 (1.0)	<0.001
Time to reach Aldrete score ≥ 9 (min)	17.4 (7.8)	25.2 (2.4)	<0.001
Propofol consumed (mg)	1808.96 (840.8)	2419.66 (693.9)	<0.001
Remifentanil consumed (µg)	1373.81 (620.4)	1910.2 (556.7)	<0.001

Values are expressed as mean (standard deviation)

Discussion

In the current study, SPV was evaluated during a target-controlled infusion anesthesia and compared to a standard BIS-guided practice group. Our findings show that SPV guidance resulted in significant reductions of propofol, and remifentanil use as well as shorter recovery times. Except for the development of deeper hypotension following induction in the BIS Group, hemodynamic stability was comparable in both groups.

Target-controlled infusion (TCI) adjusts intravenous drug infusion rates to meet target plasma concentrations using conceptual modeling. Previous research suggests that total intravenous anesthesia with TCI propofol and remifentanil is a useful technique for controlling responses to tracheal intubation and intense surgical stimulation while preserving cerebral

autoregulation and allowing for rapid emergence from anesthesia after supratentorial tumor craniotomy [11].

A number of clinical trials investigated the impact of intraoperatively administered anesthetics on hemodynamic stability, cerebral protection, recovery patterns, and nociception after supratentorial craniotomy [11-14]. Still, it is unclear whether the anesthetics or anesthesia technique used makes a substantial difference in the patient outcome [15]. Even though each anesthetic drug has a unique effect, how anesthetics are adjusted or optimized is likely to have a greater impact on anesthesia quality. Optimizing anesthetics throughout the perioperative period of neurosurgery has a significant impact on hemodynamics, cerebral blood flow, metabolism, and brain protection, as well as the quality of emergence, postoperative course, and recovery, all of which are used to assess anesthesia quality.

Anesthesia administration based on pharmacological models, which considers pharmacokinetic and pharmacodynamic responses to maintain optimal depth of anesthesia and analgesia, may ensure better drug titration [7, 17]. Response surface models were developed to illustrate the combined clinical effects of two or more drug concentrations pharmacologically [18, 19]. The hypnotic and opioid concentrations are assessed on the x and y axes, respectively, and the synergistic effects of drugs known as isoboles are shown on the z axis. Some commercial products, such as SPV, incorporated these synergistic interactions into its operating principles. A new anesthetic depth index, the Noxious Stimulation Response Index (NSRI), was developed based on these response surface models and runs from 100 to 0 [20]. The NSRI measures the likelihood of tolerating and anticipating an intraoperative reaction to a noxious stimulus: NSRI 100 implies a 100 percent probability of response; as the NSRI approaches 0, the response declines [21]. The anesthetist can use this index to evaluate the level of anesthesia that would be appropriate for the procedure and the patient's characteristics. In 44 subjects, NSRI was shown to be better in predicting the response to noxious stimulation than parameters derived from electroencephalography and effect-site concentrations of drugs [20].

The SmartPilot® View graphically depicts the interaction of hypnotic and analgesic drugs with isoboles and uses NSRI to measure the depth of anesthesia. Another benefit of SPV is that it displays the current depth of anesthesia as well as the expected level for the next 10 minutes [8, 10]. When opioids and intravenous anesthetics are co-administered for anesthesia maintenance, fifty percent probability to tolerate laryngoscopy (TOL 50) is equal to NSRI 50, and ninety percent probability to tolerate laryngoscopy (TOL 90) is equal to NSRI 20. A deeper anesthesia than TOL 90 means high probability for tolerating highly painful stimuli, which is equal to a NSRI between 0 to 20. In our study, SPV-guided depth of anesthesia was maintained to keep anesthesia deeper than TOL 90 (NSRI $\leq$ 20) for intubation, Mayfield pin placement, skin incision, craniotomy, and dural opening and TOL 50-TOL 90 (NSRI 20-50) for the remainder of the surgery. In a patient undergoing semi-awake craniotomy, Mai and colleagues [22] successfully used SPV and TCI during intraoperative neurophysiological monitoring. In that case, BIS of the patient was maintained within the range of 80 to 90 that was approximately equal to fifty percent probability to tolerate shout and shake (TOSS 50 equal to NSRI 90). When BIS was within the range of 50 to 79 and the anesthesia depth increased to ninety percent probability to tolerate shout and shake (TOSS 90) level, neurophysiological monitoring was affected and considered poorly reproducible. The SPV made it possible to maintain and coordinate the required depth of anesthesia, which would be difficult to achieve with BIS monitoring only.

The optimal control of systemic and cerebral hemodynamics should be addressed during anesthesia for craniotomy. Both arterial hypotension and, as a result, cerebral hypoperfusion, as well as an undesired hypertensive response to a painful stimulation during craniotomy and recovery from anesthesia, are associated with increased morbidity, mortality, and poor neurologic outcomes. In the current study, SPV-guided anesthesia reduced the incidence of post-induction hypotension and intubation-induced hypertension. Hemodynamic responses in both groups were comparable during other painful stimulations, maintenance of surgery and following extubation. This finding can be attributed to the effect of scalp block, which was adjusted to all patients.

Early post-anesthesia recovery is critical following supratentorial surgeries and ensuring that neurocognitive function is quickly restored after surgery is an important goal in the anesthetic management of these patients [13]. BIS monitoring, which is the most often used monitor to evaluate the depth of anesthesia, has been shown to have an impact on recovery in previous studies [3, 4]. Mostly, BIS is accurate in determining solely the hypnotic component of anesthesia, it may not adequately reflect the even hypnotic state in some instances [23]. Unusual BIS readings were observed as a result of inaccurate low-voltage EEG analysis, particularly during anesthesia recovery [24]. Furthermore, SPV gives a priori anesthetic depth estimation, allowing anesthetic depth to be changed, whereas BIS only provides posteriori information, usually after a delay in response.

There was a significant difference in recovery times between patients monitored with SPV and patients who underwent normal anesthetic follow-up in our study. These findings are parallel those of a previous study searched the usefulness of SPV for a fast recovery from desflurane anesthesia [25]. Morimoto et al. [25] discovered that the time it took patients to open their eyes and restore orientation was much shorter in the SPV group, concluding that SPV-guided anesthesia is faster than BIS-guided anesthesia. Unlike our study, Morimoto et al. [25] used SPV at the end of the surgery, because they were solely interested in the recovery period. During the whole anesthetic phases in our research, SPV was utilized continuously in the SPV group.

In another non-randomized controlled research, Cirillo et al. [8] reported that in SPV-guided anesthesia administered groups, volatile anesthetic consumption was reduced. The authors, however, did not actually specify which MAC values they used for anesthesia maintenance or at what depths anesthesia was maintained. We can explain the reduced consumption of sevoflurane and remifentanil in the group monitored with SPV in our study, as SPV displays the hypnotic

level as well as the responsiveness to noxious stimuli compared to BIS.

Leblanc et al. [10] examined the effect of SPV on postoperative results in patients undergoing hip fracture surgery compared with standard anesthesia administration, assuming that the use of SPV in older patients may be particularly advantageous. Patients in the SPV group had better postoperative outcomes, including a shorter hospital stay [10]. Although our study showed a reduction in anesthetic consumption, the consequences on patient outcomes, postoperative mortality, and morbidity were not studied.

Limitations

The major shortcoming in this study is that it was underpowered due to its retrospective design. Prospective randomized controlled studies are needed to determine the influence of SPV on overall patient outcome and justify its usage in routine clinical practice.

Conclusion

In the current study, we investigated the effects of SPV on hemodynamics, anesthetic drug requirements, and recovery profile following supratentorial craniotomies and the display of the level of anesthesia on the SPV enabled the steady maintenance of neuroanesthesia. SmartPilot® View was effective in maintaining intraoperative hemodynamic stability, shortening postoperative recovery time, and reducing propofol and remifentanil requirement.

References

1. Bilotta F, Guerra C, Rosa G. Update on anesthesia for craniotomy. Curr Opin Anaesthesiol. 2013 Oct;26(5):517-22. doi: 10.1097/01.aco.0000432513.92822.c2. PMID: 23995058.
2. van den Berg JP, Vereecke HE, Proost JH, Eleveld DJ, Wietasch JK, Absalom AR, et al. Pharmacokinetic and pharmacodynamic interactions in anaesthesia. A review of current knowledge and how it can be used to optimize anaesthetic drug administration. Br J Anaesth. 2017 Jan;118(1):44-57. doi: 10.1093/bja/aew312.
3. Lewis SR, Pritchard MW, Fawcett LJ, Punjasawadwong Y. Bispectral index for improving intraoperative awareness and early postoperative recovery in adults. Cochrane Database Syst Rev. 2019;9:CD003843. doi: 10.1002/14651858.CD003843.pub4.
4. Chiang MH, Wu SC, Hsu SW, Chin JC. Bispectral Index and non-Bispectral Index anesthetic protocols on postoperative recovery outcomes. Minerva Anestesiol. 2018;84:216-28. doi: 10.23736/S0375-9393.17.12033-X.
5. Struys MM, Vereecke H, Moerman A, Jensen EW, Verhaeghen D, De Neve N, et al. Ability of the bispectral index, autoregressive modelling with exogenous input-derived auditory evoked potentials, and predicted propofol concentrations to measure patient responsiveness during anesthesia with propofol and remifentanil. Anesthesiology 2003; Oct;99(4):802-12. doi: 10.1097/00000542-200310000-00010. PMID: 14508310.
6. Gruenewald M, Harju J, Preckel B, Molnár Z, Yli-Hankala A, Rosskopf F, et al.; AoA Study Group. Comparison of adequacy of anaesthesia monitoring with standard clinical practice monitoring during routine general anaesthesia: An international, multicentre, single-blinded randomised controlled trial. Eur J Anaesthesiol. 2021 Jan;38(1):73-81. doi: 10.1097/EJA.0000000000001357.
7. Kennedy RR. Application of pharmacokinetics and pharmacodynamics and signal analysis to drug administration in anaesthesia. In: Gambus PL, Hendrickx JFA, editors. Personalized anaesthesia. Targeting physiological systems for optimal effect. Cambridge: Cambridge University Press; 2019. p. 82-102.
8. Cirillo V, Zito Marinosci G, De Robertis E, Iacono C, Romano GM, Desantis O, et al. Navigator® and SmartPilot® View are helpful in guiding anesthesia and reducing anesthetic drug dosing. Minerva Anestesiol. 2015 Nov;81(11):1163-9.
9. Velik-Salchner C. Computed advisory systems in daily practice for predicting concentrations and effects of combined anesthetics: a new field in anesthesia? Minerva Anestesiol. 2015;81:1151-2.
10. Leblanc D, Conté M, Masson G, Richard F, Jeanneteau A, Bouhours G, et al. SmartPilot® view-guided anaesthesia improves postoperative outcomes in hip fracture surgery: a randomized blinded controlled study. Br J Anaesth. 2017 Nov 1;119(5):1022-9. doi: 10.1093/bja/aex317.
11. Gruenbaum SE, Meng L, Bilotta F. Recent trends in the anesthetic management of craniotomy for supratentorial tumor resection. Curr Opin Anaesthesiol. 2016 Oct;29(5):552-7. doi: 10.1097/ACO.0000000000000365.
12. Xing Y, Lin N, Han R, Bebawy JF, Peng Y, Li J, et al. Sevoflurane versus PRopofol combined with Remifentanil anesthesia Impact on postoperative Neurologic function in supratentorial Gliomas (SPRING): protocol for a randomized controlled trial. BMC Anesthesiol. 2020 May 19;20(1):117. doi: 10.1186/s12871-020-01035-5.
13. Ayrian E, Kaye AD, Varner CL, Guerra C, Vadivelu N, Urman RD, et al. Effects of Anesthetic Management on Early Postoperative Recovery, Hemodynamics and Pain After Supratentorial Craniotomy. J Clin Med Res. 2015 Oct;7(10):731-41. doi: 10.14740/jocmr2256w.
14. Prabhakar H, Singh GP, Mahajan C, Kapoor I, Kalaivani M, Anand V. Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery. Cochrane Database Syst Rev. 2016 Sep 9;9(9):CD010467. doi: 10.1002/14651858.CD010467.pub2.
15. Flexman AM, Meng L, Gelb AW. Outcomes in neuroanesthesia: What matters most? Can J Anaesth. 2016 Feb;63(2):205-11. doi: 10.1007/s12630-015-0522-9.
16. Huang YH, Wu ZF, Lee MS, Lou YS, Wu KL, Cheng KI, et al. Propofol-based total intravenous anesthesia is associated with better survival than desflurane anesthesia in glioblastoma surgery. PLoS One. 2021 Aug 5;16(8):e0255627. doi: 10.1371/journal.pone.0255627.
17. Strus MMRF, Sahinovic M, Lichtenbelt BJ, Vereecke HEM, Absalom AR. Optimizing intravenous drug administration by applying pharmacokinetic/pharmacodynamic concepts. Br J Anaesth. 2011;107:38-47.
18. Mertens MJ, Olofsen E, Engbers FHM, Burm AGL, Bovill JG, Vuyk J. Propofol reduces perioperative remifentanil requirements in a synergistic manner: Response surface modeling of perioperative remifentanilpropofol interactions. Anesthesiology. 2003;99(2):347-59.
19. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology. 2004;100(6):1353-72.
20. Luginbühl M, Schumacher PM, Vuilleumier P, Vereecke H, Heyse B, Bouillon TW, et al. Noxious stimulation response index: a novel anesthetic state index based on hypnotic-opioid interaction. Anesthesiology. 2010 Apr;112(4):872-80. doi: 10.1097/ALN.0b013e3181d40368.
21. Hannivoort LN, Vereecke HE, Proost JH, Heyse BE, Eleveld DJ, Bouillon TW, et al. Probability to tolerate laryngoscopy and noxious stimulation response index as general indicators of the anaesthetic potency of sevoflurane, propofol, and remifentanil. Br J Anaesth. 2016 May;116(5):624-31. doi: 10.1093/bja/aew060.
22. Mai S, Ami S, Takayuki K. Complementary Use of Effect Site-Target Controlled Infusion and SmartPilot View for Anesthetic Management in Semi-awake Craniotomy Near BIS 85. J Neurosurg Anesthesiol. 2018 Jan;30(1):78-9. doi: 10.1097/ANA.0000000000000388.
23. Hagihira S, Okitsu K, Kawaguchi M. Unusually low bispectral index values during emergence from anesthesia. Anesth Analg. 2004;98:1036-8.
24. Dahaba A. Different conditions that could results in the bispectral index indicating an incorrect hypnotic state. Anesth Analg. 2005;101:765-73.
25. Morimoto Y, Shiramoto H, Yoshimura M. The usefulness of Smart Pilot View for fast recovery from desflurane general anesthesia. J Anesth. 2021 Apr;35(2):239-45. doi: 10.1007/s00540-021-02905-z.

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Prognostic value of preoperative glucose to lymphocytes ratio in patients with resected gastric cancer

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Ethics committee approval was obtained from Hitit University Clinical Research Ethics Committee (Date: 2021 Issue: 107).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: There are no definitive tests that determine postoperative survival in gastric cancer. Simple and cheap laboratory markers are needed for clinicians to guide them preoperatively. The aims of our study were to analyze the importance of preoperative glucose-lymphocyte ratio (GLR) in the prognosis of patients with gastric cancer (GC), and to compare the success of GLR in predicting prognosis with the success of neutrophil-lymphocyte ratio (NLR) and C-reactive protein-albumin ratio (CAR).

Methods: We carried out a cross-sectional study on 196 GC patients. CAR, NLR and GLR values were calculated from the blood samples taken 24 hours before the surgery. Lymphovascular invasion, serosal invasion, and the number of metastatic lymph nodes were determined, and the prediction ability of glucose to lymphocyte ratio (GLR), neutrophil to lymphocyte ratio (NLR), and C-reactive protein to albumin ratio (CAR) were evaluated. In addition, the effect of GLR and NLR on the ability to predict overall survival was assessed. The mean follow-up period was 37 (6-69) months.

Results: A moderate and weak positive correlation was found between GLR, NLR and the number of metastatic lymph nodes (r=0.415, $P<0.001$; r=0.193, $P=0.007$, respectively). GLR and NLR were significant for predicting lymphovascular and serosal invasion ($P<0.001$). CAR was insufficient in lymphovascular invasion differentiation (AUC (95% CI): 0.582 (0.501-0.662)) ($P=0.529$) and serosal invasion differentiation ($P=0.529$). GLR significantly predicted overall survival ($P=0.002$). Patients with a GLR value of <4.12 had a significantly longer overall survival than those with GLR>4.12. NLR was insignificant for overall survival ($P=0.233$).

Conclusion: GLR value may contribute to the planning of the therapy process by predicting both the prognosis of the disease and the overall survival before surgery.

Keywords: Overall survival, Gastric cancer, Predict, Glucose-Lymphocyte ratio

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Introduction

Gastric cancer is the fifth most common cancer and ranks second among gastrointestinal tract cancers. It ranks fourth among cancer-related deaths in the world. More than one million new diagnoses were made in 2020, and it caused approximately 760,000 deaths [1]. The high mortality of gastric cancer is because most cases are end-stage at the time of diagnosis. The five-year survival rate of even stage II-III gastric cancers that have a chance of surgery is around 35-50% [2]. Although there are many subtypes of gastric cancers, adenocarcinoma is the most common, with a rate of 95% [3]. Currently, the only curative treatment for gastric cancer is post-surgical chemoradiotherapy [4]. An average of twenty-five thousand gastrectomies are performed each year in the United States because of gastric cancer [5].

Knowing whether the operation will affect the patient's survival or whether it will be curative is especially important for the physician and the patient in terms of treatment decisions in the preoperative period. For this reason, the stage of the disease should be evaluated in detail before the operation with imaging methods and clinical examination. There are many prognostic evaluation methods such as histological grade, lymph node involvement, distant metastasis, and vascular invasion. Distant metastasis revealed by the imaging methods are unresectable. However, even if the patients are diagnosed at an operable stage, the 5-year survival rate after surgery is below 20%, especially in stage 3 cancers [6]. Currently, there are no definitive tests that determine postoperative survival; however, some markers, such as those of the inflammatory process, may help determine the prognosis [7, 8]. The neutrophil-lymphocyte ratio (NLR), C-reactive protein albumin ratio (CAR), platelet-lymphocyte ratio (PLR), and mean platelet volume were frequently researched [8, 9]. The glucose requirement increases secondary to the rapid growth around the tumor cells. Oxidative phosphorylation increases both to increase local immune suppression and meet the glucose requirement of these cells, thereby increasing the number of immature neutrophils in the blood [10]. It is also known that diabetes and increased blood sugar increase the risk of multiple neoplasms in the gastrointestinal tract, and elevated blood glucose values may affect clinical overcome and overall survival in cancer patients [11]. An increase in the rate of glucose-lymphocyte ratio (GLR) due to hyperglycemia and immunosuppression is expected in cancer patients. The ratio of preoperative blood glucose level and lymphocyte counts significantly predicts prognosis in pancreatic cancers [12]. There is still a need for a more accurate and comprehensive assessment system with improved sensitivity and specificity for the assessment of prognosis. Based on this preliminary information, the power of GLR to predict prognosis, lymphovascular invasion, serosal invasion, and survival of patients with gastric cancer were compared with NLR and CAR.

Materials and methods

The data of the patients who underwent gastrectomy with the diagnosis of gastric cancer at Hitit University Erol Olcok Training and Research Hospital between 01/01/2016 and 08/01/2021 were retrospectively analyzed after obtaining the approval of Hitit University Clinical Research Ethics Committee (Date: 2021 Issue: 107). Patients over the age of 18 years who were diagnosed with gastric adenocarcinoma and who underwent total or subtotal gastrectomy and lymph node dissection were included in the study. Patients with unavailable data, patients with acute inflammatory disease, diabetes patients, patients with comorbidities (Cushing's syndrome, glucagonoma, hyperthyroidism, etc.), patients using drugs that increase blood sugar glucose, individuals under the age of 18 years who underwent gastrectomy for pathological diagnoses other than adenocarcinoma, patients with early-stage gastric cancer, patients who received neoadjuvant chemotherapy and patients with end-stage disease who underwent surgery for gastric cancer but could not undergo gastrectomy were excluded. The reason for the exclusion of patients with early-stage gastric cancer is that serosal invasion is not detected because the tumor does not extend beyond the submucosa. The study was conducted per the Declaration of Helsinki after obtaining written consent from all patients.

Study protocol and definitions

The data of the patients, namely, age, gender, operation time, laboratory results, hospital stay, and pathological diagnoses were obtained from the hospital registry. Lymphovascular invasion, serosal invasion, the lymph node number of the patients were found, and the prediction ability of glucose lymphocyte ratio (GLR), neutrophil lymphocyte ratio (NLR), and C-reactive protein albumin ratio (CAR) were compared. In addition, the effect of GLR and NLR on the ability to predict overall survival was evaluated.

Follow-up

Overall survival (OS) was defined as the interval between the date of pathologically confirmed diagnosis and the date of death or last follow-up. All patients in this study were followed up regularly by an independent researcher by a telephone call or medical record review.

Statistical analysis

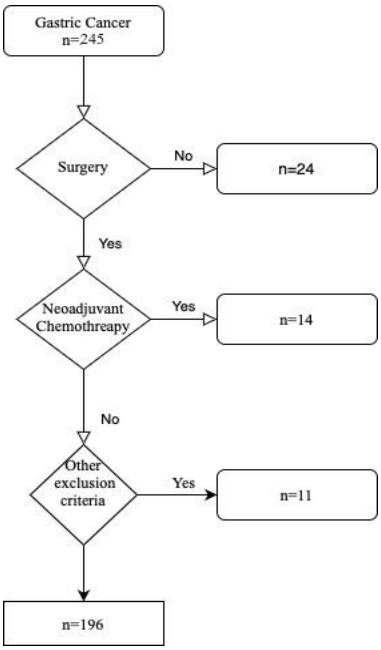
Statistical analysis was carried out using SPSS (Version 22,0, SPSS Inc., Chicago, IL, USA) software. Normally and non-normally distributed numerical data were presented as mean (standard deviation) and median (min-max), respectively. Categorical data were given as frequency and percentage (%). The Shapiro-Wilk test was used to determine whether the data were normally distributed. In the comparison of numerical variables between two independent groups, Student's t-test or Mann-Whitney U test was used depending on whether the data were normally distributed. Correlation analysis between numerical variables was conducted with the Spearman correlation coefficient per the data distribution. ROC (Recipient Operating Characteristic) analysis was used to decide whether GLR and NLR values were significant in predicting lymphovascular and serous invasion. The interpretation of the area under the curve (AUC) calculated by ROC analysis was as follows: 0.9-1: Excellent, 0.8-0.9: Good, 0.7-0.8: Fair, 0.6-0.7: Poor and 0.5-0.6: Unsuccessful. Youden index (maximum sensitivity and specificity) was used to calculate the best cut-off point in ROC analysis. Sensitivity, specificity, positive-negative predictive values (PPV-NPV), and likelihood ratio (L+) values were calculated to assess the discriminating power of cut-off

points calculated after ROC analysis in predicting lymphovascular and serosal invasion. Proportion comparisons between categorical variables were carried out using the Chi-square test. The Kaplan-Meier test was used to figure out the survival times of the groups formed according to the cut-off points determined for GLR and NLR, and the Log Rank (Mantel-Cox) test was used to compare the survival times. $P<0.05$ was considered statistically significant.

Results

After implementing the exclusion criteria, 196 patients were included in the study (Figure 1), who were divided into two groups according to the presence of lymphovascular invasion (Group I, n=91) and serosal invasion (Group II, n=57).

Figure 1: Flowchart



The gender distribution of the patients in groups I and II ($P=0.889$, $P=0.835$, respectively), their mean ages ($P=0.188$, $P=0.424$, respectively), and the hospital stay ($P=0.077$, $P=0.499$, respectively) were similar. Lymphovascular invasion and serosal invasion were significant in terms of mortality ($P<0.001$) (Table 1).

Table 1: Demographic data

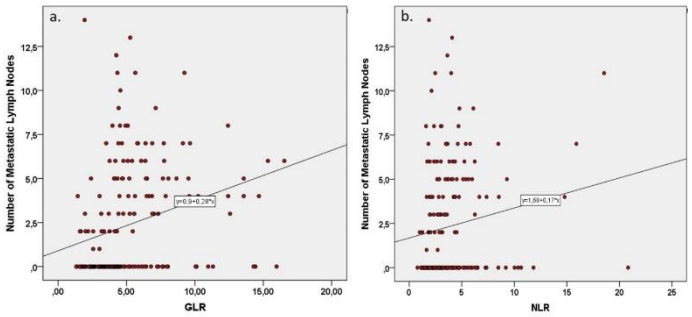
		Lymphovascular Invasion		*P*-value	Serosal Invasion		*P*-value
		No (n=105)	Yes (n=91)		No (n=139)	Yes (n=57)	
Gender	Female	28 (26.7%)	25 (27.5%)	0.899[a]	37 (26.6%)	16 (28.1%)	0.835[a]
	Male	77 (73.3%)	66 (72.5%)		102 (73.4%)	41 (71.9%)	
Mortality	Alive	70 (66.7%)	16 (17.6%)	<0.001[a]	74 (53.2%)	12 (21.1%)	<0.001[a]
	Dead	35 (33.3%)	75 (82.4%)		65 (46.8%)	45 (78.9%)	
Age		68.44(12.05)	70.7(12.5)	0.188[b]	69.06(11.77)	70.61(13.51)	0.424[b]
Duration of hospitalization (day)		15 (2-85) 17.13 (9.54)	16 (4-69) 19.35 (10.94)	0.077[c]	15 (2-85) 17.65 (9.39)	16 (8-69) 19.40 (12.08)	0.499[c]

[a] Chi-square test, [b] Student's t-test with mean (standard deviation), [c] Mann-Whitney U test with median (min-max)

The operation time was 183 (62) minutes in patients with lymphovascular invasion and 177 (64) minutes in patients without, 185 (68) minutes in those with serosal invasion and 178 (61) minutes in those without. No significant difference was found between groups in the duration of surgery.

There was a moderate and weak positive correlation between GLR, NLR and the number of metastatic lymph nodes (r=0.415, $P<0.001$, r=0.193, $P=0.007$, respectively). CAR and the number of metastatic lymph nodes were not correlated ($P=0.094$) (Figure 2).

Figure 2: Correlation between GLR and NLR and metastatic lymph node



GLR and NLR were significant for predicting lymphovascular and serosal invasion ($P<0.001$) (Table 2). CAR was insufficient in differentiating lymphovascular invasion (AUC (95% CI): 0.582 (0.501-0.662)) ($P=0.529$) and serosal invasion ($P=0.529$).

Table 2: Predictive power of GLR, NLR, and CAR to predict lymphovascular and serosal invasion

	Lymphovascular Invasion		*P*-values	Serosal Invasion		*P*-values
	No (n=105)	Yes (n=91)		No (n=139)	Yes (n=57)	
GLR	3.27 (1.3-15.9) (4.03(2.67))	5.23 (1.3-16.5) (6.13(3.16))	<0.001	3.82 (1.3-15.9) (4.56(2.93))	5.21 (1.3-16.5) (6.08(3.21))	<0.001
NLR	2.83 (0.7-11.8) (3.26(2.05))	3.56 (1.5-20.8) (4.47(3.37))	<0.001	2.91 (0.7-20.8) (3.62(2.79))	3.65 (1.5-15.9) (4.32(2.79))	0.012
CAR	4.13 (0.5-40.5) (5.98(6.85))	4.56 (0.6-82.8) (8.48(11.65))	0.049	4.31 (0.5-82.8) (7.31(10.2))	4.52 (0.7-44.1) (6.72(7.09))	0.529

Mann-Whitney U test with median (min-max) (mean, standard deviation)

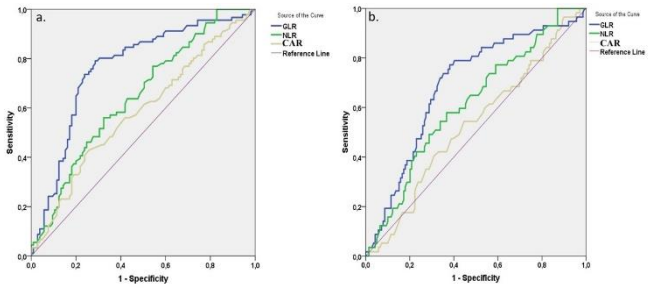
ROC (Receiver Operating Characteristic) analysis results and sensitivity, selectivity, positive-negative predictive values, and likelihood ratio (+) values of GLR and NLR values are presented in Table 3. The ROC curves are shown in Figure 3. ROC analysis showed that the GLR parameter was significant in lymphovascular invasion differentiation at a reasonable level (0.7<AUC<0.8, Table 3), and in terms of serosal invasion, it was at an acceptable level (0.6<AUC<0.7, Table 3). NLR parameter was significant at an acceptable level in the differentiation of both lymphovascular invasion (0.6<AUC<0.7, Table 3) and serosal invasion (0.6<AUC<0.7, Table 3).

Table 3: ROC (Receiver Operating Characteristic) analysis results for GLR and NLR values with sensitivity, specificity, positive-negative predictive values, and likelihood ratio (+) values

	Lymphovascular Invasion		Serosal Invasion	
	GLR	NLR	GLR	NLR
AUC (95%CI)	0.762 (0.692-0.831)	0.646 (0.569-0.722)	0.689 (0.608-0.770)	0.615 (0.530-0.700)
Cut-off	4.12	3.335	4.21	3.375
Sensitivity	79.1% (69.1-86.6)	56% (45.2-66.3)	77.2% (63.8-86.8)	57.9% (44.1-70.5)
Specificity	71.4% (61.6-79.6)	67.6% (57.6-76.2)	61.9% (53.2-69.8)	63.3% (54.6-71.1)
PPV	70.5% (60.6-78.9)	60% (48.7-70.3)	45.3% (35.3-55.7)	39.2% (28.9-50.5)
NPV	79.7 (69.9–87)	63.9 (54.2–72.7)	86.8% (78.2-92.5)	78.5% (69.6-85.5)
LR +	2.76 (2.01-3.81)	1.73 (1.24-2.41)	2.02 (1.56-2.61)	1.57 (1.15-2.15)

GLR: Glucose to lymphocyte ratio, NLR: Neutrophil to lymphocyte ratio, AUC: Area Under the ROC Curve, CI: Confidence Interval, PPV: Positive Predictive Values, NPV: Negative Predictive Values, LR: Likelihood Ratio

Figure 3: ROC curves



The cut-off points of GLR for predicting lymphovascular and serosal invasion were 4.12 and 4.21, respectively. The classification success rates of these values were 56% (45.2-66.3), and 57.9% (44.1-70.5), respectively, and selectivity were 71.4% (61.6-79.6) and 61.9% (53.2-69.8), respectively (Table 3).

The cut-off points of NLR were 3.33 and 3.37, respectively. The classification success rates of these values were 79.1% (69.1-86.6), and 77.2% (63.8-86.8), respectively, and selectivity were 67.6% (57.6-76.2), and 63.3% (54.6-71.1), respectively (Table 3).

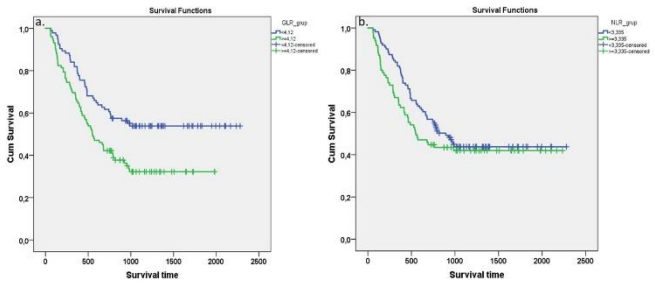
Survival times significantly differed between the GLR groups (P=0.002). Patients with a GLR value below 4.12 had a significantly longer life expectancy than patients with a GLR value above 4.12 (Table 4). There was no statistically significant difference in survival times between the NLR groups (Figure 4).

Table 4: Kaplan Meier survival analysis results: means and medians for survival time

	Groups	Mean				Median				*P*-values
		Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	Estimate	Std. Error	95% Confidence Interval Lower Bound	Upper Bound	
GLR	<4.12	1430.1	96.65	1240.6	1619.5	1075	101.4	896.1	1201.1	0.002[a]
	>=4.12	913.6	77.74	761.2	1066	549	82.9	386.5	711.4	
NLR	<3.335	1272.6	87.58	1101	1444.3	894	102.6	692.9	1095.1	0.233[a]
	>=3.335	1123.7	104.3	919.1	1328.2	549	116.7	320.1	777.8	

[a] Log Rank (Mantel-Cox) test

Figure 4: Survival Time



Discussion

This study analyzed the relationship between gastric cancer and the ability of GLR, NLR, and CAR to determine the prognosis. CAR and NLR are inflammatory response markers that effectively predict the prognosis in various cancers [13-15]. Zhong et al. stated that GLR has an essential role in determining the prognosis in pancreatic cancer patients, and that GLR alone is more effective in determining the average overall survival than NLR and CAR [12]. In another study, CAR and NLR were shown to have strong prognostic predictive values for gastric cancer [16]. No study investigated the value of GLR in gastric cancer. In our study, GLR and NLR were effective both in demonstrating lymphovascular and serosal invasion. However, CAR could not significantly differentiate lymphovascular invasion or serosal invasion (Table 2). A GLR cut-off value of 4.12 was significant in showing lymphovascular invasion, with 79.1% sensitivity and 71.4% specificity. Although NLR successfully predicts lymphovascular invasion with a cut-off value of 3.33, it has lower specificity and sensitivity than GLR. In predicting serosal invasion, the GLR and NLR cut-off values were 4.21 and 3.37, respectively. GLR is better in predicting serosal invasion than NLR. In particular, the 86.8% negative predictive value of GLR for serosal invasion plays a critical role in deciding neoadjuvant therapy before surgery. Lymphovascular and serosal invasion are the most critical factors in determining the prognosis and aggressiveness of gastric cancer [17-19]. Our results showed that mortality was significantly higher in the patient group with lymphovascular or serosal invasion. Previous studies have shown that gastric cancer patients with serosal invasion have a higher rate of peritoneal involvement and need neoadjuvant chemoradiotherapy [20–22].

One of the important factors determining the overall survival of gastric cancer is the number of metastatic lymph nodes [23–26]. In this study, while NLR and GLR were significantly related to the number of metastatic lymph nodes, CAR was not. Since D1 and D2 lymph node dissection for gastric cancers is still controversial, it may be useful to decide on D2 lymph node dissection by considering the preoperative NLR and GLR values. There are many survival analyses with NLR and CAR values in terms of gastric cancer. A meta-analysis conducted in 2015 revealed that increased NLR value was inversely proportional to survival [27]. However, we observed that the NLR value was not effective enough to predict the overall survival, while GLR value was (P=0.002). Kaplan Meier survival analysis revealed that the overall survival was 1430 days in patients with a GLR value below 4.12, and 913.6 days in patients with a GLR value above 4.12. Since there is no study on GLR in predicting survival among gastric cancer patients, this article may guide the future studies.

Limitations

This study inevitably has limitations as it was planned retrospectively, including small sample size, its single-center design, and not including gastric cancer subtypes other than adenocarcinoma. However, we believe that we obtained important findings, considering the absence of any other studies examining GLR values in gastric cancer. We aim to provide clinicians with a new and helpful tool that can be easily accessed and calculated, in addition to traditional methods and staging systems, while planning individualized treatment for gastric cancer.

Conclusion

GLR value is a successful immunological indicator in predicting lymphovascular and serosal invasion without added cost before surgery. The correlation between the number of metastatic lymph nodes and GLR can guide the surgeon for the width of the lymph node dissection. Furthermore, GLR value contributes to the planning of the therapy process by predicting both the prognosis of the disease and overall survival before surgery. Prospective randomized controlled studies are needed for predictivity success of GLR value on overall survival in gastric cancer patients.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: A Cancer Journal for Clinicians. 2021;71(3):209–49.
2. Survival for stomach cancer | Cancer Research UK [Internet]. [cited 2021 Aug 29]. Available from: https://www.cancerresearchuk.org/about-cancer/stomach-cancer/survival
3. Zali H, Rezaei-Tavirani M, Azodi M. Gastric cancer: prevention, risk factors and treatment. Gastroenterol Hepatol Bed Bench. 2011;4(4):175–85.
4. Jiang L, Yang K-H, Guan Q-L, Zhao P, Chen Y, Tian J-H. Survival and recurrence free benefits with different lymphadenectomy for resectable gastric cancer: A meta-analysis. Journal of Surgical Oncology. 2013;107(8):807–14.
5. Solanki S, Chakinala RC, Haq KF, Khan MA, Kifayat A, Linder K, et al. Inpatient burden of gastric cancer in the United States. Annals of Translational Medicine. 2019 Dec;7(23):772–772.
6. Sano T, Coit DG, Kim HH, Roviello F, Kassab P, Wittekind C, et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. Gastric Cancer. 2017 Mar;20(2):217–25.
7. Kim M-R, Kim A-S, Choi H-I, Jung J-H, Park JY, Ko H-J. Inflammatory markers for predicting overall survival in gastric cancer patients: A systematic review and meta-analysis. PLOS ONE. 2020 Jul 27;15(7):e0236445.
8. Toyokawa T, Muguruma K, Yoshii M, Tamura T, Sakurai K, Kubo N, et al. Clinical significance of prognostic inflammation-based and/or nutritional markers in patients with stage III gastric cancer. BMC Cancer. 2020 Jun 3;20(1):517.
9. Jiang X, Hiki N, Nunobe S, Kumagai K, Kubota T, Aikou S, et al. Prognostic importance of the inflammation-based Glasgow prognostic score in patients with gastric cancer. Br J Cancer. 2012 Jul;107(2):275–9.
10. Rice CM, Davies LC, Subleski JJ, Maio N, Gonzalez-Cotto M, Andrews C, et al. Tumour-elicited neutrophils engage mitochondrial metabolism to circumvent nutrient limitations and maintain immune suppression. Nat Commun. 2018 Nov 30;9(1):5099.
11. Hirakawa Y, Ninomiya T, Mukai N, Doi Y, Hata J, Fukuhara M, et al. Association Between Glucose Tolerance Level and Cancer Death in a General Japanese Population: The Hisayama Study. American Journal of Epidemiology. 2012 Nov 15;176(10):856–64.
12. Zhong A, Cheng C-S, Kai J, Lu R, Guo L. Clinical Significance of Glucose to Lymphocyte Ratio (GLR) as a Prognostic Marker for Patients With Pancreatic Cancer. Front Oncol. 2020;10:520330.
13. Sahiner Y. Can the C-reactive protein-to-plasma albumin ratio be an alternative scoring to show mortality and morbidity in patients with colorectal cancer? Ulus Travma Acil Cerrahi Derg [Internet]. 2020 [cited 2021 Aug 29]; Available from: http://www.tjtes.org/eng/jvi.aspx?pdir=travma&plng=eng&un=UTD-34412
14. Sert ÖZ, Bozkurt H, Ölmez T, Aray E, Uzun O, Gülmez S, et al. C-Reactive Protein to Albumin Ratio: A Reliable Marker in Colorectal Cancer. tjcd. 2021 Mar 1;31(1):35–42.
15. Yalav O, Topal U, Ünal AG, Eray İC, Rencüzoğulları A. Clinical Value of Neutrophil/Lymphocyte Ratio in Predicting Postoperative Complications and Prognosis in Patients with Colorectal Cancer Undergoing Surgical Treatment. tjcd. 2020 Mar 1;30(1):49–56.
16. Saito H, Kono Y, Murakami Y, Shishido Y, Kuroda H, Matsunaga T, et al. Prognostic Significance of the Preoperative Ratio of C-Reactive Protein to Albumin and Neutrophil–Lymphocyte Ratio in Gastric Cancer Patients. World J Surg. 2018 Jun 1;42(6):1819–25.
17. Lee J-H, Kim MG, Jung M-S, Kwon SJ. Prognostic significance of lymphovascular invasion in node-negative gastric cancer. World J Surg. 2015 Mar;39(3):732–9.
18. Chen S, Cai M-Y, Chen Y-B, Li Y-F, Feng X-Y, Zhou Z-W. Serosa-penetration in human T4aN0M0 gastric carcinoma correlates with worse prognosis after D2 gastrectomy. Chin Med J (Engl). 2012 Mar;125(6):1158–62.
19. Yasuda K, Shiraishi N, Inomata M, Shiroshita H, Izumi K, Kitano S. Prognostic significance of macroscopic serosal invasion in advanced gastric cancer. Hepatogastroenterology. 2007 Nov;54(79):2028–31.
20. Takiguchi N, Nunomura M, Koda K, Oda K, Suzuki H, Miyazaki M. Neoadjuvant chemotherapy with CDDP and 5-fluorouracil for gastric cancer with serosal invasion. Oncol Rep. 2003 Apr;10(2):433–8.
21. Xu A-M, Huang L, Liu W, Gao S, Han W-X, Wei Z-J. Neoadjuvant Chemotherapy Followed by Surgery versus Surgery Alone for Gastric Carcinoma: Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLOS ONE. 2014 Jan 30;9(1):e86941.
22. Togano S, Yashiro M, Miki Y, Yamamato Y, Sera T, Kushitani Y, et al. Microscopic distance from tumor invasion front to serosa might be a useful predictive factor for peritoneal recurrence after curative resection of T3-gastric cancer. PLOS ONE. 2020 Jan 15;15(1):e0225958.
23. Zhao B-W, Chen Y-M, Jiang S-S, Chen Y-B, Zhou Z-W, Li Y-F. Lymph Node Metastasis, a Unique Independent Prognostic Factor in Early Gastric Cancer. PLOS ONE. 2015 Jul 8;10(7):e0129531.
24. Ding Y-B, Chen G-Y, Xia J-G, Zang X-W, Yang H-Y, Yang L, et al. Correlation of tumor-positive ratio and number of perigastric lymph nodes with prognosis of gastric carcinoma in surgically-treated patients. World J Gastroenterol. 2004 Jan 15;10(2):182–5.
25. Berkeşoğlu M, Çağlar R, Ölmez A, Canbaz H, Taşdelen B, Dirlik MM, et al. Evaluation of the Factors Affecting Survival in Patients with Gastric Cancer According to the 8th Edition of the Tumor, Node and Metastasis Classification. Haseki. 2019 Jun 1;57(2):153–61.
26. Koşmaz K, Bostancı MT, Çaparlar MA, Başak F, Şişik A, Kalcan S, et al.. Predicting survival in gastric cancer: A prospective cohort study with 102 patients. J Surg Med. 2019; 3(5):361-5.
27. Xin-Ji Z, Yong-Gang L, Xiao-Jun S, Xiao-Wu C, Dong Z, Da-Jian Z. The prognostic role of neutrophils to lymphocytes ratio and platelet count in gastric cancer: A meta-analysis. Int J Surg. 2015 Sep;21:84–91.

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Percutaneous cholecystostomy results of 136 acute cholecystitis patients: A retrospective cohort study

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Ethics Committee Approval
The Ethical Review Committee of University of Health Sciences, Okmeydani Training and Research Hospital approved this study (date: 23.05.2017 and number: 668).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Percutaneous cholecystostomy (PC) is an alternative procedure to surgery in selected patients with acute cholecystitis (AC). This study aimed to review the clinical and surgical results of patients who underwent percutaneous cholecystostomy.
Methods: The records of patients who underwent PC for AC were evaluated for age, gender, comorbidities, survey, catheterization timing, complications, control, removal timing, operation type, interval time, pathology, C-reactive protein (CRP) level and white blood cell count (WBC), ultrasonography (USG) and computed tomography (CT) results.
Results: One hundred and thirty-six AC patients who underwent PC were included in the study. The median age was 73 (32-96) years and 57.3% of the patients were male. Out of the 136, 106 (78%) had an American Society of Anesthesiologists (ASA) classification score of 3 or 4. The median Charlson's comorbidity index (CCI) score was 5 (0-13). The median timing of catheterization was 23 (20-144) hours and length of hospital stay (LOS) was 3 (1-25) days. Dislocation was the most common complication of PC, and 7.4% (n=10) had recurrent AC. The median time until tube removal was 26.5 (1-238) days. Among all, 41.2% (n=56) of the patients underwent interval cholecystectomy, which equates to 76.8% of the those performed laparoscopically. The median time until the operation was 100 (1-264) days. Chronic cholecystitis was the most common pathology of cholecystectomy after PC. Bacterial bile cultures were analyzed in 36 of the patients and showed positive results in 66.7%, with no overall effect on the outcome. Nine patients (6.6%) died.
Conclusion: The importance of PC in AC increased with the Covid19 pandemic. PC was performed especially for old patients with ASA ≥3, and CCI ≥5 due to lower complication and recurrence rates. PC could be the final treatment for selected AC patients. Interval cholecystectomies performed after 8 weeks had a shorter LOS and a lower rate of complication.

Keywords: Acute cholecystitis, Comorbidities, Percutaneous cholecystostomy, Recurrence

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Introduction

Acute cholecystitis (AC) is the inflammation of the gallbladder and mostly occurs due to the obstruction of the cystic duct by gallstones. Five percent of the ACs are acalculous. The prevalence of gallstone is 15-20% in the population, 2% being symptomatic, and 20% of the symptomatic patients present with AC [1, 2]. The most common diagnostic criteria and severity grading for AC is Tokyo Guidelines (TG). AC is divided into mild, moderate, and severe according to TG18 severity grading. Treatment of AC varies from supportive (antibiotic) treatment to cholecystectomy due to severity and/or patients' comorbidities or health conditions [3].

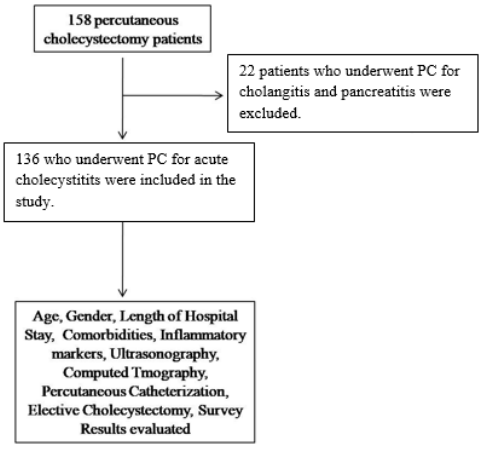
Percutaneous cholecystostomy (PC) is an ultrasonography (USG)-guided, percutaneously performed drainage procedure, which is an alternative to surgery in selected AC patients [4]. PC is indicated in severe cholecystitis (according to TG18), AC patients with American Society of Anesthesia (ASA) classification ≥3 or Charlson's comorbidity index ≥ 6 score, in malignant biliary tract lesions, bile duct stricture dilatation, bile duct fistula output diversion, or biliary tract decompression in cholangitis [5]. PC became more important for AC treatment during the Covid-19 pandemic independent from comorbidities or surgical high risk [6]. There is no literature on the optimal timing for tube placement of PC. However, lower procedure-related bleeding and lower hospital stay were reported with early tube placement (≤24 hours) [7]. Tube removal is suggested 3-6 weeks after placement because of tract maturation. However, the mean tube removal time was reported as 89 days in the literature [8]. Major or minor complication rate varies from 2.4 to 16%, and mortality rate ranges between 0-1.4% [9]. PC can be the final treatment in selected patients with higher surgical risk and/or patent cystic duct at cholecystography with or without cholecystolithotomy, or a bridge treatment for early or elective cholecystectomy [10].

This study aimed to assess the percutaneous cholecystostomy results of 136 acute cholecystitis patients.

Materials and methods

The Ethics Review Committee of University of Health Sciences, Okmeydanı Training and Research Hospital approved this study (Decision no: 668, date: 23.05.2017). The records of the patients who underwent percutaneous cholecystostomy for acute cholecystitis between 01 January 2015 and 01 January 2021 were evaluated retrospectively (Figure 1).

Figure 1: Flowchart showing the patients included in the study



An interventional radiologist performed US-guided PC with the transhepatic approach (Figure 2) and checked it with a cholecystography (Figure 3).

Figure 2: Ultrasound-guided transhepatic percutaneous cholecystostomy images: A: The catheter is on the gallbladder wall, B: The catheter is within the gallbladder.

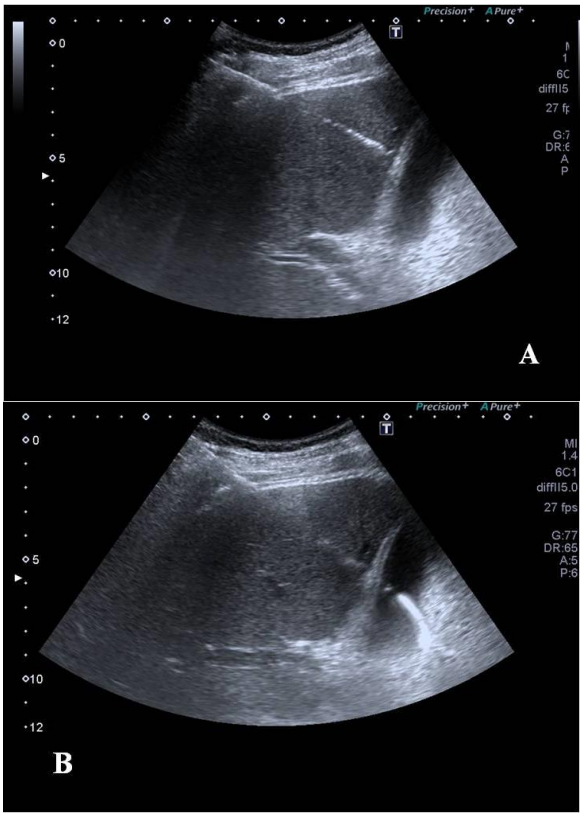
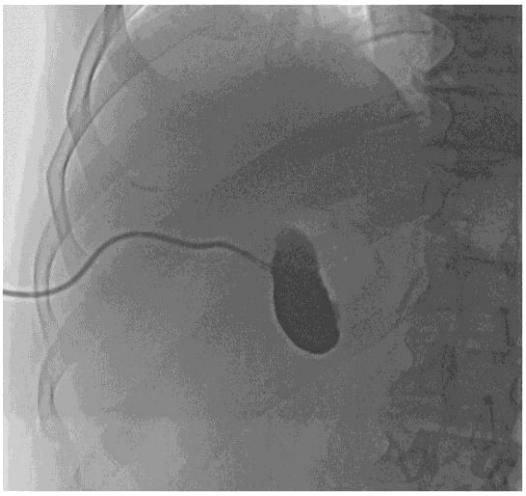


Figure 3: Cholecystography



Patients' age, gender, comorbidities, catheterization timing, length of hospital stay (LOS), endoscopic retrograde cholangiopancreatography (ERCP), CCI, ASA classification score, time until surgery, and survey were noted. Charlson's Comorbidity Index (CCI) was calculated as Charlson et al. [11] described. Baseline, pre-procedural and discharge levels of C-Reactive protein (CRP) (g/dl), white blood cell count (WBC) (10^6/dl), baseline levels of neutrophil percentage (Neu%), neutrophil lymphocyte ratio (NLR), platelet count (PLT) (10^3/dl), international normalization ratio (INR), creatinine (mg/dl) levels were assessed. The size of the gallbladder, wall thickness, contents of gallbladder, and size of major calculi were determined using USG and CT. The size and complications of the catheter, bile culture results, isolated pathogens, imaging for catheter control, time until removal, and catheter removal

indications were considered the catheterization results. Operation type and indications of initial open surgery and conversion to open surgery, time until the operation, postoperative intensive care unit requirement, and postoperative pathology results were evaluated as the cholecystectomy results.

Whether the patient underwent operation was recorded as yes/no, survival was noted as alive or exitus, the size of gallbladder, as hydropic or normal, the contents of the gallbladder, as sludge, the size of the stones as <3 mm, or ≥3 mm, and CT results, as not performed, performed but negative or performed and positive. Catheter complications were noted as none, dysfunction, dislocation, abscess, removed, and recurrence. Whether bile culture was obtained was assessed as no or yes (if yes, negative or positive). Catheters were controlled ultrasonographically or with a cholecystography. Catheter removal indication was grouped as final treatment, during surgery, removal without surgery and exitus. Operation types included laparoscopic, initial open surgery, or conversion to open surgery. Postoperative pathological examination results were grouped as chronic cholecystitis, active chronic cholecystitis, xanthogranulomatous cholecystitis, ulcerous active cholecystitis, ulcerous active follicular cholecystitis, or chronic follicular cholecystitis.

In addition to the comparisons of the PC patients in our dataset according to the mentioned criteria, treatment types of the AC cases from the first wave of the Covid-19 outbreak were compared with those treated during the study period. The first wave of the Covid19 outbreak was defined as the period between 11.03.2020 and 01.07.2020. The number of all AC patients during the evaluated period was 993, 31 of which were treated during the first wave of the Covid-19 pandemic. This being a retrospective study, any potential bias which may be introduced from the fact that the study groups were not randomized should be kept in mind.

Statistical analysis

Statistical analysis performed with SPSS 16.0 (Chicago, SPSS Inc.), The age, LOS, catheterization timing, wall thickness, major calculi size, laboratory results, catheter removal time, and operative time were reported as median (minimum-maximum).

Results

Out of the 158 patients who underwent percutaneous cholecystostomy, 136 patients who had acute cholecystitis were included in the study. The median age was 73 (32-96) years and 57.3% (n=78) were male. The median CCI was 5 (0-13). Only 8% (n=11) of the patients had no comorbidities. The most common comorbidities were hypertension (HT) (50.7%, n=69), diabetes mellitus (DM) (46.3%, n=63), coronary artery disease (CAD) (34.5%, n=47), and chronic obstructive pulmonary disease (24.2%, n=33). The median time until catheterization was 23 (20-144) hours, and the median length of hospital stay was 3 (1-25) days. Fourteen percent (n=19) of the patients underwent ERCP, 41.2% (n=56) underwent cholecystectomy, and 6.6% (n=9) of the patients died (Table 1).

The median of CRP at admission (baseline), before the cholecystostomy and at discharge were 184.02 (0.92-426.72) g/dl, 211.5 (8.75-494.17) g/dl, and 104 (3.3-382), respectively. The median WBC count at admission, before the cholecystostomy and at discharge were 15.35 (3.43-32.2) 10^6/dl, 13.07 (3.3-33.1) 10^6/dl, and 9.14 (2.9-20.5), respectively. The median Neu%, NLR, PLT count, INR and serum creatinine values were 86.2 (61.8-95.8) %, 12.14 (2.1-68.4), 233.5 (86-512) 10^3/dl, 1.16 (0.88-2.58), and 0.93 (0.53-6.71) mg/dl, respectively (Table 2).

One hundred and twelve patients (82.4%) had hydropic gallbladders. The median gallbladder wall thickness was 5 (4-17) mm. Other radiologic findings (USG and CT) are shown in Table 3.

Table 1: Patient demographics (n=136)

Age (years)*	73 (32-96)
Gender	n (%)
Male	78 (57.3%)
Female	58 (42.7%)
Charlson's Comorbidity Index*	5 (0-13)
Comorbidities	n (%)
None	11(8%)
Hypertension	69 (50.7%)
Diabetes	63 (46.3%)
Coronary Arter Disease	47 (34.5%)
Chronic Obstructive Pulmonary Disease	33 (24.2%)
Tumor	13 (9.5%)
Cerebrovascular Disease	12 (8.8%)
Alzheimer	11 (8.1%)
Chronic Renal Failure	10 (7.3%)
Congestive Heart Failure	8 (5.9%)
ASA classification score	n (%)
ASA 1-2	30 (22%)
ASA 3	83 (61%)
ASA 4	23 (17%)
Catheterization timing (hours)*	23 (20-144)
Length of hospital stay (day)*	3 (1-25)
ERCP	n (%)
No	117 (86%)
Yes	19 (14%)
Operation	n (%)
No	80 (58.8%)
Yes	56 (41.2%)
Survey	n (%)
Alive	127 (96.3%)
Exitus	9 (6.6%)

* Median (Minimum-Maximum)

Table 2: Patients' laboratory findings

CRP (g/dl)*	
A	184.02 (0.92-426.72)
BC	211.5 (8.75-494.17)
D	104 (3.3-382)
WBC (10^6/dl)*	
A	15.35 (3.43-32.2)
BC	13.07 (3.3-33.1)
D	9.14 (2.9-20.5)
Neu%*	86.2 (61.8-95.8)
NLR*	12.14 (2.1-68.4)
PLT (10^3/dl)*	233.5 (86-512)
INR*	1.16 (0.88-2.58)
Creatinine (mg/dl)*	0.98 (0.53-6.71)

* Median (Minimum-Maximum) PLT: Platelet, INR: International Normalization Ratio, WBC: White blood cells, Neu%: Neutrophil (%), NLR: Neutrophil lymphocyte ratio, CRP: C-reactive protein, (A) Administration (BC) Before Cholecystostomy (D) Discharge

Table 3: Results of the patients' radiologic findings

Ultrasound Size of gallbladder	n	%
Hydrops	112	82.4
Normal	24	17.6
Wall thickness (mm)*	5 (4-17)	
Contents of gallbladder	n	%
Sludge	21	15.3
Calculi (<3mm)	36	26.5
Calculi (≥3mm)	79	58.2
Size of major calculi (mm)*	13.9 (3-39)	
Computed tomography	n	%
Not Performed	79	58.2
Performed but negative	7	12
Performed and positive	50	88

* Median (Minimum-Maximum)

The most common catheter size was 8F, used in 83% (n=113). Two patients (1.5%) had catheter dysfunction, 2.2% (n=3) had catheter dislocation, and 7.4% (n=10) had recurrence.

Among the thirty-six patients (26.4%) who had their bile cultures obtained, no pathogens were isolated in 33.3% (n=12). Escherichia coli was the most common pathogen isolated

from the bile culture with a rate of 50.0% (n=12), with Klebsiella pneumonia, and Enterobacter cloaca both following with 12.5% (n=3). Only 23.5% (n=32) of the patients had their catheter controlled with a cholecystography. The median catheter removal time was 27 (1-228) days, 41.2% (n=56) of the patients had their catheter removed during surgery, while 22.8% (n=31) had their catheter removed as final treatment (Table 4).

Among 56 patients who were operated, 76.8% (n=43) underwent laparoscopic cholecystectomy, and the operations of 14.3% (n=8) began laparoscopically but were converted to open surgery. Previous upper GIS surgery and ventriculoperitoneal shunt were the indications of initial open surgery, while severe adhesions and organ injury were the indications of conversion to open surgery. The median time until the operation was 100 (1-264) days. Twenty-one operated patients (38.2%) required intensive care. The most common postoperative pathological examination results were xanthogranulomatous cholecystitis in 23.2% (n=13), chronic cholecystitis in 21.4% (n=12), and active chronic cholecystitis in 19.7% (n=11) (Table 5).

Table 4: Results of percutaneous catheterization (n=136)

Size of catheter	n	%
8F	113	83
10F	17	12.5
7F or 9F	6	4.5
Complication of catheter	n	%
None	128	94.1
Dysfunction	2	1.5
Dislocation	3	2.2
Subcutaneous abscess	1	0.7
Remove	2	1.5
Recurrence	10	7.4
Bile culture	n	%
No	100	73.6
Yes	36	26.4
Negative	12	33.3
Positive	24	66.7
Isolated pathogens	n	%
Escherichia coli	12	50.0
Klebsiella pneumoniae	3	12.5
Enterobacter cloacae	3	12.5
Citrobacter freundii	1	4.2
Serratia marcescens	1	4.2
Pseudomonas aureginosa	1	4.2
Enterococcus faecalis	1	4.2
Enterococcus raffinosus	1	4.2
Enterococcus durans	1	4.2
Catheter control imaging	n	%
Ultrasonography	104	76.5
Cholecystography	32	23.5
Catheter Removal Time (day)*	26.5 (1-238)	
Catheter removal indication	n	%
Final treatment	31	22.8
During surgery	56	41.2
Removal without Surgery	42	30.8
Exitus	7	5.2

* Median (Minimum-Maximum)

Table 5: Results of cholecystectomy (n=56)

Operation Type	n	%
Laparoscopic	43	76.8
Open	5	8.9
Previous Upper GIS Surgery	4	80
Ventriculoperitoneal Shunt	1	20
Laparoscopic Conversion Open	8	14.3
Severe Adhesions	7	87.5
Organ Injury	1	12.5
Operation Interval Time (day)*	100 (1-264)	
Postoperative Intensive Care Unit	n	%
No	34	61.8
Yes	21	38.2
Pathology of Gallbladder	n	%
Chronic	12	21.4
Active Chronic	11	19.7
Xanthogranulomatous	13	23.2
Ulcerous Active	7	12.5
Ulcerous Active Follicular	9	16.1
Chronic Follicular	4	7.1

*Median (Minimum-Maximum)

Among the cholecystectomies performed ≤8 weeks, the rate of conversion to open surgery was higher (18.8%), mean LOS was longer (3.8 days), and the rate of perioperative complications was higher (12.5%) (Table 6).

Comparing the treatment types of the patients from the first wave of the Covid-19 pandemic with all AC patients in the study period revealed a lower rate of cholecystectomy and a higher rate of PC during the pandemic period (Table 7).

Table 6: Results of cholecystectomy by interval (n=56)

Interval*	≤8-week, n=16		>8-week, n=40	
	n	%	n	%
Laparoscopic	11	68.8	32	80.0
LCO**	3	18.8	5	12.5
Open	2	12.5	3	7.5
Complication	2	12.5	3	7.5
LOS (day)	3.8		3.1	

*Operation interval time (day), ** Laparoscopic Convert to Open

Table 7: AC treatment type comparison between the first wave of the Covid-19 pandemic and the total evaluated period

	1.1.2015 / 1.1.2021*		11.3.2020 / 1.7.2020**	
	n	%	n	%
AC	993		31	
Treatment Type				
Medical	521	52.4	21	67.7
PC	136	13.7	7	22.6
Cholecystectomy	337	33.9	3	9.7

* All patients, ** First wave of the Covid-19 pandemic

Discussion

Percutaneous cholecystostomy (PC) has a life-saving role for severe AC patients who cannot tolerate surgery. The indications of PC include (1) failure of medical treatment, (2) severe sepsis or intensive care requirement, (3) suspicion of gallbladder necrosis/perforation, (4) suspicion of gallbladder empyema, (5) surgeon's choice, (6) rejecting surgery, and (7) old age [12].

PC can be performed under USG, CT or endoscopic USG (EUS) guidance. The disadvantages of CT and EUS-guided PC are radiation exposure, the need for more experience, and sedation or general anesthesia requirement [13, 14]. In our study, PC was performed by an experienced interventional radiologist with 100% technical and clinical success under USG guidance with the transhepatic approach. The indications of PC in our study were CCI >5, ASA ≥3, and/or old patients who did not respond to medical treatment.

Older age is an important criterion for PC. The mean age of PC patients varies between 54.7-83 years, and it is predominant among males with rates of 52.7-78.3% reported in the literature [12]. Anderson et al. [15] studied 3,961 PC patients and reported the mean age of PC as 72.9 years, older than that of cholecystectomy patients (54.4 years), and the rate of male patients who underwent PC and cholecystectomy as 52.7%, and 38.9%, respectively. We reported the mean age for cholecystectomy as 51.76 years and the rate of males as 53.4% in our previous study [16]. In our current study, the median age was 73 years and 57.3% of the patients were male, both of which were similar to those reported in the literature.

Comorbidities affect not only surgical but also anesthetic morbidity and mortality. In the literature, the comorbidities were evaluated with ASA classification or CCI and only diabetes, coronary arterial disease or tumor were reported [12]. Bakkaloğlu et al. [17], Hiesh et al. [18], and Peters et al. [19] used ASA classification to assess the comorbidities and stated that three quarters of PC patients were ASA 3 and the rest were ASA 4. In our study, the percentage of ASA 3 and 4

patients was 78%. Anderson et al. [15], Bolues et al. [20], and Kawasneh et al. [21] used CCI for evaluating the comorbidities, and reported the mean CCI values as 3.9, 3.2 and 5.5 respectively. DM, HT, and CAD are the most common comorbidities of the elderly. Lin et al. [20] reported the comorbidities of elderly AC patients as HT (54.1%), DM (39.3%), CVD (24.6%) and CAD (22.9%). In our study, the median CCI was 5 (0-13), and the most common comorbidities were HT, DM, and CAD with rates of 50.7%, 46.3%, and 34.5%, respectively.

Ninety-five percent of AC patients had calculous cholecystitis (CC); therefore, PC was most performed for CC. The rates of PC performed for acalculous cholecystitis (ACC) varies from 3.1% to 42.5% in literature [12]. PC without cholecystectomy was reported as the final treatment of ACC in 76.3% [13, 22]. In our study, 15.4% of the PC was performed for ACC, and PC was the final treatment for only 19% (n=4) of those with ACC.

CRP and WBC count were the most used inflammatory biomarkers for AC, and important predictors of severity [16]. WBC increased early and decreased quickly as a response to treatment; however, CRP increased later and decreased slowly. The decreased CRP, WBC and fever were signs of inflammatory response to PC. WBC decreased from 19.97 to 8.37 $10^3/\mu L$, and CRP, from 248.7 to 25 mg/l in 72 hours after PC [23]. In our study, the median WBC decreased from 15.36 to $9.14x10^6$/dl; however, CRP increased before cholecystostomy compared to the level at admission, but decreased at discharge (211.5, 184.02, and 104 g/dl respectively).

Increased wall thickness, and pericholecystic fluid are the most common findings in the radiologic evaluation of AC. USG and/or contrast-enhanced CT were used for imaging in acute gallbladder pathologies. Hydropic gallbladder is an important finding for performing PC and a sign of obstruction of cystic duct. A hydropic gallbladder was reported in 74.2%, and the mean wall thickness was 6 (1.93) mm among patients with AC [24]. In our study, 82.4% of the patients had hydropic gallbladders, and their median wall thickness was 5 (4-17) mm. Also, 12.3% of the CT-performed patients had false negative findings.

Hemorrhage, dislocation, dysfunction, self-removal, or bile leakage are the complications of PC. In the literature, the complication rates of transabdominal and transhepatic PC were 32.3% and 12.1%, respectively [13]. Recurrence rate varied from 18-20.6%, and the mean time until recurrence, from 65 to 660 days. Malignancy, calculous cholecystitis, common bile duct stone, shorter than 44 days of PC duration were the risk factors of recurrence. Thirty-eight percent of the recurrence patients' catheters were functional [25, 26]. The removal time of catheters varied from 2 to 193 days, and there was no correlation between clinical outcomes [27].

In our study, the complication rate was 5.9% (n=8), and the dislocation of catheter was the most common complication, seen in 37.5% (n=3). Ten patients (7.4%) had recurrent AC after PC, which is lower than those reported in the literature. Ninety percent of the recurrent diseases were CC, only 30% (n=3) had their tube removed within the first 44 days following PC, and none had any tumors. The median removal timing of the catheter was 27 (1-228) days.

Bile cultures were obtained from 93.5% of the patients who underwent PC, among which 60.3% came back positive. The most common isolated pathogen was Escherichia coli (28.7%), which was followed by Klebsiella spp, and Enterobacter spp with rates of 17.14% each [28]. In our study, bile cultures could be obtained from 26.4% (n=36) of the patients, and a positive culture result was reported in 66.7% (n=24). Escherichia coli was the most common isolated pathogen with 50% (n=12), followed by Klebsiella pneumoniae and Enterobacter cloacae both at 12.5% (n=3).

Interval or delayed cholecystectomy, cholecystoscopy with lithotripsy, cystic duct stenting or removal after cholecystography would be performed after PC. Cholecystectomy was performed in 30-43% of the PC patients within 30-120 days [10, 29]. Initial open approach (16% vs 3%) or conversion to open surgery (26% vs 13%) were significantly higher in cholecystectomies performed after PC [30]. In the literature, there is no consensus about the favorable timing of interval cholecystectomy after PC. Woodward et al. [31] recommended a waiting period of 4 to 8 weeks after PC, due to increased surgical complication risk before 4 weeks, and after 8 weeks, whereas Altieri et al. [37] suggests that performing an early cholecystectomy (≤ 8 weeks) is associated with a higher risk of complications and longer hospital LOS compared to those performed at >8 weeks.

In our study, 40.4% of the PC patients underwent cholecystectomy within a median of 100 days, and cholecystectomies performed within ≤8 weeks were associated with a higher risk of complications (11.8%, n=17) and a longer LOS (3.8 days). Initial open approach and conversion to open surgery rates were lower than those in the literature, with 9% and 12.8%, respectively.

The most common postoperative pathological findings of the gallbladder among 1960 samples include chronic cholecystitis (67%), follicular cholecystitis (12%), and xanthogranulomatous cholecystitis (0.3%). Xanthogranulomatous cholecystitis is a rare, uncommon variant of chronic cholecystitis. The reported incidence varies from 0.3 to 1.9% in western countries, but increases up to 9% India [32, 33]. In our study, chronic cholecystitis was the most common pathology (41.1%), and the rate of xanthogranulomatous cholecystitis was 23.2%, higher than that reported in the literature.

PC was the final treatment for AC patients whose bile drainage from the gallbladder to the common bile duct was observed with a cholecystography, those not suitable for surgery, patients with malignancy, or acalculous cholecystitis. USG could not show the drainage of bile but revealed dislocation or other complications, such as abscess. The rate of PC performed as the final treatment of AC was varies between 43%-94% in the literature [34]. In our study, only 23.5% of the PCs were controlled with cholecystography, PC was the final treatment of 22.8% AC patients, and 5.2% of the patients' tubes were removed because of death.

In the literature, the thirty-day mortality rate of PC varies between 2.5-16.7%. The higher mortality rate of PC was

related with older age and comorbidities (especially malignancy) more than cholecystectomy [35, 36]. In our study, the mortality rate was 6.6%, similar with the literature.

The importance of PC increased with the Covid-19 pandemic worldwide [6]. Due to the decrease in resources (staff, ICU beds, operating rooms, etc.) because our hospital became a pandemic hospital during this period, AC patients which required cholecystectomy were treated conservatively or with PC more frequently.

Limitations

Its retrospective design and lack of comparison with AC patients who were conservatively or surgically treated were the two main limitations of our study. Additionally, the number of patients who underwent surgery post-PC was relatively low. High-quality prospective randomized trial studies about post-PC management are needed to reach a consensus on the topic.

Conclusion

PC is an important low-recurrence, low-complication alternative procedure to surgery in AC, especially for old patients with multiple comorbidities and high surgical risk. Its significance was revealed even more during the first wave of the Covid-19 where institution resources for surgery were scarcer. USG-guided transhepatic approach is a common and safe technique of PC. Some AC, especially ACC, could be treated with PC. Dislocation is the most common complication of PC. Recurrence of AC is another important problem of PC and may require further treatment such as surgery. Interval or delayed cholecystectomy could be performed after PC in selected patients. Xanthogranulomatous cholecystitis is rare, but it must be kept in mind that it is more common in cholecystectomies performed after PC. Our study suggests interval cholecystectomies performed after 8 weeks results in shorter LOS and lower rates of complication.

References

1. Indar AA, Beckingham IJ. Acute cholecystitis. BMJ. 2002 Sep 21;325(7365):639-43. doi: 10.1136/bmj.325.7365.639.
2. Halpin V. Acute cholecystitis. BMJ Clin Evid. 2014 Aug 20;2014:0411. PMID: 25144428.
3. Yokoe M, Hata J, Takada T, Strasberg SM, Asbun HJ, Wakabayashi G, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):41-54. doi: 10.1002/jhbp.515.
4. Mori Y, Itoi T, Baron TH, Takada T, Strasberg SM, Pitt HA, et al. Tokyo Guidelines 2018: management strategies for gallbladder drainage in patients with acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2018 Jan;25(1):87-95. doi: 10.1002/jhbp.504.
5. Morales-Maza J, Rodríguez-Quintero JH, Santes O, et al. Percutaneous cholecystostomy as treatment for acute cholecystitis: What has happened over the last five years? A literature review. Rev Gastroenterol Mex. 2019 Oct-Dec;84(4):482-91. English, Spanish. doi: 10.1016/j.rgmx.2019.06.004.
6. Somuncu E, Kara Y, Kızılkaya MC, Bozdağ E, Yıldız ZB, Özkan C, et al. A. Percutaneous cholecystostomy instead of laparoscopy to treat acute cholecystitis during the COVID-19 pandemic period: single center experience. Ulus Travma Acil Cerrahi Derg. 2021 Jan;27(1):89-94. English. doi: 10.14744/tjtes.2020.69804.
7. Chou CK, Lee KC, Chan CC, Perng CL, Chen CK, Fang WL, et al. Early Percutaneous Cholecystostomy in Severe Acute Cholecystitis Reduces the Complication Rate and Duration of Hospital Stay. Medicine (Baltimore). 2015 Jul;94(27):e1096. doi: 10.1097/MD.0000000000001096.
8. Masrani A, Young D, Karageorgiou JP, Mani NB, Picus DD, Kim SK. Management algorithm of acute cholecystitis after percutaneous cholecystostomy catheter placement based on outcomes from 377 patients. Abdom Radiol (NY). 2020 Apr;45(4):1193-7. doi: 10.1007/s00261-020-02449-y.
9. Gulaya K, Desai SS, Sato K. Percutaneous Cholecystostomy: Evidence-Based Current Clinical Practice. Semin Intervent Radiol. 2016 Dec;33(4):291-6. doi: 10.1055/s-0036-1592326
10. Bundy J, Srinivasa RN, Gemmete JJ, Shields JJ, Chick JFB. Percutaneous Cholecystostomy: Long-Term Outcomes in 324 Patients. Cardiovasc Intervent Radiol. 2018 Jun;41(6):928-34. doi: 10.1007/s00270-018-1884-5.
11. 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(5):373-83. doi: 10.1016/0021-9681(87)90171-8.
12. Elsharif M, Forouzanfar A, Oaikhinan K, Khetan N. Percutaneous cholecystostomy… why, when, what next? A systematic review of past decade. Ann R Coll Surg Engl. 2018 Oct 5;100(8):1-14. doi: 10.1308/rcsann.2018.0150.
13. Dvorak P, Hoffmann P, Renc O, Dusek T, Rejchrt S, Slezak O, Vyroubal P. Percutaneous cholecystostomy in the management of acute cholecystitis - 10 years of experience. Wideochir Inne Tech Maloinwazyjne. 2019 Dec;14(4):516-25. doi: 10.5114/wiitm.2019.84704.
14. Luk SW, Irani S, Krishnamoorthi R, Wong Lau JY, Wai Ng EK, Teoh AY. Endoscopic ultrasound-guided gallbladder drainage versus percutaneous cholecystostomy for high risk surgical patients with acute cholecystitis: a systematic review and meta-analysis. Endoscopy. 2019 Aug;51(8):722-32. doi: 10.1055/a-0929-6603.
15. Anderson JE, Chang DC, Talamini MA. A nationwide examination of outcomes of percutaneous cholecystostomy compared with cholecystectomy for acute cholecystitis, 1998-2010. Surg Endosc. 2013 Sep;27(9):3406-11. doi: 10.1007/s00464-013-2924-5.
16. Karakaş DO, Yeşiltaş M. Validity of the Glasgow prognostic score and modified systemic inflammation score in predicting complicated cholecystitis. Hippokratia. 2020 Jan-Mar;24(1):15-20.
17. Bakkaloglu H, Yanar H, Guloglu R, Taviloglu K, Tunca F, Aksoy M, et al. Ultrasound guided percutaneous cholecystostomy in high-risk patients for surgical intervention. World J Gastroenterol. 2006 Nov 28;12(44):7179-82. doi: 10.3748/wjg.v12.i44.7179.
18. Hsieh YC, Chen CK, Su CW, Chan CC, Huo TI, Liu CJ, et al. Outcome after percutaneous cholecystostomy for acute cholecystitis: a single-center experience. J Gastrointest Surg. 2012 Oct;16(10):1860-8. doi: 10.1007/s11605-012-1965-8.
19. Peters R, Kolderman S, Peters B, Simoens M, Braak S. Percutaneous cholecystostomy: single centre experience in 111 patients with an acute cholecystitis. JBR-BTR. 2014 Jul-Aug;97(4):197-201. doi: 10.5334/jbr-btr.101.
20. Boules M, Haskins IN, Farias-Kovac M, Guerron AD, Schechtman D, Samotowka M, et al. What is the fate of the cholecystostomy tube following percutaneous cholecystostomy? Surg Endosc. 2017 Apr;31(4):1707-12. doi: 10.1007/s00464-016-5161-x.
21. Khasawneh MA, Shamp A, Heller S, Zielinski MD, Jenkins DH, Osborn JB, et al. Successful laparoscopic cholecystectomy after percutaneous cholecystostomy tube placement. J Trauma Acute Care Surg. 2015 Jan;78(1):100-4. doi: 10.1097/TA.0000000000000498.
22. Gulaya K, Desai SS, Sato K. Percutaneous Cholecystostomy: Evidence-Based Current Clinical Practice. Semin Intervent Radiol. 2016 Dec;33(4):291-96. doi: 10.1055/s-0036-1592326.
23. Carrafiello G, D'Ambrosio A, Mangini M, Petullà M, Dionigi GL, Ierardi AM, et al. Percutaneous cholecystostomy as the sole treatment in critically ill and elderly patients. Radiol Med. 2012 Aug;117(5):772-9. doi: 10.1007/s11547-012-0794-2.
24. Sureka B, Rastogi A, Mukund A, Thapar S, Bhadoria AS, Chattopadhyay TK. Gangrenous cholecystitis: Analysis of imaging findings in histopathologically confirmed cases. Indian J Radiol Imaging. 2018 Jan-Mar;28(1):49-54. doi: 10.4103/ijri.IJRI_421_16.
25. Bhatt MN, Ghio M, Sadri L, Sarkar S, Kasotakis G, Narsule C, et al. Percutaneous Cholecystostomy in Acute Cholecystitis-Predictors of Recurrence and Interval Cholecystectomy. J Surg Res. 2018 Dec;232:539-46. doi: 10.1016/j.jss.2018.06.051.
26. Park JK, Yang JI, Wi JW, Park JK, Lee KH, Lee KT, et al. Long-term outcome and recurrence factors after percutaneous cholecystostomy as a definitive treatment for acute cholecystitis. J Gastroenterol Hepatol. 2019 Apr;34(4):784-90. doi: 10.1111/jgh.14611.
27. Macchini D, Degrate L, Oldani M, Leni D, Padalino P, Romano F, et al. Timing of percutaneous cholecystostomy tube removal: systematic review. Minerva Chir. 2016 Dec;71(6):415-26.
28. Nitzan O, Brodsky Y, Edelstein H, Hershko D, Saliba W, Keness Y, et al. Microbiologic Data in Acute Cholecystitis: Ten Years' Experience from Bile Cultures Obtained during Percutaneous Cholecystostomy. Surg Infect (Larchmt). 2017 Apr;18(3):345-9. doi: 10.1089/sur.2016.232.
29. Hung YL, Chen HW, Fu CY, Tsai CY, Chong SW, Wang SY, et al. Surgical outcomes of patients with maintained or removed percutaneous cholecystostomy before intended laparoscopic cholecystectomy. J Hepatobiliary Pancreat Sci. 2020 Aug;27(8):461-9. doi: 10.1002/jhbp.740.
30. Sakran N, Kopelman D, Dar R, Abaya N, Mokary SE, Handler C, et al. Outcome of Delayed Cholecystectomy after Percutaneous Cholecystostomy for Acute Cholecystitis. Isr Med Assoc J. 2018 Oct;20(10):627-31.
31. Woodward SG, Rios-Diaz AJ, Zheng R, McPartland C, Tholey R, Tatarian T, et al. Finding the Most Favorable Timing for Cholecystectomy after Percutaneous Cholecystostomy Tube Placement: An Analysis of Institutional and National Data. J Am Coll Surg. 2021 Jan;232(1):55-64. doi: 10.1016/j.jamcollsurg.2020.10.010.
32. Limaiem F, Sassi A, Talbi G, Bouraoui S, Mzabi S. Routine histopathological study of cholecystectomy specimens. Useful? A retrospective study of 1960 cases. Acta Gastroenterol Belg. 2017 Jul-Sep;80(3):365-70.
33. Frountzas M, Schizas D, Liatsou E, Economopoulos KP, Nikolaou C, Apostolou KG, et al. Presentation and surgical management of xanthogranulomatous cholecystitis. Hepatobiliary Pancreat Dis Int. 2021 Apr;20(2):117-27. doi: 10.1016/j.hbpd.2021.01.002.
34. Stanek A, Dohan A, Barkun J, Barkun A, Reinhold C, Valenti D, et al. Percutaneous cholecystostomy: A simple bridge to surgery or an alternative option for the management of acute cholecystitis? Am J Surg. 2018 Sep;216(3):595-603. doi: 10.1016/j.amjsurg.2018.01.027.
35. Fleming CA, Ismail M, Kavanagh RG, Heneghan HM, Prichard RS, Geoghegan J, et al. Clinical and Survival Outcomes Using Percutaneous Cholecystostomy Tube Alone or Subsequent Interval Cholecystectomy to Treat Acute Cholecystitis. J Gastrointest Surg. 2020 Mar;24(3):627-32. doi: 10.1007/s11605-019-04194-0.
36. Kuan LL, Oyebola T, Mavilakandy A, Dennison AR, Garcea G. Retrospective Analysis of Outcomes Following Percutaneous Cholecystostomy for Acute Cholecystitis. World J Surg. 2020 Aug;44(8):2557-61. doi: 10.1007/s00268-020-05491-5.
37. Altieri MS, Yang J, Yin D, Brunt LM, Talamini MA, Pryor AD. Early cholecystectomy (≤8 weeks) following percutaneous cholecystostomy tube placement is associated with higher morbidity. Surg Endosc. 2020 Jul;34(7):3057-63. doi: 10.1007/s00464-019-07050-z..

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The impact of Covid-19 on ECG: A case-control study

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Ethics Committee Approval
The Ethical Review Committee of Harran University, HRU/21.12.19, has approved this study.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Coronavirus Disease 2019 (Covid-19) is a pandemic with fatal effects on the respiratory and cardiovascular systems. Early recognition of complications in the cardiovascular system in Covid-19 disease will guide our treatment management. Therefore, we aimed to examine the changes that occurred in the ECGs of patients with a Covid-19 infection in the last year who were admitted with palpitations.

Methods: Patients who presented to the Cardiology and Internal Medicine outpatient clinics with a complaint of palpitation between June 2021 and July 2021 and who had a Covid-19 infection in the last year were included in this study. A total of 212 patients with a history of Covid-19 and a control group of 185 people without Covid-19 history and cardiac diseases were compared. At admission, QTc, Tp-e interval, frontal QRS-T angle, and fragmented QRS were evaluated on Electrocardiography (ECG).

Results: Among patients with a history of Covid-19 disease, there were 127 (59.91%) males and 85 (40.09%) females. Within the control group, 71 (38.38%) were males and 114 (61.62%) were females. In patients who had a Covid-19 infection, QTc (OR: 1.071, 95% CI: 1.042-1.100, $P<0.001$), frontal QRS-T angle (OR: 1.054, 95% CI: 1.015-1.095, $P=0.007$), and Tp-e interval (OR: 1.253, 95% CI: 1.140-1.377, $P<0.001$) were significantly increased. The difference in fragmented QRS ($P=0.230$) was not significant in logistic regression analysis.

Conclusion: We found increased QTc, Tp-e, and fQRS-T angles in patients who had Covid-19 disease, all of which indicate ventricular repolarization abnormality. Therefore, those with Covid-19 infection should be followed up for malignant arrhythmias.

Keywords: Covid-19, ECG, fQRS-T angle, QTc, Tp-e interval

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Introduction

Coronavirus disease (Covid-19) is defined as "severe acute respiratory syndrome (SARS-CoV-2)" by the World Health Organization [1, 2]. Clinical manifestations range from fever and cough, which are the symptoms of simple respiratory infection, to severe acute respiratory syndrome (ARDS) in Covid -19 infection [3]. Covid-19 can also cause undesirable effects on the heart and cardiovascular system [4], and various clinical conditions such as acute coronary syndrome, myocarditis, arrhythmias, and heart failure were reported [5, 6]. Electrocardiography (ECG) has a vital role in demonstrating cardiac damage and arrhythmic events to explain the clinical changes occurring during Covid-19 infection and give an idea about the problems that may occur in the future. Therefore, the primary aim of our study was to examine the arrhythmic state after cardiac injury, based on ECG findings such as QTc, Tp-e interval, frontal QRS-T angle (fQRS-T), and fragmented QRS (fQRS) in patients who had Covid-19.

Materials and methods

Study design

Patients who visited the Şanlıurfa Mehmet Akif Inan Training and Research Hospital Cardiology Outpatient Clinic and Internal Medicine Outpatient Clinic with complaints of palpitation between June 2021 and July 2021 and who were Covid-19-positive in real-time reverse-transcription (RT-PCR) test within the last year were included in the study. The patients included in the study were divided into two groups. The ECG and laboratory findings of those with a history of Covid-19 in the 1st group (n=212) and those of the healthy population without a history of Covid-19 infection in the 2nd group (n=185) were compared. Patients with ECG abnormalities such as a bundle branch block or atrioventricular block as well as a history of coronary artery disease, previous cerebrovascular event, systolic heart failure, left ventricular hypertrophy, severe heart valve disease, permanent pacemaker, chronic kidney or liver failure, hyperthyroidism, hypertension, pregnancy, electrolyte imbalance were also excluded.

In this prospective study, demographic characteristics, age, gender, hypertension (HT), diabetes mellitus (DM), and smoking history were recorded from the patients' history. Laboratory findings included glucose, urea, creatinine, sodium, potassium, AST, ALT, hemoglobin values, lymphocyte, and neutrophil counts. The Harran University ethics committee approved this study, and written informed consent was obtained from all patients (decree no: HRU/21.12.19).

Electrocardiographic examination

After resting in supine position for 10 minutes, 12-lead ECG recordings were obtained from all cases, with a paper speed of 25 mm per second, a height of 10 mm/mV, and a filter range of 0.16-100 Hz. QT and Tp-e interval measurements were calculated. The QT interval was defined as the distance from the beginning of the Q wave until the end of the T wave. The corrected QT interval (QTc) according to the heart rate was calculated using Bazett's formula. The Tp-e interval was defined as the distance between the peak of the T wave and the endpoint. Tp-e interval measurements were made in the precordial leads [7, 8]. The frontal QRS axis and T-axis were obtained from the automatic report of the ECG device, and these angles were controlled. Frontal QRS-T angle (fQRS-T angle) was defined as the absolute difference between the QRS axis and T-axis (frontal QRST angle = QRS axis – T-axis). When this angle exceeded 180°, the current angle was subtracted from 360° and recalculated [9]. Fragmented QRS was defined as the RSR pattern in at least two consecutive leads and/or the presence of notching in the R and S waves [10].

Statistical analysis

All analyses were performed with SPSS v21 (SPSS Inc. Chicago, Illinois, USA). Shapiro-Wilk test was used to check whether the data were normally distributed. Data were presented as mean (1st quartile – 3rd quartile) for continuous variables and frequency (percentage) for categorical variables. Non-normally distributed variables were analyzed with the Mann-Whitney U test. The Pearson chi-square test was used to assess categorical variables. Logistic regression analysis was performed to determine the risk factors for the presence of Covid 19. Variables that were statistically significant in univariate analyses were included in the regression models. *P*-values of less than 0.05 were considered statistically significant.

Results

The distribution of age, presence of DM, level of ALT was similar among the two groups. Gender, hypertension, smoking, WBC, MPV, neutrophil count, lymphocyte count, monocyte count, platelet count, glucose, potassium, urea, AST, albumin, QT, QTc, fQRS-T angle, and Tp-e interval were related with the presence of Covid-19 (Table 1). The distribution of ECG variables by groups is shown in Figures 1-4.

Figure 1: QT value by groups

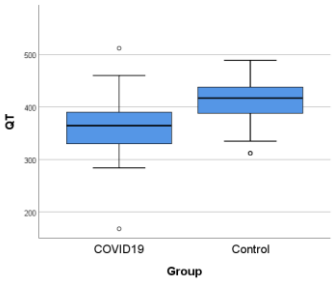


Figure 2: QTc value by groups

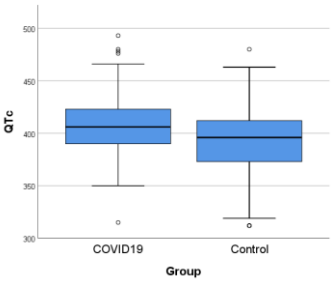


Figure 3: Frontal QRS value by groups

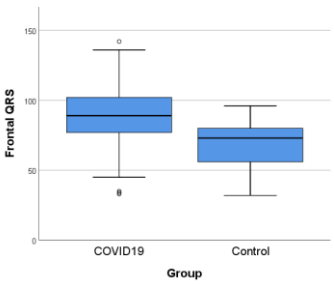
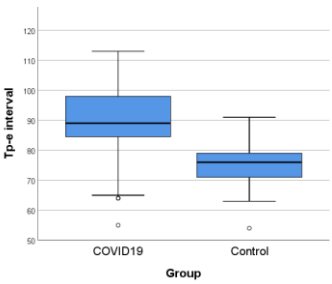


Figure 4: Tp-e interval value by groups



Multiple logistic regression analysis was performed to identify the important factors related to Covid-19. Smoking (OR: 0.182, 95% CI: 0.049-0.675, *P*=0.011), neutrophil count (OR: 1.094, 95% CI: 1.053, 1.138, *P*<0.001), urea level (OR: 1.074, 95% CI: 1.011-1.141, *P*=0.020), AST level (OR: 1.057, 95% CI: 1.003-1.114, *P*=0.040), QT (OR: 0.915, 95% CI: 0.886-0.945, *P*<0.001), QTc (OR: 1.071, 95% CI: 1.042-1.100, *P*<0.001), frontal QRS-T angle (OR: 1.054, 95% CI: 1.015-1.095,

P=0.007), Tp-e interval (OR: 1.253, 95% CI: 1.140-1.377, *P*<0.001) were associated with COVID 19. Other variables included in the sample, such as gender (*P*=0.280), hypertension (*P*=0.304), WBC (*P*=0.142), MPV (*P*=0.686), RDW (*P*=0.404), lymphocyte (0.565), platelet (*P*=0.547), glucose (*P*=0.464), K (*P*=0.727), and fQRS (*P*=0.230) were not (Table 2).

Table 1: Clinical variables by groups

	Group		
	COVID-19	Control	*P*-value
Gender			
Male	127 (59.91%)	71 (38.38%)	<0.001
Female	85 (40.09%)	114 (61.62%)	
Age (years)	54.00 (33.00 - 70.00)	51.00 (44.00 - 57.00)	0.356
DM	51 (24.06%)	34 (19.32%)	0.261
HT	54 (25.47%)	26 (14.29%)	0.006
Smoking	55 (25.94%)	72 (41.11%)	0.001
WBC	8.92 (6.3.00 - 12.00)	8.07 (6.87 - 9.52)	0.010
MPV	10.40 (9.70 - 11.00)	10.50 (9.90 - 11.20)	0.039
RDW	13.20 (12.60 - 14.65)	13.80 (13.00 - 14.50)	0.033
Neutrophils	8.74 (4.17 - 71.00)	4.83 (4.00 - 6.00)	<0.001
Lymphocyte	2.31 (1.51 - 8.00)	2.40 (1.69 - 2.90)	0.034
Monocytes	0.91 (0.56 - 4.20)	0.64 (0.51 - 0.80)	<0.001
Hgb	14.10 (12.35 - 15.25)	13.50 (12.50 - 15.00)	0.143
Hct	42.05 (37.85 - 45.45)	41.10 (38.60 - 45.30)	0.575
Platelet	245.00 (193.50 - 288.50)	268.00 (222.00 - 323.00)	0.001
Glucose	122.50 (102.00 - 177.50)	102.00 (91.90 - 110.20)	<0.001
Sodium	139.00 (136.00 - 141.00)	139.00 (137.00 - 141.00)	0.551
Potassium	4.48 (4.10 - 4.80)	4.29 (4.00 - 4.58)	0.001
Urea	33.00 (24.5 - 44)	27.90 (23.60 - 37.50)	<0.001
Creatinine	0.96 (0.78 - 1.14)	0.82 (0.71 - 0.94)	0.501
ALT	18.85 (11.40 - 30.50)	18.00 (14.50 - 27.50)	0.057
AST	22.65 (16.40 - 33.95)	21.00 (16.00 - 27.00)	<0.001
Albumin	39.27 (32.95 - 44.85)	4.40 (4.00 - 4.60)	<0.001
QT	364.50 (330.00 - 390.00)	417.00 (388.00 - 438.00)	<0.001
QTc	406.00 (390.00 - 423.00)	396.00 (373.00 - 412.00)	<0.001
Fragmented QRS	25 (11.79%)	9 (4.86%)	0.014
Frontal QRS	89.00 (77.00 - 102.00)	73.00 (56.00 - 80.00)	<0.001
Tp-e interval	89.00 (84.50 - 98.00)	76.00 (71.00 - 79.00)	<0.001
Death	23 (10.85%)	0 (0%)	N/A

AST: Alanine Aminotransferase; ALT: Alanine Aminotransferase; QTc: Corrected QT range, DM: Diabetes mellitus, Hgb: Hemoglobin, Hct: Hematocrit, HT: Hypertension, MPV: Mean platelet volume, RDW: Erythrocyte distribution width, WBC: White blood cell count Data were presented as mean (1st quartile – 3rd quartile) for continuous variables and as frequency (percentage) for categorical variables.

Table 2: Key factors of COVID 19, multiple logistic regression analysis

	β coefficient	Standard Error	Wald	*P*-value	Exp(β)	95.0% Confidence Interval for Exp(β)	
Smoking	-1.706	0.67	6.482	0.011	0.182	0.049	0.675
Neutrophils	0.090	0.020	20.949	<0.001	1.094	1.053	1.138
Urea	0.072	0.031	5.411	0.020	1.074	1.011	1.141
AST	0.055	0.027	4.238	0.040	1.057	1.003	1.114
QT	-0.089	0.016	29.253	<0.001	0.915	0.886	0.945
QTc	0.068	0.014	24.696	<0.001	1.071	1.042	1.100
Frontal QRS	0.053	0.019	7.402	0.007	1.054	1.015	1.095
Tp-e interval	0.225	0.048	21.92	<0.001	1.253	1.140	1.377
Continuous	-19.596	5.273	13.812	<0.001	<0.001		

Dependent variables: COVID-19; Nagelkerke R2=0.919

Discussion

This study determined increased QTc, Tp-e interval, and fQRS-T angle, which are vital markers of potentially fatal arrhythmias on surface ECG. The increase in these parameters occurs with the delay in the action potential, which indicates myocardial repolarization. Since ECG is a non-invasive test used to obtain rapid results in evaluating the cardiovascular system, we can also evaluate myocardial repolarization using parameters such as QT interval first and then Tp-e interval and QRS-T angle [11]. As previously known, increased QT and QTc values can result in malignant arrhythmias and sudden cardiac death [12, 13]. Although the measurement of the QT interval and the calculation of the Tp-e interval are not easy, they are unlikely to be repeated. Hence, researchers have started to use the fQRS-T angle, which both shows ventricular repolarization and is automatically calculated by the devices in ECG because of its repeatability [14]. The QRS angle is easily and reproducibly calculated as the difference of the automatically calculated QRS and T-angles in the frontal plane [15]. The fQRS-T angle can be affected by the variables in the action potential. The fQRS-T angle is safer in clinical use compared to the QT interval [16]. Various studies were performed, especially on ventricular repolarization, and a study by Mayet et al. [17] found QTc to be longer in left ventricular hypertrophy (LVH). Using a different method, Zülküf et al. [9] found that the reflection of these parameters, which indicate repolarization, on the ECG significantly increased the fQRS-T angle in patients with LVH. Excluding those with ECG findings suggesting left ventricular hypertrophy in our study renders the increased QTc values more significant. Parameters indicating myocardial repolarization are closely associated with ventricular arrhythmias and mortality [18]. This may cause myocardial damage and subsequent fatal arrhythmias in Covid-19 infection [12]. To the best of our knowledge, there is no study in which QTc, Tp-e, and fQRS-T values are examined together in patients with Covid-19 infection. This study investigated the potential for ventricular repolarization abnormality and arrhythmia with myocardial damage after Covid-19 infection. This finding may be important for the approach to arrhythmias associated with Covid-19. Sinus tachycardia and ST-T changes are observed in most of these patients [19]. Again, Bertini et al. [20] detected atrial fibrillation in 22% of those who had palpitations among those who had Covid-19 infection. The increase in QTc, Tp-e interval, and fQRS-T-angle, which are indicators of myocardial repolarization observed in the ECG in our study, may cause arrhythmic events. Conduction, repolarization abnormalities, and ventricular arrhythmias, including ECG changes such as QTc prolongation, may reflect myocardial injury directly or indirectly associated with Covid-19 pneumonia [21]. fQRS, another parameter examined in our study, reflects non-specific myocardial depolarization and is an indicator of myocardial fibrosis on the ECG. In a study conducted by HA Barman et al., fQRS was observed more frequently in patients who needed intensive care, but this was associated with cardiac damage and mortality [21]. While fQRS was significant in intergroup variables in our study, its absence in multivariate analysis suggests that acute myocardial damage may heal over time or that depolarization abnormality that does not progress to fibrosis is reversible.

Limitations

Although we obtained crucial findings in our study, there are some limitations, some of which are the need for more patients, and the wide age distribution. Also, our control group was not similar to the COVID-19 group regarding gender and smoking frequency distribution, which causes a limitation. However, since both gender and smoking status were stated as risk factors in some literature studies, we did not form the control group in a matched way concerning these factors, and our results were in accordance with the literature in general. In addition, we tried to find out how effective these variables were by performing multivariate analyses. We reduced the likelihood of bias that could occur consequently.

Conclusion

In conclusion, the increase in QTc, Tp-e, and fQRS-T values in those who had Covid-19 infection, especially in those admitted with palpitations, may cause cardiac events that may result in malignant arrhythmias after ventricular repolarization abnormality.

References

1. Mehraeen E, SeyedAlinaghi S, Nowroozi A, Dadras O, Alilou S, Shobeiri P, et al. A systematic review of ECG findings in patients with Covid-19. Indian Heart Journal. 2020;72(6):500-7
2. He J, Wu B, Chen Y, Tang J, Liu Q, Zhou S, et al. Characteristic electrocardiographic manifestations in patients with Covid-19. Canadian Journal of Cardiology. 2020;36(6):966.
3. Cheng ZJ, Shan J. 2019 Novel coronavirus: where we are and what we know. Infection. 2020;48(2):155-63.
4. Kaya BC, Çekici Y, Berna K, Çelik A, Demir HA, Sahin NY. A prospective study on the relationship between Covid-19 disease progress and cardiovascular damage. Journal of Surgery and Medicine. 2021;5(4):322-6.
5. Zheng Y-Y, Ma Y-T, Zhang J-Y, Xie X. Covid-19 and the cardiovascular system. Nature Reviews Cardiology. 2020;17(5):259-60.
6. Long B, Brady WJ, Bridwell RE, Ramzy M, Montrief T, Singh M, et al. Electrocardiographic manifestations of Covid-19. The American Journal of Emergency Medicine. 2020;41:96-103
7. Panikkath R, Reinier K, Uy-Evanado A, Teodorescu C, Hattenhauer J, Mariani R, et al. Prolonged Tpeak-to-tend interval on the resting ECG is associated with increased risk of sudden cardiac death. Circulation: Arrhythmia and Electrophysiology. 2011;4(4):441-7.
8. Öztürk F, Karaduman M, Çoldur R, İncecik Ş, Güneş Y, Tuncer M. Interpretation of arrhythmogenic effects of Covid-19 disease through ECG. The Aging Male. 2020;23(5):1362-5.
9. Tanrıverdi Z, Beşli F, Güngören F, Attıparmak İH, Yeşilay AB, Erkuş ME, ve ark. Esansiyel hipertansiyonlu hastalarda sol ventrikül hipertrofisinin bir göstergesi olarak frontal QRS-T açısı. Dokuz Eylül Üniversitesi Tıp Fakültesi Dergisi.32(2):77-87.
10. Eyüboğlu M, Akdeniz B. Fragmente QRS kompleksleri koroner anjiyografi uygulanan stabil koroner arter hastalarında daha yüksek Gensini skorunu öngördürmektedir. Ege Tıp Dergisi. 2018;57(2):71-4.
11. Kors JA, van Eck HJR, van Herpen G. The meaning of the Tp-Te interval and its diagnostic value. Journal of electrocardiology. 2008;41(6):575-80.
12. Han H, Xie L, Liu R, Yang J, Liu F, Wu K, et al. Analysis of heart injury laboratory parameters in 273 Covid-19 patients in one hospital in Wuhan, China. Journal of medical virology. 2020;92(7):819-23.
13. Sinkeler F, Berger F, Muntinga H, Jansen M. The risk of QTc-interval prolongation in Covid-19 patients treated with chloroquine. Netherlands Heart Journal. 2020;28(7):418-23.
14. Oehler A, Feldman T, Henrikson CA, Tereshchenko LG. QRS-T angle: a review. Annals of Noninvasive Electrocardiology. 2014;19(6):534-42.
15. Macfarlane PW. The frontal plane QRS-T angle. Oxford University Press; 2012;14(6):773-5
16. Raposeiras-Roubín S, Virgós-Lamela A, Bouzas-Cruz N, López-López A, Castiñeira-Busto M, Fernández-Garda R, et al. Usefulness of the QRS-T angle to improve long-term risk stratification of patients with acute myocardial infarction and depressed left ventricular ejection fraction. The American journal of cardiology. 2014;113(8):1312-9.
17. Mayet J, Shahi M, McGrath K, Poulter NR, Sever PS, Foale RA, et al. Left ventricular hypertrophy and QT dispersion in hypertension. Hypertension. 1996;28(5):791-6.
18. Kaplan Ö, İzmir Güner Ş. Lösemi Hastalarında Kemoterapötiklerin Frontal QRS-T Açısı Üzerine Etkisi. Kocaeli Tıp Dergisi. 2020;9(2):14-9.
19. Bergamaschi L, D'Angelo EC, Paolisso P, Toniolo S, Fabrizio M, Angeli F, et al. The value of ECG changes in risk stratification of Covid-19 patients. Annals of Noninvasive Electrocardiology. 2021;26(3):12815.
20. Bertini M, Ferrari R, Guardigli G, Malagu M, Vitali F, Zucchetti O. Electrocardiographic 636 features of 431 consecutive, critically ill Covid-19 patients: an insight into the mechanisms of cardiac 637 involvement. ESC. 2020;22(12):1848-54
21. Haseeb S, Gul EE, Çinier G, Bazoukis G, Alvarez-Garcia J, Garcia-Zamora S, et al. Value of electrocardiography in coronavirus disease 2019 Covid-19. Journal of Electrocardiology. 2020;62:39-45.

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Research article

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Our experience of treating children with primary monosymptomatic enuresis nocturna in a pediatric bedwetting clinic

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Ethics Committee Approval
Kahramanmaras Sutcu Imam University Faculty of Medicine Non-invasive Clinical Research Ethics Committee, Date, no: 17.08.2021 decision no: 07, session: 2021/26.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Enuresis nocturna is an important problem that negatively affects the self-confidence and quality of life of millions of children. Controversial points still exist regarding the treatment algorithm of enuresis. This study aimed to discuss the approach to this condition which deeply affects the child and their family and contribute to the literature by analyzing the success in the treatment steps.
Methods: This study was conducted by reviewing the files of the patients who presented to the pediatric bedwetting outpatient clinic between May 2017 and March 2019 with the complaint of nocturia. The diagnoses and treatment outcomes were recorded from the patient files. The first step was motivation therapy, the second step was alarm treatment, and the third step was drug therapy, which were combined if necessary.
Results: Among 95 primary monosymptomatic enuresis nocturna patients with a mean age of 8.5 years, all patients received supportive treatment to increase motivation as the first step. The second step consisted of alarm treatment administered to 32 patients and as the third step, medical drug treatment was prescribed to eight. Enuresis decreased in 58% of the patients receiving motivation therapy, 63% of the patients receiving alarm therapy and >90% of the patients receiving drug therapy; however, it relapsed when the medication was discontinued.
Conclusion: According to the experience acquired in this study, a specific enuresis polyclinic is important in terms of ease of presentation for patients, and motivation treatment should be the first line of treatment. Other treatment steps can be added as necessary. All three steps in primary monosymptomatic enuresis nocturna can be combined or administered alone.

Keywords: Enuresis, Bedwetting clinic, Children, Treatment

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Introduction

Enuresis is defined as involuntary urination while asleep for no organic reason and is inappropriate in a child older than 5-7 years, which is considered the age of developing urinary control [1-3]. Enuresis nocturna is seen in approximately 25% of children aged 5 years, and with a spontaneous recovery rate of 15% each year, this rate falls to <10% at the age of 7 years [4]. Monosymptomatic enuresis indicates involuntary urination [4-6]. Polysymptomatic enuresis refers to the presence of an added lower urinary system symptom, such as the patient feeling urgency, frequent urination, dysuria, or dripping [4].

Primary enuresis nocturna is defined as the child not having had a dry night for at least 6 months, and secondary enuresis originates from the onset of a new medical condition such as urinary infection, obstructive sleep apnea, diabetes insipidus, diabetes mellitus, hypothyroidism, kidney disease, or a new psychological stress [7-9]. Primary monosymptomatic enuresis nocturna (PMEN) cases constitute more than 80% of all enuresis patients [4, 6].

PMEN leads to problems affecting both the child and their family. Children with PMEN may not wish to see a doctor because of guilt and shame as a result of psychological pressure from the family. The most important step in the treatment of monosymptomatic enuresis nocturna is making enough time for the patient and motivating the child and family to follow the treatment. To achieve this, it is necessary to form a good relationship with the child. When it is explained that there is nothing to be ashamed of and the patient and the family are reassured that it will get better, the patient relaxes and has increased motivation for treatment. Treatment consists of non-pharmacological approaches such as behavioral interventions, alarm devices, bladder exercises, and treatment for constipation if present. Pharmacological agents include desmopressin, tricyclic anti-depressants, and anti-cholinergic medication [3].

The aim of this study was to discuss the treatment approach to patients who presented to the pediatric bedwetting outpatient clinic and were diagnosed with PMEN, and to contribute to the literature by analyzing the success in the treatment steps.

Materials and methods

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethics approval was obtained from the tertiary university hospital ethics committee before starting the study (Ethical Committee Approval Number: 07/26/2021).

A retrospective examination was made of the files of 108 patients aged 6-18 years who presented to the pediatric bedwetting outpatient clinic between May 2017 and March 2019 with the complaint of nocturia. A total of 13 patients with secondary or polysymptomatic enuresis nocturna were excluded from the study. Ninety-five patients over the age of 6 years whose only symptom was urination during sleep were included in the study with the diagnosis of PMEN. The anamnesis, physical examination and ultrasound findings of the patients were recorded from the files, together with the treatment protocols applied and the outcomes during follow-up. Following the described treatment protocol and current guidelines [3], the treatment consisted of three stages: The first stage was behavioral and supportive treatment (encouraging communication, giving rewards when the number of dry wakes increases, etc.), the second stage was alarm treatment, and the third stage was drug (only desmopressin) prescription. Other medications were not used due to side effects. The next stage was tried if unsuccessful in the prior stages, or the treatment steps were combined. The age, gender, and treatment outcomes of the patients were recorded, and the results were evaluated.

Statistical analysis

Statistical analysis was conducted using the Statistical Package for the Social Sciences for Windows (SPSS Inc., Chicago) 22 package program. Variables were expressed as mean (standard deviation) or minimum-maximum. Proportional data about the children were expressed as numbers (n) and percentages (%).

Results

Evaluation was made of a total of 95 patients diagnosed with PMEN, comprising 63 (66%) males and 32 (34%) females with a mean age of 8.5 years (range, 6-18 years). The physical examination, urine examination and urinary system ultrasound examination results were normal in all patients before beginning the treatment. As the first step, all the patients received behavioral therapy, fluid was restricted, and all patients underwent detailed motivational interviews. Alarm treatment was the second stage. The use of the alarm was explained to the family, who used it at their discretion. A total of 32 (34%) patients used the alarm devices. As the third stage, desmopressin was prescribed to 8 (8.4%) patients who attended boarding school. There was no patient who received alarm and drug therapy together.

In all 55 (58%) patients who only received first-stage treatment, the frequency of urination decreased from the first week onwards in all cases, but because of an increase again after 6-8 weeks, there was a request for a further motivational interview. Of the patients who received first and second stage treatment, 20/32 (63%) reported benefit from the alarm treatment, and in these patients there was no loss of motivation and subsequent request for a further motivational interview. In the third stage treatment, desmopressin was used for 3 months, after which the frequency of urination decreased by >90% in all the patients. After terminating the desmopressin treatment, the frequency of urination increased. No drugs other than desmopressin were used. Difficulty in waking from sleep was reported by 82 (86%) patients and not by 13 (14%). There was a history of PMEN in at least one parent of 53 (56%) patients.

Discussion

Enuresis is not only a disease affecting millions of children worldwide, with negative effects on self-confidence and quality of life, but also constitutes a social problem [3]. Involuntary urination creates a feeling of embarrassment in children and they do not wish anyone outside the family to know of it. Treatment of PMEN patients has been attempted by physicians of several branches [3]. To raise awareness and to be able to persuade children to consult doctors comfortably, we

designed a "pediatric bedwetting outpatient clinic" within the Pediatric Surgery Outpatient Clinic. The patients and their parents stated that their concerns about the department and physician to which they should apply were eliminated because of this separate outpatient clinic. The establishment of such a specialized clinic in hospitals will be more useful for PMEN patients than the main branch polyclinics.

It has been reported that when one of the parents has a history of PMEN, the likelihood of seeing it in the child is 44%, and this rate increases to 77% when there is such a history in both parents [3]. In the current study, 56% of the patients had at least one parent with a history of PMEN.

PMEN is considered a benign disease that does not require comprehensive investigation. The most important approach is the taking a detailed history and performing a thorough physical examination during the first evaluation. The American Pediatric Academy and the International Child Continence Association do not recommend routine renal ultrasound in children who present with PMEN [10]. In some publications, urine analysis and/or a bladder diary have been suggested [3-8]. Kovacevic et al. [10] reported that according to their clinical experience, the use of urine analysis as a single test in children with PMEN was generally worrying for parents as they wished to discount anatomic disorders in the urinary tract. All patients in the current study underwent urine analysis and a urinary ultrasound, which turned out normal. Performing these tests in addition to a detailed history and physical examination is debatable and it has been suggested that there is no need for further investigation.

Success in PMEN treatment is the correct diagnosis of the underlying agent. After a diagnosis of PMEN, the child should be talked to and evaluated with at least one of the parents present. Various studies suggest that it should be explained to the child in a comprehensible way that this condition is not a fault of the child, there is no shame, it is extremely common in children and will recover as the child grows [3, 4]. All patients in the current study underwent interviews to motivate and increase the self-confidence of the child. The parents reported that after each interview, the urination reduced.

In recent years, alarm treatment is used extremely frequently, either alone or in combination and as the first option in treatment [11]. Alarm treatment has been reported to condition the nervous system and can increase bladder capacity [3, 12]. When alarm treatment is used regularly for a sufficient period, a success rate of 75% has been reported [3]. However, problems can be experienced such as the family not adapting to the alarm device and abandoning the treatment. In the current study, the use of alarm treatment and the outcomes were explained to the families, who used it at their discretion. In 32 patients, alarm treatment was administered throughout 3 months in addition to the supportive motivation treatment. Of those who used the alarm treatment, 20 (62.5%) reported that they had seen a benefit in the form of staying dry for 2 consecutive weeks.

Pharmacological drugs are recommended as the third line PMEN treatment, and include desmopressin, anti-cholinergic agents, and tricyclic anti-depressants [11, 13]. The efficacy of drug treatments alone or in combination is not clear [3, 13]. Desmopressin was administered to eight of the current study patients who attended boarding school, as the onset of the effect of this drug is rapid and it has a lower side-effect profile than other drugs. Adolescents at boarding school are embarrassed by their peers but with the early effect of desmopressin taken one hour before going to bed, the number of dry nights increased. However, when desmopressin was discontinued, the frequency of bedwetting increased again.

Alternative treatment methods such as acupuncture, hypnosis, and psychotherapy are also used in PMEN treatment, albeit not routinely. No alternative treatment was given to any of the patients in this study.

Limitations of this study include its retrospective design and the relatively low number of patients. There is a need for further, prospective comparative studies with a greater number of patients.

Conclusion

The status of the patient and their family must be taken into consideration in the selection of treatment. Based on our experience, a specific enuresis outpatient clinic is important in terms of ease of presentation, and motivation treatment should be the first line treatment, with other treatment steps added as necessary. All three steps in PMEN treatment can be administered combined or alone.

References

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., (DSM-5). Washington, DC: American Psychiatric Publishing; 2013.
2. Neveus T, von Gontard A, Hoebeke P, Hjälmås K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol. 2006;176(1):314–24. doi: 10.1016/S0022-5347(06)00305-3.
3. Önen A, Günşar C, Alkan M, Karaman A. Çocuk Ürolojisi. In: Avlan D, eds. Enurezis. İzmir, US akademi, 2021, pp:221-230.
4. Walker RA. Nocturnal Enuresis, Prim Care Clin Office Pract. 2019;46:243–8.
5. Haque M, Ellerstein NS, Grundy JH, Shelov SP, Weiss JC, McIntire MS, et al. Parental perceptions of enuresis: A collaborative study. Am J Dis Child. 1981;135:809-11.
6. Oğraş MS, Ağlamış E, Yücel MÖ, Taşdemir C, Selçuk EB. Treatment and follow up results of patients with monosymptomatic enuresis nocturna. Dicle Med J. 2013;40(3):410-3.
7. Vande Walle J, Rittig S, Bauer S, Eggert P, Marschall -Kehrel D, Tekdul S, et al, Practical consensus guidelines for the management of enuresis. Eur J Pediatr. 2012;171:971–83. doi: 10.1007/s00431-012-1687-7.
8. Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgul S, et al. Evaluation of and treatment for monosymptomatic enuresis: a standardization document from the International Children's Incontinence Society. J Urol. 2010;183:441. doi: 10.1016/j.juro.2009.10.043.
9. Robson WL, Leung AK. Secondary Nocturnal Enuresis. Clin Pediatr (Phila). 2000;39:379. doi: 10.1177/000992280003900701.
10. Kovacevic L, Wolfe-Christensen C, Mirkovic J, Yih J, Lakshmanan Y. Renal bladder ultrasound evaluation in monosymptomatic primary nocturnal enuresis: is it really necessary? Pediatr Nephrol. 2014;29(7):1189-94. doi 10.1007/s00467-013-2742-y.
11. Glazener CMA, Evans JHC,Peto RE. Alarm interventions for nocturnal enuresis in children. Cochrane Database Syst Rev. 2005,2:CD002911. doi: 10.1002/14651858.CD002911.pub2.
12. Taneli C, Ertan P, Taneli F, Genc A, Günsar C, Sencan A, et al. Effect of alarm treatment on bladder storagec capacities in monosymtomatic nocturnal enuresis. Scand J Urol Nephrol. 2004;38:(3):207-10. doi: 10.1080/00365590310022653.
13. Austi PF, Ferguson G, Yan Y, Campigotto MJ, E Royer M, E Coplen D. Combination therapy with desmopressin and an anticholinegic medication for nonresponders to desmopressinfor monosymptomatic nocturnal enuresis: a randomized, double-blind, placebo-controlled trial. Pediatrics. 2008;122:1027-32. doi: 10.1542/peds.2007-3691.

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The effect of the Covid-19 outbreak on the management of acute appendicitis: A retrospective comparative cohort study

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Abstract

Background/Aim: Covid-19 pandemic (Cov19) has affected the world since December 2019. The management of acute appendicitis (AA) has also changed distinctly during the Cov19 outbreak. The aim of this study is to evaluate and compare the results of AA during the pre-pandemic period and the first wave of the Cov19 outbreak.

Methods: Patients diagnosed with AA from March to July 2019 (pre-pandemic, 2019), and from March to July 2020 (first wave of the pandemic, 2020) were included in this study, and evaluated for age, gender, nationality, length of stay (LOS), ultrasonography (USG), computed tomography (CT) findings, C-reactive protein level (CRP), white blood cell count (WBC), treatment results, operation type, and pathological examination results retrospectively.

Results: One hundred patients from 2019, and seventy-seven patients from 2020 were included in the study. The male ratio, false negative USG, number of CTs performed (especially among conservatively treated patients), CRP levels, the rate of conservative treatment were higher, and LOS was longer among patients treated in 2020 ($P<0.05$ for all). In 2019, 91.8% of the AA operations were performed laparoscopically, whereas in 2020, 73.2% of them were open operations ($P<0.001$). Complicated AA was more frequent in 2019 than in 2020 (12.2% vs 9.8%).

Conclusion: During the Cov19 pandemic, a longer LOS, and a higher ratio of male to female AA patients were observed. CT was more useful during the Cov19 pandemic for diagnosing AA and especially for choosing the suitable patients for conservative treatment. Conservative treatment was preferred more frequently than surgery with a lower recurrence rate in selected uncomplicated patients; and for surgery, the open technique was preferred more frequently during the Cov19 pandemic.

Keywords: Acute appendicitis, Covid-19 pandemic, Conservative treatment, Appendectomy

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Ethics Committee Approval
The ethics committee of Prof. Dr Cemil Taşçıoğlu City Hospital (16 June 2020 date and 249 number)
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Introduction

Covid 19 (Cov19) pandemic, which started in December 2019 in Wuhan, China, affected the world from January 2020 until today. All healthcare services and staff had to deal with Cov19 patients due to the high intensity and severity of disease. Curfew, the flexible working hours of health institutions and the risk of Cov19 contamination from hospitals caused decreased admission of patients to the hospital and increased the number of more complicated diseases [1]. In addition, treatment algorithms of surgery, as well as emergency surgery, were changed to protect the patients, health professionals and critical resources, namely, hospital and intensive care unit (ICU) beds [2].

Acute appendicitis (AA) is the most common emergency surgery disease and mostly treated with surgical intervention. Detailed examination and imaging have become more important and difficult due to complaint of abdominal pain, vomiting, diarrhea, and fever which are the gastrointestinal symptoms of Cov19 as well as AA [3]. Appendectomy is the surgical treatment of AA and is performed with the open (OA) or laparoscopic (LA) methods. LA has fewer wound infections and post-operative pain, shorter length of hospital stays and earlier return to work; however, the intra-abdominal abscess rate is higher than OA. Conservative treatment of acute appendicitis is recommended in selected uncomplicated patients with 41-85% effectiveness and 20% recurrence rate [4]. Conservative treatment or OA was recommended during the initial stages of the Cov19 outbreak by some study groups [5]. This study aimed to compare the differences in the management of acute appendicitis during the Cov19 pandemic with the same period a year ago.

Materials and methods

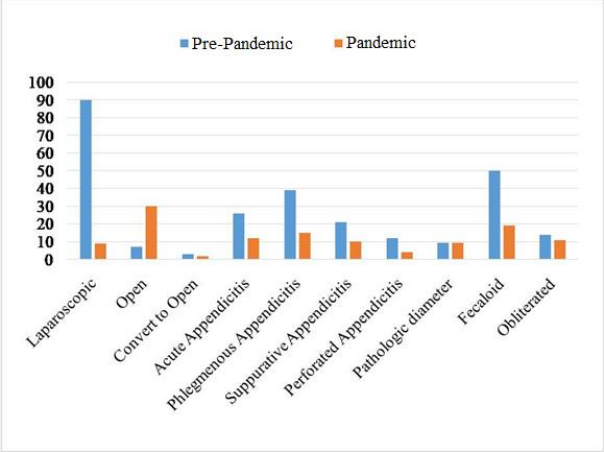
After receiving institutional approval from the ethics committee of Prof. Dr Cemil Taşçıoğlu City Hospital (16 June 2020 date and 249 number), the accessible records of AA patients from March 2019 to July 2019, and from March 2020 to July 2020, were evaluated retrospectively.

The period from March to July 2020, the first wave of the Cov19 pandemic, is hereinafter referred to as the pandemic, and the one from March to July 2019, the same period a year ago, is hereinafter referred to as the pre-pandemic period.

Patients' age, gender, nationality, length of hospital stays (LOS), ultrasonography (USG), and computed tomography (CT) findings, white blood cell (WBC) count, C-reactive protein (CRP) levels, and treatment were evaluated in terms of the pandemic and the pre-pandemic period retrospectively. The nationality criterion was classified as a citizen or a noncitizen. USG and CT criteria were classified as not performed, performed but negative, performed and positive, and the diameter of appendix was evaluated from the USG or the CT result. Treatment was evaluated as conservative or operated. Patients' results were evaluated according to the treatment type in the pandemic and the pre-pandemic period.

Operated patients were additionally evaluated according to the operation type, pathology, pathological diameter of the appendix, luminal pathology, and additional pathology comparing the pandemic and the pre-pandemic periods (Figure 1). The operation type was evaluated as laparoscopic, open, or laparoscopic converted to open. Pathological examination results were categorized as acute appendicitis, phlegmonous appendicitis, suppurative appendicitis and complicated appendicitis (appendicitis which is complicated by a local or contained perforation with an appendiceal abscess or mass formation). Luminal pathology was evaluated as fecaloid and obliterated. Additional pathology was evaluated as neuroma, serrated adenoma, diverticulum, and neuroendocrine tumor.

Figure 1: Surgical and pathological results of operated patients by period



Statistical analysis

Statistical analysis was performed with SPSS 16.0 (Chicago, SPSS Inc.). Age (years), LOS (days), USG diameter (mm), CT diameter (mm), CRP (mg/dl), WBC (10^6/uL), and pathological diameter (mm) were presented as mean (SD). Nonparametric values were evaluated with the Mann Whitney U test, and parametric values were evaluated with the t-test. $P<0.05$ was considered significant.

Results

One hundred patients from the pre-pandemic period and seventy-seven patients from the pandemic were included in the study. The mean age was 34.4 (13.9) in the pre-pandemic period, and 34.7 (15.7) during the pandemic ($P=0.87$). During the pandemic, the percentage of male patients was higher, and the percentage of noncitizen patients was lower. The mean LOS was 1.45 (1.1) days in the pre-pandemic period, and 2.48 (1.8) days during the pandemic. The difference in gender distribution, nationality and LOS were significant ($P=0.002$, $P=0.024$, and $P<0.001$ respectively) (Table 1). While USG was preferred more often in the pre-pandemic period, CT was preferred more often during the pandemic (Table 1). There was no significant difference in the mean appendix diameter on USG and CT between the two periods ($P=0.394$, and $P=0.157$ for USG and CT results respectively) (Table 1). The mean CRP in the pre-pandemic and pandemic periods were 56.7 (75.1) mg/dl and 93.4 (97.9) mg/dl, respectively ($P=0.006$). There was no significant difference in WBC counts between the pre-pandemic and pandemic periods (Table 1).

Table 1: The results of patients by period

Parameters	Pre-pandemic		Pandemic		*P*-value
Age*	34.4(13.9)		34.7 (15.7)		0.87
Gender	n	%	n	%	0.002
Female	38	38	13	16.9	
Male	62	62	64	83.1	
Nationality	n	%	n	%	0.024
Citizens	82	82	72	93.5	
Noncitizens	18	18	5	6.5	
LOS*	1.45 (1.1)		2.48 (1.8)		<0.001
USG	n	%	n	%	0.001
Not Performed	0	0	6	7.8	
Performed	100	100	71	92.2	
USG Diameter*	9.5 (2.1)		9.9 (3.3)		0.394
CT	n	%	n	%	<0.001
Not Performed	57	57	21	27.3	
Performed	43	43	56	72.3	
CT Diameter*	11.5 (2.8)		10 (4.1)		0.157
WBC*	15.1 (4.4)		14.6 (4.3)		0.51
CRP*	56.7 (75.1)		93.4 (97.9)		0.006
Treatment	n	%	n	%	<0.001
Conservative	2	2	36	46.8	
Operated	98	98	41	53.2	

*Median (standard deviation), LOS: Length of Stay, USG: Ultrasonography, CT: Computed Tomography, WBC: White Blood Cell, CRP: C-Reactive Protein

In the pre-pandemic period, the mean age of the conservatively treated patients was 63.5 (7.8) years, while that of the operated ones was 33.8 (13.3) years. The difference in age was statistically significant (*P*=0.002). There was no significant difference in gender, nationality, and LOS between the conservatively treated and operated patients during this period (Table 2). None (0/2) of the conservative, 27.3% (27/98) of the operated had negative USG findings (*P*=0.549). None (0/2) of the conservative and 58.2% (57/98) of the operated had no CT; 0% (0/2) of the conservative, 7.3% (3/41) of the operated had negative CT findings (*P*=0.162). There was no significant difference in the mean appendix diameter in USG and CT, WBC levels, and CRP levels between the conservatively treated and operated patients (*P*=0.771, *P*=0.443, *P*=0.185, and *P*=0.668 respectively) (Table 2).

During the pandemic, there was no significant difference in age, gender, nationality, or LOS between the conservatively treated and operated patients. 8.3% (n=3) of the conservative, 7.3% (n=3) of the operated had no USG; 42.4% (14/33) of the conservative, 44.7% (17/38) of the operated had negative USG findings (*P*=0.936). Four (11.1%) of the conservative and 41.5% (n=17) of the operated had no CT; 12.5% (4/32) of the conservative, 12.5% (3/24) of the operated had negative CT findings. The difference in those without CTs was statistically significant (*P*=0.007). Like it was the case in the pre-pandemic period, there was no significant difference in the mean appendix diameter in USG and CT, WBC levels, and CRP levels between the conservatively treated and operated patients (*P*=0231, *P*=0.854, *P*=0.069, and *P*=0.441 respectively) (Table 2).

Table 2: The results of patients by period with treatments

Parameters	Pre-Pandemic				Pandemic				
	Conservative		Operated		*P*	Conservative		Operated		*P*
Age*	63.(7.8)		33.8 (13.3)		0.002	38.3 (17.9)		31.6 (12.8)		0.063
Gender	n	%	n	%	0.782	n	%	n	%	0.208
Female	1	50	37	37.8		4	11.1	9	22.0	
Male	1	50	61	62.2		32	88.9	32	78.0	
Nationality	n	%	%	%	0.679	n	%	n	%	0.542
Citizens	2	100	80	81.6		33	91.7	39	95.1	
Noncitizens	0	0	18	18.4		3	8.3	2	4.9	
LOS*	1.5 (0.7)		1.45 (1.1)		0.947	2.81 (1.6)		2.2 (1.8)		0.133
USG	n	%	n	%	0.549	n	%	n	%	0.936
Not Performed	0	0	0	0,0		3	8.3	3	7.3	
Performed	2	100	98	100		33	91.7	38	92.7	
USG Diameter*	9.1 (1.3)		9.5 (2.1)		0.771	9.3 (1.6)		10.6 (4.3)		0.231
CT	n	%	n	%	0.162	n	%	n	%	0.007
Not Performed	0	0	57	58.2		4	11.1	17	41.5	
Performed	2	100	41	41.8		32	88.9	24	58.5	
CT Diameter*	10 (1.4)		11.6 (2.9)		0.443	9.9 (4.1)		10.1 (4.3)		0.854
WBC*	11 (0.4)		15.1 (4.4)		0.185	13.7 (3.5)		15.5 (4.8)		0.069
CRP*	34.1 (40)		57.2 (75.7)		0.668	102.6 (82.8)		85.1 (110)		0.441

* Mean (Standard Derivation), LOS: Length of Stay, USG: Ultrasonography, CT: Computed Tomography, WBC: White Blood Cell, CRP: C-Reactive Protein

Evaluation of the results of operated patients by period revealed that 91.8% (n=90) in the pre-pandemic period had LA, whereas 73.2% (n=30) in the pandemic had OA (*P*<0.001) (Table 3).

Out of the conservatively treated patients during the pandemic, only two patients (5.5%) had recurrence in the 6 months that followed the treatment. More specifically, one recurred in 13 days, and the other in 29 days. Both patients were treated conservatively again.

The occurrence rate of any of the evaluated pathologies, namely, perforated appendicitis (*P*=0.818), obliterated appendicitis or fecaloid (*P*=0.13), and diameter of appendix (*P*=0.925) were similar between the two periods. The pathology results by period are shown in Table 3.

Table 3: The results of operated patients by period

Parameters	Pre-Pandemic		Pandemic		*P*-value
Type of operation	n	%	n	%	<0.001
Laparoscopic	90	91.8	9	22	
Open	7	7.1	30	73.2	
Laparoscopic convert open	3	3.1	2	4.8	
Pathology	n	%	n	%	0.818
Acute appendicitis	26	26.5	12	29.3	
Phlegmonous appendicitis	39	39.8	15	36.6	
Suppurative appendicitis	21	21.4	10	24.4	
Perforated appendicitis	12	12.2	4	9.8	
Pathologic diameter *	9.4 (2.3)		9.5 (3)		0.925
Luminal pathology	n	%	n	%	0.13
Fecaloid	50	51	19	46.3	
Obliterated	14	14.3	11	26.8	
Added pathology	n	%	n	%	0.004
Neuroma	0	0	1	2.4	
Serrated adenoma	1	1	2	4.9	
Diverticulum	0	0	4	9.8	
Neuroendocrine tumor	1	1	0	0	

* Mean (Standard Derivation)

Discussion

Appendicitis occurs with luminal obstruction of the appendix by lymphoid hyperplasia (related to viral illnesses, upper respiratory infection, mononucleosis, and gastroenteritis), appendicoliths, parasites, foreign bodies, Crohn's disease, cancers or carcinoid syndrome [6]. Appendicitis which occurs by lymphoid hyperplasia or spontaneous passage of appendicolith can heal without an appendectomy [7]. However, phlegmonous, suppurative, or complicated appendicitis (gangrenous, perforated or with abscess) require appendectomy [8].

The most common emergency surgical disease was AA with 31.84%, followed by anal abscess with 13.8%, and acute cholecystitis with 9.45% during the first wave of the Cov19 pandemic [9]. Tankel et al. [10] reported a decreasing incidence of AA during Cov19. During the Cov19 pandemic, the ratio of AA patients to the total number of patients admitted to the emergency department increased (1.35% (77/5707) vs. 1.16% (100/8624)) in our hospital.

Romero et al. [11] and Finkelstein et al. [12] reported the mean age as 38.2 and 41 years, respectively, in the pre-pandemic period, and as 36.6 and 44 years, respectively, during the pandemic. They stated that female was the most common gender with 52% and 73%, respectively, before the pandemic, and 56% and 61.8%, respectively, during the pandemic. There was no significant difference in terms of age and gender in the comparative studies about AA during the Cov19 pandemic. Also, there was no difference in the mean age of acute care surgery patients between the pre-pandemic and pandemic periods; however, there was a significant change in the most common

gender between the periods with female being the most common gender with 50.9% before the pandemic, but male being the most common gender with 66.6% during pandemic [9]. There was no difference in terms of age and gender (higher male ratio) between the conservatively treated or operated patients by period [13, 14]. The rate of noncitizen AA patients our previous study was 15.1% (95/628) from 2014 to 2018 [15].

In our study the mean age was 34.4 (13.9) in the pre-pandemic, and 34.7 (15.7) in the pandemic period. There was no difference in age between conservatively treated and operated patients during the pandemic; however, conservatively treated patients were older before the pandemic. Eighteen percent (n=18) and 6.5% (n=5) of the patients were non-citizens during the pre-pandemic and pandemic periods, respectively. Third decade and male gender were the risk groups of AA during the pandemic for both conservatively treated and operated patients. Travel bans significantly decreased the rate of noncitizen AA patients during the pandemic.

Lower length of hospital stay is desired and favored during the pandemic to decrease the contamination of Cov19 and to empty the beds for a new outbreak. Some studies reported no differences in LOS between these periods [16-17]; however, Kvasnovsky et al. [18] reported a significantly higher LOS for AA during the pandemic. Conservatively treated AA patients had longer LOS than the operated patients in both periods [14, 19]. In our study, LOS was significantly higher among all AA patients during the pandemic. Conservatively treated patients in both periods had insignificantly longer LOS. During the pandemic, the number of conservatively treated patients was higher than the surgically treated, hence, a longer LOS was expected.

History and physical examination are the essential parameters for diagnosing and differential diagnosing acute abdominal pain (AAP) as well as AA with 43-59% accuracy. Plain radiographies have limited indication for diagnosing AAP, USG is the initial imaging with advantages of ease of accessibility, cheaper cost, and safety. The correct diagnosis rates of AAP in USG and CT were 53-83%, and 61.6-96%, respectively. The sensitivity and specificity of diagnosing AA by USG were 76% and 95%, respectively, and 99% and 84%, respectively, for CT imaging [20, 21]. Cov19 has gastrointestinal symptoms which mimic AAP such as AA, and CT becomes more useful and important for diagnosing AA during the Cov19 outbreak [22]. Somers et al. [23] reported that the rate of imaging used for AA was 70.27% in the pre-pandemic, and 89.9% in the pandemic periods. CT was the most common imaging method used for AA with 54.05% during the pre-pandemic, and 69.64% during the pandemic periods; however, USG was used in 10.8% before the pandemic, in 12.5% during the pandemic. Antakia et al. [16] reported a significant decrease in USG use (16.5% vs 24.1%); however, a significant increase was observed in CT use (87.5% vs 69.8%) during the pandemic for AA imaging. The diameter of the appendix being ≥ 7mm was a sign of AA. In our study, USG was performed to all AA patients during the pre-pandemic period but was performed to 92.2% of AA patients in the pandemic with a higher false negativity rate (27% vs 40.3%). CT was performed more frequently during the pandemic (72.3% vs 43%), with higher false negativity rates (12.5% vs 7%). The performance and false negativity rates of USG were similar for the conservatively treated and operated patients in both periods, but CT was preferred more frequently, especially for conservatively treated patients during the pandemic. The diameter of the appendix at both USG and CT during both periods was not a predictor for surgery.

WBC and CRP are the most common inflammatory markers for diagnosis, and also a part of scoring system which is used to diagnose and predict the severity of AA. WBC ≥ $14x10^6$u/l, and CRP > 5mg/dl supports the diagnosis of AA [24]. In previous studies, there is contradicting results for differences in WBC and CRP levels between the two periods. Gannesh et al. [25] reported lower levels of WBC (12.9 vs 13.2 $x10^9$/L), and higher levels of CRP (82 vs 69 mg/dl), but Mai et al. [26] reported higher levels of WBC (14 vs 12.2 $x10^9$/L), and lower levels of CRP (43 vs 56 mg/dl) in AA during the pandemic. Lower WBC and CRP were reported for conservatively treated AA both in the pre-pandemic (14.2 vs 15.3 $x10^9$/L, and 25.9 vs 64.8 mg/dl respectively), and the pandemic periods (12.5 vs 15.9 $x10^9$/L, and 24.5 vs 50 mg/dl respectively) [13, 14]. In our study, overall WBC levels were insignificantly lower during the pandemic, while overall CRP levels were higher. CRP levels were also higher independently for both the conservatively treated and operated patient groups during the pandemic. Another observation was that while in the pre-pandemic period, the mean CRP levels of the operated patients were higher than those of conservatively treated patients, it was the opposite in the pandemic period. However, since the number of conservatively treated patients was only 2 in the pre-pandemic period, no statistical analysis was performed on this observation.

Nonoperative treatment for uncomplicated and selected AA is recommended and have been a part of guidelines, with 27.4% recurrence rate in one year. Hansson et al. [27] reported that AA patients with CRP <60 g/L, WBC <12 × 10^9/L, and age <60 years could be treated conservatively with 89% accuracy [21]. The management algorithms of emergency disease have changed during Cov19 [28, 29]. The management of acute appendicitis involves, if possible, conservative treatment as an outpatient, short hospitalization, operation with an open technique and under regional anesthesia [16]. AA was managed conservatively in 5.4-22.2% of the patients during the pre-pandemic period, which increased to 7.8-100% during the pandemic [30]. In our study, conservative treatment was performed in 46.8% (36/77) of the AA patients with 5.5% (n=2) recurrence rate during the pandemic.

Phlegmonous, suppurative, and complicated AA were treated surgically. LA was performed more frequently than OA for AA recently, with lower postoperative pain, LOS, wound infection, and higher intraabdominal abscess rate. Sixty to eighty percent of the appendectomies were performed laparoscopically in tertiary centers with 1-2 days LOS, and 1-3% complication rate [31]. Javanmard-Emamghissi et al. [32] reported the OA rate as 56.1%, and conversion to open surgery rate as 10.7%; however, Lotfallah et al. [14] reported the OA rate as 35.5% and conversion to open surgery rate as 3.2% during the pandemic. In our study, while 91.2% of the AA underwent LA in the pre-pandemic with 3.1% conversion rate, OA was performed in 72% of the AA patients during the pandemic.

Gao et al. [33] reported an increased rate of complicated appendicitis due to delayed admission or surgery and decreased intention to seek treatment at Cov19. Fonseca et al. [17] reported the rate of complicated AA as 15.2% in the pre-pandemic period, and as 33.3% during the pandemic. In our study, the lower rate of complicated AA and luminal pathology implied the accurate indication and timing of appendectomy during the pandemic.

Limitation

The main limitation of this study was the fact that it was not a prospective randomized controlled trial. The number of conservatively treated patients during the pre-pandemic was only two, therefore, conservatively treated patients could not be evaluated statistically. Also, the differences in the management of AA patients during the initial and later stages of the Cov19 pandemic should be evaluated.

Conclusion

During the first wave of the Cov19 pandemic, the ratio of AA patients to the total number of patients admitted to the emergency department was larger compared to the pre-pandemic period. The mean LOS was longer, and a higher ratio of male to female AA patients was seen in our department. USG had no effect on choosing conservative or surgical treatment; however, CT was particularly useful for the diagnosis of AA and choosing suitable patients for conservative treatment, and it was performed more frequently during the Cov19 pandemic. CRP levels of conservatively treated AA patients increased in the Cov19 pandemic. We saw more patients being treated with no surgery with lower recurrence rates for selected uncomplicated cases during the pandemic. The open surgical technique was performed more often. As a result, even though surgery is the widely accepted method for treating AA for centuries, this study, albeit limited, suggests that in conditions where the resources of a hospital may be limited, the treatment of uncomplicated AA can be managed conservatively with a low recurrence rate.

References

1. Orthopoulos G, Santone E, Izzo F, Tirabassi M, Pérez-Caraballo AM, Corriveau N, et al. Increasing incidence of complicated appendicitis during COVID-19 pandemic. Am J Surg. 2021 May;221(5):1056-60. doi: 10.1016/j.amjsurg.2020.09.026.
2. Coimbra R, Edwards S, Kurihara H, Bass GA, Balogh ZJ, Tilsed J, et al. European Society of Trauma and Emergency Surgery (ESTES) recommendations for trauma and emergency surgery preparation during times of COVID-19 infection. Eur J Trauma Emerg Surg. 2020 Jun;46(3):505-10. doi: 10.1007/s00068-020-01364-7.
3. Zhou Y, Cen LS. Managing acute appendicitis during the COVID-19 pandemic in Jiaxing, China. World J Clin Cases. 2020 Oct 6;8(19):4349-59. doi: 10.12998/wjcc.v8.i19.4349.
4. Gorter RR, Eker HH, Gorter-Stam MA, Abis GS, Acharya A, Ankersmit M, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc. 2016 Nov;30(11):4668-90. doi: 10.1007/s00464-016-5245-7.
5. Ielpo B, Podda M, Pellino G, Pata F, Caruso R, Gravante G, et al.; ACIE Appy Study Collaborative. Global attitudes in the management of acute appendicitis during COVID-19 pandemic: ACIE Appy Study. Br J Surg. 2020 Oct 8:10.1002/bjs.11999. doi: 10.1002/bjs.11999.
6. Hardin DM Jr. Acute appendicitis: review and update. Am Fam Physician. 1999 Nov 1;60(7):2027-34.
7. Hernigou J, Condat B, Giaoui A, Charlier A. Resolution of appendiceal colic following migration of an appendicolith. J Visc Surg. 2014 Sep;151(4):323-5. doi: 10.1016/j.jviscsurg.2014.04.008.
8. Perez KS, Allen SR. Complicated appendicitis and considerations for interval appendectomy. JAAPA. 2018 Sep;31(9):35-41. doi: 10.1097/01.JAA.0000544304.30954.40.
9. Cano-Valderrama O, Morales X, Ferrigni CJ, Martín-Antona E, Turrado V, García A, et al. Acute Care Surgery during the COVID-19 pandemic in Spain: Changes in volume, causes and complications. A multicentre retrospective cohort study. Int J Surg. 2020 Aug; 80:157-61. doi: 10.1016/j.ijsu.2020.07.002. 10.
10. Tankel J, Keinan A, Blich O, Koussa M, Helou B, Shay S, et al.. The Decreasing Incidence of Acute Appendicitis During COVID-19: A Retrospective Multi-centre Study. World J Surg. 2020 Aug;44(8):2458-63. doi: 10.1007/s00268-020-05599-8.
11. Romero J, Valencia S, Guerrero A. Acute Appendicitis During Coronavirus Disease 2019 (COVID-19): Changes in Clinical Presentation and CT Findings. J Am Coll Radiol. 2020 Aug;17(8):1011-3. doi: 10.1016/j.jacr.2020.06.002.
12. Finkelstein P, Picado O, Muddasani K, Wodnicki H, Mesko T, Unger S, et al. A Retrospective Analysis of the Trends in Acute Appendicitis During the COVID-19 Pandemic. J Laparoendosc Adv Surg Tech A. 2021 Mar;31(3):243-6. doi: 10.1089/lap.2020.0749.
13. Talan DA, Saltzman DJ, Mower WR, Krishnadasan A, Jude CM, Amii R, et al.; Olive View–UCLA Appendicitis Study Group. Antibiotics-First Versus Surgery for Appendicitis: A US Pilot Randomized Controlled Trial Allowing Outpatient Antibiotic Management. Ann Emerg Med. 2017 Jul;70(1):1-11.e9. doi: 10.1016/j.annemergmed.2016.08.446.
14. Lotfallah A, Aamery A, Moussa G, Manu M. Surgical Versus Conservative Management of Acute Appendicitis During the COVID-19 Pandemic: A Single-Centre Retrospective Study. Cureus. 2021 Mar 24;13(3):e14095. doi: 10.7759/cureus.14095.
15. Karakaş D, Yeşiltaş M, Gökçek B, Eğin S, Hot S. Is language disability a risk factor for complicated appendicitis? A retrospective cohort study. J Surg Med. 2020;4(8):631-5. doi:10.28982/josam.770774
16. Antakia R, Xanthis A, Georgiades F, Hudson V, Ashcroft J, Rooney S, et al. Acute appendicitis management during the COVID-19 pandemic: A prospective cohort study from a large UK centre. Int J Surg. 2021 Feb;86:32-7. doi: 10.1016/j.ijsu.2020.12.009.
17. Kumaira Fonseca M, Trindade EN, Costa Filho OP, Nácul MP, Seabra AP. Impact of COVID-19 Outbreak on the Emergency Presentation of Acute Appendicitis. Am Surg. 2020 Nov;86(11):1508-12. doi: 10.1177/0003134820972098.
18. Kvasnovsky CL, Shi Y, Rich BS, Glick RD, Soffer SZ, Lipskar AM, et al.. Limiting hospital resources for acute appendicitis in children: Lessons learned from the U.S. epicenter of the COVID-19 pandemic. J Pediatr Surg. 2021 May;56(5):900-4. doi: 10.1016/j.jpedsurg.2020.06.024.
19. Horn CB, Tian D, Bochicchio GV, Turnbull IR. Incidence, demographics, and outcomes of nonoperative management of appendicitis in the United States. J Surg Res. 2018 Mar;223:251-8. doi: 10.1016/j.jss.2017.10.007.
20. Gans SL, Pols MA, Stoker J, Boermeester MA; expert steering group. Guideline for the diagnostic pathway in patients with acute abdominal pain. Dig Surg. 2015;32(1):23-31. doi: 10.1159/000371583.
21. Di Saverio S, Podda M, De Simone B, Ceresoli M, Augustin G, Gori A, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg. 2020 Apr 15;15(1):27. doi: 10.1186/s13017-020-00306-3.
22. Ashcroft J, Hudson VE, Davies RJ. COVID-19 gastrointestinal symptoms mimicking surgical presentations. Ann Med Surg (Lond). 2020 Jun 24;56:108-9. doi: 10.1016/j.amsu.2020.06.025.
23. Somers K, Abd Elwahab S, Raza MZ, O'Grady S, DeMarchi J, Butt A, et al. Impact of the COVID-19 pandemic on management and outcomes in acute appendicitis: Should these new practices be the norm? Surgeon. 2021 Feb 12:S1479-666X(21)00030-5. doi: 10.1016/j.surge.2021.01.009.
24. Wagner M, Tubre DJ, Asensio JA. Evolution and Current Trends in the Management of Acute Appendicitis. Surg Clin North Am. 2018 Oct;98(5):1005-23. doi: 10.1016/j.suc.2018.05.006.
25. Ganesh R, Lucocq J, Ekpete NO, Ain NU, Lim SK, Alwash A, et al. Management of appendicitis during COVID-19 pandemic; short-term outcomes. Scott Med J. 2020 Nov;65(4):144-8. doi: 10.1177/0036933020956316.
26. Mai DVC, Sagar A, Menon NS, Claydon O, Park JY, Down B, et al. A local experience of non-operative management for an appendicitis cohort during COVID-19. Ann Med Surg (Lond). 2021 Mar;63:102-60. doi: 10.1016/j.amsu.2021.02.006.
27. Hansson J, Khorram-Manesh A, Alwindawe A, Lundholm K. A model to select patients who may benefit from antibiotic therapy as the first line treatment of acute appendicitis at high probability. J Gastrointest Surg. 2014 May;18(5):961-7. doi: 10.1007/s11605-013-2413-0.
28. Ehmann MR, Zink EK, Levin AB, Suarez JI, Belcher HME, Daugherty Biddison EL, et al. Operational Recommendations for Scarce Resource Allocation in a Public Health Crisis. Chest. 2021 Mar;159(3):1076-83. doi: 10.1016/j.chest.2020.09.246.
29. Iftikhar M, Shah S, Shah I, Shah JA, Faisal M. Outcomes of Conservative Management of Acute Appendicitis during COVID-19 Pandemic. J Coll Physicians Surg Pak. 2021 Jan;30(1):S50-S54. doi: 10.29271/jcpsp.2021.01.S50.
30. Emile SH, Hamid HKS, Khan SM, Davis GN. Rate of Application and Outcome of Non-operative Management of Acute Appendicitis in the Setting of COVID-19: Systematic Review and Meta-analysis. J Gastrointest Surg. 2021 Mar 26:1–11. doi: 10.1007/s11605-021-04988-1.
31. Flum DR. Clinical practice. Acute appendicitis--appendectomy or the "antibiotics first" strategy. N Engl J Med. 2015 May 14;372(20):1937-43. doi: 10.1056/NEJMcp1215006. Erratum in: N Engl J Med. 2015 Jun 4;372(23):2274.
32. Javanmard-Emamghissi H, Boyd-Carson H, Hollyman M, Doleman B, Adiamah A, Lund JN, et al. COVID: HAREM (Had Appendicitis, Resolved/Recurred Emergency Morbidity/Mortality) Collaborators Group. The management of adult appendicitis during the COVID-19 pandemic: an interim analysis of a UK cohort study. Tech Coloproctol. 2021 Apr;25(4):401-11. doi: 10.1007/s10151-020-02297-4.
33. Gao Z, Li M, Zhou H, Liang Y, Zheng C, Li S, et al. Complicated appendicitis are common during the epidemic period of 2019 novel coronavirus (2019-nCoV). Asian J Surg. 2020 Oct;43(10):1002-5. doi: 10.1016/j.asjsur.2020.07.01.

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Correlation between neck circumference measurement and obesity type with difficult intubation in obese patients undergoing elective surgery

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Ethics Committee Approval
This study was approved by the Marmara University Pendik Training and Research Hospital ethics committee (approval no 09.2021.135). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The number of obese patients undergoing elective surgery is increasing day by day. However, there are conflicting data in the literature about factors predicting difficult tracheal intubation in obese patients. The aim of this study was to evaluate the commonly used predictors of difficult intubation in obese patients (body mass index (BMI) >35 kg/m^2) who wish to undergo elective surgery and to examine the association of neck circumference and obesity type with difficult intubation.

Methods: This observational, cross-sectional, prospective study was performed after obtaining approval from the ethics committee. Obese patients over the age of 18 years, requiring tracheal intubation, undergoing elective surgery, and with a BMI greater than 35 were included in this study. Patients with a history of cervical spine anomaly or trauma, congenital facial anomaly or trauma affecting this region, those who would undergo emergency surgery, patients with a known history of difficult airway or upper respiratory tract disease, and those with planned awake intubation were excluded from the study. Preoperative anesthetic evaluation was performed for all patients, their relevant measurements were obtained, and medical histories were taken as required for the study. The association of the patients' BMI, Mallampati classification, thyromental distance, Cormack–Lehane grade, obstructive sleep apnea, neck circumference, and obesity type with difficult intubation was evaluated. Preoperative and peroperative measurements were recorded in the follow-up forms.

Results: A total of 85 patients, 62 females and 23 males, between the ages of 19 and 77 years were included in this study. A significant difference was found in the patients' BMI, neck circumference, thyromental distance, Mallampati classifications, and Cormack–Lehane grades in terms of intubation difficulty (P<0.001, P<0.001, P<0.001, P<0.01, P<0.01, respectively). Patients who underwent difficult intubation had lower thyromental distance but greater BMI, neck circumference, Mallampati classification, and Cormack–Lehane grade. It was determined that a neck circumference of >50 cm increased the risk of difficult intubation 8.323 times.

Conclusion: Neck circumference and thyromental distance are significant predictors for difficult intubation and laryngoscopy in morbidly obese patients.

Keywords: Obesity, Difficult intubation, Neck circumference, BMI

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Introduction

Difficult airways, one of the major causes of perioperative mortality and morbidity, are a major cause of concern for anesthesiologists. Difficulty in managing the airway is the single most common cause of anesthesia-related death and brain damage [1]. Therefore, predicting a potentially difficult intubation means that measures can be taken to minimize the risk [2].

The number of obese patients undergoing elective surgery is increasing with each passing day, and anesthesiologists must be prepared to handle all perioperative care of obese patients. In particular, they should understand the effects of obesity on the airway and be prepared to manage the airway correctly [3, 5]. Several reviews in the literature reported that endotracheal intubation is more difficult in obese patients than in lean patients [6]. However, this claim is controversial because no other studies such an association [7-11]. While one study stated that morbid obesity increases the rate of difficult intubation three times, there are others in the literature that reported that there is no relationship between morbid obesity and difficult intubation [12, 13]. However, in general, airway management in obese patients is considered a challenge for many anesthetists [12].

Many attempts have been made to develop reliable predictors of difficult intubation and difficult laryngoscopy, but none of them have high diagnostic accuracy, particularly in obese patients [14]. The best known and recommended predictors include parameters such as the Mallampati classification, thyromental distance measurement, obstructive sleep apnea (OSA), male gender, and increased age [14, 15]. However, some studies in the literature report that none of these predictors yield satisfactory results in obese patients. There is limited literature and conflicting results about the relationship between neck circumference and difficult intubation [16, 17]. Contrary to two studies that reported that neck circumference greater than 43 cm was associated with difficult intubation, Neligan et al. [13] could not find a relationship between the neck circumference and difficult intubation in their study.

There are few studies examining the relationship between neck circumference and difficult intubation in obese patients and no studies on whether the obesity type is a significant risk factor for difficult intubation. Therefore, in this study, we sought to evaluate the predictors of difficult intubation such as the Mallampati classification, BMI, thyromental distance, OSA in obese patients (>35 kg/m^2) undergoing elective surgery in our clinic, and we aimed to investigate the association of the neck circumference and obesity type with difficult intubation.

Materials and methods

The study protocol was approved by Marmara University Medical Faculty, Ethics Committee for Clinical Studies (no: 09.2021.135) and conducted in accordance with the Declaration of Helsinki.

Patients above 18 years of age, with an American Society of Anesthesiologists (ASA) score of I–III, who were candidates for elective surgery, and whose BMI was >35 kg/m^2 were included in the study to investigate whether the neck circumference and obesity type constituted risk factors for difficult intubation in obese patients. The patients were operated under general anesthesia and underwent endotracheal intubation. Before the surgery, the patients were informed about the measurements and tests that would be performed on the face and neck, and they gave their informed consent. Patients with a history of cervical spine anomaly or trauma, congenital facial anomaly or trauma affecting this region, those who would undergo emergency surgery, patients with a known history of difficult airway or upper respiratory tract disease, and those with planned awake intubation were excluded from the study. The patients were evaluated by resident anesthesiologists before the operation. Pre-anesthetic evaluations were made by assessing for age, gender, physical condition according to the ASA, and the presence of OSA. The patients underwent physical examinations for height and weight measurements; the BMI was calculated on the basis of height and weight of the patients. The Mallampati score and thyromental distance assessments were noted. With the help of a tape measure, the neck circumference was measured at the level of the thyroid cartilage with the patient in neutral position. Before induction, patients underwent electrocardiogram, pulse oximetry, and noninvasive arterial blood pressure monitoring. Preoxygenation was administered for 3 minutes. Operating tables were set in the ramp position. Mask ventilation, performed with a face mask of appropriate size, was evaluated using the Han Classification, and difficult intubation was assessed with the IDS. Tracheal intubation was considered successful when a capnography waveform was observed, and the sounds of both lungs could be equally heard by auscultation.

Statistical analysis

For statistical analysis, the statistical software R version 2.15.3 (R Core Team, 2013) was used. The study data were reported using minimum, maximum, mean, standard deviation, median, first quartile, third quartile, frequency, and percentage. The Shapiro–Wilk test and graphical reviews were used to check whether quantitative data were normally distributed. The Mann–Whitney U test was used for inter-group assessments of non-normally distributed variables. Pearson's chi-squared test, Fisher's exact test, and Fisher–Freeman–Halton exact test were used to compare qualitative data. Multivariate logistic regression analysis was performed to identify the factors affecting difficult intubation. Statistical significance was set at $P<0.05$.

Results

The data associated with the patients included in our study are presented in Table 1. The patients were between the ages of 19 and 77 years, with a mean age of 45.87 (13.33) years.

The BMI values of the cases ranged from 35 to 60 kg/m^2, with an average of 43.79 (6.05) kg/m^2; neck circumference ranged from 36 to 59 cm, with an average of 47.83 (6.41) cm; and thyromental distance ranged from 4.5 to 10 cm, with an average of 6.84 (1.13) cm. Neck circumference was <42 cm in 18.8% of the cases (n = 16) and ≥42 cm in 81.8% (n = 69).

The Mallampati classification of the cases ranged from 1 to 4, with an average of 2.31 (1.13) and the Cormack–Lehane grades ranged from 1 to 4, with an average of 1.96 (0.81). The

number of intubation attempts made on the cases ranged from 1 to 4, with an average of 1.59 (0.82).

Table 1: Information on demographic features

	Min-Max (Median)	Mean (SD)
Age	19-77 (45)	45.87 (13.33)
BMI	35-60 (43)	43.79 (6.05)
Neck circumference	36-59 (47)	47.83 (6.41)
Thyromental distance	4.5-10 (7)	6.84 (1.13)
Mallampati	1-4 (2)	2.31 (0.93)
Cormaclehen degree	1-4 (2)	1.96 (0.81)
Number attempt	1-4 (1)	1.59 (0.82)
	n	%
Gender		
Female	62	72.9
Male	23	27.1
DM		
+	50	58.8
-	35	41.2
HT		
+	50	58.8
-	35	41.2
OSA		
+	66	77.6
-	19	22.4
Neck circumference		
<42	16	18.8
≥42	69	81.2
Restricted neck movement		
+	67	78.8
-	18	21.2
Obesity type		
Peripheral	20	23.5
Central	65	76.5
Ramp		
No	0	0.0
Yes	85	100.0
Difficult Mask		
No	47	56.0
Yes	37	44.0
Instrument used for intubation		
Direct laryngoscope (DL)	57	67.1
DL+Guide	14	16.5
VL	11	12.9
VL+Guide	3	3.5
Intubation		
Resident (experience <2 years)	16	18.8
Resident (experience 2 years)	44	51.8
Specialist	25	29.4

Approximately 72.9% of the patients (n = 62) were female and 27.1% (n = 23) were male.

Diabetes mellitus (DM) was present in 41.2% of the cases, hypertension (HT) in 41.2%, and OSA in 22.4%. Approximately 21.2% of the patients had limited neck mobility. About 23.5% had peripheral obesity and 76.5% had central obesity.

Ramps were used in all cases. Mask ventilation was difficult in 44% of the cases.

Approximately 67.1% of the patients were intubated with the Macintosh blade, 16.5% with the Macintosh blade and guide, 12.9% with a video laryngoscope, 3.5% with a video laryngoscope and guide.

There was no difference in the age of the patients in terms of intubation difficulty (P>0.05). A significant difference was found in the patients' BMI, neck circumference, thyromental distance, Mallampati classifications, and Cormack–Lehane grades in terms of intubation difficulty (P<0.001, P<0.001, P<0.001, P<0.01, P<0.01, respectively). Patients who underwent difficult intubation had lower thyromental distance but greater BMI, neck circumference, Mallampati classification, and Cormack–Lehane grade. There was no significant difference in the percentage of intubation difficulty in terms of gender, DM, HT, OSA, and neck circumference (P>0.05).

The percentage of intubation difficulty was higher in patients with neck circumferences ≥42 cm, limited neck mobility, presence of central obesity, and difficult mask ventilation (P=0.002, P=0.001, P=0.029, and P<0.001, respectively). The cut-off values associated with difficult intubation were established for BMI, neck circumference, thyromental distance, Mallampati classification, and Cormack–Lehane grades. According to the evaluations, these cut-off values were >46 kg/m^2 for BMI, >50 cm for neck circumference, ≤6.5 cm for thyromental distance, >2 for Mallampati classification, and >2 for Cormack–Lehane grade.

Multivariate logistic regression analysis was performed to identify the factors affecting difficult intubation (Table 2). Intubation difficulty was included in the analysis as a dependent variable, and BMI, neck circumference, thyromental distance, Mallampati classification, Cormack–Lehane grade, restricted neck mobility, obesity type, and mask ventilation difficulty were included as independent variables. The model derived from the analysis performed using the backward elimination method was statistically significant (χ^2=73.640, P<0.001). Neck circumference, thyromental distance, Mallampati classification, and Cormack–Lehane grade were found to have significant effects in the model. A neck circumference of >50 cm increased the risk of difficult intubation 8.323 times [odds radio (OR) (95% confidence interval (CI)) = 8.323 (1.175, 58.970); P=0.034]. A thyromental distance of ≤6.5 cm increased the risk of difficult intubation 40,475 times [OR (95% CI) = 40.475 (3.227, 507.637); P=0.004]. A Mallampati classification score >2 was increased the risk of difficult intubation 16,129 times [OR (95% CI) = 16,129 (1.606, 161.967); P=0.018]). A Cormack–Lehane grade >2 increased the risk of difficult intubation by a factor of 13.449 [OR (95% CI) = 13.449 (1.294, 139.827); P=0.030].

Table 2: Comparisons for difficult intubation

	Difficult Intubation		Test value	P-value
	No Median (Q1,Q3)	Yes Median (Q1,Q3)		
Age	47 (38.5, 56.5)	43 (37, 50)	-1.410	[a]0.159
BMI	41 (38, 45.25)	50 (47, 51)	-4.008	[a]<0.001*
Neck Circumference	45 (41.25, 48.5)	53 (51, 57)	-4.897	[a]<0.001*
Thyromental distance	7 (6.75, 8)	6 (5.5, 6)	-5.293	[a]<0.001*
Mallampati	2 (1, 2)	3 (3, 3)	-5.595	[a]<0.001*
Cormaclehen level	2 (1, 2)	3 (2, 3)	-6.054	[a]<0.001*
	n (%)	n (%)	Test value	P-value
Gender			1.435	[c]0.231
Female	46 (74.2)	16 (25.8)		
Male	14 (60.9)	9 (39.1)		
Diabetes Mellitus (DM)			1.713	[c]0.191
DM (-)	38 (76)	12 (24)		
DM (+)	22 (62.9)	13 (37.1)		
Hypertension (HT)			0.392	[c]0.531
HT(-)	34 (68)	16 (32)		
HT(+)	26 (74.3)	9 (25.7)		
Obstructive Sleep Apnea (OSA)			1.899	[c]0.168
OSA(-)	49 (74.2)	17 (25.8)		
OSA(+)	11 (57.9)	8 (42.1)		
Neck circumference (cm)			8.213	[b]0.002*
<42	16 (100)	0 (0)		
≥42	44 (63.8)	25 (36.2)		
Restricted Neck Mobility (RNM)			11.053	[c]0.001*
RNM(-)	53 (79.1)	14 (20.9)		
RNM(+)	7 (38.9)	11 (61.1)		
Obesity type			4.747	[c]0.029*
Peripheral	18 (90)	2 (10)		
Central	42 (64.6)	23 (35.4)		
Face Mask Difficulty			33.850	[b]<0.001*
Difficult(-)	46 (95.8)	2 (4.2)		
Difficult(+)	14 (37.8)	23 (62.2)		

[a] Mann-Whitney U test, results are presented as median (first quartile, third quartile), [b] Fisher's exact test, [c] Pearson chi-square test, * P<0.05

Discussion

The number of obese patients undergoing elective emergency operations is increasing with every passing day. Difficult intubation and difficult mask ventilation defined as difficult airways are observed at increased rates in obese and morbidly obese patients. In our study, we determined that neck circumference, thyromental distance, Mallampati classification and Cormack–Lehane grade are independent risk factors for difficult intubation in obese patients.

There is conflicting evidence in the literature about the relationship between obesity and difficult tracheal intubation [17]. Although Butler et al. [18] found the Mallampati classification to be useless in evaluating preoperative intubation difficulty in their study, there are other studies showing that the Mallampati test is a more valuable predictor when supported by other airway assessment tools. Ittichaikulthol et al. [19] found the modified Mallampati test alone to have low sensitivity and specificity as a predictor of difficult intubation, but they reported that the combined use of thyromental distance and modified Mallampati test yielded significant results. Shailaja et al. [20] and Özdilek et al. [21] showed that a score of III–IV in Mallampati classification in obese patients is a predictor of difficult intubation. In our study, we found that the Mallampati classification was an independent risk factor for difficult intubation in obese patients, and that the risk of difficult intubation increased 16.129 times when the Mallampati score was >2.

There are different interpretations in the literature as to whether obesity alone is a risk factor for difficult intubation [22]. While some studies failed to associate obesity and BMI with difficult intubation, others concluded that obesity increases the risk of difficult intubation [12, 23]. The reason for this difference is that there is no universal definition of difficult tracheal intubation and there is no linear relationship between BMI and difficult intubation and the threshold value for BMI. Lundstrom et al. [2] reported that a BMI >35 kg/m^2 is an independent risk factor for difficult and unsuccessful intubation. In their study which compared normal-weight and obese patients (n = 263), Juvin et al. [16] found that the rate of difficult intubation was higher in obese patients. In contrast, Brodsky et al. studied 100 morbidly obese patients and stated that obesity is not an independent risk factor for difficult intubation [10]. Riad et al. [17] showed that a high BMI is an independent predictor for difficult intubation in a study conducted in 2016, and they reported that a BMI higher than 50 kg/m^2 increased the risk of difficult intubation five times. In a meta-analysis by Shiga et al., the risk of difficult intubation was three times higher in morbidly obese patients than in normal-weight patients [12]. In contrast, Neligan et al. [13] and Brodsky et al. [10] did not find a relationship between morbid obesity and difficult intubation. In our study, we found that a BMI value higher than 46 kg/m^2 was significant for difficult intubation in obese patients.

OSA is a risk factor for difficult mask ventilation and difficult intubation in obese patients. Considering the high closing pressure of the pharyngeal airway in OSA patients, this association is easily understood [24]. Some studies in the literature showed high rates of OSA in patients with difficult tracheal intubation. Siyam et al. [25] and Kim et al. [26] showed that tracheal intubation with direct laryngoscopy is more difficult in OSA patients than in patients without OSA, but no comparison was made between the BMIs of the patients in these studies.

There is limited data and conflicting evidence in the literature regarding the relationship between neck circumference and difficult intubation. In addition, the cut-off value for neck circumference, which may be associated with difficult intubation, has not been exactly established [17]. In addition to publications stating that neck circumference alone is not a significant predictor for difficult intubation, Gonzalez et al. [7] conducted a study with 70 morbidly obese and 61 non-obese patients, in which intubation was categorized as difficult at IDS >5 and not difficult at IDS = 5 and below, and they found that a neck circumference of >43 cm increased the risk of difficult intubation in both obese and non-obese patients. Langeron et al. [21] also emphasized that a neck circumference of >43 cm is a risk factor for difficult intubation. In their study conducted in 2002, Brodsky et al. [10] reported that neck circumference is an independent risk factor for difficult intubation and that the risk of difficult intubation increases seven times as the neck circumference increases from 40 cm to 60 cm. Riad et al. [17] conducted a study with 104 morbidly obese patients in 2016 and showed that neck circumference >42 cm was an independent risk factor for difficult intubation, and it increased the risk of difficult intubation five times. Contrary to these studies, in their study conducted with 180 obese patients in 2009, Neligan et al. [13] stated that neck circumference was significant in the prediction of difficult laryngoscopy but was not useful in the prediction of difficult intubation. However, in their study conducted with 120 obese patients in 2018, Özdilek et al. [21] reported that neck circumference was not a risk factor for difficult mask ventilation or for difficult laryngoscopy. In line with studies using ultrasound measurement, which reported that large neck circumference contributes to difficult intubation due to fat deposition in the anterior soft tissue of the neck, Raju Vegesna et al. [27] showed that neck circumference has the highest significance as a parameter in terms of difficult intubation [28]. In their study that compared 123 obese and 125 non-obese patients, Kim et al. [26] found that neck circumference/thyromental distance ratio is a better predictor of difficult intubation than the Mallampati classification or neck circumference measurement alone. Consistent with the studies by Brodsky et al. [10] and Riad et al. [17], our study found that neck circumference was an independent risk factor for difficult intubation in obese patients, and neck circumference >50 cm increased the risk of difficult intubation eight times.

There are some studies in the literature claiming that BMI cannot distinguish between adipose tissue and lean body mass; therefore, a high BMI alone is not significant for obesity and accompanying complications. These studies stated that obesity pathology is closely related to body fat distribution [4, 29-31]. These views emphasize that what matters is not the patient's actual BMI, but visceral adiposity, which defines where this excess weight is stored. Whether a person has an apple- or pear-shaped body morphology matters. Apple-shaped individuals have proportionally more abdominal fat, a case defined as central obesity. Many studies have found them to be at higher risk for

perioperative complications [31, 32]. Although waist circumference and BMI are related to each other, it has been frequently stated in the literature that waist/height ratio (central obesity) means a higher risk rate in terms of type 2 diabetes, dyslipidemia, HT, and cardiovascular diseases [32]. However, there are very limited data in the literature on the relationship between obesity type and difficult airway/difficult intubation. In a study examining the effects of morbid obesity on the difficult airway, it was found that the risk of difficult intubation is higher in males than in females because most morbidly obese women carry excess weight on their hips and thighs (classical "pear" shape), whereas morbidly obese men carry excess weight on their trunks and abdomen. They also reported that morbidly obese men have more pretracheal fat mass and larger back fat pads, resulting in anatomical changes in the upper neck and airway that increase the risk of difficult intubation. This view is supported by some studies suggesting that there is a significant relationship between neck circumference and central obesity and that the height of the neck circumference is an indicator for central obesity. The multivariate logistic regression analysis performed in this study showed that central obesity type is not an independent risk factor for difficult intubation but has a significant association with difficult intubation.

Limitations

One of the limitations of our study was the inability to standardize the evaluation of patients in terms of difficult intubation owing to the different levels of education, skill, and experience of the anesthetists who performed intubation.

Secondly, our use of a video laryngoscope as the first choice instead of the Macintosh blade in some patients who were believed to be at high risk for difficult intubation may have resulted in a failure to make objective evaluations among patients in defining difficult intubation.

In addition, because there are few studies examining whether the type of obesity is significant in terms of difficult intubation in obese patients, we believe that new studies with a larger number of patients should be performed by a single anesthesiologist and practitioner following standardized techniques.

Conclusion

Thus, the findings of this study showed that BMI, neck circumference, thyromental distance <6.5 cm and Mallampati classification >2 are important predictor factors in morbidly obese patients. These important measurements should be evaluated in the pre-anesthesia examination for possible difficult intubation.

References

1. Henderson JJ, Popat MT, Latto IP, Pearce AC; Difficult Airway Society. Difficult Airway Society guidelines for management of the unanticipated difficult intubation. Anaesthesia. 2004 Jul;59(7):675-94. doi: 10.1111/j.1365-2044.2004.03831.x.
2. Lundstrøm LH, Møller AM, Rosenstock C, Astrup G, Wetterslev J. High body mass index is a weak predictor for difficult and failed tracheal intubation: a cohort study of 91,332 consecutive patients scheduled for direct laryngoscopy registered in the Danish Anesthesia Database. Anesthesiology. 2009 Feb;110(2):266-74. doi: 10.1097/ALN.0b013e318194cac8.
3. Aceto P, Perilli V, Modesti C, Ciocchetti P, Vitale F, Sollazzi L. Airway management in obese patients. Surg Obes Relat Dis. 2013 Sep-Oct;9(5):809-15. doi: 10.1016/j.soard.2013.04.013
4. Bray, G.A., et al., Management of obesity. The Lancet, 2016. 387(10031): p. 1947-1956.
5. Hodgson LE, Murphy PB, Hart N. Respiratory management of the obese patient undergoing surgery. J Thorac Dis. 2015 May;7(5):943-52. doi: 10.3978/j.issn.2072-1439.2015.03.08.
6. Moon TS, Fox PE, Somasundaram A, Minhajuddin A, Gonzales MX, Pak TJ, et al. The influence of morbid obesity on difficult intubation and difficult mask ventilation. J Anesth. 2019 Feb;33(1):96-102. doi: 10.1007/s00540-018-2592-7.
7. Gonzalez H, Minville V, Delanoue K, Mazerolles M, Concina D, Fourcade O. The importance of increased neck circumference to intubation difficulties in obese patients. Anesth Analg. 2008 Apr;106(4):1132-6. doi: 10.1213/ane.0b013e3181679659.
8. Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. Br J Anaesth. 1988 Aug;61(2):211-6. doi: 10.1093/bja/61.2.211. PMID: 3415893.
9. Bond A. Obesity and difficult intubation. Anaesth Intensive Care. 1993 Dec;21(6):828-30. doi: 10.1177/0310057X9302100614.
10. Brodsky JB, Lemmens HJ, Brock-Utne JG, Vierra M, Saidman LJ. Morbid obesity and tracheal intubation. Anesth Analg. 2002 Mar;94(3):732-6. doi: 10.1097/00000539-200203000-00047.
11. Sinha A, Jayaraman L, Punhani D. Predictors of difficult airway in the obese are closely related to safe apnea time! J Anaesthesiol Clin Pharmacol. 2020 Jan-Mar;36(1):25-30. doi: 10.4103/joacp.JOACP_164_19.
12. Shiga T, Wajima Z, Inoue T, Sakamoto A. Predicting difficult intubation in apparently normal patients: a meta-analysis of bedside screening test performance. Anesthesiology. 2005 Aug;103(2):429-37. doi: 10.1097/00000542-200508000-00027.
13. Neligan PJ, Porter S, Max B, Malhotra G, Greenblatt EP, Ochroch EA. Obstructive sleep apnea is not a risk factor for difficult intubation in morbidly obese patients. Anesth Analg. 2009 Oct;109(4):1182-6. doi: 10.1213/ane.0b013e3181b12a0c.
14. Kim WH, Ahn HJ, Lee CJ, Shin BS, Ko JS, Choi SJ, et al. Neck circumference to thyromental distance ratio: a new predictor of difficult intubation in obese patients. Br J Anaesth. 2011 May;106(5):743-8. doi: 10.1093/bja/aer024.
15. Bindra A, Prabhakar H, Singh GP, Ali Z, Singhal V. Is the modified Mallampati test performed in supine position a reliable predictor of difficult tracheal intubation? J Anesth. 2010 Jun;24(3):482-5. doi: 10.1007/s00540-010-0905-6.
16. Juvin P, Lavaut E, Dupont H, Lefevre P, Demetriou M, Dumoulin JL, et al. Difficult tracheal intubation is more common in obese than in lean patients. Anesth Analg. 2003 Aug;97(2):595-600. doi: 10.1213/01.ANE.0000072547.75928.B0.
17. Riad W, Vaez MN, Raveendran R, Tam AD, Quereshy FA, Chung F, et al. Neck circumference as a predictor of difficult intubation and difficult mask ventilation in morbidly obese patients: A prospective observational study. Eur J Anaesthesiol. 2016 Apr;33(4):244-9. doi: 10.1097/EJA.0000000000000324.
18. Butler PJ, Dhara SS. Prediction of difficult laryngoscopy: an assessment of the thyromental distance and Mallampati predictive tests. Anaesth Intensive Care. 1992 May;20(2):139-42. doi: 10.1177/0310057X9202000202.
19. Ittichaikulthol W, Chanpradub S, Amnoundetchakorn S, Arayajarernwong N, Wongkum W. Modified Mallampati test and thyromental distance as a predictor of difficult laryngoscopy in Thai patients. J Med Assoc Thai. 2010;93(1):84-9.
20. Shailaja S, Nichelle SM, Shetty AK, Hegde BR. Comparing ease of intubation in obese and lean patients using intubation difficulty scale. Anesth Essays Res. 2014 May-Aug;8(2):168-74. doi: 10.4103/0259-1162.134493.
21. Özdilek A, Beyoglu CA, Erbabacan ŞE, Ekici B, Altındaş F, Vehid S, et al. Correlation of Neck Circumference with Difficult Mask Ventilation and Difficult Laryngoscopy in Morbidly Obese Patients: an Observational Study. Obes Surg. 2018 Sep;28(9):2860-7. doi: 10.1007/s11695-018-3263-3
22. Langeron O, Birenbaum A, Le Saché F, Raux M. Airway management in obese patient. Minerva Anestesiol. 2014 Mar;80(3):382-92.
23. Ezri T, Medalion B, Weisenberg M, Szmuk P, Warters RD, Charuzi I. Increased body mass index per se is not a predictor of difficult laryngoscopy. Can J Anaesth. 2003 Feb;50(2):179-83. doi: 10.1007/BF03017853.
24. Hora F, Nápolis LM, Daltro C, Kodaira SK, Tufik S, Togeiro SM, Nery LE. Clinical, anthropometric and upper airway anatomic characteristics of obese patients with obstructive sleep apnea syndrome. Respiration. 2007;74(5):517-24. doi: 10.1159/000097790.
25. Siyam MA, Benhamou D. Difficult endotracheal intubation in patients with sleep apnea syndrome. Anesth Analg. 2002 Oct;95(4):1098-102, table of contents. doi: 10.1097/00000539-200210000-00058.
26. Kim JA, Lee JJ. Preoperative predictors of difficult intubation in patients with obstructive sleep apnea syndrome. Can J Anaesth. 2006 Apr;53(4):393-7. doi: 10.1007/BF03022506. PMID: 16575040.
27. Raju Vegesna AR, Al-Anee KN, Bashah MMM, Faraj JH. Airway management in bariatric surgery patients, our experience in Qatar: A prospective observational cohort study. Qatar Med J. 2020 Mar 2;2020(1):2. doi: 10.5339/qmj.2020.2
28. Ünal Kantekin Ç, Erkoç M, Talih G. The measurement of skin to epiglottis length for difficult airway prediction by ultrasonography in obese pregnant women: Prospective cohort study. Journal of Surgery and Medicine. 2019; 3(10): 759-762.
29. Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, et al. The Science of Obesity Management: An Endocrine Society Scientific Statement. Endocr Rev. 2018 Apr 1;39(2):79-132. doi: 10.1210/er.2017-00253.
30. Shearer ES. Obesity anaesthesia: the dangers of being an apple. Br J Anaesth. 2013 Feb;110(2):172-4. doi: 10.1093/bja/aes471.
31. Coe AJ, Saleh T, Samuel T, Edwards R. The management of patients with morbid obesity in the anaesthetic assessment clinic. Anaesthesia. 2004 Jun;59(6):570-3. doi: 10.1111/j.1365-2044.2004.03733.x.
32. Kurt AK. Birinci Basamakta Obezite Yönetimi. Aile Hekimliği. 2019;11(2):55-60.

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Comparison of anterior tab flap and underlay tympanoplasty techniques in anterior tympanic membrane perforations

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Ethics Committee Approval
Kocaeli University Ethics Committee of Non-invasive Clinical Research in 11/12/2019 approved this study with the number of GOKAEK 2019/349.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Closure of anterior tympanic membrane perforation is surgically demanding with high rates of graft failure. The anterior tab flap (ATF) technique is a modification of underlay tympanoplasty which claims higher success rates for repairing anterior and subtotal perforations. Our main aim was to compare graft take rates of ATF and underlay techniques in anterior tympanic membrane perforations.
Method: In this retrospective cohort study, 41 patients with anterior tympanic membrane perforations who underwent tympanoplasty at a tertiary referral center were analyzed. The patients were grouped according to the technique used. Demographic, clinical, and follow-up information as well as preoperative and postoperative 6th-month audiometric data were collected and compared between the groups.
Results: Four patients were lost to follow-up. Eighteen patients in the ATF arm and 19 patients in the underlay arm were compared. Graft take rates were 94.4% in the ATF group and 73.7% in the underlay group (P=0.180). An air conduction threshold average of <30 dB was observed in 76.5% in the ATF group and 63.1% in the underlay tympanoplasty group (P>0.05). The postoperative ABG of the ATF and underlay group patients were less than 20 dB in 76.5% and 78.9%, respectively (P>0.05). No graft lateralization, anterior blunting, or cholesteatoma were observed.
Conclusion: ATF is a safe and effective technique with a higher success rate for repairing anterior tympanic membrane perforation.

Keywords: Anterior tab flap, Tympanoplasty, Anterior pull-through, Kerr flap, Underlay

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Introduction

Tympanoplasty is one of the widely performed and understood otologic procedures over the years [1]. Maintaining a healthy middle ear cleft and restoration of hearing are its main goals. Although graft take rates are high for posterior and central perforations, anterior tympanic membrane perforation is clinically challenging for surgeons. The absence of medial support mechanism for grafts, relatively less vascularity of the region, scarcity of anterior epithelial reserve, and poor exposure are the main reasons for graft failure in anterior tympanic membrane perforations [2-3].

Several different tympanoplasty techniques and modifications were described to establish an intact tympanic membrane for anterior perforations. The underlay technique is an easy to perform and less time-consuming method that is commonly used throughout the world. The absence of reliable support and resulting graft medialization is the main drawback of the underlay technique [4-5]. To prevent anterior reperforations and decrease graft medialization, the anterior tab flap (ATF) method, a modification of the underlay technique was advocated with higher success rates. In this modification, the tip of the graft is anchored to a 1-2 mm tunnel created lateral to the anterior fibrous annulus and external auditory canal wall skin [5-7].

This study aimed to compare graft take rates of the ATF and underlay techniques in anterior tympanic membrane perforations.

Materials and methods

The patients with anterior tympanic membrane perforations operated on between 2015-2019 in a tertiary referral center were the subjects of this study. After institutional review board approval was granted from the Kocaeli University Ethics Committee of Non-invasive Clinical Research on 11/12/2019 with the number of GOKAEK 2019/349, a retrospective chart review was performed. Data regarding the preoperative and the postoperative 6th-month air conduction thresholds (ACT), bone conduction thresholds (BCT), air-bone gaps (ABG), the postoperative 6th-month tympanic membrane status, surgical technique, operative details, and follow-up information were collected.

We included the patients with perforations affecting more than 30% of the whole tympanic membrane, with a perforation margin to the anterior fibrous annulus of less than 1 mm. All procedures were performed under general anesthesia using an operating microscope through a retroauricular approach. Temporalis muscle fascia and conchal cartilage with one-sided perichondrium were used as graft materials. Patients with cholesteatoma or retraction pockets were excluded, but those with ossicular chain discontinuity were included in the study.

The decision of the technique to be used was made intraoperatively. The underlay technique was used in patients with a clear view and access to the anterior tympanic membrane remnant. The ATF technique was preferred in patients with less than 1 mm anterior tympanic membrane remnant after disepitelization or anterior marginal perforations with an unhindered view of the anterior tympanomeatal angle.

ATF Technique

The ATF technique is well described in the literature [6-8]. The retroauricular approach is preferred in our clinic to increase the exposure of the anterior tympanomeatal angle and the anterior extent of the perforation. Temporalis muscle fascia and conchal cartilage with the perichondrium are harvested routinely. The edges of the perforation are refreshed. During tympanomeatal flap elevation, the manubrium of the malleus is carefully freed from the membrane. Sclerotic plaques which are close to the perforation and the larger ones causing hearing impairment are removed. Ossicular movement is controlled at this step and ossiculoplasty is performed if required. A 2-mm anterior stab incision 2 mm lateral to the annulus is made on the anterior meatal skin usually at the 2 to 4 o'clock position in right ears and the 8 to 10 o'clock position in the left ears. An anterior meatal tunnel is created deep into the annulus, carefully preserving the fibrous annulus, and the middle ear is entered. Temporalis fascia graft is fashioned according to the perforation, leaving an anterior tab, or pointed tip to be delivered through the meatal tunnel. Temporalis fascia graft is then positioned under the tympanomeatal flap over the manubrium of the malleus. The anterior tab portion is placed near the anterior meatal tunnel and pulled through the tunnel with micro-suction tubes, alligator forceps, or right-angled hooks. This maneuver anchors the fascia graft anteriorly. To further support the temporalis fascia medially, a thinned cartilage perichondrium composite graft of 5 mm is positioned on the malleus handle under the fascia graft and dry gel foam is placed into the anterior mesotympanum to further support the grafts medially. The tympanomeatal flap is then placed back into the anatomic position and stabilized laterally with gel foam soaked in antibiotic solution. The incision is closed in layers, antibiotic-coated ribbon gauze is inserted in the ear canal, and a standard pressure dressing is applied.

Underlay Technique

The underlay technique used in our clinic for anterior perforations is similar to the classical underlay technique [6]. The difference is the release of the malleus handle from the tympanic membrane to use for medial support. Temporalis fascia graft is placed over the manubrium of the malleus under the tympanomeatal flap. In this approach, a larger (~6-8 mm) cartilage perichondrium composite graft is positioned onto the malleus handle to support the fascia graft anteriorly. Also, dry gel foam is inserted into the anterior mesotympanum to support both grafts medially. The rest of the procedure is the same in both techniques.

Patients are called for routine control visits on the 2nd postoperative day, first week, 3rd week, 2nd month, and 6th month. Ribbon gauze in the ear canal is removed on the 2nd day and the patients start using 0.3% ciprofloxacin and 0.1% dexamethasone ear drops three times a day for 3 weeks. Stitches are removed at 1 week postoperatively. Tympanic membrane repair is expected at the 3rd week but hearing status is evaluated at 2nd and 6th-month postoperative controls.

Audiologic Assessment

Patients' audiometry tests were performed per the ISO standards within a maximum of one month before the surgery, and at the last control after surgery (Audiometer: Interacoustic, AC40, Denmark). ACT, BCT, and ABG are evaluated at 500,

1000, 2000, and 4000 Hz. An ABG within 20 dB, or a hearing level within 30 dB considering the average pure tone thresholds of 500, 1000, 2000 Hz, 4000 Hz, are considered functional hearing success [1].

Statistical analysis

IBM SPSS statistics 21 (IBM Corp, Armonk, NY) software was used for data analysis. The chi-square test was used to compare graft take rates and hearing improvement. Odds ratio (OR) and 95% confidence intervals (CI) were given in parenthesis. Shapiro-Wilk test was used for the analysis of normality. ABG closure rates were evaluated using related samples Wilcoxon signed-rank test. *P*-values of less than 0.05 were considered significant.

Results

Forty-one patients with anterior tympanic membrane perforations were operated on between 2015-2019 in our tertiary referral center. All patients had chronic tubotympanic otitis media with anterior tympanic membrane perforation. Of these patients, four were lost to follow-up, so 37 patients were included in the study. Nineteen patients underwent underlay tympanoplasty, and 18 patients underwent ATF modification of underlay tympanoplasty.

In the ATF group, the median age of 18 patients was 30.4 (20.8, 43.8) years. The female to male ratio was 8/10. Tympanoplasty was performed on the right ear in 11 cases and on the left ear in 7 patients. Four patients were revision cases, previously operated with other techniques, but perforation persisted. The ossicular chain was mobile in 16 patients and immobile in 2. In one of these immobile ossicular chain patients, the incus was removed, and a partial ossicular replacement prosthesis was inserted between the cartilage composite graft and stapes head for hearing restoration. The incus lenticular process and stapes suprastructure were eroded in the remaining patient, and a total ossicular replacement prosthesis was positioned on the mobile footplate.

In the underlay group, the female to male ratio was 12/7, and the median age of 19 patients was 35.0 (26.0-48.0) years. The right to left ear ratio was 8/11. Three cases were revision surgeries. The ossicular chain was mobile in 17 patients. The lenticular process was eroded and incudostapedial conduction was ensured with glass-ionomer bone cement in one patient. In the other one, the incus was removed and malleostapedopexy was performed. Malleostapedial connection was established with the glass-ionomer bone cement. The clinical data of both groups are given in Table 1.

Table 1: Clinical summary of both groups

	Anterior tab flap group	Underlay group	*P*-value
Number of patients	18	19	
Age	30.4 (20.8,43.8)	35.0 (26.0,48.0)	0.461
Female to Male Ratio	8/10	12/7	0.343
Right Ear/Left Ear	11/7	8/11	
Revision Surgery	4	3	
Ossiculoplasty	2	2	
Graft take rate	17/18 (94.4%)	14/19 (73.7%)	

Age is presented as median (25-75%).

The average follow-up time was 18 months in the ATF group and 9 months in the underlay group. Graft take rates were 17/18 (94.4%) in the ATF group and 14/19 (73.7%) in the underlay group. No statistical difference was found between the two groups in terms of graft success rate (P=0.180). One of the graft failure patients in the ATF group was re-operated for slit-like re-perforations, and complete tympanic membrane closure was achieved afterward. One of five patients with postoperative defective graft in the underlay group was re-operated, but the perforation persisted. None of the patients exhibited graft lateralization or anterior blunting. Two patients in the ATF group and one patient in the underlay group had a postoperative purulent discharge. These infections had resolved with appropriate care and antibiotics. After the treatment, complete tympanic membrane closure was achieved in all 2 patients in the ATF group, however, perforation persisted in the infected ear in the underlay group. The patient in the underlay group did not agree to a revision.

One cochlear implant candidate patient was not evaluated for hearing statistics. In terms of hearing status, the median of the average of 500-1000-2000-4000 Hz preoperative ACT and BCT values were 32.5 dB and 10.0 dB, respectively, in the ATF group, versus 42.5 dB and 15.0 dB, respectively, in the underlay group (Table 2). The median of sixth-month postoperative air and bone conduction thresholds were 22.5 dB and 11.3 dB, respectively, in the ATF group versus 23.8 dB and 16.3 dB, respectively, in the underlay group. The differences in the ACT were significantly better in both groups. The BCT levels did not deteriorate statistically. The preoperative and postoperative median of the ABG in the ATF group were 22.5 and 12.5, respectively (P=0.023). The preoperative and postoperative median of the ABG in the underlay group were 25.0 and 12.5, respectively (P=0.003). One patient in the ATF group was operated on to prepare for cochlear implantation, so she was excluded from hearing assessment.

Table 2: Audiological outcomes of both groups

		Pre-operative	Post-operative	p value
Anterior Tab Flap Group (N=17)	ACT	32.5 (30.0-40.0)	22.5 (18.1-30.0)	0.031
	BCT	10.0 (8.1-16.3)	11.3 (7.5-17.5)	0.118
	ABG	22.5 (18.1-29.4)	12.5 (3.8-18.8)	0.023
Underlay Group (N=19)	ACT	42.5 (26.3-50.0)	23.8 (18.8-40.0)	0.004
	BCT	15.0 (8.8-25.0)	16.3 (8.8-23.8)	0.135
	ABG	25.0 (17.5-32.5)	12.5 (3.8-18.8)	0.003

Median and range values of 500-1000-2000-4000 Hz pure tone audiometry and air-bone gap results are presented in the table (Unit: dB). ACT: Air-Conduction Threshold, BCT: Bone-Conduction Threshold, ABG: Air-Bone Gap

Air conduction threshold of under 30 dB was reached in 76.5% in the ATF group, and 63.1% in the underlay tympanoplasty group (P>0.05). The ATF and underlay group patients had postoperative ABGs less than 20 dB in 76.5% and 78.9% (P>0.05). No difference for functional hearing success was detected among the groups (P=0.586, OR: 1.15, 95% CI: 0.24-5.56).

Analyses of the preoperative and postoperative ABG closure rates alone demonstrated a significant difference in the underlay group (pre-op ABG: Median: 25, interquartile range: 19 vs post-op ABG: Median: 15, interquartile range: 12) (P=0.031). However, the decrease in ABG was not significant in the ATF group (pre-op ABG: Median: 23, interquartile range: 9 vs post-op ABG: Median: 13, interquartile range: 14) (P=0.083).

Discussion

Tympanoplasties for anterior tympanic membrane perforations are surgically demanding, thus, surgical approaches have lower closure rates compared to other perforations [1-2]. Reasons for graft failure include scarcity of vascular supply,

difficulty in access, and lack of medial support for the graft [2]. Many different techniques and modifications of underlay and overlay tympanoplasties have been described with increased graft survival in anterior tympanic membrane perforations [2-3]. The ATF technique is one of the modifications of the underlay technique described to solve this problem. In this technique, a small tab of fascia is anchored to the anterior wall to provide durability for the graft while preserving the anterior acute tympanomeatal angle.

The proposed technique was first introduced by Bailey in 1976 [6]. In his underlay fixation technique, small tongues of the fascia graft were drawn under the fibrous annulus both superiorly and anteriorly through 2-4 mm tunnels on the anterior bony canal wall. In 1986, Primrose and Kerr defined the anterior hitch method for anterior marginal perforations [7]. This method was a modification of the underlay fixation technique using only one anterosuperior tunnel. Sharp et al. exercised the Kerr flap in 47 patients with a 97.5% graft take rate [8]. Later in 1996, Kerr published his series with a 100% success rate in 20 patients [9]. Instead of creating an anterior tunnel, Harris et al. [5] made the anterior incision just lateral to the annulus. With their anterior pull-through technique, they reported an 84.6% perforation closure rate in 13 patients. They proposed that performing this modification was easier and less time-consuming than the anterior hitch method.

Our experience with the ATF method was similar to the previous reports [5,8,9]. In contrast to overlay techniques, creating a small tunnel on the anterior wall did not cause anterior blunting. The decision to do underlay or ATF can be made intraoperatively, just before trimming the fascia. Indeed, the ATF method requires more time and experience [5,7]. We believe creating a 2 mm tunnel provides more support for the graft and pulling the anterior tab through the tunnel is not very difficult. However, in cases with obstructed views of the anterior tympanic annulus due to anterior bony overhang or anatomical reasons, the ATF method may not be feasible. Although this technique can be used in the transcanal, endaural, and postauricular approaches, the postauricular route provides a better view of the anterior wall and more mobility to the surgeon [6].

In the literature, 84.6% to 100% graft take rates were published with the ATF method [5, 7-11]. However, there is only one study comparing the ATF method with the underlay techniques. In this random prospective clinical trial, D'Ereditá and Lens [11] compared the ATF technique with standard underlay myringoplasty in children. The closure rate at 2 years of follow-up was 93.2% in the ATF technique and 84.6% in the underlay technique. Although they achieved insignificantly better results with the ATF technique, their results were not limited to anterior perforations. In anterior perforations, they still achieved better results with the ATF technique (91.3% vs 78.9%) [11]. Our results were consistent with this study (94.4% in the ATF arm and 73.7% in the underlay tympanoplasty arm).

The most common graft failure in our underlay group was medialization of the anterior border of the cartilage. If this medialization occurs without fascia or pericondrium on the free margin, it is difficult to restore.

The main drawbacks of our study were the small sample size, lack of randomization, and non-homogeneity of the groups in terms of ABG and ossicular problems.

Conclusion

ATF is a safe and effective technique for repairing anterior tympanic membrane perforations. None of the patients had anterior blunting or graft lateralization at 18 months follow-up. Although insignificant, higher graft take rates were achieved with the ATF technique compared to underlay tympanoplasty.

References

1. Baba S, Fujikura T, Pawankar R, Yagi T.Subjective evaluation of post-tympanoplasty hearing in relation to the pure tone threshold. AurisNasus Larynx.2004 Dec;31(4):347-51.
2. Barake R, El Natout T, Bassim M, El Natout MA. Loop underlay tympanoplasty for anterior, subtotal and total tympanic membrane perforations: a retrospective review. J Otolaryngol Head Neck Surg. 2019;48:12.
3. FischU, May JS, Linder T. Tympanoplasty, Mastoidectomy and Stapes Surgery. Second Edition.Thieme Group. 2008: page 45.
4. Faramarzi A, Hashemi SB, Rajaee A. "Mucosal pocket" myringoplasty: a modification of underlay technique for anterior or subtotal perforations. Am J Otolaryngol. Nov-Dec 2012;33(6):708-13.
5. Harris JP, Wong YT, Yang TH, Miller M. How I do it: Anterior pull-through tympanoplasty for anterior eardrum perforations. Acta Otolaryngol. 2016;136(4):414-9.
6. Bailey HAT Jr. Symposium: Methods of reconstruction in tympanoplasty. II. Maintenance of the anterior sulcus-tympanic membrane relationships in tympanoplastic surgery. Laryngoscope. 1976 Feb;86(2):179-84.
7. Primrose WJ, Kerr AG. The anterior marjinal perforation. Clin Otolaryngol Allied Sci. 1986 Jun;11(3):175-6.
8. Sharp JF, Terzis TF, Robinson J. Myringoplasty for the anterior perforation: experience with the Kerr flap. J Laryngol Otol .1992 Jan;106(1):14-6.
9. Scally CM, Allen L, Kerr AG. The anterior hitch method of tympanic membrane repair. Ear Nose Throat J. 1996 Apr;75(4):244-7.
10. Faramarzi M, Atashi S, Edalatkhah M, Roosta S. The effect of anterior tab flap technique on graft success rate in large tympanic membrane perforation. Eur Arch Otorhinolaryngol. 2020 Jul 27. Online ahead of print.
11. D'Eredità R, Lens MB. Anterior tab flap versus standard underlay myringoplasty in children. Otol Neurotol. 2009 Sep;30(6):777-81.

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Research article

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Evaluation of ultrasonic intravascular thrombectomy system on a rabbit model in the treatment of deep vein thrombosis

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Ethics Committee Approval
The study was initiated after approval was granted by Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision numbered 65202830-050.04.04-319. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Advanced treatment options are needed in deep venous thrombosis (DVT), which is a special subgroup of venous disease. We examined this subgroup on an animal model and aimed to evaluate the effects of the ultrasonic intravascular thrombectomy system on vascular endothelial damage.
Methods: A total of 24 rabbits in 3 groups were used in the study. DVT was created in the common iliac vein by the administration of intravascular fibrin. One hour passed for DVT formation. The ultrasonic intravascular thrombectomy system and the mechanical thrombectomy system were used separately in the DVT groups. After one hour, samples obtained from the groups were examined histologically.
Results: Significantly less endothelial damage was detected in the ultrasonic intravascular thrombectomy system group compared to the mechanical thrombectomy group ($P<0.05$).
Conclusions: Ultrasonic intravascular thrombectomy method minimizes the thrombus load and causes minimal endothelial damage. These findings show that the ultrasonic intravascular thrombectomy method can be used successfully in DVT treatment.

Keywords: Deep vein thrombosis, Ultrasonic intravascular thrombectomy system, Animal model, Endothelial injury

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Introduction

Deep venous thrombosis (DVT) has a wide range of symptoms. If asymptomatic, it is defined as subclinical DVT. It may cause mortality due to a pulmonary embolism. Venous ulcer and postphlebitic syndrome may occur in untreated patients. Cancer, postoperative long-term bed dependency, sedentary lifestyle, advanced age, obesity, tobacco use, organ failure, neurological diseases, hereditary causes, increased platelet count, and increased red blood cell distribution width may have a predisposing effect [1, 2]. In the Caucasian race, which includes Turkey, DVT cases are observed at a rate of 50-124/100,000 per year [3]. Innovations are needed in the prevention, diagnosis, follow-up, and treatment of DVT because it is a very common disease with high morbidity and mortality due to venous thromboembolism [4]. There are many treatment methods of DVT, including interventional techniques. However, no studies are comparing these methods with each other in terms of vascular endothelial damage. The absence of endothelial damage is essential for the effectiveness of the treatment and prevention of recurrence. In this study, a comparison was made between mechanical thrombectomy and the ultrasonic intravascular thrombectomy system in terms of endothelial damage.

Materials and methods

The study was initiated after the approval was granted by Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision numbered 65202830-050.04.04-319. The study was conducted on a total of three groups and twenty-four rabbits. There were eight rabbits in each group (New Zealand white rabbits, 6-8 months old, males weighing 3.2-3.5 kg, females weighing 2.75-3 kg). The rabbits were housed in equally sized cages and at a constant temperature of twenty degrees, in a laboratory environment capable of receiving twelve hours of the night and twelve hours of daylight. Standard rabbit food was used in all rabbits and their water was changed every other day. 90 mg/kg subcutaneous ketamine and 3 mg/kg intraperitoneal xylazine were administered to the animals for anesthesia before surgical applications.

Group 1: No procedures were performed on the animals in this group. At the end of the experiment, iliac vein samples were obtained after sacrification.

Group 2: DVT was created in the iliac vein and a mechanical thrombectomy was performed. At the end of the experiment, iliac vein samples were obtained after sacrification.

Group 3: DVT was created in the iliac vein and thrombectomy was performed with the ultrasonic intravascular thrombectomy system. At the end of the experiment, iliac vein samples were obtained after sacrification.

Acute DVT was induced in each study group by catheter-mediated fibrin application previously described by Itoh et al. [5]. The common iliac vein was thrombosed with a fibrin-coated catheter of 0.9 mm in diameter. In the study of Itoh et al., thrombosis was observed to start approximately within 2 minutes after fibrin administration and reached the desired level at the 20^{th} minute. Therefore, thrombectomy began 1 hour after thrombosis developed. Surgical procedures were performed under general anesthesia and per the ethical rules. The iliac veins of the animals were explored and a thrombectomy was performed so that both the thrombectomy catheters were visible and manually felt. A mechanical thrombectomy catheter (Fogarty catheter) and an ultrasonic intravascular thrombectomy system catheter (Mavera Medical Devices Inc.) were used for thrombectomy. The samples removed after the animals were sacrificed were evaluated histopathologically and comparisons were made separately for each group.

Histopathological method

The common iliac vein tissues were fixed in 10% neutral formalin solution and embedded in paraffin blocks after routine alcohol-xylol procedure. The 5 µ sections on the polylysine slides were stained with hematoxylin-eosin, the size of the thrombotic mass was evaluated under a light microscope, and the damage to the endothelium was evaluated as shown in the table (Table 1).

Table 1: Histopathological scoring system of endothelial damage

Histopathological Score	
Thrombus in the entire lumen (3)	Damage to the entire endothelium (3)
Thrombus in half of the lumen (2)	Damage to half of the endothelium (2)
Thrombus in a quarter of the lumen (1)	Damage to the quarter of the endothelium (1)
No thrombus (0)	No damage (0)

Statistical analysis

The data were analyzed with the SPSS 20.00 program (StataCorp LP, College Station, TX, USA). The difference between the groups was determined by the Kruskal Wallis test, one of the nonparametric tests, and the differing group was assessed with the Mann Whitney U test. A *P*-value of <0.05 was considered statistically significant.

Results

Statistically significant differences were found between the groups in terms of both thrombosis and endothelial damage in the common iliac veins (Table 2).

Table 2: Statistical comparison of groups according to results

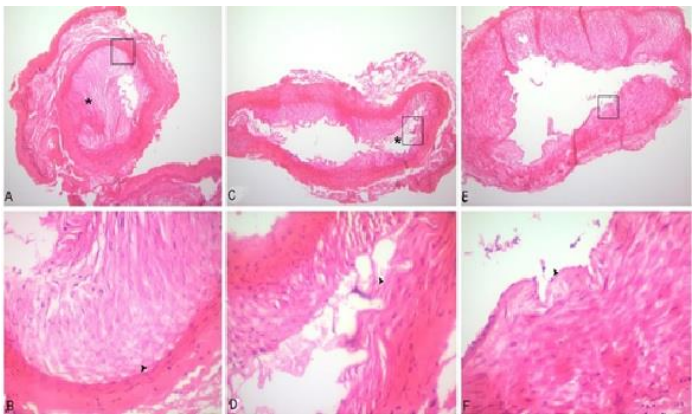
Groups	Thrombosis	Endothelial Damage
Group 1 (Control group)	0.16(0.40)c	1.33(0.51)b
Group 2 (Mechanical thrombectomy group)	2.16(0.40)a	2.16(0.40)a
Group 3 (Ultrasonic intravascular thrombectomy system group)	1.16(0.40)b	2.16(0.40)a
Statistical Significance (*P*-value)	<0.05	<0.05

Table 3: Differences between the groups in terms of endothelial damage in the post-hoc Dunn test (Std: Standard)

Sample 1-Sample 2	Test Statistic	Std. Error	Std. Test Statistic	*P*-value
Ultrasonic intravascular thrombectomy system vs. the control group	1.063	4.464	0.238	0.812
Mechanical thrombectomy vs. the control group	-18.937	4.464	-4.242	0.000
Ultrasonic intravascular thrombectomy system vs. mechanical thrombectomy	-20.000	4.464	-4.480	0.000

The lumen of the iliac vein was completely covered with a thrombotic mass in the mechanical thrombectomy group, and leukocyte infiltration was observed in the thrombotic mass. The ultrasonic thrombectomy group had a mild thrombotic mass and mild leukocyte infiltration, while no thrombotic mass was found in the control group. In the ultrasonic thrombectomy group, the vascular endothelial structure had a normal histological appearance, whereas in the mechanical thrombectomy group, moderate degeneration and desquamation were observed in the vascular endothelial cells. There was no endothelial injury in the control group ($P<0.001$) (Figure 1) (Table 3).

Figure 1: Common iliac vein sections stained with hematoxylin-eosin, light microscope images showing thrombotic masses and endothelial damage



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Discussion

Although venous thrombosis can be seen in any vein, lower extremity DVTs cause life-threatening complications such as pulmonary thromboembolism and postphlebitic syndrome more often. DVT, seen at a rate of 1% in older ages, is most common in the lower extremities and pelvic veins [6]. The postphlebitic syndrome is seen in 5-10% of the lower extremity DVT patients [7].

Symptoms begin to appear in most patients shortly after thrombosis develops. The first 2 weeks are considered acute DVT, 2-4 weeks, subacute DVT, and >4 weeks, it is defined as chronic DVT. DVT treatment can also vary depending on the stage of the disease. Medical, interventional, and surgical methods are used according to the stage of the disease. Commonly used interventional treatment methods include mechanical thrombectomy, aspiration thrombectomy, pharmacomechanical thrombectomy, and ultrasonic thrombectomy [8, 9].

Each of the methods used to prevent postphlebitic syndrome has a great advantage. All significantly reduce the development of postphlebitic syndrome as a result of vein recanalization [10-12]. These methods help not only to prevent changes in the chronic phase but also to eliminate complaints in the acute phase, reduce thrombus burden and shorten lysis time [13-15]. In addition, they reduce hospital costs by preventing long hospitalizations [16]. However, the use of significant amounts of fibrinolytic agents in pharmacomechanical methods increases the risk of bleeding [17].

Open surgical methods are still an option in the treatment of acute DVT. Studies are reporting that it has a reliability of close to 100% in preventing postphlebitic syndrome [18]. All the methods and techniques listed can be used alone or in combination [19, 20] in lower and upper extremity thrombosis [21].

This study compared conventional mechanical thrombectomy and ultrasonic thrombectomy methods on a rabbit DVT model in terms of thrombus load, presence of thrombus, and endothelial damage. Based on our results, ultrasonic thrombectomy was superior to conventional thrombectomy in clearing the thrombus and reducing the thrombus load as well as endothelial damage.

This study was designed to evaluate the early phase of acute deep vein thrombosis. In daily life, most patients clinically transform from acute deep vein thrombosis to chronic deep vein thrombosis. This shows that it is more effective to monitor long-term results. The most important outcome expected in the early period in the treatment of acute DVT is the reduction or complete elimination of the thrombus load. Therefore, the lower thrombus load in ultrasonic thrombectomy is an indication that the device has the desired feature. In addition, minimal endothelial damage in the ultrasonic thrombectomy group can be considered a positive sign of long-term results.

Limitations

There are several limitations to our study. First, only two of the thrombectomy methods were compared. The study being an animal experiment limited the chance of a long-term follow-up. In addition, clinical studies including long-term follow-ups are needed.

Conclusion

We observed that the ultrasonic thrombectomy method minimized early thrombus load and caused minimal endothelial damage. These findings suggest that the ultrasonic thrombectomy method can be successfully used in the treatment of acute deep vein thrombosis.

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References

1. Cay N, Unal O, Kartal MG, Ozdemir M, Tola M. Increased level of red blood cell distribution width is associated with deep venous thrombosis. Blood Coagulation & Fibrinolysis. 2013;24(7):727-31.
2. Ada F, Polat V. Evaluation of platelet indices in acute, subacute and, chronic phases of deep venous thrombosis. Cumhuriyet Medical Journal. 2019;41(3):544-50.
3. Han JS, Park TS, Cho SY, Joh JH, Ahn HJ. Increased mean platelet volume and mean platelet volume/platelet count ratio in Korean patients with deep vein thrombosis. Platelets. 2013;24(8):590-3.
4. Willans DJ, Mill SC, Ranney EK. Common thrombotic disorders defined by CBC platelet parameters. Clinical and Applied Thrombosis/Hemostasis. 1995;1(3):188-201.
5. Itoh K, Ieko M, Hiraguchi E, Kitayama H, Tsukamoto E. In vivo kinetics of 99m Tc labeled recombinant tissue plasminogen activator in rabbits. Annals of Nuclear Medicine. 1994;8(3):193-9.
6. Wiwanitkit V. Plateletcrit, mean platelet volume, platelet distribution width: its expected values and correlation with parallel red blood cell parameters. Clinical and Applied Thrombosis/Hemostasis. 2004;10(2):175-8.
7. Lichtenberg M, de Graaf R, Jalaie H. Acute and chronic venous outflow obstructions–a global burden. Vasa. 2021;50(1):1.
8. Kasirajan K, Gray B, Ouriel K. Percutaneous AngioJet thrombectomy in the management of extensive deep venous thrombosis. Journal of Vascular and Interventional Radiology. 2001;12(2):179-85.
9. Delomez M, Beregi JP, Willoteaux S, Bauchart JJ, d'Othée BJ, Asseman P, et al. Mechanical thrombectomy in patients with deep venous thrombosis. CardioVascular and Interventional Radiology. 2001;24(1):42-8.
10. Biuckians A, Meier III GH. Treatment of symptomatic lower extremity acute deep venous thrombosis: role of mechanical thrombectomy. Vascular. 2007;15(5):297-303.
11. Augustinos P, Ouriel K. Invasive approaches to treatment of venous thromboembolism. Circulation. 2004;110(9_suppl_1), I-27.
12. Chandra V, Dwyer D, Quadri R, Sharma A, Khaja M, Matson J. Initial Experience with Inari Thrombectomy Systems for Single-Session Suction Thrombectomy of Iliocaval Thrombus. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2021;9(2):540-1.
13. Shi HJ, Huang YH, Shen T, Xu Q. Percutaneous mechanical thrombectomy combined with catheter-directed thrombolysis in the treatment of symptomatic lower extremity deep venous thrombosis. European Journal of Radiology. 2009;71(2):350-5.
14. Murphy KD. Mechanical thrombectomy for DVT. Techniques in Vascular and Interventional Radiology. 2004;7(2):79-85.
15. Vedantham S, Vesely TM, Parti N, Darcy M, Hovsepian DM, Picus D. Lower extremity venous thrombolysis with adjunctive mechanical thrombectomy. Journal of Vascular and Interventional Radiology. 2002;13(10):1001-8.
16. Lin PH, Zhou W, Dardik A, Mussa F, Kougias P, Hedayati N, et al. Catheter-direct thrombolysis versus pharmacomechanical thrombectomy for treatment of symptomatic lower extremity deep venous thrombosis. The American Journal of Surgery. 2006;192(6):782-8.
17. Blackwood S, Dietzek AM. Pharmacomechanical thrombectomy: 2015 update. Expert Review of Cardiovascular Therapy. 2016;14(4):463-75.
18. Kutsukata N, Mashiko K, Matsumoto H, Hara Y, Sakamoto Y, Yokota H, et al. Surgical venous thrombectomy for Japanese patients with acute deep vein thrombosis: a review of 5 years' experience. Journal of Nippon Medical School. 2010;77(3):155-9.
19. Kasirajan K, Milner R, Chaikof EL. Combination therapies for deep venous thrombosis. Seminars in Vascular Surgery. 2006;19(2):116-21.
20. Karthikesalingam A, Young EL, Hinchliffe RJ, Loftus IM, Thompson MM, Holt PJE. A systematic review of percutaneous mechanical thrombectomy in the treatment of deep venous thrombosis. European Journal of Vascular and Endovascular Surgery. 2011;41(4):554-65.
21. Arko FR, Davis CM, Murphy EH, Smith ST, Timaran CH, Modrall JG, et al. Aggressive percutaneous mechanical thrombectomy of deep venous thrombosis: early clinical results. Archives of Surgery. 2007;142(6):513-9.

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Nano-based ceramic surgical blade accelerates wound healing

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Ethics Committee Approval
This study was approved with the decision of No. 65202830-050.04.04-33 by the Animal Review Board of Sivas Cumhuriyet University.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Many factors affect the results of a surgical operation, one of which is the harmony of the materials used during surgery with the tissue. Zirconia is a material with antimicrobial properties, high surface sensitivity and robustness. This study was conducted to observe the acute and subacute effects of the nano-based zirconia surgical blade on living tissue.

Methods: The study was conducted after approval was granted by the Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision number 65202830-050.04.04-33. A total of 16 rats were used in the study. Eight were incised with classic steel surgical blade and eight, with nano-based zirconia surgical blade. A total of 4 incisions were performed to each rat and the incisions were closed with 3.0 polypropylene suture. Tissue samples were obtained from the incisions on day 0, 3, 7 and 21, and examined histologically.

Results: The epidermis layer thickness on days 7 and 21 (P=0.030, P=0.025), the dermis layer thickness on days 3 and 7 (P=0.035, P=0.030), muscle layer thickness on days 7 and 21 (P=0.030, P=0.025) were significantly increased and inflammatory cells were significantly less on days 3, 7 and 21 (P=0.030, P=0.020, P=0.025) in the nano-ceramic surgical blade compared to the other group. Collagen tissue density was significantly higher in favor of the nano-ceramic blade on the 3rd and 7th days (P=0.025, P=0.020).

Conclusion: Nano-based zirconia surgical blade has been shown to have positive effects on wound healing. The use of nano-based zirconia surgical blade should be kept in mind in patient groups with wound healing problems.

Keywords: Ceramic, Healing, Histological, Nano-based, Scalpel, Steel, Surgical blade, Wound

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Introduction

The final goals after a surgical operation are the rapid and scarless healing of the wound, and the absence of infection. The wound healing process depends on many factors [1]. Some of these components are interchangeable and technological advances have contributed positively to the wound healing process. One of the disciplines contributing to these positive developments is nanotechnology. With its advancement, the design of the materials changed, their effectiveness increased, and their advantageous properties have been brought to the fore. Nano-based drugs, diagnostic and therapeutic tools have begun to be used in clinical practice. It will be possible to use many nano-based instruments in surgical operations in the near future. One of the factors affecting wound healing is the features of the instruments used in surgery. Today, many methods are used to make a surgical incision, such as a conventional steel surgical blade, laser, CO_2, and electrocautery, with each having their advantages and disadvantages. Our study is the first animal experiment on nano-based zirconia surgical blade, but there are publications of material science of this issue [2-4]. This study aimed to investigate the histological changes in the surgical wound created with a nano-based zirconia surgical blade in a rat model.

Materials and methods

Animals

All experimental protocols were performed according to the guidelines for the ethical procedures of experimental animals and approved by the Sivas Cumhuriyet University local ethics committee for laboratory animal care and use. Male/female Wistar rats weighing 220-240 g were obtained from experimental animal center of Sivas Cumhuriyet University. The animals were kept under a 12-h-light-dark cycle in a room temperature of 20–22 °C and a relative humidity of 50–65% and had free access to standard laboratory food and water. After the back hair was removed by a clipper, the rats were anesthetized with intraperitoneal injection of ketamine (30 mg/kg, CEVA SanteAnimale, Brussels, Belgium) and xylazine (10 mg/kg, Rompun, Bayer Animal Health, Brussels, Belgium). For the first 3 days after surgery, each animal was administered ceftriaxone sodium intramuscularly (30 mg/kg). In all rats, euthanasia was performed under ketamine/xylazine anesthesia.

Experimental groups and treatments

The study was carried out after approval was granted by Sivas Cumhuriyet University Animal Experiments Local Ethics Committee with the decision number 65202830-050.04.04-33. The animals were cared for and housed in the experimental animal laboratory of Sivas Cumhuriyet University. A total of sixteen rats were included, among which 8 were incised with nano-based zirconia surgical blades (H2 Zir Medikal, Kütahya/Turkey) (Figures 1-2) and eight, with classic steel surgical blades (Braun, Tuttlingen/Germany), the latter comprising the control group. A total of four incisions were made on each rat, two to the right and two to the left, with 1 cm to the middle part of the dorsum. A specimen was taken from the near right side cranial incision for histological examination on postoperative day 0, at the 12th hour. Three days after the first incision, a specimen was taken from the incision near the left side. Seven days after the first incision, a specimen was taken from the right caudal incision. Finally, after 21 days, the specimen was taken from the caudal incision near the left side for histological examination. All incisions were closed with prolene sutures and daily dressings were performed with standard povidone iodine solution. The procedure was performed separately for each group and under general anesthesia. No rats died during the procedures. On the 21st day, after the last tissue samples were taken, all rats were sacrificed with high dose anesthetic agents.

Figure 1: Nano-based ceramic surgical blade

Figure 2: Appearance of the surgical model of the study

Histological examination

Wound skin tissue samples were obtained from the control and experimental groups on days 0 (12 h), 3, 7, and 21 by a scalpel for histological observation. After a 36-hour fixation in Bouin's solution, all the investigated tissues were embedded in paraffin blocks, cut into 5-µm-thick serial sections, mounted on glass slides coated with poly-L-lysine, and subjected to hematoxylin-eosin (HE; Thermo Fisher Scientific) staining for morphological assessment.

Skin sections were examined for depth of epidermis, dermis, and muscle layer at the center of each wound. Specific features were used based on location and characteristics of the layer to measure the thickness. The epidermis is the outermost layer of the skin composed of keratinized, stratified squamous epithelium. Directly lying beneath the epidermis and above the subcutaneous layer is the dermis, which consists of connective tissue, cellular elements, and ground substance. Inferior to the subcutaneous layer is the muscle layer composed of mature myocytes. In this study, dermis and subcutaneous layers were evaluated together as a single layer due to thickness differences between skin sections. The thicknesses of the layers were measured using ImageJ software (ImageJ; National Institutes of Health, Bethesda, MD). The percentage of each skin section occupied by resident mononuclear cells was measured using the

IHC Toolbox plug in for ImageJ software. Briefly, the numbers of dark purple-colored pixels were identified with "color deconvolution function" by separating the HE stains. It was quantified and represented as a percentage relative to the total number of pixels per skin section. Skin sections were also stained with Masson's trichrome to observe the site of collagen deposition per skin section. The percentage of collagen was calculated using the ImageJ software as described previously [5]. An algorithm was used to deconvolve the color information acquired with stained sections. The number of blue colored pixels was quantified and represented as a percentage relative to the total number of pixels per skin section.

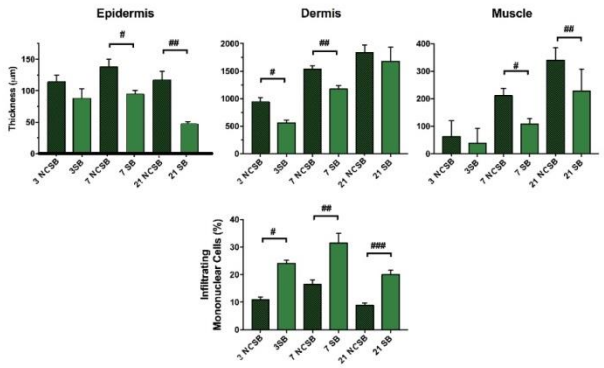
Statistical analysis

Statistical analysis was performed using the SPSS (version 24.0, StataCorp LP, College Station, TX, USA) software package. The Kruskal Wallis test was used to compare the differences between the groups in the histopathological examination of the data obtained semi-quantitatively. The differing groups were identified by the Mann Whitney U test. A *P*-value of <0.05 was considered statistically significant.

Results

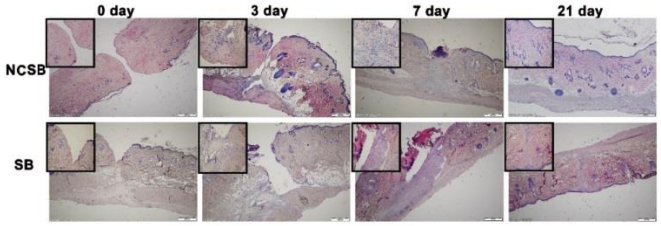
The epidermis, dermis, muscle tissue, collagen tissue and inflammatory cells were similar in the samples taken at the 12th hour of the first incision. The epidermis layer thickness on days 7 (140µm vs 100µm) (*P*=0.030), and 21 (110µm vs 40µm) (*P*=0.025), the dermis layer thickness on days 3 (900µm vs 500µm) (*P*=0.030), and 7 (1500µm vs 1100µm) (*P*=0.035), muscle layer thickness on days 7 (200µm vs 100µm) (*P*=0.025), and 21 (320µm vs 210µm) (*P*=0.030) were significantly increased and inflammatory cells were significantly less on days 3 (10% vs 25%)(*P*=0.030), 7 (15% vs 30%)(*P*=0.020), and 21 (8% vs 20%) (*P*=0.025) in the nano-ceramic surgical blade compared to the steel blade group (Figure 3, 4). Collagen tissue density was significantly higher in favor of the nano-ceramic blade on the 3rd (38% vs 30%) (*P*=0.025) and 7th (30% vs 15%) days (*P*=0.020) (Figures 5, 6).

Figure 3: Epidermis: $^{\#,\#\#}P$=0.030 vs. NSCB 7d, SB 7d, NSCB 21d, and SB 21d.
Dermis: $^{\#,\#\#}P$=0.035 vs. NSCB 3d, SB 3d, NSCB 7d, and SB 7d.
Muscle: $^{\#,\#\#}P$=0.030 vs. NSCB 7d, SB 7d, NSCB 21d, and SB 21d.
Infiltrating Mononuclear Cells: $^{\#,\#\#,\#\#\#}P$=0.020 vs. NSCB 3d, SB 3d, NSCB 7d, SB 7d, NSCB 21d, and SB 21d.



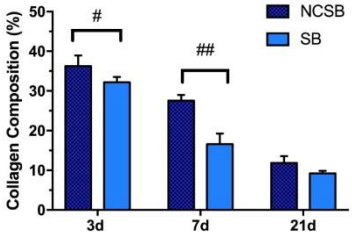
NCSB: nano-ceramic surgical blade, SB: surgical blade

Figure 4: Representative images of skin sections stained with hematoxylin and eosin. Infiltrating mononuclear cells were assessed by color deconvolution followed by quantification of dark purple stain. Thickness of the epidermis, dermis, and muscle layers of skin (mean with SD).



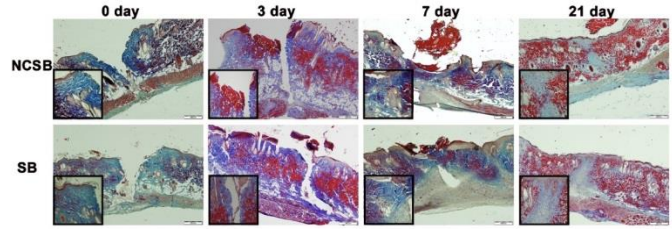
#, ##, ### *P*<0.05 between nano ceramic surgical blade and steel surgical blade group. NCSB: nano-ceramic surgical blade, SB: surgical blade

Figure 5: Collagen Composition: $^{\#,\#\#}P$=0.025 vs. NSCB 3d, SB 3d, NSCB 7d, and SB 7d.



NCSB: nano-ceramic surgical blade, SB: surgical blade

Figure 6: Representative images of skin sections stained with Masson's trichrome. Collagen composition was assessed by color deconvolution followed by quantification of blue stain (mean with SD). #, ## *P*=0.025 *P*<between nano ceramic surgical blade and steel surgical blade group.



NCSB: nano-ceramic surgical blade, SB: surgical blade

Discussion

Wound healing is a complex process involving cytokines, as well as matrix and components. This process is divided into three phases, namely, the inflammation, proliferation, and maturation phases [6, 7]. The inflammation phase includes the first 5-day period, when fibrin formation and angiogenesis are highest for the stabilization of the wound. The cellular elements that dominate the wound tissue are neutrophils and monocytes. The proliferation phase covers days 5 to 14, and collagen production from fibroblasts is highest. In this phase, wound contraction is achieved by the action of myofibroblasts, and the wound size begins to decrease [8]. Maturation phase refers to the process after the 14th day and sometimes takes years. In this phase, type 3 collagen is transformed into to the more robust type 1 collagen, helping to restore tissue to its original strength. It is observed that the tissue regains approximately 95% strength after about 6 weeks of wound is formed [7, 9]. Local and systemic factors play a major role in wound healing. Local factors include tissue blood flow (oxygenation), hematoma or seroma development in the wound site, infection, over-pressure wound dressing, surgical technique, foreign bodies, necrotic tissue, local steroid use, tissue edema, and radiotherapy. Systemic factors include advanced age, anemia, lack of nutrition, systemic steroid use, cytotoxic drug use, sepsis, diabetes, uremia, severe pain, and connective tissue diseases [1, 10, 11]. Although there are a number of studies on the various components of

wound healing, studies on the effects of the materials used in the surgical incisions on wound healing are limited.

Studies show that methods such as CO_2 assisted incision, ultrasound-assisted incision, and laser incision are superior to conventional steel surgical blades. Ryu et al. conducted a study on wound healing in the oral mucosa of the Guinea pig and showed that Er, Cr: YSGG laser incision group had less TNF-α and TGF-ß1 expression in the wound tissue compared to CO_2 scalpel, indicating better wound healing [12]. Carreira and colleagues showed that the CO_2 laser surgical blade had a better healing process than the conventional surgical blade, resulting in fewer leukocytes, minor tissue trauma, and reduced albumin extravasation in the skin incision. It was also noted that postoperative patient comfort was increased due to less pain and, better cosmetic results were obtained in CO_2 laser group [13]. Jawad and colleagues studied wound healing on the rabbit model with the steel scalpel. They found that the best wound healing occurred after the 14^{th} day of surgery [14].

Demir and colleagues studies the rabbit oral mucosa and demonstrated that Neodymium-Doped Yttrium Aluminium Garnet (Nd-YAG) laser facilitates soft tissue operations and provides faster wound healing [15]. Tuncer et al. compared the conventional surgical blade and CO_2 laser surgical blade in terms of postoperative pain relief need and showed that CO_2 laser surgical blade group needed less painkillers [16]. In the study conducted by Kara et al. Nd-YAG laser was shown to cause less pain and fewer postoperative side effects compared to the conventional surgical blade [17]. Pearce and colleagues compared the microscalpel with the conventional surgical blade in a rat model and found similar results among the two surgical blades in terms of all surgical outcomes, including inflammation [18].

The elevated cost of the mentioned methods, the lack usability in every surgical field and the unique structure of each tissue are the main obstacles against the widespread use of these devices. For this reason, the classic steel surgical blade is still widely used and seems indispensable for practical surgical life. There are also studies on changing the structure of the classical surgical blade. As reported by Tsai et al., the sharpness of the surgical blade increased with coating. Coating of the traditional surgical blades with ZrCuAlAgSi in the form of thin glass film may render them more useful in surgery [19]. Kelley et al. reported that the classical steel double-blade tissue cutters for microtomes yielded much better results in tissue sampling [20]. Mftah et al. investigated the properties, cytotoxicity, and antimicrobial properties of sulphated nano-zirconia. Sulphated nano-zirconia was found to have strong antibacterial properties against gram-positive and gram-negative bacteria, and its wide use was proposed in biomedical applications [2]. There are many methods to increase the sharpness of surgical blades. Sharpness is an important aspect of ceramic scalpels. To provide this sharpness, Kuai and colleagues used ELID grinding technology and demonstrated that more feasible results were achieved compared to traditional methods [3]. Kuai and his colleagues reported that a sharper surface was obtained in the nano ceramic scalpel along with ELID grinding technology [4].

According to our quantitative comparison of the histomorphological data, nano-based zirconia surgical blade has positive effects on wound healing. Increased collagen composition and epidermis, dermis, and muscle layer thickness, along with reduced levels of inflammatory cell infiltration indicate that the nano-based zirconia surgical blade results in better wound healing compared to the traditional steel scalpel.

Limitations

There are several limitations to our study. First, only two types of the surgical blade were compared. Second, conducting an animal experiment limited the chance of a long-term follow-up.

Conclusion

The nano-based zirconia surgical blade has been shown to accelerate wound healing process compared to the conventional steel surgical blade. It seems likely in the near future that the nano-based zirconia surgical blade will be preferred for surgical interventions in selected patients with wound healing problems.

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References

1. Parsak CK, Sakman G, Çelik, Ü. Yara iyileşmesi, yara bakımı ve komplikasyonları. Arşiv Kaynak Tarama Dergisi. 2007;16(2):145-59.
2. Mftah A, Alhassan FH, Al-Qubaisi MS, El Zowalaty ME, Webster TJ, Sh-eldin M, et al. Physicochemical properties, cytotoxicity, and antimicrobial activity of sulphated zirconia nanoparticles. International Journal of Nanomedicine. 2015;10: 765.
3. Kuai JC, Zhang FH, Liu YZ. ELID Grinding Technology of Nano-Material Cutting Tool. In Applied Mechanics and Materials. 2012;155:960-4.
4. Kuai JC, Zhang FH, Liu YZ. ELID Grinding Technology of Nano-Ceramic Scalpel. In Advanced Materials Research. 2012;468:1560-3.
5. Strong AL, Bowles AC, MacCrimmon CP, Frazier TP, Lee SJ, Wu X, et al. Adipose stromal cells repair pressure ulcers in both young and elderly mice: potential role of adipogenesis in skin repair. Stem Cells Translational Medicine. 2015;4(6):632-42.
6. Barbul A. Wound healing. Schwartz's Principles of Surgery. Mc Graw Hill Eight edition. 2005;223.
7. Sherris DA, Kern EB. The Wound. In Basic Surgical Skills, Mayo Foundation for medical Education and research, Rochester, 1999:8-12.
8. Pakyari M, Farokhi A, Jalili RB, Kilani RT, Brown E, Ghahary, A. Local Expression of Indoleamine 2, 3, Dioxygenase Prolongs Allogenic Skin Graft Take in a Mouse Model. Advances in Wound Care. 2018;8(2):58-70.
9. Özpolat B, Gürpınar Aylin Ö, Ayva Şebnem E, Gazyağcı S, Niyaz M. The effect of basic fibroblast growth factor and adipose tissue-derived mesenchymal stem cells on wound healing, epithelization and angiogenesis in a tracheal resection and end-to-end anastomosis rat model. Turkish Journal of Thoracic and Cardiovascular Surgery. 2013;21:1010-9.
10. Gupta A, Kumar P. Assessment of the histological state of the healing wound. Plastic and Aesthetic Research. 2015;2(5):239.
11. Durgun M, Durgun Ögücü S, Özakpınar Rıfat H, Eryılmaz Tolga A, Öktem Fatih H, İnözü E, et al. Approach to of infected sternotomy wounds in the management of mediastinitis. Turkish Journal of Thoracic and Cardiovascular Surgery. 2012;20:820-5.
12. Ryu SW, Lee SH, Yoon HJ. A comparative histological and immunohistochemical study of wound healing following incision with a scalpel, CO2 laser or Er, Cr: YSGG laser in the Guinea pig oral mucosa. Acta Odontologica Scandinavica. 2012;70(6):448-54.
13. Carreira LM, Azevedo P. Comparison of the Influence of CO2-laser and Scalpel Skin Incisions on the Surgical Wound Healing Process. ARC Journal of Anesthesiology. 2016;1(3):1-8.
14. Jawad MM, Alam MK, AbdulQader ST, Al-Azzawi LM, Husein A, Mahmood AS. Histological evaluation of incision healing response made by metallic scalpel on rabbits skin: preliminary study. International Medical Journal. 2013;20(4):496-8.
15. Demir T, Kara C, Özbek E, Kalkan Y. Evaluation of neodymium-doped yttrium aluminium garnet laser, scalpel incision wounds, and low-level laser therapy for wound healing in rabbit oral mucosa: a pilot study. Photomedicine and laser surgery. 2010;28(1):31-7.
16. Tuncer I, Özçakır-Tomruk C, Şencift K, Çöloğlu S. Comparison of conventional surgery and CO2 laser on intraoral soft tissue pathologies and evaluation of the collateral thermal damage. Photomedicine and laser surgery. 2010;28(1):75-9.
17. Kara C, Süleyman H, Tezel A, Orbak R, Cadirci E, Polat B, Kara I. Evaluation of pain levels after Nd: YAG laser and scalpel incisions: an experimental study in rats. Photomedicine and laser surgery. 2010;28(5):635-8.
18. Pearce EC, Hall JE, Boyd KL, Rousseau B, Ries WR. The Ophthalmology Microscalpel versus Standard Scalpels and Wound Healing in a Rat Model. Otolaryngology-Head and Neck Surgery. 2014;151(3):424-30.
19. Tsai PH, Lin YZ, Li JB, Jian SR, Jang JSC, Li C, et al. Sharpness improvement of surgical blade by means of ZrCuAlAgSi metallic glass and metallic glass thin film coating. Intermetallics. 2012;31:127-31.
20. Kelley DB, Abt AB. Uniform Tissue Sections Cut with a Double-Bladed Scalpel. Journal of Histotechnology.2013;16(4):363-4.

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The effect of online education during the pandemic on ocular surface symptoms

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Ethics Committee Approval
Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (Decision no:06, dated:12/04/21). Registered at Clinical Trial Registry (ClinicalTrials.gov Identifier: NCT04960696). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: During the pandemic, eye symptoms increased. This study aimed to investigate the effects of online education on ocular surface symptoms, which was a part of the distance learning model during the COVID-19 pandemic, to be able to prevent the formation of irreversible damage.
Methods: This cohort study included 315 students who were undertaking online education and presented at the Ophthalmology Department of a university hospital. The sociodemographic data, Schirmer test results, tear break-up time (TBUT) and Ocular Surface Disease Index (OSDI) scores of the students were noted. The data were analyzed using SPSS v. 22.0 software and a value of $P<0.05$ was considered statistically significant.
Results: Evaluation was made of 315 students with a mean age of 14.48 (5.86) years (range: 6-29 years). Of these, 159 were studying at a high school or university, and 267 had been participating in online education for ≥6 hours per week. New symptoms had developed in the eyes of 213. The Schirmer test results were 8.74 (3.76) mm in the right eye and 8.90 (3.86) mm in the left eye. TBUT was 9.95(3.60) seconds in the right eye and 10.15 (3.58) seconds in the left. The mean OSDI score was 26.39 (11.85). OSDI was significantly negatively correlated with the Schirmer results and TBUT (r= -0.883, $P<0.05$, r= -0.793, $P<0.05$, respectively), while Schirmer and TBUT were positively correlated (r=0.871, $P<0.05$).
Conclusion: With the continuation of education online during the COVID-19 pandemic, televisions, computers, and tablets were commonly used. This increased screen time led to the development of new symptoms causing significant changes in the OSDI, TBUT, and Schirmer tests.

Keywords: COVID-19, Online education, Tear break-up time, Schirmer, OSDI

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Introduction

At the end of 2019, a series of treatment-resistant cases of pneumonia of unknown cause was determined in Wuhan, China, by Dr. Wenliang Li. He warned that this could become an epidemic, and in March 2020, the novel coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 virus infection was declared a global pandemic by the World Health Organization (WHO) [1, 2]. This virus was one of the most rapidly spreading viruses in history. By 1 January 2021, 83.5 million cases had been diagnosed worldwide in 222 countries, with 1.82 million deaths [2].

With rapidly increasing numbers of cases from the beginning of the pandemic, national leaders and the WHO started to implement measures to protect public health. One of the most important was quarantine and the immediate temporary cessation of face-to-face education [3]. With these quarantine measures, 20 million students were no longer physically attending school, and in Turkey, as throughout the world, education was converted to a distance learning model [2, 4]. Televisions, computers, and tablets became an indispensable part of daily life as a part of the online education model. Exposure to digital screens is known to harm eye health [5, 6]. With the prolonged time spent using televisions, computers, and tablets for education during the pandemic, there was an increase in ocular complaints. The main reasons for these symptoms are ocular surface disorders and accommodation problems stimulated or exacerbated by digital screen exposure [7-9].

This study aimed to investigate the effects of online education on the ocular surface symptoms of the students, which was a part of the distance learning model during the COVID-19 pandemic, to be able to prevent irreversible damage with early diagnosis and treatment. With simple recommendations, it was aimed to protect ocular health.

Materials and methods

This cohort study was conducted in the Ophthalmology Department of a tertiary level university hospital. Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaras Sutcu Imam University Faculty of Medicine (Decision no:06, dated:12/04/21). This study is registered in the Clinical Trial Registry (ClinicalTrials.gov Identifier: NCT04960696). All procedures followed the principles of the Helsinki Declaration. The study sample consisted of 315 students, aged 6-30 years, participating in online education who presented at the Ophthalmology Polyclinic within 2 months. Patients were excluded from the study if they were aged <6 years or >30 years, had communication difficulties, were not students, or were not continuing education online.

All patients underwent the Schirmer test, the Tear Break-Up Time (TBUT) test, and the Ocular Surface Disease Index (OSDI) scoring, and filled a sociodemographic form created by literature review. The sociodemographic data were collected by face-to-face interviews. The OSDI scoring was performed face-to-face with a questionnaire consisting of 12 items in 3 sections regarding ocular symptoms, sight-related functions, and environmental factors. Each item is scored between 0-4 points, and the final score is calculated by multiplying the total points by 25 and dividing the result by the number of items. Thus, the total points range between 0-100 and are evaluated as follows: 0-12 points: Normal, 13-22 points: Mild, 23-32 points: Moderate, and 33-100 points: Severe ocular surface damage.

In the TBUT test, fluorescein is dropped into both eyes, and after several blinks, the cornea is examined biomicroscopically under cobalt blue. The time of the formation of two black dots is considered the tear break-up time. A time of >10 secs is normal.

In the Schirmer test, the results are obtained from a special filter paper placed between the eye and the lower eyelid outer third. The cut-off value is 10mm and values >10mm are considered normal.

Statistical analysis

Data obtained in the study were analyzed using SPSS v. 22.0 software. Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test. Categorical data were analyzed with the Chi-square test. The ANOVA test was used for comparisons between the groups. Spearman correlation analysis was utilized for group correlations. Continuous data were presented as mean (standard deviation (SD)), and categorical data, as number (n) and percentage (%). A value of $P<0.05$ was considered statistically significant.

Results

An evaluation was made of a total of 315 students with a mean age of 14.48 (5.86) years. The sociodemographic data and responses to the questionnaire are shown in Table 1.

Table 1: Sociodemographic and survey data of the students included in the study

	Groups	n	Percent (%)
Gender	Male	153	48.6
	Female	162	51.4
Education status	Primary school	78	24.8
	Middle school	78	24.8
	High school	78	24.8
	University	81	25.7
Weekly Online Education Period	<6 hours	48	15.2
	6-12 hours	117	37.1
	>12 hours	150	47.6
Online Education-related Screen Exposure	<30 minutes	51	16.2
	30-60 minutes	60	19.0
	61-120 minutes	99	31.4
	>120 minutes	105	33.3
Developed New Symptoms	Yes	213	67.6
	No	102	32.4
What Symptoms Have Developed	Sensitivity	156	49.5
	Itching	123	39.0
	Redness	135	42.8
	Sting-Burning	74	23.5
	Watering	75	23.8
	Blurred vision	90	28.5

N: Numbers of subjects

The data showing the quality, amount, and evaluations of the tears of the students are shown in Table 2. The overall mean Schirmer test results were 8.74 (3.76) mm in the right eye and 8.90 (3.86) mm in the left eye. Mean TBUT was 9.95 (3.60) secs in the right eye and 10.15 (3.58) secs in the left eye. According to the OSDI grading, 86 (27.3%) students were within normal limits, 95 (30.1%) had mild, 54 (17.1%) had moderate, and 80 (25.3%) had severe ocular surface damage. The mean OSDI score of the whole sample indicated moderate ocular surface damage.

The subgroup examinations (education status, duration of online education per week, education-related screen exposure) of the OSDI, Schirmer, and TBUT results and the post-hoc analyses are shown in Table 3.

Table 2: The results of the Shirmer test, tear break-up time and OSDI score of the students participating in the study

	Minimum	Maximum	Mean
Shirmer Test			
Right eye(mm)	2	15	8.74 (3.76)
Left eye(mm)	3	12	8.90 (3.86)
Total(mm)	2	15	8.82 (3.66)
TBUT			
Right eye(sn)	4	18	9.95 (3.60)
Left eye(sn)	6	15	10.15 (3.58)
Total(sn)	4	18	10.15 (3.58)
OSDI scores	4.5	61.6	26.39 (11.85)

TBUT: Tear Break Up Time, OSDI: Ocular Surface Disease Index

Table 3: Group comparisons of the test results measured by the questionnaire answers of the students participating in the study

		OSDI scores			Shirmer test		TBUT	
		N	Mean	*P*-value*	Mean	*P*-value*	Mean	*P*-value*
Education status	Primary school[a]	78	14.00 (15.46)[b,c,d]	<0.05	11.54 (3.25)[b,c,d]	<0.05	12.08 (3.21)[b,c,d]	<0.05
	Middle school[b]	78	27.47 (21.75)[a,d]		8.69 (3.99)[a,d]		10.00 (4.00)[a,d]	
	High school[c]	78	22.33 (21.29)[a,d]		8.35 (2.90)[a,d]		9.96 (3.30)[a,d]	
	University[d]	81	41.19 (18.73)[a,b,c]		6.78 (2.66)[a,b,c]		8.22 (2.63)[a,b,c]	
Weekly online education period	<6 hours[a]	48	13.47 (23.37)[b,c]	<0.05	11.06 (3.88)[b,c]	<0.05	12.38 (3.38)[b,c]	<0.05
	6-12 hours[b]	117	28.30(19.19)[a]		8.46 (3.50)[a]		9.38 (3.26)[a]	
	>12 hours[c]	150	29.04 (21.84)[a]		8.38 (3.44)[a]		9.82 (3.59)[a]	
Online education-related screen exposure	<30 minutes[a]	51	8.01 (16.42)[b,c,d]	<0.05	10.41 (2.40)[d]	<0.05	12.35 (3.09)[c,d]	<0.05
	30-60 minutes[b]	60	20.07 (20.91)[a,d]		10.35 (4.29)[d]		11.35 (3.66)[c,d]	
	61-120 minutes[c]	99	25.29 (18.61)[a,d]		9.27 (3.58)[d]		9.88 (3.31)[a,b,d]	
	>120 minutes[d]	105	39.98 (18.75)[a,b,c]		6.74 (2.79)[a,b,c]		8.34 (3.08)[a,b,c]	
Developed new symptoms	Yes	213	31.10 (18.06)	<0.05	7.63 (3.19)	<0.05	8.79 (2.97)	<0.05
	No	102	7.93 (12.51)		11.88 (2.92)		13.28 (2.92)	

TBUT: Tear Break Up Time, OSDI: Ocular Surface Disease Index, *ANOVA, **Groups that were significant in the post-hoc analysis were given as superscript.

OSDI was significantly negatively correlated with the Schirmer results and TBUT (r= -0.883, $P<0.05$, r= -0.793, $P<0.05$, respectively), while Schirmer and TBUT were positively correlated (r=0.871, $P<0.05$).

Discussion

One of the main precautions taken during the COVID-19 pandemic was the conversion of education to an online model. This model was of great importance concerning the quarantine and lockdown but resulted in students spending more time using televisions, computers, and tablets. The longer digital screen exposure increased the ocular complaints of the students. Ocular surface disorders and accommodation problems stimulated or exacerbated by digital screen exposure are the main reasons for these symptoms.

Of the total 315 study participants, 162 were female and 50.4% were studying at a high school or university. Among all, 52.3% undertook an online education of ≤12 hours per week, and a screen time exposure of >1 hour before and/or after online education was reported by 64.8%. In the study by Bostanci in 2016 [10], ocular symptoms increased with digital screen exposure, and in a study on computer use and sight, Shantakuri [11] reported that as digital screen time use increased, new symptoms were developing in the eyes, the most common being redness and burning. In the current study, new ocular symptoms were had developed after the introduction of online education in 213 students. The most common included sensitivity in the eyes in 49.5%, redness in 42.8%, and itching in 39%. It is thought that as a result of increased digital screen exposure, the amplitude of blinking is disrupted, and with the development of epithelial damage, more sensitivity, redness, and secondary itching develop.

The OSDI results of the middle school and high school students were similar according to the post-hoc test, while the other subgroups showed significant differences. In a study by Schiffman [12] and Simavli [7], the OSDI score was correlated with screen exposure. In the current study, the highest mean points were found among university students, and these were classified as severe ocular surface damage. There may be several effective factors, such as the longer lesson hours of university students, weaker family, and social ties, and auto-control mechanisms, and spending a longer time on extra-curricular projects, thesis preparation, social media, and digital gaming platforms.

The OSDI score was significantly high in those who were studying ≥6 hours per week online, but there was no significant difference between the groups who undertook 6-12 hours and >12 hours of online education. OSDI scores were highest in the group who received more than 2 hours of online education per week, who were considered to have severe ocular surface damage. Students who developed new symptoms after online education were determined to have a moderate level of ocular surface damage. In a study of young adults by Pang in 2020 [13], screen time was reported to affect dry eye symptoms, and in another study by Mishra [14], entitled, "The effect of digital screen exposure on the ocular surface", it was reported that as digital screen time exposure increased, so did the OSDI score and dry eye symptoms. Associated with the decrease in blink reflex in digital screen-focused education, there is thought to be insufficient irrigation of the corneal surface epithelium and impaired tear functions. It must also not be forgotten that another main factor is that the screen light is not at an equal level to that of the environment.

The Schirmer test results were examined within the sub-groups. The lowest measurement was obtained among the university students, who were considered to have dry eyes. The results of the middle school and high school students were similar, and there was a statistically significant difference between the other groups. In the group receiving ≥6 hours per week online education, dry eye was determined at a significantly higher rate. The results of the groups receiving 6-12 hours and >12 hours online education were similar. A significant difference was found between the group with >2 hours of education-related screen exposure and the other groups concerning dry eye classification. The results of the groups with ≤2 hours of exposure were similar. Dry eye was significantly more common in the group that developed new symptoms after online education. Similar results were reported in a study by Mehra et al. [15], as an increase in the rate of dry eye in parallel with an increase in digital screen exposure. In a study of office workers by Uchino et al. [16], the extent of dry eye disease was determined at a high rate associated with the duration of screen exposure. Kawashima et al. [17] also investigated office workers and determined an increase in tired eyes and the diagnosis of dry eye with increased screen exposure. With a series of simple precautions, these diagnoses were reduced by 75%.

In the current study, the Schirmer test results were negatively affected in parallel with screen exposure. The high Schirmer test values measured in primary school students, those with few online lesson hours, and those with low education-related screen time were an indicator of this finding. Unlike the previous studies in literature, the reason that this study was conducted on a sample of students with no known systemic ocular disease was to be able to determine ocular surface problems which may develop associated with the use of televisions, computers, and tablets in online education during the pandemic.

The TBUT measurements were low (below the cut-off value) in university students, those with ≥6 hours per week online education, and those with > 1-hour education-related screen exposure, with significant differences between these and the other groups. The TBUT was affected in the group that developed new ocular symptoms after the onset of online education. In a study of dry eye patients, Yiğit et al. [18] showed that the TBUT value decreased as screen exposure increased. Gümüş et al. [19] examined the effect of computer use on ocular parameters and determined a negative relationship between TBUT and increased periods of computer work. In the workplaces and social life of the modern technological age, digital screen use has increased even more with the pandemic. The mandatory increase of screen exposure for students can be considered the reason for the decrease in TBUT values. In the current study, OSDI was significantly negatively correlated with Schirmer and TBUT, and a significant positive correlation was found between Schirmer and TBUT.

Similar results were seen in the study of Gümüş et al. [19]. In a study of the relationship between OSDI and ocular parameters by Balyen [20], OSDI was significantly correlated with Schirmer and TBUT. These results in the literature and those of the current study demonstrate that increased digital screen exposure due to online education harms ocular health.

The limitations of this study include the small sample size, limited follow-up time, and differences in the digital materials used.

Conclusion

The continuation of education online during the COVID-19 pandemic significantly increased the use of televisions, computers, and tablets. In addition to the development of new symptoms, this increase caused significant changes in the OSDI, TBUT, and Schirmer tests. It can be recommended that easily applicable measures be conveyed to students before, during, and after online education, and information given in various ways can draw the attention of the families.

The development of eye symptoms in students should be noticed by the family, and the student should immediately be taken to a primary level family healthcare center and/or an ophthalmologist for early diagnosis and treatment. Eye symptoms that initially seem unimportant may cause irreversible eye diseases in the future. The results of this study suggest that there is a need for studies of more extensive series at the national level.

References

1. Malik YS, Kumar N, Sircar S, Kaushik R, Bhat S, Dhama K, et al. Coronavirus disease pandemic (COVID-19): challenges and a global perspective. Pathogens. 2020;9(7):519.
2. World Health Organization Coronavirus disease 2019 (COVID-19). Situation report - 81.
3. Lee SJ, Ward KP, Chang OD, Downing KM. Parenting activities and the transition to home-based education during the COVID-19 pandemic. Children and Youth Services Review. 2021;122:105585.
4. Seymour-Walsh AE, Bell A, Weber A, Smith T. Adapting to a new reality: COVID-19 coronavirus and online education in the health professions. Rural Remote Health. 2020 May;20(2):6000.
5. Paudel P. Online education: Benefits, challenges and strategies during and after COVID-19 in higher education. International Journal on Studies in Education. 2021;3(2):70-85.
6. Wong CW, Tsai A, Jonas JB, Ohno-Matsui K, Chen J, Ang M, et al. Digital Screen Time During the COVID-19 Pandemic: Risk for a Further Myopia Boom? Am J Ophthalmol. 2021 Mar;223:333-7.
7. Simavlı H, Önder Hİ, Bucak YY, Erdurmuş M, Güler E, Hepşen İF. Bilgisayar Kullanıcılarında Oküler Yüzey Hastalık İndeksi ile Kuru Göz Testleri ve Demografik Özellikler Arasındaki İlişki. Turkish Journal of Ophthalmology/Turk Oftalmoloji Dergisi. 2014;44(2).
8. Alvarez-Peregrina C, Sánchez-Tena MÁ, Martinez-Perez C, Villa-Collar C. The Relationship Between Screen and Outdoor Time With Rates of Myopia in Spanish Children. Front Public Health. 2020 Oct 14;8:560378.
9. Bahkir FA, Grandee SS. Impact of the COVID-19 lockdown on digital device-related ocular health. Indian J Ophthalmol. 2020 Nov;68(11):2378-83.
10. Bostancı B. Dijital Göz Yorgunluğu Sendromu ve Kuru Göz. MN Oftalmoloji 2016;23:96-9
11. Shantakumari N, Eldeeb R, Sreedharan J, Gopal K. Computer use and vision. related problems among university students in Ajman, United Arab Emirate. Annals of medical and health sciences research. 2014;4(2):258-63.
12. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and Validity of the Ocular Surface Disease Index. Archives of Ophthalmology. 2000;118(5):615-21.
13. Pang Y, Madro S. Effect of Screen time on Dry Eye Symptoms in Young Adults. Investigative Ophthalmology & Visual Science. 2020;61(7):341.
14. Mishra G. Impact of prolonged digital screens exposure on ocular surface and management. International Journal of Health and Clinical Research. 2021;4(3):136-8.
15. Mehra D, Galor A. Digital Screen Use and Dry Eye: A Review. Asia Pac J Ophthalmol (Phila). 2020 Dec;9(6):491-7.
16. Uchino M, Yokoi N, Uchino Y, Dogru M, Kawashima M, Komuro A, et al. Prevalence of dry eye disease and its risk factors in visual display terminal users: the Osaka study. Am J Ophthalmol. 2013 Oct;156(4):759-66.
17. Kawashima M, Sano K, Takechi S, Tsubota K. Impact of lifestyle intervention on dry eye disease in office workers: a randomized controlled trial. J Occup Health. 2018 Jul 25;60(4):281-8.
18. Yiğit U, Evcimen Y, Kırık F, Ağaçhan A. Kuru Göz Hastalarında Gözyaşı Osmolarite Ölçümünün Gün İçi Değişiklikleri. Turk J Ophthalmol. 2013;43:437-41.
19. Gümüş K, Arda H, Öner AÖ, Kaküçük S, Mirza E. Bilgisayar kullanımının kuru göz parametreleri üzerine olan etkisinin değerlendirilmesi. Türk Oftalmoloji Dergisi. 2009;39(4):244-9.
20. Balyen L. Bilgisayar Kullanıcılarında Oküler Yüzey Hastalığı İndeksi ve Kuru Göz Testi Parametreleri Arasındaki İlişkinin Değerlendirilmesi. Kafkas Tıp Bilimleri Dergisi. 2019;9(3):169-79.

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The relationship between renal oxygen saturation and renal function in patients with and without diabetes following coronary artery bypass grafting surgery

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Ethics Committee Approval
The approval of the Ankara University School of Medicine ethics committee (23.11.2015/18-763-15).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Acute kidney injury may occur due to renal ischemia and hypoxia during coronary artery bypass surgery. Monitoring of renal regional tissue oxygenation might be useful to determine renal hypoxia. We aimed to investigate whether renal oxygen saturation values differ between diabetic and non-diabetic patients and evaluate the relationship between intra-operative renal oxygen saturation values and postoperative renal function.

Methods: Forty consecutive patients aged 18-65 years, who underwent elective coronary artery bypass grafting, were included in this prospective case-control study. Body mass index ≥30 kg/m^2 and the presence of renal damage were considered the exclusion criteria. Group I consisted of diabetic patients (n = 20), and Group II consisted of non-diabetic patients (n = 20). Near Infrared Spectroscopy (NIRS) recorded renal saturation values just before the intubation as the basal value and every 10 minutes after intubation in all patients. Creatinine clearances and glomerular filtration rates were calculated along with blood urea nitrogen and creatinine values on the postoperative 1st and 3rd days of all patients.

Results: The two groups were similar in terms of gender, age, body mass index, duration of surgery, cross-clamp time, and total cardiopulmonary bypass duration (P>0.05). While there was no difference between baseline values, significant differences were found between preoperative BUN and creatinine and POD 3 BUN and creatinine values in Group 1 (P=0.003 and P=0.046, respectively) and Group 2 (P=0.018 and P=0.030, respectively). There was no significant difference between two groups in renal oxygen saturation values considering both basal and post-intubation measurements (P>0.05 for all). However, an earlier decrease in renal oxygen saturation values was seen in diabetic patients (P<0.05). There was no significant relationship between the changes in intraoperative renal oxygen saturation values and postoperative renal function (P>0.05 for all).

Conclusion: Although coronary artery graft bypass surgery does not lead to a significant difference in renal saturation values, as determined by Near Infrared Spectroscopy, in diabetic patients compared to non-diabetic patients, NIRS may be helpful and beneficial to show renal ischemia in these patients.

Keywords: Diabetes mellitus, Coronary artery bypass grafting, Near-infrared spectroscopy, Acute kidney injury

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Introduction

Acute kidney injury (AKI) is seen after coronary artery bypass grafting (CABG) with an incidence of up to 45%. It is generally associated with prolonged mechanical ventilation and intensive care unit stay and is probably accompanied by increased mortality [1-4].

Near-Infrared Spectroscopy (NIRS) noninvasively monitors the regional oxygen saturation. It works continuously by measuring the concentration of oxygenated and non-oxygenated hemoglobin in the local tissue area of selected organs [5].

A correlation was shown between urinary biomarkers and low renal saturation values, as detected by NIRS, including the need for renal replacement therapy after cardiac surgery [6]. Contrary to these findings, there was no correlation with the development of AKI [2-4]. Although urinary output amount, blood urea nitrogen (BUN) and creatinine levels have been used as the preliminary indicators for renal function in CABG patients perioperatively, studies which compare renal oxygen saturation values by NIRS with postoperative renal functions are rare [1]. Therefore, evaluation of such a relationship remains controversial.

Even in diabetic patients without nephropathy, a known micro-vascular complication of chronic diabetes, the risk of developing AKI after cardiac surgery is higher than in non-diabetic patients [7]. Therefore, early prediction of the development of AKI in diabetic patients who undergo cardiac surgery may have an impact on the morbidity and mortality.

This study aimed to compare the peri-operative renal oxygen saturation values measured by NIRS in diabetic and non-diabetic adult patients undergoing CABG and evaluate the possible relationship between the peri-operative renal oxygen saturation values with postoperative urinary indicators including urine output, BUN and serum creatinine values.

Materials and methods

This study prospectively investigated patients aged 18-65 years who underwent elective CABG between January 2015 and January 2016 at Ankara University Faculty of Medicine Department of Cardiovascular Surgery after the approval of the Ankara University School of Medicine ethics committee (23.11.2015/18-763-15). The study was conducted in compliance with the Declaration of Helsinki. Written consent was obtained from all patients.

Patients with coronary artery disease and those undergoing elective CABG were included in the study. Emergent surgery, BMI >30 kg/m^2 and diabetes-induced renal micro- or macro-vascular complications were regarded as the exclusion criteria.

The patients were grouped into two as diabetic (Group 1) and non-diabetic (Group 2). Patients with type II diabetes mellitus who were taking oral antidiabetic and/or insulin therapy without any known renal micro- or macro-vascular complications were included in Group I.

An a priori power analysis was conducted using G*Power3 (Faul, Erdfelder, Lang, & Buchner, 2007) to test the difference between two independent group means using a two-tailed test, a medium effect size of d=0.50, and an alpha of 0.05. Result showed that a total of 32 participants with two equal sized groups of n = 16 was required to achieve a power of 0.80. So, it was planned to have at least 20 patients in both groups. Patients were consecutively included in the groups from the beginning of the study, considering the presence or absence of diabetes.

Demographic and clinical features of the patients (age, gender, and BMI) and perioperative (duration of the surgery, cross-clamp time, and total cardiopulmonary bypass duration) and postoperative findings were recorded using a prospectively held database. Hematocrit (%) levels were recorded preoperatively, after induction, pre-CABG, post-CABG, and before the transfer to the intensive care unit in all patients. Urine output was monitored hourly until discharge from the ICU. BUN (mg/dL) and creatinine (mg/dL) values of all patients were measured preoperatively, and on the 1st and 3rd postoperative days (POD 1 and POD 3, respectively). Creatinine clearance (ml/min) and glomerular filtration rate (GFR) were calculated according to following formulas [8]:

- For creatinine clearance, the Cockcroft-Gault formula was used:

Creatinine Clearance (ml/min) = [[140 - age (years)] x weight (kg)] / [72 x serum creatinine (mg/dL)] (multiply by 0.85 in females).

- For GFR calculation, the simplified Modification of Diet in Renal Disease Study equation was used:

GFR [ml/ min/1.73 m^2] = 186 x [serum creatinine (mg/dL)]$^{-1.154}$ x [age (years)]$^{-0.203}$ x (0.742 if female).

Peri-operative follow-up

All patients were routinely monitored via electrocardiography, pulse oximetry and non-invasive blood pressure tracing before the induction of anesthesia. Invasive radial artery monitoring was performed before the induction in patients with an ejection fraction (EF) of <50%. Following monitoring, midazolam (0.06 mg/kg) (Demizolam, ampoule, 15 mg/3 ml, Actavis, Istanbul, Turkey) was administered after intravenous access. For induction of anesthesia, 6 mg/kg thiopental sodium (Pentothal Sodium, ampoule, 1 g, Abbott, Istanbul, Turkey), 0.1 mg/kg vecuronium bromide (Norcuron, ampoule, 4 mg, Schering Plough, Istanbul, Turkey) and 1 mcg/kg fentanyl (Fentanyl, ampoule, 0.05mg-ml, 10 ml, Johnson & Johnson, Istanbul, Turkey) were administered. After intubation, oxygen and air mixture was given at 2-4 L per minute. The tidal volumes of patients were set at 6 mL/kg, aiming to have an end-tidal carbon dioxide pressure value of 33-35 mmHg.

Direct blood pressure monitoring with radial artery cannulation was performed in all patients whose blood pressures were non-invasively monitored, and central venous pressure monitoring was performed with right internal jugular vein catheterization. In addition to sevoflurane (Sevoran Liquid, liquid, Abdi Ibrahim, Istanbul, Turkey) with a minimum alveolar concentration of 1.3, remifentanil infusion at a dose of 0.05 mcg/kg/min (Ultiva, vial, 1 mg, Glaxo Smith Kline, Istanbul, Turkey), intermittent doses of midazolam and muscle relaxant vecuronium bromide were used in maintenance anesthesia.

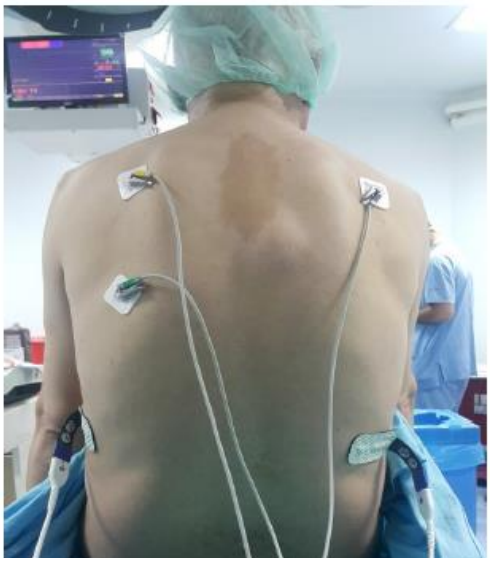
Partial oxygen saturation, lactate, and hematocrit levels were routinely recorded. Renal saturation values were recorded

with NIRS at baseline, and every 10 minutes following intubation. After the termination of maintenance anesthesia following CABG, all patients with stabilized vital parameters were transferred to the cardiovascular surgery intensive care unit, intubated.

Renal NIRS technique

NIRS electrodes were placed at the intersection of the posterior axillary line with the 12th rib on both sides of all patients to evaluate intraoperative renal perfusion. To decide the exact value of renal oxygen saturation, the lowest value obtained from both sides was regarded as the final measurement. Renal oxygen saturation (rO_2) values were obtained as the basal measurement before the intubation and 10 minutes after intubation (Figure 1).

Figure 1: Renal NIRS measurement



Statistical analysis

Patients in both groups were compared in terms of gender, age, ejection fraction, BMI, operation time, cross-clamp and cardiopulmonary bypass periods and concomitant disease.

The data were analyzed in the SPSS for Windows 15 package program (SPSS, Inc., Chicago, IL, USA). Mean (standard deviation) values were presented for variables with a normal distribution, median (min-max) values were used for non-normally distributed variables, and the number of cases (%) were used for nominal variables. The significance of differences between the groups was determined by the t-test, and those between the median values was assessed by the Mann Whitney U test. Nominal variables were evaluated by Pearson Chi-Square or Fisher exact test. The paired t-test was used if the variation distribution according to time was normal before and after the treatment, and the Wilcoxon test was used in case of non-normal distribution. Analysis of variance was used for repeated measures if the variation of the distribution of the repeated measures obtained before and during the treatment period was normal. In case of non-normal distribution, the Friedman test was used. Spearman correlation test was utilized when the relationship between continuous variables was non-normal, and the Pearson correlation test was used when it was normal. *P* values of <0.05 were considered statistically significant.

Results

There were 14 males and 6 females in Group 1 and 16 males and 4 females in Group 2. The groups were similar in terms of gender distribution, age, BMI, duration of the surgery, cross-clamp time, and total cardiopulmonary bypass duration (P>0.05 for all) (Table 1).

Table 1: Demographic and clinical data of the groups

	Group 1 n=20	Group 2 n=20	*P*-value
Age (year)[¥]	62.2 (10.7)	63.7 (8.2)	0.602
Gender (F/M)	6/14	4/16	0.465
BMI (kg/m^2)[¥]	27.3 (2.1)	26.7 (2.3)	0.289
Duration of surgery (min)[¥]	262.7 (45.2)	264.5 (45.1)	0.640
Cross-clamp time (min)[¥]	56.6 (21.6)	60.1 (19.9)	0.620
Total cardiopulmonary bypass duration (min)[¥]	104.2 (35.8)	116.1 (22.4)	0.149

[¥]: mean (standard deviation), F: Female, M: Male, BMI: Body mass index

There was no significant difference between the groups considering hematocrit values in the preoperative period and during the surgical procedures (Table 2). However, there was a significant decrease in hematocrit values before CABG, after CABG and at the end of surgery compared to the preoperative values in intra-group analyses. In Group 1, the hematocrit value of 39.07 (6.5) % decreased to 32.30 (6.7) % just before CABG, to 24.6 (4.0) % after CABG and to 26.79 (3.7) % at the end of the surgery (P<0.05 for all). Such significant decreases were also seen in Group 2 (Table 2).

There was no significant difference between the two groups in terms of BUN, creatinine, creatinine clearance and GFR values during the preoperative period, at POD 1 and POD 3 (Table 3).

Table 2: Hematocrit values (%)

	Preoperative	After induction	Before CABG	After CABG	At the end of surgery
Group 1	39.07 (6.5)	34.98 (6.2)	32.30 (6.7)	24.6 (4.0)	26.79 (3.7)
Group 2	37.07 (8.7)	34.98 (5.4)	33.64 (6.3)	25.60 (3.0)	26.46 (3.5)
P-value[β]	0.862	0.495	0.620	0.429	0.947

[¥]: mean (standard deviation), [β]: *P*-value between the groups

Table 3: Intra- and intergroup comparison of the urinary indicators

Parameter[¥]	Group 1	Group 2	*P*-value [0]	*P*-value [1]	*P*-value [2]
BUN (mg/dL)	16.9 (6.9)	15.4 (5.6)	0.602	--	--
BUN (mg/dL) POD 1	16.7 (6.4)	16.9 (6.3)	0.947	0.920	0.224
BUN (mg/dL) POD 3	22.6 (7.7)	19.8 (7.0)	0.253	0.003	0.018
Creatinine (mg/dL)	1.0 (0.2)	0.9 (0.1)	0.640	--	--
Creatinine (mg/dL) POD 1	1.0 (0.3)	1.1 (0.3)	0.277	0.145	0.014
Creatinine (mg/dL)POD 3	1.1 (0.3)	1.1 (0.3)	0.495	0.046	0.030
CrCl (ml/min)	90.8 (36.2)	90.8 (21.1)	0.820	--	--
CrCl (ml/min) POD 1	87.0 (40.7)	79.6 (27.8)	0.758	0.263	0.027
Cr Cl (ml/min) POD 3	83.5 (39.2)	83.1 (24.8)	0.512	0.126	0.040
GFR (ml/ min/1.73 m^2)	84.3 (27.3)	86.5 (15.9)	0.495	--	--
GFR (ml/ min/1.73 m^2) POD 1	79.7 (28.3)	74.4 (25.9)	0.414	0.247	0.024
GFR (ml/ min/1.73 m^2) POD 3	76.0 (30.1)	78.1 (21.9)	0.461	0.117	0.044

[¥]: mean (standard deviation), BUN: Blood urea nitrogen, POD 1: postoperative day 1, POD 3: postoperative day 3, CrCl: creatinine clearance, GFR: Glomerular filtration rate, [0]: When two groups are compared. [1]: When the values of group I are compared with baseline (preoperative value). [2]: When the values of group II are compared with baseline (preoperative value).

In group 1, there were significant differences between preoperative BUN and creatinine values and POD 3 BUN and creatinine values (P=0.003 and P=0.046, respectively). However, no significant association was found between creatinine clearance and GFR (Table 3).

Similar to Group 1, significant differences were found between preoperative BUN and creatinine values and POD 3 BUN and creatinine values in Group 2 (P=0.018 and P=0.030, respectively). In addition, creatinine clearance and GFR values significantly decreased at POD 3 compared to preoperative values (P=0.040 and P=0.044, respectively) (Table 2),

There was no significant difference between Groups 1 2 in terms of urine volume (ml) before, during and after CABG (Table 4).

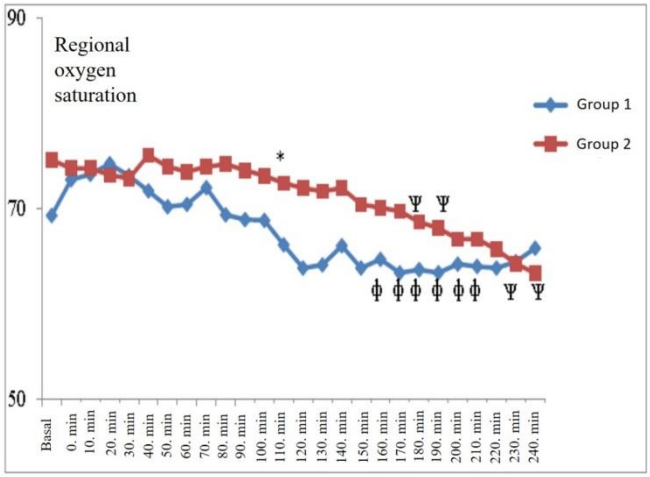
Table 4: Comparison of total urinary volume (ml) during POD 1

	Before CABG¥	During CABG¥	After CABG¥
Group 1	195 (158)	916 (464)	500 (343)
Group 2	195 (180)	1044 (473)	556 (238)
P-value	0.620	0.355	0.383

¥: mean (standard deviation)

There was no significant difference between the baseline rO_2 levels of the patients (Figure 2). Although the pattern for the decrease in rO_2 measurements was similar until an average of 110 minutes after the start of surgery, there was a significant difference at this point between Group 1 and 2 ($P<0.05$). In addition, an earlier decrease was observed from the baseline value of rO_2 in Group 1 compared to Group 2 (Figure 2).

Figure 2: rO_2 changes over time



*: $P<0.05$ when compared to Group 1 and Group 2, ϕ: $P<0.05$ when compared to baseline values in Group 1, Ψ: $P<0.05$ when compared to baseline values in Group 2

Discussion

Renal oxygen saturation levels measured by NIRS was lower compared with basal in diabetic and non-diabetic patients undergoing CABG. Although it was significantly lower in diabetics than in non-diabetics, it did not make sense clinically when creatinine and urine output levels were considered.

During open heart surgery, ischemic changes that may occur in splanchnic organs such as the liver and the kidney lead to an increase in postoperative hospital stay, morbidity, and mortality rates. Ascione et al. [9] found that damage to the splanchnic organs was more prominent in patients who were treated with extracorporeal circulation. They also mentioned that more than 24 hours is required for the development of such symptoms. In a case series of 500 patients who underwent cardiopulmonary bypass and who were alive after 24 hours, Khilji et al. reported that acute renal failure rate (creatinine >2.5 mg/dl) was 7%, rate of acute renal dysfunction (creatinine 1.6-2.4 mg/dl) was 20.4% and the mortality rate in patients with AKI was 88% [10]. This shows how important it is to follow the circulation in the splanchnic organs during open heart surgery.

Owens et al. [5] observed renal oxygenation of the patients who underwent pediatric cardiac surgery in the peri-operative and postoperative 48-hour period with NIRS and found that low renal oximetry follow-up was correlated with acute renal failure. In our study, the change in the values of renal oxygen saturation in each patient did not exceed 20%. Reductions of more than 20% from the baseline tissue oxygen saturation values with the NIRS method are considered significant. In addition, there was no significant difference between the baseline measurements of renal oxygen saturation in terms of NIRS values between the diabetic and non-diabetic groups in the present study. No significant correlation was found between changes in intra-operative renal NIRS values and postoperative renal function. However, although there was no significant between the renal NIRS values between the two groups, rO_2 started to fall earlier in Group 1 (the diabetic group) than Group 2 (the non-diabetic group). This decrease reached a significant level at the 110th minutes of the operation. In both groups, the decrease in rO_2 levels was increased as the duration of surgery was prolonged (not given in the text).

This is considered undetected nephropathy, a microvascular complication that develops in diabetic patients. Even 20-30% of the patients undergoing coronary artery surgery have diabetes, the patients with diabetic nephropathy were not included in the study [11, 12]. Although the duration of the diagnosis of diabetes mellitus was not considered in patients with type II diabetes in our study, exclusion of the patients with nephropathy could not be effective to prevent such co-existence.

Although there is no clear and precise information on the use of NIRS in adult patients, we are convinced that NIRS may be useful in monitoring liver and the kidney oxygenation, particularly in patients at risk for renal and ischemic events in appropriate (non-obese patients) cases. The present study was conducted on the diabetic and non-obese patients (BMI <30 kg/m^2) who may be at risk for peri-operative renal ischemia. Therefore, the NIRS method may be a meaningful way to evaluate the somatic oxygen saturation in appropriate adult patients.

Hyperglycemia, which may be present in diabetic patients, is known to adversely affect overall postoperative outcomes [13]. Thus, DM is an independent and potent risk factor for renal insufficiency [14]. In a study by Stallwood and colleagues [15], CABG has been shown to increase the risk of renal insufficiency 2.6-fold. Although this may suggest that the cardiac surgical procedures in diabetic patients may further increase renal insufficiency, there was no significant difference in BUN, creatinine, creatinine clearance and GFR between the diabetic and the non-diabetic groups in our study. Therefore, large-scale prospective studies are needed to clarify this controversial issue.

AKI, a common complication following CABG, is associated with high mortality, extended hospital stays, and increased health expenditures [16]. The frequency of AKI after open heart surgery ranges between 5-48%. The short- and long-term mortality risk increased significantly in the postoperative period in patients with AKI [17]. In the present study, although the longer follow-up periods following CABG were not studied, there was no short-term mortality in both groups.

Serum creatinine level and/or GFR values are used to evaluate the renal functions in the peri-operative periods for almost all types of major surgical procedures. These variables are strong indicators for AKI that can develop postoperatively [18]. In this study, serum creatinine and BUN values were within

normal limits in all patients preoperatively due to the inclusion criteria. In addition, there was no statistically significant difference between GFR and creatinine clearance in both groups preoperatively. However, significant increases at POD 3 BUN and creatinine values were observed in both groups. Although creatinine clearance and GFR values significantly decreased at POD 3 in Group 2, the small size of the groups may cause such difference.

Anemia predisposes to AKI [19]. The presence of anemia before CABG alone or in combination with pre- and post-CABG is known to be associated with postoperative AKI development and increased mortality [20]. Prolonged duration of CABG causes an increased rate of hemolysis, and as a result, free hemoglobin acts as an endogenous toxin causing pigment nephropathy. Therefore, the increased duration of CABG also causes an increased risk of AKI [21]. In this study, the decrease in renal NIRS by the duration of the surgery was correlated; therefore, it may have a significant impact on prospective studies.

Some of the challenges we face in this study suggest that there is a need for novel studies on NIRS for evaluation of somatic oxygenation in adult patients undergoing open heart surgery. Since the distance between the somatic organs and the skin is close in pediatric patients, the data obtained with NIRS are reliable, but the reliability of the data obtained with NIRS may be decreased, especially in adult and obese patients. The ideal way to overcome this problem is to locate the NIRS probes where the kidneys are closest to the skin via preoperative ultrasonographic evaluations. That way, it can be possible to find exact points in which the distance between the skin and the kidney is within 2 to 2.5 cm- the optimum distance for these probes. Failure to perform such an evaluation may disturb the interpretation of the results. For that reason, the patients with BMI <30 kg/m^2 were included in the study.

Limitations

This study has some limitations. First, the number of patients in both groups was low, and AKI did not develop in the study group, so the results could not be evaluated in relation to the development of AKI. Second, ultrasound was not used for the placement of renal NIRS probes; therefore, it was not possible to determine whether the distance between the skin and the kidney was 2-2.5 cm. This can have an impact on the reliability of the results obtained.

Conclusion

NIRS may be helpful and beneficial to show renal ischemia in patients following CABG. Although it was significantly lower in diabetics than in non-diabetics, it did not correlate with creatinine and urine output levels. However, large-scale prospective studies including adult obese patients and use of ultrasonography to localize the NIRS probes are needed.

References

1. Choi DK, Kim WJ, Chin JH, Lee EH, Don Hahm K, Yeon Sim J, Cheol Choi I. Intraoperative Renal Regional Oxygen Desaturation Can Be a Predictor for Acute Kidney Injury after Cardiac Surgery. J Cardiothorac Vasc Anesth. 2014;28:564-71.
2. Li S, Krawczeski CD, Zappitelli M, Devarajan P, Thiessen-Philbrook H, Coca SG, et al. Incidence, risk factors, and outcomes of acute kidney injury after pediatric cardiac surgery: a prospective multicenter study. Crit Care Med. 2011;39:1493–9.
3. Pedersen K. Acute kidney injury in children undergoing surgery for congenital heart disease. Eur J Pediatr Surg. 2012;22:426–33.
4. Aydin SI, Seiden HS, Blaufox AD, Parnell VA, Choudhury T, Punnoose A, et al. Acute kidney injury after surgery for congenital heart disease. Ann Thorac Surg. 2012;94:1589–95.
5. Owens GE, King K, Gurney JG, Charpie J R. Low Renal Oximeter Correlates With Acute Kıdney Injury After Infant Cardiac Surgery. Pediatr Cardiol. 2011;32:183-8.
6. Hazle MA, Gajarski RJ, Aiyagari R, Yu S, Abraham A, Donohue J, et al. Urinary biomarkers and renal near-infrared spectroscopy predict intensive care unit outcomes after cardiac surgery in infants younger than 6 months of age. J Thorac Cardiovasc Surg. 2013;146:861–7.
7. Cao Z, Cooper ME. Pathogenesis of diabetic nephropathy. J Diabetes Investig. 2011;2:243-7.
8. Pöge U, Gerhardt T, Stoffel-Wagner B, Klehr HU, Sauerbruch T, Woitas RP. Calculation of glomerular filtration rate based on cystatin C in cirrhotic patients. Nephrol Dial Transplant. 2006;21:660-4.
9. Ascione R, Talpahewa S, Rajakaruna C, Reeves BC, Lovell AT, Cohen A, Angelini GD. Splanchnic organ injury during coronary surgery with or without cardiopulmonary bypass a randomized controlled trial. Ann Thorac Surg. 2006;81:97-103.
10. Khilji SA, Khan AH. Acute renal failure after cardiopulmonary bypass surgery. J Ayub Med Coll Abbottabad. 2004;16:25-8.
11. Raza JA, Movahed A. Current concepts of cardiovascular diseases in diabetes mellitus. Int J Cardiol. 2003;89:123-34.
12. Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases shorter mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol. 2002;40:418-23.
13. McDonnell ME, Alexanian SM, White L, Lazar HL. A primer for achieving glycemic control in the cardiac surgical patient. J Card Surg. 2012;27:470-7.
14. Saran R, Robinson B, Abbott KC, Agodoa LYC, Bhave N, Bragg-Gresham J, et al. US Renal Data System 2017 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis. 2018;71:7.
15. Stallwood MI, Grayson AD, Mills K, Scawn ND. Acute renal failure in coronary artery bypass surgery: independent effect of cardiopulmonary bypass. Ann Thorac Surg. 2004;77:968-72.
16. Bahar I, Akgul A, Ozatik MA, Vural KM, Demirbag AE, Boran M, et al. Acute renal failure following open heart surgery: risk factors and prognosis. Perfusion. 2005 Oct;20:317-22.
17. Thakar CV, Liangos O, Yared JP, Nelson D, Piedmonte MR, Hariachar S, et al. ARF after open-heart surgery: Influence of gender and race. Am J Kidney Dis. 2003;41:742-51.
18. Cooper WA, O'Brien SM, Thourani VH, Guyton RA, Bridges CR, Szczech LA, et al. Impact of renal dysfunction on outcomes of coronary artery bypass surgery: results from the Society of Thoracic Surgeons National Adult Cardiac Database. Circulation. 2006;113:1063-70.
19. Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, et al. Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg. 2005;129:391-400.
20. Oprea AD, Del Rio JM, Cooter M, Green CL, Karhausen JA, Nailer P, et al. Pre- and postoperative anemia, acute kidney injury, and mortality after coronary artery bypass grafting surgery: a retrospective observational study. Can J Anaesth. 2018;65:46-59.
21. Kumar AB, Suneja M. Cardiopulmonary bypass-associated acute kidney injury. Anesthesiology. 2011;114:964-70.

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Long-term results of laparoscopic Heller myotomy with Dor-fundoplication in surgical treatment of achalasia: A single-center experience

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Ethics Committee Approval
Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee (HNEAH-KAEK 2021/212).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
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Abstract

Background/Aim: Laparoscopic Heller myotomy with Dor fundoplication (LHD) is a widely used surgical method in achalasia treatment. However, it has not been well studied in terms of symptomatic relief effect and anti-reflux success in the long term. This study aimed to investigate the long-term success of LHD on symptom relief and acid reflux control.

Methods: Patients who underwent LHD between February 2011 and June 2020 were included in this retrospective cohort study. Patients' demographics, post-operative follow-up outcomes and esophagitis signs on endoscopy were retrieved from the institutional database. Eckardt scores of all study patients were calculated. Those with insufficient follow-up data were excluded. Disease free rates were calculated using the Kaplan-Meier analysis.

Results: A total of 24 patients, 11 males and 13 females, were included. The mean age of all patients was 47.9 (11.3) years. The median follow-up time was 71.0 (12.0-117.0) months. Cumulative symptomatic relief (Eckardt ≤3) rate of LHD was 87.5% (21/24). Kaplan-Meier analysis showed that the time-dependent probability of Eckardt score being ≤3 at 3 and 5 years after the surgery were 100% and 94.7%, respectively. The mean expected survival time with Eckardt score ≤3 was 102.5 (95% CI: 87.6-117.3) months. The post-LHD esophagitis rate was 20.8% (5/24). The probability of no reflux esophagitis at 3 and 5 years after the surgery were 95.0% and 89.4%, respectively. The mean expected esophagitis-free survival was 94.2 (95% CI: 80.6-107.7) months.

Conclusion: LHD seems successful and safe in terms of long-term symptomatic relief and acid reflux control in the surgical treatment of achalasia.

Keywords: Achalasia, Laparoscopic Heller-myotomy with Dor-fundoplication, Long-term results, Esophagitis

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Introduction

Achalasia is a rare primary esophageal motility disorder characterized by the lack of peristaltic activity and partial or total loss of lower esophageal sphincter (LES) relaxation in response to swallowing [1]. Selective degeneration of inhibitory neurons in the myenteric plexus responsible for esophageal peristalsis and LES relaxation is the culprit mechanism. Since a functional obstruction occurs in gastroesophageal junction, esophageal dilatation is seen. The most common complaints include dysphagia, regurgitation, chest pain and weight loss. Diagnosis is made by esophagogastroduodenoscopy, barium esophagogram and manometry [2].

Treatment protocols are not curative, and the primary goal is to relieve symptoms and help foods pass through esophagus by decreasing LES pressure. Non-surgical approaches include pharmacological agents, endoscopic botulinum toxin injection, pneumatic dilatation and peroral endoscopic myotomy (POEM). The surgical treatment methods are Heller myotomy and esophagectomy [3].

The gold standard surgical treatment is laparoscopic Heller myotomy (LHM) with added partial anti-reflux procedures. Although some centers suggest a myotomy of 3 cm on the gastric side, performing a myotomy of at least 6 and 2.5 cm on the esophageal and gastric sides, respectively, is a well-accepted approach [2, 4]. The partial anti-reflux procedure to be preferred is not clear. The most used partial fundoplication methods include Toupet (posterior, 270 degrees) and Dor (anterior, 180 degrees). In Toupet, the edges of the myotomy are kept separate, the abdominal esophagus is totally mobilized and gastrica breves are totally cut to obtain a mobile fundus [4]. In Dor fundoplication, however, the mucosa exposed following the myotomy is covered by the fundus and since total mobilization of abdominal esophagus is not necessary, posterior dissection is useless. Plus, gastrica breves are not necessarily cut given no need of extended fundal mobilization [5]. Toupet versus Dor fundoplication procedures were compared in randomized controlled studies with no significant differences in terms of post-operative reflux [6-8]. These results suggest that the fundoplication method of choice is at the surgeon's discretion. We prefer LHM with Dor fundoplication (LHD) in our center. In this context, we designed this study to report our experiences in terms of intra and post-operative complications, long-term symptomatic relief and success of acid reflux control.

Materials and methods

Patients with achalasia who presented with LHD between February 2011 and June 2020 were included in this retrospective cohort study. Diagnoses of all included patients were made based on esophagogastroduodenoscopy, esophagogram and esophageal manometry findings. The patients' demographics, pre- and post-operative weights, disease durations, esophageal dilatation size, operation notes, intra- and post-operative complications, and duration of post-operative follow-up and endoscopic findings were retrieved from the institutional database. Eckardt scores were calculated. Those with insufficient follow-up data were excluded. The study was conducted in accordance with the Helsinki Declaration and approved by Haydarpasa Numune Training and Research Hospital Clinical Research Ethics Committee (HNEAH-KAEK 2021/212).

Preoperative esophagograms were obtained with barium until 2018. Since it was not available in our country from that year on, water-soluble opaque agents were used. Japanese Esophageal Society (JES) classification was used to determine the dilatation degree in the esophagogram [9]. Accordingly, the patients were divided into three, as those with grade I (maximal esophageal diameter of less than 3.5 cm), grade II (between 3.5 and 6 cm) and grade III (more than 6 cm) dilation. Manometry was performed with the conventional method (5-channel catheter).

Eckardt score is a widely used and well-established grading system in the assessment of symptom and treatment effectiveness [10]. Four major symptoms are inquired (dysphagia, regurgitation, chest pain and weight loss) and graded between 0-4. A total score of equal to or lower than 3 is considered successful in the evaluation of the treatment. Those with post-operative Eckardt scores of >3 were asked when their first complaint began and the duration between surgery and the beginning of complaints was considered successful post-surgical time. Time to detection of post-operative esophagitis via endoscopy was also noted. The Los Angeles classification was used to determine severity of esophagitis in our center [11]. Los Angeles grade A or higher (B, C, D) was defined as endoscopic esophagitis.

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 25.0 software (IBM Corporation, Armonk, NY, US). Categorical data were expressed as numbers (n) and percentage (%) while quantitative data were given as mean (SD) and median (min-max). The clinical success (Eckardt score ≤3) and esophagitis-free survival rates were displayed by the Kaplan-Meier survival curves. Cumulative survival rates for 3 and 5 years, and the mean expected duration of life without reflux were also calculated at a 95% confidence interval.

Results

A total of twenty-four patients, 11 males (48.8%) and 13 females (51.2%), had undergone LHD between February 2011-June 2020. The mean age of the patients was 47.9 (11.3) years. Half of patients had undergone pneumatic dilatation before surgery. Preoperative degree of dilatations were grade I in 3 (12.5%), grade II in 15 (62.5%) and grade III in 6 (25%) patients. Table 1 shows the patients' characteristics.

Table 1: Baseline characteristics of patients

	n=24
Age (years)	47.9 (11.3)
Gender	
Male	11 (45.8%)
Female	13 (54.2%)
Pre-op BMI (kg/m^2)	23.0 (5.6)
Duration of disease (months)	48.0 (12.0-360.0)
Prior history of pneumatic dilation	12 (50.0%)
Maximum esophageal diameter (cm)	5.12 (1.04)
Pre-op ECKARDT score	8.5 (5.0-12.0)
Degree of dilation	
Grade I (<3.5 cm)	3 (12.5%)
Grade II (≥3.5 cm <6.0 cm)	15 (62.5%)
Grade III (≥6.0 cm)	6 (25.0%)

Three trocars of 5 mm and 2 trocars of 12 mm (5 ports in total) were used in LHD. The median operation time was 150

(120-210) minutes. Mucosal injury occurred in 2 patients (8.3%) and were repaired. One (4.2%) patient had a bleeding of 300 cc and 1 (4.2%) patient had vagal injury. Operation was switched to open surgery in 1 patient owing to adhesions secondary to previous intra-abdominal surgery. The median duration of hospital stay was 4 (3-5) days. Among post-operative complications, 1 (4.2%) patient had atelectasis and 1 (4.2%) had wound infection (open surgery case). No perforation or delayed peritonitis was noted in the post-operative period. The median follow-up time was 71 (12-117) months (Table 2).

Table 2: Other clinical findings

Parameter	Value
Operative time (min)	150.0 (120.0-210.0)
Blood loss (ml)	0.0 (0.0-300.0)
Intraoperative complications	4 (16.7%)
Esophageal/gastric mucosal injury	2 (8.3%)
Blood loss > 200 ml	1 (4.2%)
Vagus nerve injury	1 (4.2%)
Length of hospital stay (days)	4.0 (3.0-5.0)
Postoperative complications	2 (8.3%)
Atelectasis	1 (4.2%)
Surgical site infections	1 (4.2%)
Post-op BMI (kg/m^2)	26.4 (4.5)
Post-op Eckardt score	2.0 (0.0-5.0)
Post-op Eckardt score >3	3 (12.5%)
Post-op esophagitis	5 (20.8%)
Follow-up time (months)	71.0 (12.0-117.0)

LHD resulted in symptomatic relief in 21 of 24 patients (87.5%) (Eckardt ≤3). We had 3 patients with a post-operative Eckardt score of more than 3 (12.5%). Kaplan-Meier analysis showed that the time-dependent probability of Eckardt score ≤3 at 3 and 5 years after surgery were 100% and 94.7%, respectively (Figure 1). The mean expected survival time with Eckardt score ≤3 was 102.5 (95% CI: 87.6 – 117.3) months. Five (20.8%) of 24 patients had post-operative esophagitis. Severity was Los Angeles grade A in 4 patients and B in one. Figure 2 shows the Kaplan-Meier esophagitis-free survival curve. Accordingly, the probability of no reflux esophagitis at 3 and 5 years after the surgery were 95.0% and 89.4%, respectively. The mean expected esophagitis-free survival time was 94.2 (95% CI: 80.6 – 107.7) months.

Figure 1: Kaplan-Meier analysis on time-dependent probability of patients with Eckardt score ≤3

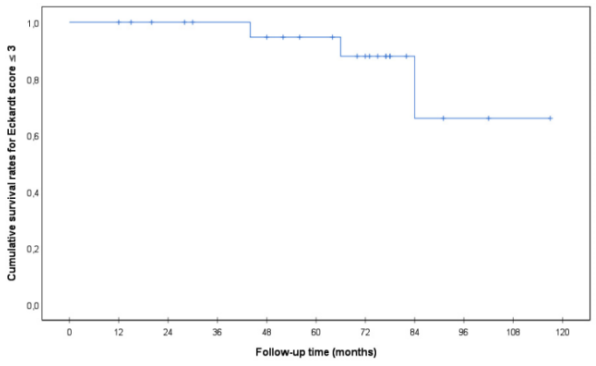
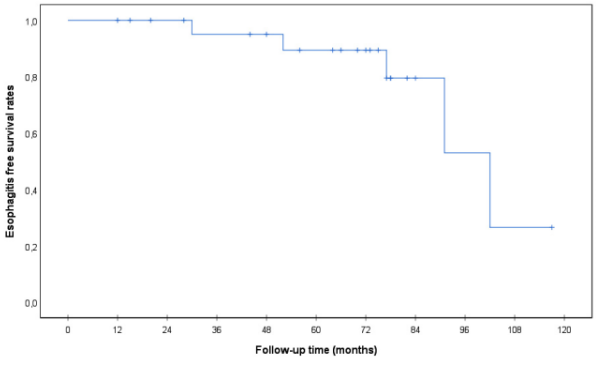


Figure 2: Kaplan-Meier analysis on esophagitis-free survival



Discussion

Dr. Heller first performed the transabdominal myotomy in the gastric cardia and esophagus approximately 100 years ago [12]. The myotomy technique was modified over the years. The first LHM was performed by Shimi et al. [13] in 1991. Post-operative reflux rates were reported as high as 60% when Heller myotomy was performed alone; however, thanks to the addition of Dor fundoplication, this rate decreased down to 17% [14]. Eventually, the gold standard treatment was established as Heller myotomy plus partial anti-reflux procedures. Since it does not necessitate posterior dissection and covers the exposed esophageal mucosa, we prefer the Dor fundoplication (anterior, 180 degrees).

LHM has favorable results. Zaninotto et al. [15] reported a success rate of 90% in their study with a median follow-up duration of 2.5 years covering 407 patients. Schlottmann et al. [16] noted a 87% success rate (Eckardt <3) in a study including 147 patients with a median follow-up duration of 22 months. In their study on 896 patients with a median follow-up duration of 5.2 years, Costantini et al. [17] reported that LHM resulted in esophageal symptom control in 84.3% of patients over 10 years. Fukushima et al. reported the success rates of LHM as 95.3%, 86.5% and 73.5% over 1, 5 and 10 years, respectively, in their study on 530 patients with a median follow-up duration of 50.5 months [18]. In our study with 70.1 months of median follow-up duration, which included 24 patients, the cumulative symptom relief rate of LHM (Eckardt ≤3) was %87.5. Kaplan-Meier analysis showed that the probability of Eckardt score ≤3 over 3 and 5 years were 100% and 94.7%, respectively. Mean expected survival time with Eckardt score ≤3 was 102.5 (95% CI: 87.6 – 117.3) months. In light of these data, it can be concluded that LHM is still one of the most effective methods in long-term achalasia treatment.

We had 3 patients with a post-operative Eckardt score >3. One of these underwent pneumatic dilatation because of severe dysphagia. Two (one of them who underwent pneumatic dilatation) of these 3 patients were consistent with JES grade I (<3.5 cm), while the other one was consistent with JES grade III. Fukushima et al. reported that JES grade I patients had the highest risk of recurrent dysphagia [18]. High-resolution manometry (HRM) has recently been used in the diagnosis of achalasia. Achalasia was divided into three in the Chicago classification based on HRM findings for a better treatment algorithm, as type I, II and III [19]. Type III is also named as spastic achalasia. Studies suggest that the risk of recurrent dysphagia following LHM is the highest in type III patients. Besides, the vast majority of those with type III disease correspond to JES grade I (<3.5 cm) [18]. Costantini et al. [17] reported that symptomatic recurrences mostly occurred in type III disease. Of the 3 patients with Eckardt score >3 following LHD in our study, 2 were in the JES grade I group, suggesting that these patients had type III spastic achalasia. Although similar results were recently reported in the study comparing the newly popular POEM versus LHM in terms of symptom control, in Type III spastic achalasia, POEM is preferred over LHM since it yields a longer myotomy line [20]. We would probably recommend POEM if we have had the chance to know whether these two cases to had type III disease or not. However, it should

be kept in mind that POEM carries a risk of reflux esophagitis in 50% of cases [2]. Nowadays, POEM seems to be preferable in recurrent cases and in the primary treatment of type III achalasia.

Nearly all centers add partial anti-reflux procedures to LHM to better control the reflux. Rawling et al. [6] conducted a multicenter randomized controlled study to investigate which partial fundoplication should be performed. They noted no difference between Dor and Toupet regarding acid reflux symptoms. These data were confirmed by two additional randomized controlled studies and two meta-analyses [7, 8, 21, 22]. Considering these data, which fundoplication method to be used was left to the surgeon's preference. We have been using the Dor fundoplication. Post-LHD reflux esophagitis occurrence rates vary between 6-35% [18, 23-25]. This wide range of recurrence rates may be due to the different times elapsed until post-operative endoscopy and follow-up durations. Fukushima et al. [18] reported the rate of post-LHD reflux esophagitis as 34.4% in those with a follow-up duration of more than 10 years. In our study with a median of 71 month-follow-up time, the post-LHD esophagitis rate was 20.8%. Although this finding seems relatively high, 4 of 5 patients had mild (Los Angeles grade A) and 1 had moderate (Los Angeles grade B) esophagitis. No one had Los Angeles grade C or D disease. The Kaplan-Meier analysis predicted an esophagitis-free survival of 3 and 5 years as 95% and 89.4%, respectively. Besides, the mean expected esophagitis-free survival was 94.2 (95% CI: 80.6 – 107.7) months. All these data suggest that LHD is successful in long-term acid reflux control.

Limitations

Limitations of the study include its retrospective design, lack of HRM, confirmation of reflux esophagitis findings without 24 h ambulatory pH monitoring and low sample size. Its non-comparative nature is another limitation. Although self-reporting of symptoms may yield a potential bias regarding objectivity, we used the Eckardt scoring system, which is widely used in the symptom assessment of achalasia.

Conclusion

LHD seems successful and safe in terms of symptomatic relief and acid reflux control in the surgical treatment of achalasia. However, determining the subtypes of achalasia via HRM before the treatment may possibly lead to more successful results. Further studies with a higher patient number and longer follow-up period are needed to verify our findings.

References

1. Schlottmann F, Neto RML, Herbella FAM, Patti MG. Esophageal achalasia: Pathophysiology, clinical presentation, and diagnostic evaluation. Am Surg. 2018;4:84:467–4.
2. Schlottmann F, Patti MG. Esophageal achalasia: current diagnosis and treatment. Expert Rev Gastroenterol Hepatol. 2018;12:711-21. doi: 10.1080/17474124.2018.1481748.
3. Zaninotto G, Bennett C, Boeckxstaens G, Costantini M, Ferguson MK, Pandolfino JE, et al. The 2018 ISDE achalasia guidelines. Dis Esophagus. 2018;31. doi: 10.1093/dote/doy071.
4. Inaba CS, Wright AS. Laparoscopic Heller myotomy and Toupet fundoplication for achalasia. J Laparoendosc Adv Surg Tech. 2020;30: doi:10.1089/lap.2020.0158
5. Schlottmann F, Nurczyk K, Patti MG. Laparoscopic Heller Myotomy and Dor Fundoplication: How I Do It? J Laparoendosc Adv Surg Tech A. 2020 Jun;30(6):627-9. doi:10.1089/lap.2020.0157.
6. Rawlings A, Soper NJ, Oelschlager BK. Laparoscopic Dor versus Toupet fundoplication following Heller myotomy for achalasia: Results of a multicenter, prospective, randomized-controlled trial. Surg Endosc. 2012;26:18–26. doi: 10.1007/s00464-011-1822-y. Epub 2011 Jul 26.
7. Kumagai K, Kjellin A, Tsai JA, Thorell A, Granqvist S, Lundell L, et al. Toupet versus Dor as a procedure to prevent reflux after cardiomyotomy for achalasia: Results of a randomised clinical trial. Int J Surg. 2014;12:673–80. doi: 10.1016/j.ijsu.2014.05.077. Epub 2014 Jun 2.
8. Torres-Billalobos G, Coss-Adame E, Furuzawa-Carballeda J, Romero-Hernandez F, Blancas-Brena B, Torres-Landa S, et al. Dor vs Toupet fundoplication after laparoscopic Heller myotomy: Long-term randomized controlled trial evaluated by high-resolution manometry. J Gastrointest Surg. 2018;22:13–22. doi: 10.1007/s11605-017-3578-8. Epub 2017 Sep 18.
9. Japan Eshophageal Society. Descriptive rules for achalasia of the esophagus, June 2012: 4th edition. Esophagus. 2017;14:275–89. doi: 10.1007/s10388-017-0589-1
10. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology. 1992;103:1732–8. doi: 10.1016/0016-5085(92)91428-7.
11. Lundell L, Dent J, Bennett J, Blum A, Armstrong D, Galmiche J, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut. 1999;45:172–80. doi: 10.1136/gut.45.2.172.
12. Heller E. Extramukose cardioplastik beim chronischen kardiospasmus mit dilatation des oesophagus. Mitt Grenzgeb Med Chir. 1914;27:141–9.
13. Shimi S, Nathanson LK, Cuschieri A. Laparoscopic cardiomyotomy for achalasia. J R Coll Surg Edinb. 1991;36(3):152–4.
14. Patti MG, Pellegrini CA, Horgan S, Arcerito M, Omelanczuk P, Tamburini A, et al. Minimally invasive surgery for achalasia: an 8-year experience with 168 patients. Ann Surg. 1999;230(4):587–93. doi: 10.1097/00000658-199910000-00014.
15. Zaninotto G, Costantini M, Rizzetto C, zanatta L, Guirroli E, Portale G, et al. Four hundred laparoscopic myotomies for esophageal achalasia: a single centre experience. Ann Surg. 2008;248(6):986–93. doi: 10.1097/SLA.0b013e3181907bdd.
16. Schlottmann F, Andolfi C, Kavitt RT, Konda VJA, Patti MG. Multidisciplinary approach to esophageal achalasia: a single center experience. J Laparoendosc Adv Surg Tech A. 2017;27(4):358–62. doi: 10.1089/lap.2016.0594
17. Costantini M, Salvador R, Capovilla G, Vallese L, Costantini A, Nicoletti L, et al. A thousand and one laparoscopic heller myotomies for esophageal achalasia: a 25-year experience at a single tertiary center. J Gastrointest Surg. 2019;23:23–35. doi: 10.1007/s11605-018-3956-x
18. Fukushima N, Masuda T, Yano F, Omura N, Tsuboi K, Hoshino M, et al. Over ten year outcomes of laparoscopic Heller myotomy with Dor fundoplication with achalasia: single center experience with annual endoscopic surveillance. Surg Endosc. 2020;Nov 13. doi: 10.1007/s00464-020-08148-5. Online ahead of print.
19. Pandolfino JE, Ghosh SK, Rice J, Clarke JO, Kwiatek MA, Kahrilas PJ. Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. Am J Gastroenterol. 2008;103(1):27–37. doi: 10.1111/j.1572-0241.2007.01532.x
20. Kumbhari V, Tieu AH, Onimaru M, El Zein MH, Teitelbaum EN, Ujiki MB, et al. Peroral endoscopic myotomy (POEM) vs laparoscopic Heller myotomy (LHM) for the treatment of type III achalasia in 75 patients: a multicenter comparative study. Endosc Int Open. 2015;3(3):E195–201. doi: 10.1055/s-0034-1391668
21. Aiolfi A, Tornese S, Bonitta G, Cavalli M, Rausa E, Micheletto G, et al. Dor versus Toupet fundoplication after laparoscopic Heller myotomy: Systematic review and Bayesian meta-analysis of randomized controlled trials. Asian J Surg. 2020;43:20–8. doi: 10.1016/j.asjsur.2019.03.019
22. Siddaiah-Subramanya M, Yunus RM, Khan S, Memon B, Memon MA. Anterior Dor or posterior Toupet with Heller myotomy for achalasia cardia: A systematic review and meta-analysis. World J Surg. 2019;43:1563–70. doi: 10.1007/s00268-019-04945-9
23. Boeckxstaens GE, Annese V, des Varannes SB, Chaussade S, Costantini M, Cuttutta A, et al. Pneumatic Dilation versus Laparoscopic Heller's Myotomy for Idiopathic Achalasia. N Engl J Med. 2011;364:1807–16. doi: 10.1056/NEJMoa1010502
24. Campos G, Vittinghof E, Rabl C, Takata M, Gadenstätter M, Lin F, et al. Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis. Ann Surg. 2009;249:45–57. doi: 10.1097/SLA.0b013e31818e43ab
25. Costantini A, Familiari P, Costantini M, Salvador R, Valmasoni M, Capovilla G, et al. Poem versus laparoscopic heller myotomy in the treatment of esophageal achalasia: a case control study from two high volume centers using the propensity score. J Gastrointest Surg. 2020;24:505–15. doi: 10.1007/s11605-019-04465-w.

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Which anti-TNF is most effective for my patient? Which one should I choose?

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Ethics Committee Approval
The approval for the study was obtained from the local ethics committee (Malatya Clinical Research Ethics Committee, İnönü University, 17.02.2021, Approval number: 2021/74).
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Abstract

Background/Aim: Multicenter controlled studies were conducted on the effect of anti-Tumor Necrosis Factor (TNF) agents in rheumatoid arthritis (RA) and varying effectiveness rates were reported. These agents have different advantages over each other. We aimed to compare the disease activation parameters in patients with RA at the beginning and the 52nd week of therapy in patients who were followed up in our center and started on anti-TNF (etanercept, adalimumab, and golimumab), and examine the effects of the drugs that are used by comparing them with each other.

Methods: This retrospective cohort study included 187 patients with RA who were started on anti-TNF therapy because the disease activity could not be controlled by the concomitant use of at least three different conventional Disease-Modifying Anti-Rheumatic drugs, and whose adequate response to anti-TNF were observed at the 12th-week follow-up. RA disease activity was measured using the 28-joint Disease Activity Score incorporating erythrocyte sedimentation rate (DAS-28 ESR) and the patients were evaluated by a Health Assessment Questionnaire (HAQ). For each drug group, disease activation and laboratory parameters were compared before treatment initiation and at 52 weeks of treatment. These values were then compared between the drug groups.

Results: The mean age of 187 patients included in the study was 52.70 (10.17) years, 119 (63.6%) were female and 68 (36.4%) were male. Of the patients, 63 (33.7%) were using adalimumab, 62 (33.2%) were using etanercept and 62 (33.2%) were using golimumab. In all patients, there was a significant improvement in all parameters except mean corpuscular hemoglobin, gamma-glutamyl transferase, and creatinine. There were significant changes in hemoglobin, leukocyte and platelet count, erythrocyte sedimentation rate, C reactive protein, neutrophil count, serum albumin, DAS-28 ESR, and HAQ levels in all three groups ($P<0.05$).

Conclusion: There were no differences in efficacy between adalimumab, etanercept and golimumab therapies, which were planned considering the comorbidities and drug preferences of the patients. In addition to controlled studies, real-life data to be reported by rheumatology centers will help us obtain more accurate information about the therapy results of anti-TNF agents.

Keywords: Arthritis, Rheumatoid; Adalimumab, Etanercept

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Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatic disease which inflicts irreversible damage on the joints. Although it affects the joints and periarticular structures, it can cause comorbid syndromes due to extra-articular involvement, such as rheumatoid nodules, lung involvement, and vasculitis. RA creates a significant burden for both the individual and society [1]. The individual burden consists of physical disability due to musculoskeletal dysfunction, decreased quality of life, and other comorbidities [2]. The socioeconomic burden includes medical costs, loss of workforce, and social isolation [3]. Therefore, early diagnosis and initiation of effective therapy are important to reduce inflammation and subsequent damage and functional loss. Technological developments in recent years revealed new therapeutic targets. The definition of new classification criteria and novel effective therapy strategies provided significant improvements in all outcomes of the disease [4-9].

The use of anti-tumor necrosis factor (anti-TNF) is a revolutionary therapy. Anti-TNF agents facilitate the achievement of therapy targets with their rapid and powerful effects and significantly increase the rates of controlling disease activation. Etanercept (ETN), Adalimumab (ADA), and Golimumab (GOL) are approved for use in the therapy of RA. ADA and GOL are monoclonal anti-TNF-α full IgG1 antibodies, while ETN is an extracellular domain of TNF receptor 2/IgG1-Fc fusion protein. ETN is administered once a week, ADA once every 2 weeks, and GOL once every 4 weeks by subcutaneous injection.

In the 2021 American College of Rheumatology (ACR) RA therapy guideline, it is stated that anti-TNFs can be used preferably in combination with conventional Disease-Modifying Anti-Rheumatic drugs (cDMARDs) such as methotrexate, or alone [10]**.** Although many studies report that the anti-TNF agents have similar effects, contradictions remain. Structural differences were reported to create differences in both efficacy and toxicity [11, 12]**.** In addition, the rates of primary or secondary therapy resistance that can be seen in these drugs differ [13]**.**

Response to medication delays reaching the therapy goal and requires re-evaluating the treatment alternatives. RA affects a significant part of the population and creates a serious cost burden on the healthcare system. Regular follow-up of the patients and making the necessary interventions improve the prognosis of the disease and reduce all kinds of negative outcomes.

In our daily practice as clinicians, we think it is important to know which of these drugs is the most effective for our patients and whether their effects differ. This study aimed to statistically compare the disease activation parameters in patients with RA at the beginning and in the 52nd week of anti-TNF therapy in patients who were followed up in our center, and comparatively examine the effects of these drugs.

Materials and methods

Study design

This retrospective cohort study included 187 patients who presented to the rheumatology department between August 2017-January 2021 and were diagnosed with RA according to the 2010 College of Rheumatology / European League Against Rheumatism (ACR/EULAR) classification criteria [14]**.** Patients aged 18 years and older, who were started on anti-TNF (ETN, ADA, GOL) therapy because the disease activity could not be controlled by the concomitant use of at least three different cDMARDs and who continued anti-TNF agents with an adequate response to the therapy at the 12th-week follow-ups were enrolled. The 12th-week response criterion consisted of the 28-joint Disease Activity Score, incorporating an erythrocyte sedimentation rate (DAS-28 ESR) decrease of 1.2 units from baseline and DAS-28 ESR <3.2. The patients included in the study were those who did not receive biologic DMARD (bDMARD) therapy before, did not stop or delay their medication after starting the anti-TNF therapy, and did not switch to another drug. We only included patients who received anti-TNF plus 15 mg methotrexate once a week and non-steroidal anti-inflammatory therapy if needed to ensure standard conditions. We did not include patients using cDMARD other than methotrexate and steroids.

In the clinic where the study was conducted, care is taken to use all biological drugs in equal proportions, provided that the co-morbidity and drug preferences of the patients are considered. Although our study is retrospective, the sizes of our study groups are very close.

Participants

Inclusion criteria

The study inclusion criteria were set as follows: Patients aged 18 years and over who were regularly followed up and treated by the anti-TNF agents ADA, ETN, and GOL for RA in the rheumatology clinic, without a history of bDMARD use.

Exclusion criteria

The exclusion criteria were set as follows: Patients aged under 18 years, with a history of alcohol and substance abuse, other uncontrolled medical disorders, and overlap syndromes with RA.

Data collection

All patients' demographic characteristics and clinical data were analyzed. The clinical data included duration of disease, drugs used at the time of admission and before, habits (smoking, alcohol, etc.), and history of other systemic diseases. Laboratory findings, namely, C-reactive protein (CRP, mg/L), albumin (g/dL) levels, ESR (mm/h), and complete blood count parameters were obtained from the hospital records. DAS 28 ESR and Health Assessment Questionnaire (HAQ) values calculated by the rheumatologist during follow-ups were obtained from the patient files.

Measurement tools

Disease Activity Score 28-joint count -erythrocyte sedimentation rate (DAS28-ESR): DAS28-ESR is used to determine the severity of RA using ESR along with the number of sensitive and swollen joints. The number of swollen joints is determined by a visual analog scale and ESR levels. The DAS28-ESR score ranges between 0 and 9.4.

Health Assessment Questionnaire (HAQ): HAQ is a comprehensive instrument designed to evaluate a patient's health status. HAQ is one of the measures of the ACR Core Data Set for the assessment of RA disease activity and patient-oriented outcomes, including disability, drug-associated side-effects, discomfort, cost of care, and mortality. It includes 20 items divided into the eight subcategories of dressing, arising, eating, walking, hygiene, reaching, gripping, and usual activities to determine patients' ability to use upper or lower limbs. Each item of HAQ is rated on a 4-point scale ranging from 0 to 3. The final HAQ index ranges from 0 to 3 and is scored by averaging the items from all eight categories. A HAQ score <0.3 is considered normal; however, the average HAQ of the population has been shown to increase with age [15].

Sample size

Since this is a retrospective study, the sample size was not calculated. It has been reported that at least 40 patients should be included in each group with 90% potency to evaluate the efficacy in biological drug studies used in RA [16].

Statistical analysis

Statistical Package for the Social Sciences (SPSS 22.0 for Windows) was used for data analysis. The Kolmogorov-Smirnov test was performed to check the normality of the quantitative variables. Descriptive variables were presented as mean (standard deviation (SD)) for quantitative variables, and as frequencies and percentages (%) for qualitative variables. In-group significant differences were assessed with the dependent sample T-test for quantitative variables. In addition, an ANOVA test with Bonferroni (post-hoc analysis) was utilized to assess the differences between the three groups. The significance of difference for qualitative variables was analyzed using the χ^2 test. *P*-values of <0.05 were considered statistically significant.

Results

The mean age of 187 patients included in the study was 52.70 (10.17) years, 119 (63.6%) were female and 68 (36.4%) were male. Of the patients, 63 (33.7%) were using ADA, 62 (33.2%) were using ETN and 62 (33.2%) were using GOL. Distribution and comparison of demographic characteristics of the patients according to drug groups are presented in Table 1. There was no difference between the drug groups in terms of demographic characteristics (*P*>0.05).

Table 1: Distribution and comparison of demographic characteristics of patients according to groups

	All subject n=187	Etanercept n=62	Adalimumab n=63	Golimumab n=63	*P*-value
Age, mean (SD)	52.70 (10.17)	53.03 (9.42)	52.06 (9.59)	53.00 (11.52)	0.834 *
Sex n(%)					0.940♠
Female	119 (63.6)	40 (64.5)	39 (61.9)	40 (64.5)	
Male	68 (36.4)	22 (35.5)	24 (38.1)	22 (35.5)	
Age of diagnosis (year) mean (SD)	45.61 (10.11)	46.13 (9.24)	44.65 (9.80)	46.08 (11.27)	0.651 *
Presence of additional comorbidities n(%)	29 (15.5)	11 (17.7)	11 (17.5)	7 (11.3)	0.532 ♠

SD: Standard deviation, *: ANOVA test was used; ♠:χ^2 test was used.

One hundred and thirty-nine (74.3%) patients (n=187) had RF positivity and 117 (62.6%) had Anti CCP positivity. The distribution and in-group comparison of laboratory and disease activation parameters measured before and at the 52nd week of therapy are shown in Tables 2 and 3.

In all patients, there was a significant improvement in all parameters except MCH, GGT, and creatinine (0.001<p<0.038). At the end of the first year, there was no increase in the number of additional diseases compared to pre-therapy (n=29, 15.5%). There were significant changes in the hemoglobin, leukocyte and platelet count, ESR, CRP, neutrophil, albumin, DAS-28, and HAQ levels in all three groups (*P*<0.05). A significant decrease was found in lymphocyte counts in the ETN and ADA groups, and in the ALP levels in the GOL group (Table 3).

Table 2: Comparison of the laboratory and disease activation parameters of the patients before anti-TNF therapy and in the 52nd week of treatment

	All Subject (n=187)		*P*-value*
	Before (mean (SD))	After (mean (SD))	
Hemoglobin (g/dl)	12.20 (1.62)	13.07 (0.90)	<0.001
Leukocyte (/µl)	7728.07 (1767.73)	6290.96 (1518.49)	<0.001
Thrombocyte (10^3/µl)	245.68 (63.84)	226.81 (52.77)	<0.001
MCV (fL)	86.02 (3.24)	86.44 (2.49)	0.027
MCH (pg)	26.23 (2.31)	26.06 (1.74)	0.301
ESR (mm/h)	40.30 (9.76)	12.67 (4.37)	<0.001
CRP (mg/L)	21.37 (8.68)	2.80 (1.47)	<0.001
Neutrophil (/µl)	5612.57 (1848.81)	3577.81 (1350.51)	<0.001
Lymphocyte (/µl)	1855.56 (382.33)	1617.38 (382.33)	<0.001
Albumin (g/L)	4.24 (0.18)	4.45 (0.16)	<0.001
ALT (U/L)	17.27 (7.48)	16.13 (3.09)	0.006
AST (U/L)	16.98 (4.66)	15.99 (3.11)	0.038
ALP (U/L)	84.49 (19.07)	81.14 (12.88)	0.024
GGT (U/L)	24.73 (10.45)	23.32 (7.90)	0.078
Creatinine (mg/dL)	0.73 (0.15)	0.71 (0.11)	0.115
DAS 28-ESR	5.89 (0.19)	2.60 (0.42)	<0.001
HAQ	1.30 (0.24)	0.33 (0.11)	<0.001

MCV: mean corpuscular volüme, MCH: mean corpuscular hemoglobin, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline phosphatase, GGT: Gamma glutamyl transferase, DAS 28-ESR: 28-joint Disease Activity Score incorporating erythrocyte sedimentation rate, HAQ: Health assessment questionnaire, SD: Standard deviation, *: Dependent T test was used.

Table 3: Distribution and comparison of laboratory and disease activation parameters of patients before anti-TNF treatment and in the 52nd week of treatment according to drugs

	Etanercept (n=62)		*P*-value*	Adalimumab (n=63)		*P*-value*	Golimumab (n=62)		*P*-value*
	Before Mean (SD)	After Mean (SD)		Before Mean (SD)	After Mean (SD)		Before Mean (SD)	After Mean (SD)	
Hemoglobin (g/dL)	12.29 (1.70)	13.21 (0.86)	<0.001	12.06 (1.63)	12.89 (1.04)	<0.001	12.24 (1.53)	13.11 (0.74)	<0.001
Leukocyte (/µl)	7890.48 (1798.87)	6395.97 (1557.13)	<0.001	7768.40 (1854.06)	6524.44 (1506.05)	<0.001	7524.68 (1651.54)	5948.71 (1454.04)	<0.001
Thrombocyte (10^3/µl)	238.17 (70.59)	223.80 (61.69)	<0.001	255.90 (54.73)	235.28 (44.11)	<0.001	242.80 (65.01)	221.20 (50.91)	<0.001
MCV (fL)	85.63 (2.43)	86.11 (2.36)	0.092	86.20 (4.11)	86.44 (3.03)	0.461	86.23 (2.95)	86.75 (1.97)	0.151
MCH (pg)	25.79 (2.54)	25.82 (1.83)	0.908	26.47 (2.24)	26.39 (1.75)	0.771	26.42 (2.10)	25.98 (1.62)	0.116
ESR (mm/h)	41.74 (8.84)	12.87 (4.71)	<0.001	39.56 (10.45)	12.51 (4.08)	<0.001	39.63 (9.91)	12.65 (4.37)	<0.001
CRP (mg/L)	21.59 (8.85)	2.85 (1.42)	<0.001	21.80 (4.43)	2.76 (1.50)	<0.001	20.71 (8.86)	2.79 (1.51)	<0.001
Neutrophil (/µl)	5666.29 (1773.44)	3682.90 (1433.82)	<0.001	5676.98 (2001.01)	3589.84 (1225.98)	<0.001	5493.39 (1784.92)	3460.48 (1397.30)	<0.001
Lymphocyte (/µl)	1841.77 (719.72)	1586.13 (328.07)	0.003	2078.10 (825.22)	1720.95 (421.60)	<0.001	1643.23 (489.93)	1543.39 (373.90)	0.093
Albumin (g/L)	4.26 (0.16)	4.46 (0.15)	<0.001	4.24 (0.23)	4.50 (0.17)	<0.001	4.24 (0.15)	4.41 (0.13)	<0.001
ALT (U/L)	16.36 (5.15)	16.15 (3.07)	0.766	18.15 (9.76)	16.04 (3.42)	0.064	17.30 (6.75)	16.22 (2.78)	0.238
AST (U/L)	17.10 (4.44)	16.25 (3.13)	0.152	17.46 (5.81)	16.10 (3.43)	0.071	16.38 (3.38)	15.63 (2.74)	0.160
ALP (U/L)	79.76 (17.94)	81.42 (12.05)	0.464	85.41 (20.66)	80.11 (15.83)	0.054	88.29 (17.74)	81.90 (10.21)	0.016
GGT (U/L)	24.35 (9.18)	21.65 (7.07)	0.055	27.87 (13.52)	25.57 (8.29)	0.157	21.92 (6.68)	22.71 (7.87)	0.460
Creatinine (mg/dL)	0.74 (0.17)	0.71 (0.13)	0.136	0.70 (0.15)	0.69 (0.11)	0.885	0.75 (0.12)	0.73 (0.10)	0.216
DAS 28-ESR	5.90 (0.20)	2.56 (0.49)	<0.001	5.93 (0.18)	2.61 (0.44)	<0.001	5.85 (0.17)	2.62 (0.47)	<0.001
HAQ	1.31 (0.25)	0.35 (0.14)	<0.001	1.30 (0.23)	0.32 (0.14)	<0.001	1.31 (0.23)	0.32 (0.13)	<0.001

*: Dependent T test was used.

While the pre-therapy values were similar in all three groups, the lymphocyte count, albumin, and GGT levels measured after the therapy were significantly different (*P*=0.024, *P*=0.005, and *P*=0.015, respectively). Subgroup analysis revealed that in the ADA group, lymphocyte count (*P*=0.027) and albumin (*P*=0.003) levels were higher than in the GOL group, and GGT levels were higher compared to the ETN group (*P*=0.016) (Table 4).

The distribution and comparison of the changes in therapy and evaluation parameters according to the groups are presented in Table 5. A significant difference was found in the

change in ALP and albumin levels (P=0.005 and P=0.043, respectively). In subgroup analysis, the change in albumin level was significantly higher in the ADA group compared to the GOL group (P=0.005). The decrease in ALP level was significantly higher in the GOL group compared to the ETN group (P=0.047).

No serious side effects were observed in any of the patients included in the study.

Table 4: Comparison of pre-treatment and end-of-first year values of patients receiving Etanercept, Adalimumab and Golimumab treatment

	Etanercept (n=62) Mean (SD), n(%)	Adalimumab (n=63) Mean (SD), n(%)	Golimumab (n=62) Mean (SD), n(%)	*P*-value
Before treatment				
Hemoglobin (g/dL)	12.29 (1.70)	12.06 (1.63)	12.24 (1.53)	0.710*
Leukocyte (/µl)	7890.48 (1798.87)	7768.40 (1854.06)	7524.68 (1651.54)	0.505*
Thrombocyte (10^3/µl)	238.17 (70.59)	255.90 (54.73)	242.80 (65.01)	0.274*
MCV (fL)	85.63 (2.43)	86.20 (4.11))	86.23 (2.95)	0.507*
MCH (pg)	25.79 (2.54)	26.47 (2.24)	26.42 (2.10)	0.193*
ESR (mm/h)	41.74 (8.84)	39.56 (10.45)	39.63 (9.91)	0.368*
CRP (mg/L)	21.59 (8.85)	21.80 (4.43)	20.71 (8.86)	0.790*
Neutrophil (/µl)	5666.29 (1773.44)	5676.98 (2001.01)	5493.39 (1784.92)	0.826*
Lymphocyte (/µl)	1841.77 (719.72)	2078.10 (825.22)	1643.23 (489.93)	0.053*
Albumin (g/L)	4.26 (0.16)	4.24 (0.23)	4.24 (0.15)	0.807*
ALT (U/L)	16.36 (5.15)	18.15 (9.76)	17.30 (6.75)	0.441*
AST (U/L)	17.10 (4.44)	17.46 (5.81)	16.38 (3.38)	0.423*
ALP (U/L)	79.76 (17.94)	85.41 (20.66)	88.29 (17.74)	0.059*
GGT (U/L)	24.35 (9.18)	27.87 (13.52)	21.92 (6.68)	0.052*
Creatinine (mg/dL)	0.74 (0.17)	0.70 (0.15)	0.75 (0.12)	0.133*
RF positivity	47 (75.8)	42 (66.7)	50 (80.6)	0.194♠
Anti-CCP positivity	43 (69.4)	32 (50.8)	42 (67.7)	0.059♠
DAS28-ESR	5.90 (0.20)	5.93 (0.18)	5.85 (0.17)	0.058*
HAQ	1.31 (0.25)	1.30 (0.23)	1.31 (0.23)	0.990*
After treatment				
Hemoglobin (g/dL)	13.21 (0.86)	12.89 (1.04)	13.11 (0.74)	0.125*
Leukocyte (/µl)	6395.97 (1557.13)	6524.44 (1506.05)	5948.71 (1454.04)	0.084*
Thrombocyte (10^3/µl)	223.80 (61.69)	235.28 (44.11)	221.20 (50.91)	0.285*
MCV (fL)	86.11 (2.36)	86.44 (3.03)	86.75 (1.97)	0.367*
MCH (pg)	25.82 (1.83)	26.39 (1.75)	25.98 (1.62)	0.176*
ESR (mm/h)	12.87 (4.71)	12.51 (4.08)	12.65 (4.37)	0.897*
CRP (mg/L)	2.85 (1.42)	2.76 (1.50)	2.79 (1.51)	0.941*
Neutrophil (/µl)	3682.90 (1433.82)	3589.84 (1225.98)	3460.48 (1397.30)	0.657*
Lymphocyte (/µl)	1586.13 (328.07)	1720.95 (421.60)	1543.39 (373.90)	0.024*
Albumin (g/L)	4.46 (0.15)	4.50 (0.17)	4.41 (0.13)	0.005*
ALT (U/L)	16.15 (3.07)	16.04 (3.42)	16.22 (2.78)	0.907*
AST (U/L)	16.25 (3.13)	16.10 (3.43)	15.63 (2.74)	0.518*
ALP (U/L)	81.42 (12.05)	80.11 (15.83)	81.90 (10.21)	0.725*
GGT (U/L)	21.65 (7.07)	25.57 (8.29)	22.71 (7.87)	0.015*
Creatinine (mg/dL)	0.71 (0.13)	0.69 (0.11)	0.73 (0.10)	0.228*
DAS28-ESR	2.56 (0.49)	2.61 (0.44)	2.62 (0.47)	0.752*
HAQ	0.35 (0.14)	0.32 (0.14)	0.32 (0.13)	0.444*

RF: Rheumatoid factor, Anti CCP: Cyclic Citrullinated Peptide Antibody, SD: Standard deviation, *: ANOVA test was used; ♠:χ^2 test was used.

Table 5: Comparison of the changes in Etanercept, Adalimumab and Golimumab treatments before and after the first year of treatment

	Etanercept (n=62) Mean (SD)	Adalimumab (n=63) Mean (SD)	Golimumab (n=62) Mean (SD)	*P*-value*
Hemoglobin (g/dL)	0.92 (1.38)	0.83 (1.29)	0.86 (1.57)	0.935
Leukocyte (/µl)	-1494.51 (1968.50)	-1243.95 (1981.13)	-1575.96 (1739.40)	0.596
Thrombocyte (10^3/µl)	-14.37 (162.61)	-20.61 (236.81)	-21.59 (276.52)	0.172
MCV (fL)	0.48 (2.24)	0.23 (2.56)	0.52 (2.83)	0.796
MCH (pg)	-0.03 (2.06)	-0.08 (2.24)	-0.44 (2.18)	0.444
ESR (mm/h)	-28.87 (8.95)	-27.04 (11.24)	-26.98 (9.67)	0.492
CRP (mg/L)	-18.74 (8.43)	-19.03 (7.96)	-17.92 (8.49)	0.740
Neutrophil (/µl)	-1983.38 (1649.38)	-2087.14 (2084.66)	-2032.90 (1693.54)	0.951
Lymphocyte (/µl)	-255.64 (647.99)	-357.14 (770.09)	-99.83 (460.24)	0.080
Albumin (g/L)	0.19 (0.15)	0.26 (0.19)	0.16 (0.10)	0.005
ALT (U/L)	-0.21 (5.61)	-2.10 (9.12)	-1.08 (7.15)	0.365
AST (U/L)	-0.84 (4.59)	-1.35 (5.72)	-0.74 (4.14)	0.754
ALP (U/L)	1.66 (17.75)	-5.30 (21.40)	-6.38 (20.30)	0.043
GGT (U/L)	-2.70 (10.91)	-2.30 (12.76)	0.79 (8.36)	0.147
Creatinine (mg/dL)	-0.03 (0.18)	-0.01 (0.18)	-0.01 (0.13)	0.564
DAS28-ESR	-3.33 (0.49)	-3.32 (0.41)	-3.23 (0.46)	0.362
HAQ	-0.96 (0.24)	-0.98 (0.20)	0.98 (0.20)	0.770

SD: Standard deviation, *: ANOVA test was used.

Discussion

In our study, we aimed to statistically compare the disease activation parameters at the beginning and the 52nd week of anti-TNF therapy in patients who were followed up in our center, and comparatively examine the effects of the drugs used. We showed that there was a significant decrease in DAS28-ESR, CRP, ESR, and HAQ scores at the 52nd week of therapy in patients who were started on ADA, ETN, and GOL due to RA. In addition, the effects of ADA, ETN, and GOL therapies at the end of 52 weeks were similar.

Well-defined mediators of inflammation such as interleukin 6 (IL-6), interleukin 1 (IL-1), interferon-gamma, especially the pro-inflammatory cytokine TNF secreted from B and T lymphocytes stimulated as a result of inappropriate activation of the immune system, play role in the pathogenesis of RA [17]. Among these cytokines, TNF has been shown to have the most critical role [18]. After this was discovered, controlling the inflammation pathway that starts with TNF and blocking the effects of TNF became one of the main goals of treatment in reducing the chronic effects of RA. For this purpose, anti-TNF agents with different molecular structures targeting TNF began to be used. ETN, which blocks the membrane and soluble form of TNF [19], ADA, which prevents TNF from binding to its specific receptor [20], and GOL, which blocks the soluble and transmembrane form of TNF, are three of these drugs [21].

Many studies investigated the effectiveness of ADA, ETN, and GOL therapies, albeit not comparatively. It was reported that the combination of anti-TNF agents with MTX provides permanent clinical improvement and reduces radiographic progression in patients with RA. Evaluation of the patients according to the ACR response criteria revealed that the efficacy of anti-TNF agents in patients using this combination was similar [22].

Studies report that patients using ADA plus MTX had a better clinical course and radiographic progression than patients using MTX alone [23-25]. Also, patients using ETN plus MTX had better clinical course compared to patients using ETN or MTX alone [26]. The efficacy of GOL was demonstrated by multicenter studies conducted with different patient groups investigating the efficacy and safety of the drug [27-29]. Unlike all these multicenter studies, we compared the laboratory and disease activation scores for each anti-TNF agent at therapy initiation and the end of 52 weeks and found a significant difference in inflammation parameters and disease activation scores at the 52nd week of therapy in all three anti-TNF agents. However, the effects of the three agents did not significantly differ when compared to each other. Another result of our study is that the serum ALP level was higher in patients using ETN than in patients using the other two agents, while the GGT level decreased with therapy in patients using ETN and ADA but increased with GOL therapy. Larger and controlled studies are needed to evaluate this finding more accurately.

Limitations

Its single-center and retrospective design, and the sparse number of patients are the two main limitations of this study.

Conclusion

In this retrospective study, we found that there were no significant differences in the efficacy between ADA, ETN and GOL therapies, which were planned considering the comorbidities and drug preferences of the patients. In addition to controlled studies, real-life data to be reported by rheumatology centers will help us to obtain more accurate information about the therapy results of anti-TNF agents. Larger studies with larger patient groups are needed for the reliability of these data.

References

1. Cross M, Smith E, Hoy D, Carmona L. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. 2014;73:1316-22. doi: 10.1136/annrheumdis-2013-204627. Epub 2014 Feb 18. PubMed PMID: 24550173.
2. Kitas GD, Gabriel SE. Cardiovascular disease in rheumatoid arthritis: state of the art and future perspectives. Annals of the rheumatic diseases. 2011;70:8-14. doi: 10.1136/ard.2010.142133. Epub 2010 Nov 24. PubMed PMID:21109513.
3. Sokka T, Kautiainen H, Pincus T, Verstappen SM, Aggarwal A, Alten R, et al. Work disability remains a major problem in rheumatoid arthritis in the 2000s: data from 32 countries in the QUEST-

RA study. Arthritis Res Ther. 2010;12:R42. doi: 10.1186/ar2951. Epub 2010 Mar 12. PubMed PMID: 202260118 PubMed Central PMCID: 2888189.
4. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Annals of the rheumatic diseases. 2010;69:1580-8. doi: 10.1002/art.27584.
5. Smolen JS, Aletaha D. Rheumatoid arthritis therapy reappraisal: strategies, opportunities and challenges. Nat Rev Rheumatol. 2015;11:276-89. doi: 10.1038/nrrheum.2015.8. PubMed PMID:25687177.
6. Nam JL, Ramiro S, Gaujoux-Viala C, Takase K, Leon-Garcia M, Emery P, et al. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. Annals of the rheumatic diseases. 2014;73:516-28. doi: 10.1136/annrheumdis-2013-204577. Epub 2014 Jan 7. PubMed PMID: 24399231.
7. Gaujoux-Viala C, Nam J, Ramiro S, Landewé R, Buch MH, Smolen JS, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Annals of the rheumatic diseases. 2014;73:510-5. doi: 10.1136/annrheumdis-2013-204588. Epub 2014 Jan 6. PubMed PMID: 24395555 PubMed Central PMCID:PMC3932966.
8. Ramiro S, Gaujoux-Viala C, Nam JL, Smolen JS, Buch M, Gossec L, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. Annals of the rheumatic diseases. 2014;73:529-35. doi: 10.1136/annrheumdis-2013-204575. Epub 2014 Jan 8. PubMed PMID: 24401994.
9. Stoffer MA, Schoels MM, Smolen JS, Aletaha D, Breedveld FC, Burmester G, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search update. 2016;75:16-22. doi: 10.1136/annrheumdis-2015-207526. Epub 2015 May 19. PubMed PMID: 2590290 PubMed Center PMCID: PMC4717391.
10. Fraenkel L, Bathon JM, England BR. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. 2021;73:924-39. doi: 10.1002/acr.24596. Epub 2021 Jun 8. PubMed PMID: 34101387.
11. Listing J, Strangfeld A, Kary S, Rau R, von Hinueber U, Stoyanova-Scholz M, et al. Infections in patients with rheumatoid arthritis treated with biologic agents. Arthritis and rheumatism. 2005;52:3403-12. doi: 10.1002/art.21386. PubMed PMID: 16255017.
12. Thomas SS, Borazan N, Barroso N, Duan L, Taroumian S, Kretzmann B, et al. Comparative Immunogenicity of TNF Inhibitors: Impact on Clinical Efficacy and Tolerability in the Management of Autoimmune Diseases. A Systematic Review and Meta-Analysis. BioDrugs : clinical immunotherapeutics, biopharmaceuticals and gene therapy. 2015;29:241-58. doi: 10.1007/s40259-015-0134-5. PubMed PMID:26280210.
13. Sidiropoulos PI, Boumpas DT. Differential drug resistance to anti-tumour necrosis factor agents in rheumatoid arthritis. Annals of the rheumatic diseases. 2006;65:701-3. doi: 10.1136/ard.2005.049890. PubMed PMID: 16699049 PubMed Centre PMCID: PMC1798160.
14. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, 3rd, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis and rheumatism. 2010;62:2569-81. doi: 10.1002/art.27584. PubMed PMID: 20872595.
15. Pereira AM, Tiemensma J, Romijn JA. Neuropsychiatric Disorders in Cushing's Syndrome. Neuroendocrinology. 2010;92(suppl 1):65-70. doi: 10.1159/000314317. Epub 2010 Sep 10. PubMed PMID: 20829621.
16. Celik S, Yazici Y, Yazici H. Are sample sizes of randomized clinical trials in rheumatoid arthritis too large? European journal of clinical investigation. 2014;44:1034-44. doi: 10.1111/eci.12337. Epub 2014 Oct 7. PubMed PMID: 25207845.
17. Li P, Zheng Y, Chen X. Drugs for Autoimmune Inflammatory Diseases: From Small Molecule Compounds to Anti-TNF Biologics. Frontiers in Pharmacology. 2017;8. doi: 10.3389/fphar.2017.00460. eCollection 2017. PubMed PMID:28785220 PubMed Center PMCID: PMC5506195.
18. Moudgil KD, Choubey D. Cytokines in autoimmunity: role in induction, regulation, and treatment. Journal of interferon & cytokine research : the official journal of the International Society for Interferon and Cytokine Research. 2011;31:695-703. doi: 10.1089/jir.2011.0065. Epub 2011 Sep 23. PubMed PMID: 21942420 PubMed Centre PMCID: PMC3189547.
19. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacology & therapeutics. 2008;117:244-79. doi: 10.1016/j.pharmthera.2007.10.001. Epub 2007 Oct 26. PubMed PMID: 18155297.
20. Atzeni F, Turiel M, Capsoni F, Doria A, Meroni P, Sarzi-Puttini P. Autoimmunity and Anti-TNF-α Agents. Annals of the New York Academy of Sciences. 2005;1051:559-69.
21. Shealy DJ, Cai A, Staquet K, Baker A, Lacy ER, Johns L, et al. Characterization of golimumab, a human monoclonal antibody specific for human tumor necrosis factor α. mAbs. 2010;2:428-39. doi: 10.4161/mabs.12304. Epub 2010 Jul 1. PubMed PMID: 20519961 PubMed Centre PMCID: PMC: 3180089.
22. Smolen JS, Aletaha D, Koeller M, Weisman MH, Emery P. New therapies for treatment of rheumatoid arthritis. Lancet (London, England). 2007;370:1861-74. doi: 10.1016/S0140-6736(07)60784-3. PubMed PMID: 17570481.
23. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis and rheumatism. 2006;54:26-37. doi: 10.1002/art.21519. PubMed PMID: 16385520.
24. Kavanaugh A, Fleischmann RM, Emery P, Kupper H, Redden L, Guerette B, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. Annals of the rheumatic diseases. 2013;72:64-71. doi: 10.1136/annrheumdis-2011-201247. PubMed PMID: 22562973 PubMed Centre PMCID: PMC3551224.
25. Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis and rheumatism. 2004;50:1400-11. doi: 10.1002/art.20217. PubMed PMID: 15146409.
26. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet (London, England). 2004;363:675-81. doi: 10.1016/S0140-6736(04)15640-7. PubMed PMID: 15001324.
27. Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis and rheumatism. 2009;60:2272-83.
28. Keystone E, Genovese MC, Klareskog L, Hsia EC, Hall S, Miranda PC, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: 52-week results of the GO-FORWARD study. Annals of the rheumatic diseases. 2010;69:1129-35. doi: 10.1136/ard.2009.116319. Epub 2010 May 5. PubMed PMID: 20444749.
29. Smolen JS, Kay J, Doyle MK, Landewé R, Matteson EL, Wollenhaupt J, et al. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet (London, England). 2009;374:210-21. doi: 10.1016/S0140-6736(09)60506-7. Epub 2009 Jun 26. PubMed PMID: 19560810.

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Evaluation of sinonasal complaints in obstructive sleep apnea

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Local ethics committee (Yozgat Bozok University Clinical Research Ethics Committee, Ref. No=2017-KAEK-189_2019.04.24_08).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Sinonasal complaints are frequently observed in patients with obstructive sleep apnea (OSA). This study aimed to correlate the severity of OSA with sinonasal complaints.
Methods: A total of 90 patients, including 30 patients with mild, 30 with moderate, and 30 with severe OSA, were enrolled in this cross-sectional study. None of the patients received any treatment for OSA at the time of enrollment. All participants were asked to complete the SNOT-22 questionnaire. Subdomain scores obtained from the patients with the SNOT-22 questionnaire, total scores, and scores obtained for each complaint were investigated for any correlations with severity of OSA. Also, mild, moderate, and severe OSA groups were compared with each in terms of these scores.
Results: A significant, positive correlation was found between AHI values and "nasal obstruction," "runny nose," "lack of a good night's sleep" and "waking up tired" items of the SNOT-22 (P=0.008, P=0.022, P=0.037, P=0.005, respectively) and nonrhinologic otolaryngologic subdomain scores (P=0.036). A significant, positive correlation existed between the severity of OSA and sleep subdomain score (P=0.039) and the total score (P=0.047) in addition to all the above-mentioned elements. There was no difference between mild and moderate OSA groups in nasal obstruction and runny nose complaints (P=0.858, P=0.990, respectively) but a difference was noted between mild and severe (P=0.016, P=0.011, respectively), and moderate and severe OSA groups (P=0.015, P=0.011, respectively). While there was no difference between mild and moderate (P=0.268), and moderate and severe OSA groups (P=0.036) in terms of the 'waking up tired' item, the mild and severe OSA groups differed significantly (P=0.009).
Conclusion: OSA causes various sinonasal complaints such as nasal obstruction, runny nose, and waking up tired. An increase in OSA severity leads to an increase in these complaints, and treatment may lead to increased quality of life.

Keywords: Obstructive sleep apnea, Sinonasal complaints, Apnea-hypopnea index

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Introduction

The collapse of the upper airway during sleep is the hallmark of OSA and breathing is interrupted for at least 10 seconds [1, 2]. Complete cessation of breathing is repeated many times during sleep, due to which the amount of oxygen in the blood decreases and several systems are adversely affected [3]. In the treatment of OSA, numerous methods are used to prevent the collapse of the upper respiratory tract. These therapeutic modalities generally include Positive Airway Pressure (PAP) therapy, surgical interventions, and medical treatments. The target organ in most of these treatments is the upper respiratory tract. The effects of OSA on many systems in the body were investigated in several studies in the literature [4-6]. However, there are a limited number of studies revealing the impact of OSA on the upper respiratory tract and related complaints.

This study aimed to investigate the correlation between OSA severity and sinonasal complaints.

Materials and methods

This study was conducted in the otorhinolaryngology department of a tertiary hospital after the approval of the local ethics committee (Yozgat Bozok University Clinical Research Ethics Committee, Ref. No=2017-KAEK-189_2019.04.24_08) was obtained. Ninety patients who were diagnosed with obstructive sleep apnea by a polysomnography test performed in our institution were included in the study. Thirty of these patients had mild, 30 had moderate and 30 had severe obstructive sleep apnea. The minimum sample size (30 patients in a group) was calculated for each group at a 95% significance level and 90% statistical power based on a similar study [7]. Written informed consent was obtained from all subjects before enrollment. Those with upper respiratory tract infection, allergic rhinitis, eustachian dysfunction, nasal septum deviation, nasal polyposis, previous otolaryngological operations, ear pathology, psychiatric diseases, and smokers were not included in the study. Forty-nine patients were male and 41 were female. The mean age of the patients was 54.60 years. Polysomnography was performed on all patients using a 31-channel ALICE 6 LDe device (Respironics, Murrysville, PA, USA). AHI values obtained as a result of polysomnography were recorded in all participants. The patients were divided into 3 groups according to their AHI values as mild, moderate, and severe OSA. A special effort was made to assign 30 patients to each group. Before inclusion in the study, it was ensured that the patients were not receiving any treatment for obstructive sleep apnea. All patients were asked to fill in the SNOT-22 questionnaire. There are 22 complaints including the rhinologic, nonrhinologic-otolaryngologic, sleep, and psychological complaints in the SNOT-22 questionnaire. Patients are asked to rate these complaints according to the problems they have experienced within the last 2 weeks. Each item is rated as follows: 0=No problem, 1=Very mild problem, 2=Mild or slight problem, 3=Moderate problem, 4=Severe problem, 5=Very severe problem. The rhinologic complaints subdomain contains 'need to blow nose', 'nasal obstruction', 'sneezing', 'runny nose', 'postnasal drip', 'thick nasal discharge', 'loss of smell' and 'taste complaints'; nonrhinologic-otolaryngologic subdomain includes 'cough', 'ear fullness', 'dizziness', ear pain, facial pain/pressure' complaints; the sleep subdomain comprises 'difficulty falling asleep', 'waking up at night', 'lack of a good night's sleep', 'waking up tired' complaints, and the psychological subdomain has 'fatigue', 'reduced productivity', 'reduced concentration', 'feeling frustrated/restless/irritable, sad, embarrassed' complaints. A low total SNOT-22 score indicates a better quality of life. Subdomain scores, total scores, and scores obtained for each complaint were correlated with the AHI scores and severity of OSA in the patients, obtained by the SNOT 22 questionnaire. The mild, moderate, and severe OSA groups were compared with each other in terms of subdomain scores, total scores, and scores obtained for each complaint in SNOT-22.

Statistical analysis

SPSS software (version 20.0 for Windows, IBM Corp., Armonk, NY, USA) was used for all data analyses. Spearman Correlation Analysis was used to correlate SNOT-22 parameters with AHI values and severity of OSA. A *P*-value of less than 0.05 was considered significant. The Kruskal Wallis test was used to compare mild, moderate, and severe OSA groups in terms of SNOT-22 data. Bonferroni Correction and Post hoc tests were used for the significantly differing parameters. The *P*-value obtained with Bonferroni Correction was 0.017. A *P*-value of less than 0.017 in post hoc test results was considered statistically significant.

Results

No difference was found between the groups in terms of age, gender, and body mass index (P=0.548, P= 0.140, and P=0.798, respectively).

AHI values were significantly positively correlated with 'nasal obstruction', 'runny nose', 'lack of a good night's sleep', 'waking up tired' items (P=0.008, P=0.022, P=0.037, P=0.005, respectively) and nonrhinologic-otolaryngologic subdomain scores (P=0.036, Table 1).

Table 1: Correlation between SNOT-22 items and AHI/OSA Degree

SNOT-22 items	Score	*P*-value	
	Mean (SD)	AHI	OSAS Degree
Rhinologic	5.89 (4.17)	0.172	0.102
Need to blow nose	0.88 (1.14)	0.856	0.694
Nasal Obstruction	1.47 (1.37)	0.008*	0.012*
Sneezing	1.09 (0.97)	0.371(-)	0.485(-)
Runny Nose	0.34 (0.78)	0.022*	0.006*
Postnasal Drip	1.01 (1.31)	0.992(-)	0.952
Thick Nasal Discharge	0.31 (0.74)	0.445	0.465
Loss of Smell and Taste	0.79 (1.16)	0.292	0.235
Non Rhinologic Otolaryngologic Complaints	4.09 (3.69)	0.036*	0.040*
Cough	0.93 (1.14)	0.159	0.177
Ear Fullness	1.00 (1.11)	0.212	0.155
Dizziness	1.07 (1.15)	0.531	0.600
Ear Pain	0.39 (0.80)	0.567	0.428
Facial Pain/Pressure	0.70 (1.09)	0.532	0.493
Sleep	8.09 (4.51)	0.050	0.039*
Difficulty falling asleep	1.44 (1.57)	0.797(-)	0.853
Wake up at night	2.14 (1.37)	0.123	0.146
Lack of good night's sleep	2.10 (1.58)	0.037*	0.040*
Waking up tired	2.40 (1.27)	0.005*	0.004*
Psychological	6.23 (5.27)	0.623	0.448
Fatigue	1.36 (1.34)	0.118	0.064
Reduced productivity	1.08 (1.35)	0.508	0.404
Reduced concentration	0.99 (1.31)	0.164	0.109
Frustrated/Restless/irritable	1.17 (1.33)	0.689	0.313
Sad	0.89 (1.20)	0.249	0.191
Embarrassed	0.76 (1.03)	0.790	0.843
Total	24.31(13.84)	0.072	0.047*

* Statistically significant, (-) Negatively correlated

The severity of OSA was significantly, positively correlated with the 'nasal obstruction', 'runny nose', 'lack of a good night's sleep', 'waking up tired' items (P=0.012, P=0.006, P=0.040, P=0.004, respectively) and nonrhinologic-

otolaryngologic, sleep, total SNOT-22 scores (P=0.040, P=0.039, P=0.047, respectively, Table 1).

Comparison of 3 groups concerning SNOT-22 items revealed a statistically significant difference between the three groups in 'nasal obstruction', 'runny nose', and 'waking up tired' items (P=0.019, P=0.007, P= 0.017, respectively, Table 2). While there was no statistically significant difference between mild and moderate OSA groups (P=0.858) in terms of 'nasal obstruction', a significant difference was found between mild and severe OSA groups (P=0.016) and between moderate and severe OSA groups (P=0.015). The mild and moderate OSA groups (P=0.990) were similar in terms of 'runny nose', while mild and severe OSA groups (P=0.011) and moderate and severe OSA groups (P=0.011) significantly differed. The mild and moderate OSA groups (P=0.268) and the moderate and severe OSA groups (P=0.036) did not differ in terms of the 'waking up tired' item, while the mild and severe OSA groups did (P=0.009).

Table 2: Comparison of three groups in terms of SNOT-22 items

SNOT-22 items	Kruskal Wallis	Post Hoc Tests		
		P-value		
	P-value	Mild/Moderate	Mild/Severe	Moderate/Severe
Rhinologic	0.105			
Need to blow nose	0.074			
Nasal Obstruction	0.019*	0.858	0.016*	0.015*
Sneezing	0.767			
Runny Nose	0.007*	0.990	0.011*	0.011*
Postnasal Drip	0.325			
Thick Nasal Discharge	0.088			
Loss of Smell and Taste	0.488			
Non Rhinologic	0.121			
Otolaryngologic				
Cough	0.278			
Ear Fullness	0.336			
Dizziness	0.698			
Ear Pain	0.498			
Facial Pain/Pressure	0.687			
Sleep	0.120			
Difficulty falling asleep	0.422			
Wake up at night	0.327			
Lack of good night's sleep	0.102			
Waking up tired	0.017*	0.268	0.009*	0.036
Psychological	0.312			
Fatigue	0.110			
Reduced productivity	0.384			
Reduced concentration	0.152			
Frustrated/Restless/irritable	0.373			
Sad	0.417			
Embarrassed	0.972			
Total	0.098			

* Statistically Significant

Discussion

The collapse of the upper airway during sleep is the hallmark of OSA and breathing is interrupted for longer than 10 seconds. This cessation of breathing is known as apnea, and it occurs many times during sleep. Hypoxia due to apnea adversely affects several systems. Mouth breathing is frequently observed in OSA patients [8]. The autonomic nervous system is also affected in OSA [9]. Furthermore, many craniofacial abnormalities such as mandibular insufficiency, maxillary hypoplasia, the inferior position of the hyoid bone, narrowing of the posterior airway, and drooping soft palate can be encountered [10, 11]. Tonsillar hypertrophy, hypertrophy of the base of the tongue, nasal septum deviation are also common pathologies seen in OSA. There may be also an increase in the frequency of sinonasal complaints due to the interruption of the air passage from the upper respiratory tract, frequent mouth breathing, frequent anatomical disorders related to the upper respiratory tract, and changes in the autonomic nervous system. Various studies demonstrated an increase in sinonasal complaints among OSA patients [12, 13]. In the literature, a reduction is reported in these complaints with CPAP treatment [14].

SNOT-22 is not a diagnostic test, but a method used in the follow-up of various pathologies that measures the quality of life. In previous studies, SNOT-22 items were divided into various subdomains [15, 7]. In this study, similar to previous studies, SNOT-22 items were divided into 4 groups as rhinologic, nonrhinologic-otolaryngologic, sleep, and psychological subdomains. This distinction allowed the evaluation of subdomain scores as well as the total score in various pathologies. It is not surprising that higher scores were obtained in the sleep subdomain in OSA. In many studies in the literature, sleep-related complaints were more severe in patients with OSA compared to the control group or those with other pathologies. Moxness et al. [16] found that all sleep parameters were higher in the OSA group than in the control group. However, higher scores were obtained in the OSA group in all parameters, except for 3 of the 20 items evaluated in this study. Lanchanas et al. [17] compared OSA patients with chronic rhinosinusitis patients in terms of sinonasal complaints in their study. Except for the 'difficulty falling asleep' item, higher scores were obtained for all other sleep-related items in the OSA group. On the other hand, Kuan et al. [7] did not reveal a correlation between OSA severity and sleep-related complaints in their study. However, the number of participants in this study was small. Ji et al. [18] compared patients with OSA and chronic rhinosinusitis in terms of symptom profile and found that nasal, extranasal, and ear-facial symptoms were more common in patients with chronic rhinosinusitis, while psychological and sleep subdomain scores were higher in patients with OSA. However, when the sleep-related items were analyzed one by one in this study, no significant difference was found between the two patient groups. In our study with ninety participants, a correlation was found between the "waking up tired" and "sleep" subdomain score and the AHI score. Although OSA is a sleep-related pathology, it does not result in a significant increase in all sleep-related complaints.

In numerous studies in the literature, patients with chronic sinusitis were compared with patients with OSA in terms of sinonasal complaints. Again, many studies have investigated the severity of sinonasal complaints in OSA. The reason for this is that in daily practice, rhinologic and nonrhinologic sinonasal complaints are frequently encountered in patients with OSA. When studies comparing patients with OSA with patients with chronic rhinosinusitis in the literature are reviewed, it is seen that patients with chronic rhinosinusitis have higher scores than those with OSA in postnasal drip and nasal discharge complaints [17, 18]. Considering the pathophysiology of chronic sinusitis, this result is not surprising. On the other hand, the absence of a significant difference between chronic sinusitis, which is a pathology that directly affects the upper respiratory tract, and OSA in terms of other rhinologic and non-rhinologic elements suggests that OSA causes rhinologic and non-rhinologic complaints more frequently. In our study, a correlation was found between AHI score, OSA severity and nasal obstruction, runny nose, and nonrhinologic-otolaryngologic complaints. Furthermore, a difference was found between the three groups in terms of nasal obstruction and runny nose complaints, and this

difference is more pronounced when comparing patients who suffer from severe OSA with other groups.

Depressive symptoms and cognitive impairments are frequently observed in OSA patients [19]. Sleep quality was associated with depression, anxiety, and stress [20]. Although there are more detailed tests to reveal psychiatric disorders, there is also a psychological subdomain in the SNOT-22 questionnaire. This subdomain allows evaluation of the patients in this respect as well. In several studies in the literature, in which SNOT-22 was used, high scores were found in psychological items in OSA patients [16, 17]. However, in some studies, no correlation was detected between the severity of OSA and these items [7]. Similarly, a study in the literature showed that there was no difference in terms of psychological factors in the comparison of OSA patients with chronic sinusitis patients [18]. In our study, no correlation was found between the AHI score and psychological parameters, and there was no difference between mild, moderate, and severe OSA groups concerning psychological elements. This result can be attributed to the fact that the psychological elements in the SNOT-22 test roughly assess the psychiatric condition.

The high number of patients can be considered the strength of our study. On the other hand, we had no control group. Further studies with more patients, including the control group, may provide more detailed information on this subject.

Conclusion

OSA causes various sinonasal complaints such as nasal obstruction, runny nose, and waking up tired. An increase in OSA severity leads to an increase in these complaints, and treatment may lead to an increased quality of life.

References

1. Sforza E, Roche F, Chapelle C, Pichot V. Internight variability of apnea-hypopnea index in obstructive sleep apnea using ambulatory polysomnography. Frontiers in physiology. 2019;10:849.
2. Rashid NH, Zaghi S, Scapuccin M, Camacho M, Certal V, Capasso R. The value of oxygen desaturation index for diagnosing obstructive sleep apnea: a systematic review. The Laryngoscope. 2021;131:440-7.
3. Dewan NA, Nieto FJ, Somers VK. Intermittent hypoxemia and OSA: implications for comorbidities. Chest. 2015;147:266-74.
4. Linz D, McEvoy RD, Cowie MR, Somers VK, Nattel S, Levy P, et al. Associations of obstructive sleep apnea with atrial fibrillation and continuous positive airway pressure treatment: a review. JAMA cardiology. 2018;3:532-40.
5. Seda G, Han TS. Effect of obstructive sleep apnea on neurocognitive performance. Sleep medicine clinics. 2020;15:77-85.
6. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: the road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. Sleep medicine reviews. 2018;42:211-9.
7. Kuan EC, Tajudeen BA, Peng KA, Wang MB. Sinonasal outcomes in obstructive sleep apnea syndrome. The Laryngoscope. 2015;125:2617-20.
8. Zeng YM, Hu AK, Su HZ, Ko CY. A review of the association between oral bacterial flora and obstructive sleep apnea–hypopnea syndrome comorbid with cardiovascular disease. Sleep and Breathing. 2020;24:1261-6.
9. Dissanayake HU, Bin YS, Ucak S, de Chazal P, Sutherland K, Cistulli PA. Association between Autonomic Function and Obstructive Sleep Apnea: A Systematic Review. Sleep Medicine Reviews. 2021;57:101470.
10. Cistulli PA. Craniofacial abnormalities in obstructive sleep apnoea: implications for treatment. Respirology. 1996;1:167-74.
11. Lowe AA, Santamaria JD, Fleetham JA, Price C. Facial morphology and obstructive sleep apnea. American Journal of Orthodontics and Dentofacial Orthopedics. 1986;90:484-91.
12. Soares Oliveira MC, Tufik S, Louise Martinho Haddad F, Santos-Silva R, Gregório LC, Bittencourt L. Systematic evaluation of the upper airway in a sample population: factors associated with obstructive sleep apnea syndrome. Otolaryngology--Head and Neck Surgery. 2015;153:663-70.
13. Brander PE, Soirinsuo M, Lohela P. Nasopharyngeal symptoms in patients with obstructive sleep apnea syndrome. Respiration. 1999;66:128-35.
14. Bengtsson C, Jonsson L, Theorell-Haglöw J, Holmström M, Janson C, Lindberg E. Sinonasal outcome test-22 and peak nasal inspiratory flow: valuable tools in obstructive sleep apnoea. Rhinology. 2020;58:341-8.
15. Browne JP, Hopkins C, Slack R, Cano SJ. The Sino-Nasal Outcome Test (SNOT): can we make it more clinically meaningful? Otolaryngology—Head and Neck Surgery. 2007;136:736-41.
16. Moxness MHS, Bugten V, Thorstensen WM, Nordgård S. Sinonasal characteristics in patients with obstructive sleep apnea compared to healthy controls. International journal of otolaryngology. 2017;2017:1935284
17. LachanasVA, Woodard TD, Antisdel JL, Kountakis SE. Sino-nasal outcome test tool assessment in patients with chronic rhinosinusitis and obstructive sleep apnea. ORL. 2012;74:286-9.
18. Ji K, Risoli TJ, Kuchibhatla M, Chan L, Hachem RA, Jang DW. Symptom profile of chronic rhinosinusitis versus obstructive sleep apnea in a tertiary rhinology clinic. Annals of Otology, Rhinology & Laryngology. 2019;128:963-9.
19. Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, et al. Obstructive sleep apnea, depression and cognitive impairment. Sleep Medicine. 2020;72:50-8.
20. Al-Khani AM, Sarhandi MI, Zaghloul MS, Ewid M, Saquib N. A cross-sectional survey on sleep quality, mental health, and academic performance among medical students in Saudi Arabia. BMC research notes. 2019;12:1-5.

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A new parameter for the determination of normal right ventricular function in patients with acute pulmonary embolism

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Ethics Committee Approval
The study was approved by the ethics committee of the Kahramanmaras Faculty of Medicine, and a decision was made. 2018/22.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The performance of the right ventricular myocardium is crucial in various pathological states and the right ventricular dysfunction has a prognostic value in pulmonary embolism. We sought to bring out which parameters were helpful in predicting a normal right ventricular function in patients with acute pulmonary embolism.

Methods: Consecutive 100 acute pulmonary embolism patients, who were hospitalized and confirmed by computed tomography angiography, were enrolled in this cohort study. All patients' demographics, symptoms on admission, risk factors, electrocardiography and laboratory findings, and hemodynamic parameters were assessed. Echocardiography was performed in the first 24 hours. The study group of pulmonary embolism patients was divided into two groups based on their basic characteristics: Patients with normal right ventricular function and patients with right ventricular failure.

Results: The average age of the patients was 63 (16) years, with 48 (48%) of them being male. Twenty three patients (23%) had normal RV functions. According to the multiple logistic regression analysis, age (P=0.041, OR: 1.174, 95% CI: 1.007 to 1.368), oxygen saturation (P=0.026, OR: 1.372, 95% CI: 1.039 to 1.812) and heart rate (P=0.049, OR: 1.160, 95% CI: 1.001 to 1.346) were independent predictors of normal RV function. The setting in which all three parameters (Age, Heart rate, Oxygen saturation) were positive was considered AHO index=1, with a positive predictive value of 100% a sensitivity of 44%, a negative predictive value of 85.6% and a specificity of 100% (AUC: 0.717, 95% CI: 0.619 to 0.803) for normal RV function.

Conclusion: In acute pulmonary embolism patients who were younger than 53 years of age with a heart rate of ≤118 bpm and an oxygen saturation of >90% (AHO index=1), right ventricular functions were normal. Accordingly, without the need of computed tomography angiography or echocardiography, the clinician may predict normal right ventricular function with available demographic and noninvasive hemodynamic parameters.

Keywords: Acute pulmonary embolism, Right ventricular function, Age, Heart rate, Oxygen saturation

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Introduction

Although acute pulmonary embolism (PE) is a life-threatening cardiopulmonary disease, an important decrease in its morbidity and mortality has been accomplished over the years through early diagnosis, risk assessment and recently developed treatment methods [1-4]. The development of shock or hypotension, right ventricular (RV) dysfunction and myocardial damage are the most important prognostic risk factors for acute PE patients which undertake a critical role in determining the optimal strategy of treatment [5-7].

The presence of right ventricular dysfunction indicators such as dilatation of RV in an echocardiographic image, hypokinesia or extreme pressure loading, RV dilatation in spiral BT, increase in BNP or NT-Pro BNP and increased cardiac pressure in right cardiac catheterization indicate a medium-risk PE group [8-12]. Patients with no evidence of RV dysfunction or myocardial damage are considered the low-risk PE group. With the detection of low-risk PE patients, performing outpatient follow-up and treatment will be possible [1].

In this study, we sought to bring out which hemodynamic parameters were helpful in predicting a preserved RV function in the PE population.

Materials and methods

A total of 100 participants were hospitalized after being admitted to the emergency room and subsequently diagnosed with acute PE by tomographic angiography

(CTA). The existence of RV dysfunction is considered when classifying patients with acute PE. Group I consisted of patients with RV failure (n: 77) and group II consisted of patients with normal RV function (n: 23). The following data were collected: Symptoms and time of admission to the emergency room, susceptibility conditions, history of coronary artery disease, diabetes, hypertension and chronic obstructive pulmonary disease (COPD), vital signs at the time of admission to the hospital, blood gas analysis, admission blood parameters, and the results of an electrocardiogram (ECG), transthoracic echocardiography, lower extremity Doppler ultrasound, contrast-enhanced computed tomography and ventilation perfusion imaging and other diagnostic procedures. Within the first 30 minutes after presenting to the emergency room, vital signs and blood samples were collected. Hypertension is defined as having two or more blood pressures ≥140/90 mmHg during the measurement period or taking antihypertensive medications. A fasting blood glucose level of 126 mg/dl or higher, or taking antidiabetic medications, is defined as diabetes. An abnormal stress test result, the evidence of ischemia, or a coronary angiography confirming >50% coronary artery stenosis, or a clinical history of coronary artery disease are used to determine the coronary artery disease. S1Q3T3, right bundle branch block pattern, and right preventricular T wave variation are the rhythm and ECG results related to the right ventricular load. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the Kahramanmaras Faculty of Medicine with the decision numbered 2018/22.

Echocardiography was performed within 24 hours after admission. Using 2.5 to 5 MHz probes, the Vivid 7 system (GE Healthcare, Wauwatosa, WI, USA) was used to evaluate all inspections at all participating sites. According to contemporary guidelines [13], the modified Simpson method is used to calculate ejection fraction with a defined chamber size. Echocardiography is used to evaluate RV dysfunction, RV dilation, increased tricuspid regurgitation jet rate, and pulmonary artery systolic pressure (SPAP). In addition, right ventricular dilation (right ventricular size> 3.4 cm in the basal plane or> 3.8 cm in the median plane) is associated with RV dysfunction, as is the presence of McConnell's sign [13]. According to the recommendations [14], the intensity of the color blood jet Doppler signal is combined with the width of the venous contraction to identify severe tricuspid regurgitation. The calculation of pulmonary artery systolic pressure was performed as previously described [15].

Statistical analysis

Continuous variables with a non-normal distribution were presented as mean, standard deviation (SD), or interquartile range (IQR), while categorical variables are expressed as percentages. As a measure of the test accuracy, the area under the curve (AUC) was estimated. The investigators compared AUCs using the Z test. Patients with acute PD were divided into two groups: Group A, including patients with right ventricular failure, and group B, including patients with normal right ventricular function.

When the distribution was skewed, the 2-test was used to compare categorical variables, the independent sample t-test, to evaluate normally distributed continuous data, and the Mann-Whitney U test, to compare the patient groups. The Pearson or Spearman correlation tests were used to determine the correlation between variables. To quantify the relationship between the factors and the complete RV function, we used univariate analysis. Variables that were significant in univariate analysis and other potential confounders were used in the multiple logistic regression model using forward progressive techniques to assess independent prognostic factors of maintained RV function.

Results

Of all enrolled 100 consecutive patients, the mean age was 63 (16) years. The study group was gender balanced (52% female, 48% male).

Table 1 shows the differences in hemodynamic, electrocardiographic, echocardiographic, and laboratory results between the two groups of patients with acute PE, as well as their concomitant diseases. Except for age, a history of chronic obstructive pulmonary disease, and recent surgery history, both groups had similar baseline characteristics. The group with a preserved right ventricle function (Group B) was younger and had fewer patients with COPD and a previous surgery. In physical examination, Group B patients' heart rate was significantly slower and oxygen saturation was significantly better than those in Group A. In electrocardiographic parameters, group B tended to have slightly but significantly fewer patients with atrial fibrillation. Group B also had significantly better creatinine and alanine aminotransferase levels.

Univariate analysis was performed to the parameters in Table 1 to quantify any relationship with normal right ventricular function (Table 2). The statistically significant parameters were included in the multiple logistic regression analysis (Table 3), which showed that age (P=0.041, OR: 1.174, 95% CI: 1.007 to 1.368), oxygen saturation (P=0.026, OR: 1.372, 95% CI: 1.039 to 1.812) and heart rate (P=0.049, OR: 1.160, 95% CI: 1.001 to 1.346) were independent predictors of preserved right ventricle function. ROC analysis brought out the cut-off values of these parameters for normal right ventricular function: For saturation it was >90% (60% sensitivity, 86.2% specificity, AUC: 0.750, 95% CI, 0.645 to 0.838, Figure 1) and for heart rate it was ≤ 118 bpm (100% sensitivity, 51.6% specificity, AUC: 0.803, 95% CI, 0.702 to 0.881, Figure 2). The cut-off value for age was ≤ 53 years (65.2% sensitivity, 88.3% specificity, AUC: 0.788, 95% CI, 0.695 to 0.864, Figure 3). The setting in which all three parameters were positive was considered AHO index=1, with a positive predictive value of 100%, a sensitivity of 44%, a negative predictive value of 85.6% and a specificity of 100% (AUC 0.717, 95% CI 0.577 to 0.857, figure 4) for normal right ventricle function.

Table 1: Baseline characteristics of groups

	Patients with right ventricular failure (n:77)	Patients with normal right ventricular function (n:23)	*P*-value
Mean age, years	67(14)	49(16)	<0.001
Gender, female, n, %	38 (49%)	14 (61%)	0.232
Hypertension, n, %	36 (47%)	6 (26%)	0.062
Diabetes mellitus, n, %	22 (29%)	3 (13%)	0.105
Coronary artery disease, n, %	22 (29%)	4 (17%)	0.195
COPD, n, %	22 (29%)	2 (9%)	0.040
Admission symptoms			
Dyspnea, n, %	54 (70%)	13 (57%)	0.167
Chest pain, n, %	17 (22%)	9 (39%)	0.088
Hemoptysis, n, %	7 (9%)	0 (0%)	0.150
Syncope, n, %	8 (10%)	2 (9%)	0.585
Symptom duration			
< 6 hours, n, %	3 (4%)	1 (4%)	0.655
6-12 hours, n, %	8 (10%)	1 (4%)	0.339
12-24 hours, n, %	16 (21%)	5 (22%)	0.564
> 24 hours, n, %	50 (65%)	16 (70%)	0.442
Immobilization, n, %	16 (21%)	3 (13%)	0.309
Previous history of PE, n, %	5 (7%)	1 (4%)	0.580
Previous history of DVT, n, %	4 (5%)	2 (9%)	0.420
Previous history of surgery, n, %	11 (14%)	8 (35%)	0.033
Systolic blood pressure, mm Hg	104(19)	110(17)	0.243
Diastolic blood pressure, mmHg	64(15)	68(14)	0.300
Heart rate, beats/minute	116(20)	98(13)	0.009
Oxygen saturation, %	82(9)	89(11)	<0.001
Electrocardiography parameters			
Atrial fibrillation, n, %	26 (34%)	3 (13%)	0.044
Right bundle branch block, n, %	30 (39%)	5 (22%)	0.100
S1Q3T3, n, %	18 (23%)	2 (9%)	0.102
T wave changes, n, %	33 (43%)	7 (30%)	0.206
Deep venous thrombosis, %	30 (40%)	5 (22%)	0.093
Laboratory findings			
Hemoglobin, gr/dl	13(2)	12.8(1.7)	0.643
Albumin, gr/dL	3.0(0.6)	3.2(0.7)	0.210
Creatinine, mg/dL	1.3(1.0)	0.8(0.4)	0.017
Alanine aminotransferase, IU/L	99(209)	40(36)	0.024
Troponin I, ng/mL	0.16(0.4)	0.08(0.16)	0.458
D-Dimer > 1500 ng/ml, n,%	52 (77%)	10 (56%)	0.137

COPD: Chronic obstructive pulmonary disease, DVT: Deep venous thrombosis, PE: pulmonary embolism

Table 2: Univariate predictors of normal right ventricular function

	P-value	OR	(95% CI)
Mean age, years	<0.001	0.931	0.899-0.963
Heart rate, beat/minute	0.001	0.947	0.916-0.979
Creatinine, mg/dL	0.005	0.079	0.013-0.466
Oxygen saturation, %	0.014	1.092	1.018-1.172
History of surgery, %	0.033	0.313	0.107-0.911
COPD, n,%	0.066	0.238	0.051-1.102
Atrial fibrillation, n,%	0.066	3.399	0.924-12.498
Hypertension, n,%	0.084	2.488	0.886-6.988
D-Dimer > 1500 ng/ml, n,%	0.084	0.385	0.130-1.139

All the variables from Table 1 were examined and only those significant at P<0.1 level are shown. CI: Confidence interval; OR: Odds ratio, Abbreviations in Table 1.

Table 3: Multiple predictors of normal right ventricular function

	P-value	OR	(95% CI)
Oxygen saturation, %	0.005	1.377	1.104-1.716
Heart rate, beat/minute	0.008	0.887	0.812-0.970
Mean age, years	0.010	0.867	0.777-0.967

Multiple logistic regression analysis including P<0.05 level from Table 2.
CI: Confidence interval; OR: Odds ratio

Figure 1: ROC curve for Oxygen saturation

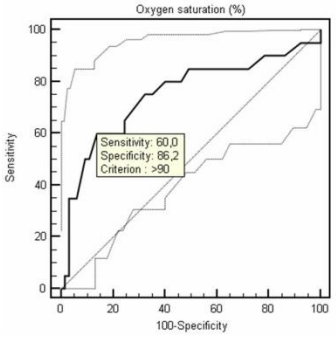


Figure 2: ROC curve for Heart rate

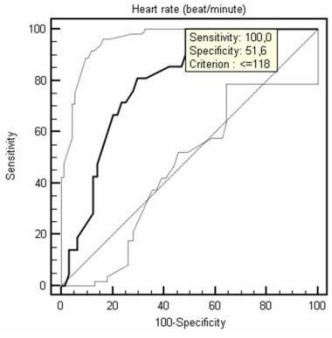


Figure 3: ROC curve for age

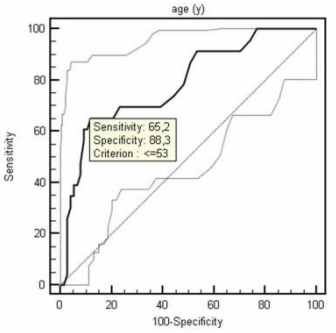
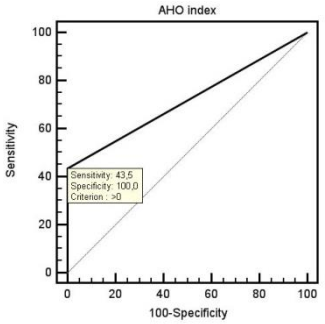


Figure 4: ROC curve for AHO index=1



Discussion

To the best of our knowledge, this is the first study demonstrating that an index comprising three quantitative parameters, age and heart rate and oxygen saturation, significantly predicts preserved RV functions in patients with sudden onset PE.

Acute PE is a complex cardiopulmonary disease and rapid risk stratification has become the most important part of treatment. A great variety of clinical, echocardiographic, and blood markers are used in this classification. Hypotension or the presence of shock is still the most important prognostic factor. Guidelines suggest the prognostic use of troponin and natriuretic peptides [1]. In addition, several laboratory parameters such as gamma glutamyl transferase [16], red cell distribution width [17], uric acid [18], heart-type fatty acid-binding protein (H-FABP) [19], copeptin, and mid-regional pro-adrenomedullin (MR-proADM) [20], were shown to be associated with mortality in PE, without adequate sensitivity and specificity.

In acute PE, it is well known that mortality is higher in patients who exhibit compromised RV functions. Right heart failure is a critical part in the vicious cycle of death in embolism: Occlusion of pulmonary arterial branch, increased pulmonary arterial pressure, decreased systemic arterial pressure, increased sympathetic tone and neuroadrenal hormones to maintain pressure, increased RV workload and wall tension of the RV due to pulmonary arterial pressure and finally, right heart failure [21-25]. It is critical to diagnose RV compromise in embolism, because it changes the therapeutic approach. Plain anticoagulation is almost enough for patients with low or intermediate risk, however; thrombolytic agents are advised for patients with cardiogenic shock (26). Guidelines advise

clinicians to check the RV status with echocardiography in patients who are not in shock but whose clinical status is concordant with heart failure [27]. Computerized tomography is another option to determine RV failure [28]. Furthermore, natriuretic peptides are also known as surrogates for right heart failure in PE. The severity of hemodynamic compromise and RV dysfunction in acute PE were demonstrated through plasma levels of natriuretic peptides [29].

At this point, we suggest an index, which is a combination of three parameters, to predict preserved RV functions. As discussed above, when all three parameters (age and heart rate and oxygen saturation values) are within determined cut-off limits, the indicator has a positive predictive value of 100 percent and a negative predictive value of 85.6%, according to research. These three parameters are obtained very easily and most importantly, in a noninvasive way.

Limitations

The current study has some limitations. Because of its monocentric nature, our research was constrained. As a result, the findings cannot be generalized to the full population of PE patients. The sample size, which is relatively small, was the most significant constraint. It should be noted that a limited sample size may have an impact on the wide percent 95 CI. It's possible that a combination of natriuretic peptides and other indicators like troponins might be utilized to monitor blood pressure. However, because we have echocardiography, natriuretic peptides are rarely used in our center.

Conclusion

Right ventricular function can be evaluated by many non-invasive methods that are not expensive, routinely available, and bedside procedures, such as computed tomography, radionuclide methods, and magnetic resonance imaging. Using the AHO index, we found that physicians can rule out RV dysfunction in acute PE with very high precision. Our findings need to be confirmed by randomized prospective studies with larger patient populations.

References

1. Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J. 2019;54(3):1901647. doi: 10.1183/13993003.01647-2019.
2. Bougouin W, Marijon E, Planquette B, Karam N, Dumas F, Celermajer DS, et al. Pulmonary embolism related sudden cardiac arrest admitted alive at hospital: Management and outcomes. Resuscitation. 2017;115:135-40. doi: 10.1016/j.resuscitation.2017.04.019.
3. Hussain ST, Bartholomew JR, Leacche M, Zhen-Yu Tong M. Retrograde Pulmonary Embolectomy for Acute Pulmonary Embolism: A Simplified Technique. Ann Thorac Surg. 2017;103(5):473-74. doi: 10.1016/j.athoracsur.2016.11.082.
4. Larsen TB, Skjøth F, Kjældgaard JN, Lip GYH, Nielsen PB, Søgaard M. Effectiveness and safety of rivaroxaban and warfarin in patients with unprovoked venous thromboembolism: a propensity-matched nationwide cohort study. Lancet Haematol. 2017;4(5):237-44. doi: 10.1016/S2352-3026(17)30054-6.
5. Sokalskis V, Peluso D, Jagodzinski A, Sinning C. Added clinical value of applying myocardial deformation imaging to assess right ventricular function. Echocardiography. 2017;34: 919-27
6. Vamsidhar A, Rajasekhar D, Vanajakshamma V, Lakshmi AY, Latheef K, Siva Sankara C, et al. Comparison of PESI, echocardiogram, CTPA, and NT-proBNP as risk stratification tools in patients with acute pulmonary embolism. Indian Heart J. 2017;69(1):68-74. doi: 10.1016/j.ihj.2016.07.010.
7. Dursunoğlu N, Dursunoğlu D, Yıldız Aİ, Rota S. Evaluation of cardiac biomarkers and right ventricular dysfunction in patients with acute pulmonary embolism. Anatol J Cardiol. 2016;16(4):276-82. doi: 10.5152/akd.2014.5828.
8. Kucher N, Rossi E, De Rosa M, Goldhaber SZ. Prognostic role of echocardiography among patients with acute pulmonary embolism and a systolic arterial pressure of 90 mm Hg or higher. Arch Intern Med. 2005;165:1777–81.
9. Coutance G, Cauderlier E, Ehtisham J, Hamon M, Hamon M. The prognostic value of markers of right ventricular dysfunction in pulmonary embolism: a meta-analysis. Crit Care. 2011;15(2):R103. doi: 10.1186/cc10119
10. Sanchez O, Trinquart L, Colombet I, Durieux P, Huisman MV, Chatellier G, et al. Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. Eur Heart J. 2008;29:1569–77.
11. Becattini C, Agnelli G, Vedovati MC, Pruszczyk P, Casazza F, Grifoni S, et al. Multidetector computed tomography for acute pulmonary embolism: diagnosis and risk stratification in a single test. Eur Heart J. 2011;32:1657–63.
12. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation. 2007;116:427–33.
13. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2010;23:685-713.
14. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, et al; European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr. 2010;11:307–32.
15. Yock PG, Popp RL. Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation. 1984;70:657–62.
16. Zorlu A, Yucel H, Bektasoglu G, Turkdogan KA, Eryigit U, Sarikaya S, Ege MR, Tandogan I, Yilmaz MB. Increased γ-glutamyl transferase levels predict early mortality in patients with acute pulmonary embolism. Am J Emerg Med. 2012;30:908-15.
17. Zorlu A, Bektasoglu G, Guven FM, Dogan OT, Gucuk E, Ege MR, Altay H, Cinar Z, Tandogan I, Yilmaz MB. Usefulness of admission red cell distribution width as a predictor of early mortality in patients with acute pulmonary embolism. Am J Cardiol. 2012;109:128-34.
18. Ozsu S, Çoşar AM, Aksoy HB, Bulbul Y, Oztuna F, Karahan SC, Ozlu T. Prognostic Value of Uric Acid for Pulmonary Thromboembolism. Respir Care. 2017;62:1091-96.
19. Qian HY, Huang J, Yang YJ, Yang YM, Li ZZ, Zhang JM. Heart-type Fatty Acid Binding Protein in the Assessment of Acute Pulmonary Embolism. Am J Med Sci. 2016;352:557-62.
20. Vuilleumier N, Simona A, Méan M, Limacher A, Lescuyer P, Gerstel E, et al. Comparison of Cardiac and Non-Cardiac Biomarkers for Risk Stratification in Elderly Patients with Non-Massive Pulmonary Embolism. PLoS One. 2016 24;11(5):e0155973. doi: 10.1371/journal.pone.0155973.
21. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. Am J Cardiol. 1971;28:288-94.
22. Smulders YM. Pathophysiology and treatment of haemodynamic instability in acute pulmonary embolism: the pivotal role of pulmonary vasoconstriction. Cardiovasc Res. 2000;48:23-33.
23. Delcroix M, Mélot C, Lejeune P, Leeman M, Naeije R. Effects of vasodilators on gas exchange in acute canine embolic pulmonary hypertension. Anesthesiology. 1990;72:77-84.
24. Huet Y, Brun Buisson C, Lemaire F, Teisseire B, Lhoste F, Rapin M. Cardiopulmonary effects of ketanserin infusion in human pulmonary embolism. Am Rev Respir Dis. 1987;135:114-7.
25. Marcus JT, Gan CT, Zwanenburg JJ, Boonstra A, Allaart CP, Götte MJ, et al. Interventricular mechanical asynchrony in pulmonary arterial hypertension: left-to-right delay in peak shortening is related to right ventricular overload and left ventricular underfilling. J Am Coll Cardiol. 2008;51:750-7.
26. Goldhaber SZ, Haire WD, Feldstein ML, Miller M, Toltzis R, Smith JL, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. Lancet 1993;341:507-11.
27. Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. Chest. 2004;125:1539-45.
28. Henzler T, Roeger S, Meyer M, Schoepf UJ, Nance JW Jr., Haghi D, et al. Pulmonary embolism: CT signs and cardiac biomarkers for predicting right ventricular dysfunction. Eur Respir J. 2012;39:919-26.
29. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med. 2008;178:425-30.

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Histological investigation of the protective effect of metformin on testis and sperm parameters in obese rats with type 2 diabetes mellitus

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Ethics Committee Approval
The study was performed in Sakarya University Animal Laboratory in accordance with international guidelines, after approval from the Animal Care and Use Ethics Committee was taken(04.09.2019/30).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Diabetes mellitus (DM) is thought to have adverse effects on the male reproductive system. Metformin (MTF) is a widely used drug in the treatment of DM. This study hypothesized that MTF can reduce the harmful effects of DM on the male reproductive system in addition to diabetes treatment.
Methods: Twenty-one adult (15-18 g, 11-12 months) C57BL6 male mice were randomly assigned to three groups, as follows: The Control group (C), Diabetes group (D), and Diabetes + Metformin (D+MTF) treatment group. Groups D and D+MTF were fed a diet composed of 60% fat for four weeks. DM was created by administering a single dose of 30 mg/kg streptozotocin intraperitoneally (i.p.). MTF was given through gavage at a dose of 300 mg/kg/day. At the end of the experiment, sperm parameters were evaluated in the testicular tissue. Histomorphology features and immune expressions of VEGF, Caspase-3, and Ki-67 were evaluated in testicular tissue sections stained with Hematoxylin and Eosin (HE).
Results: Sperm concentration, motility, and morphological characteristics of diabetic mice were significantly reduced compared to control, and MTF-treated mice. Seminiferous tubule diameters and Johnsen scores were significantly higher in the control and D+MTF groups when compared to the diabetic group. VEGF and Ki-67 immune expression were significantly higher in the control and D+MTF groups compared to the D group (P=0.001, and P=0.002, respectively). Because of D, Caspase-3 positive cell density was higher in the D group compared to the control and D+MTF groups (P=0.002).
Conclusion: Diabetes mellitus had adverse effects on sperm parameters and the testicular tissue. High glucose levels with decreased VEGF immune expression damaged spermatogenic cells and decreased proliferation and differentiation due to impaired intratesticular vascularity. MTF treatment reduced the damage in spermatogenic cells and contributed to the differentiation and division of cells through the restoration of vascularization.

Keywords: Metformin, Type 2 Diabetes, Obese

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Introduction

Diabetes mellitus (DM) is one of the most common persistent diseases affecting more than one hundred million people worldwide. It is a metabolic disease characterized by hyperglycemia that causes long-term damage to many organs, including the heart, eye, kidney, nervous system, and the vascular system. Diabetes develops a result of a deficiency in insulin secretion (T1DM) or a decrease in the sensitivity of tissue to insulin (T2DM) [1, 2].

DM may cause chronic hyperglycemia-related reproductive complications. It has been reported that high glucose causes increased oxidative stress and apoptosis in testicular cells, thus causing infertility [3-5]. A study revealed that increased oxidative stress in diabetic rats caused DNA damage in the testis, loss of sperm cells, and delay in spermatogenesis [5]. Similarly, another study proved that DM caused apoptotic cell death in germ cells in testicular tissue in rats, and the condition was the leading cause of infertility [3].

High blood glucose levels can harm blood vessels and cause endothelial disorders. Therefore, DM is considered an essential risk factor for cardiovascular diseases [6]. Vascular endothelial growth factor (VEGF), also known as vascular permeability, is a component of vessel wall endothelial cells and an angiogenic factor that causes proliferation and increased permeability [7, 8]. VEGF was effective in proliferation and differentiation during the spermatogenesis process [9]. It is known that DM causes testicular cell death by inducing the apoptosis pathway. Experimental studies have shown that cellular apoptosis results from testicular damage because of oxidative stress induced by hyperglycemia [10].

Despite increasing knowledge on T2DM risk factors, the incidence and prevalence of the disease continue to increase globally. Early diagnosis and safe and effective treatments can reduce morbidity and mortality by preventing or delaying complications [11]. MTF, a dimethyl biguanide, is a hypoglycemic drug usually prescribed for the control of T2DM. MTF has a direct eliminating effect against ROS. It improves the level of oxidative stress in DM by supporting the impaired antioxidant defense system [12].

In T2DM obesity cases, MTF treatment improves sperm abnormalities and increases the decreased sperm count. In humans, serum testosterone and LH pulsatility may be increased in individuals treated with MTF for few months [13]. This indicates that MTF can modulate testicular steroidogenesis and increases pituitary LH pulsatility, regulating Leydig cell functions [14].

This study aims to histopathological and immunohistochemically investigate the effects of MTF on obese mice with T2DM in terms of sperm parameters and testicular tissue.

Materials and methods

Test animals and ethical statement

In this study, twenty-one 11-12 week*old C57BL6 male mice, weighing an average of 15-18 grams, were used. The study was performed in the Sakarya University Animal Laboratory per the international guidelines after approval was obtained from the Animal Care and Use Ethics Committee (04.09.2019/30). All mice were adapted to the laboratory environment for one week (kept in wire cages, 12/12 h light/dark-light cycle, at 22°C, temperature, in 50-60% humidity) before the study began. The 21 mice in our study were divided into three groups, regardless of any trait. There were seven mice in each group.

Test design

Control Group (C): Mice in this group were fed average mouse food (consisting of 14.3% protein, 4% fat, 65.4% starch, and 16.3% sugar, fibers, vitamins, and minerals) and tap water for eight weeks. No further action was taken.

Three days after DM was induced, 14 animals were again randomly divided into two groups composed of 7 mice, as the diabetes and metformin treatment groups.

Diabetes Group (D): Mice in this group were underwent the diabetes induction protocol. Hyperglycemia was induced by feeding with HFD for four weeks. T2DM was created by administering 30mg/kg STZ intraperitoneally. Animals continued to be fed with HFD for another four weeks after they developed DM.

Diabetes and Metformin Group (D+M): After DM was created with the administration of 30mg/kg STZ IP, MTF (300mg/kg/day) [15] was dissolved in 0.09% isotonic solution and given through gavage for four weeks. After DM occurred, the mice were fed an average standard diet. At the end of the eight-week study, the animals were sacrificed using cervical dislocation with overdose anesthesia (pentobarbital 100 mg/kg IP) twenty-four hours after the last treatment. Tissue samples obtained for histopathological examinations were fixed in 10% buffered formalin.

Diabetes protocol

For inducing hyperglycemia in the D groups, mice were fed HFD with a total energy of 25.07 kJ/g, mostly from fats, 20% from protein, and 20% from carbohydrates (52.2% starch, 14%, 3 proteins, 17.2% fat, and 16.3% fibers, sugar, essential vitamins and minerals) [16]. The rats fasted for 16 hours at the end of 4 weeks. After 16 hours of fasting, streptozotocin (STZ), (Cayman Chemical Temno, 13104, USA) was dissolved in 0.05M citrate buffer (pH 4.5) and a single dose of 30 mg/kg was administered intraperitoneally [17]. Fasting blood glucose stages were measured with the glucometer (Roche Diagnostics, Basel, Switzerland) from blood samples taken from the tail vein 72 hours after STZ administration. Mice with fasting blood glucose levels of 150-250 mg/dL were considered hyperglycemic and used in the test.

Sperm collection

Mature sperm cells were obtained from the epididymis with the stripping method. Epididymal sperms were counted using the method described by Yokoi et al. [18]. At the end of the experiment, 10 µl of the epididymal sperm suspension was obtained from the three groups in phosphate buffer saline (PBS), and sperm count was performed in the Makler counting chamber. Their concentrations were recorded by multiplying by the dilution ratio. The morphology of 200 spermatozoa were evaluated after staining of the samples of each mouse in the three groups, which were examined at 40X magnification under the light microscope, and their percentages were calculated. Sperm morphology was evaluated according to the Kruger criteria [19].

Testicular histopathology

For evaluation under the light microscope, testicular tissue samples of mice were fixed with Bouin's fixative and embedded in paraffin. Before sectioning, samples were cooled at -20°C. Sections of 3-5 µm thickness sliced with Thermo Scientific Microm HM40E (Otto-Hahn-Strasse1a 69190 Walldorf, Germany) microtome were placed on slides after they were opened in a gelatine (Gelatine, Foodland, Ewald-GelatineGmbH, Meddersheimer Str 50, 55566 BadSobernheim, Germany) in hot water bath. Sections were stained with H-E. (Merck KGa A 6427 Darmstadt, Germany) to examine the histological structure.

The germinal layer thickness of seminiferous tubules

Testicular tissue samples were embedded in paraffin after fixation and tissue determination using 10% neutral buffered formalin. To evaluate seminiferous tubule diameters morphometrically, we took 5-micron thick sections from tissue blocks. Then the areas were stained with HE. More than 20 sections were taken from each block. The germinal layer of the seminiferous tubules was measured using the NIS-Element (USA) camera and software. Mean diameters of the germinal layer (µm) of the seminiferous tubules were measured for each testis [21].

VEGF, Caspase-3, and KI-67 IHC staining

The tissue samples, cut in 4 microns from the paraffin-embedded blocks, were deparaffinized and washed with decreasing concentrations of alcohol solutions. The preparations in citrate buffers were subjected to heat treatment for 20 minutes in the microwave. After that, all preparates were placed in blocks of 3% H2O2 with endogen peroxidase activity. The primary antibodies were Caspase-3(Genetex), VEGF(Genetex), and Kİ-67(Genetex), in 1/300 ratio, after which the secondary antibodies (UltraVisionLarge Volume DetectionSystem Anti-rabbit by LabVision, HRP) were evaluated. The producing company's procedures were implemented in each step. Diamino benzidine (DAB) was used to make the paint visible. Mayer's hematoxylin was used for contrast coloring. The preparations were covered by the mounting medium (Aqueous Mounting Medium by ScyTek). The area and intensity of brown staining were assessed using ImageJ software (ImageJ, NIH, Bethesda, MD).

Statistical analysis

Statistical analyses were performed using the SPSS 22.0 package program (SPSS Inc. and LeadTech. Inc. Chicago. USA). Numerical data were presented as mean (standard deviation) (SD). Shapiro-Wilk test was used to check the normality of distribution. The One-way ANOVA and the Kruskal Wallis tests were used to compare more than two variables. The Tukey HSD was used for variables with homogeneous in-group significance and variances, and Tamhane's T2 test was utilized for non-homogeneous variables. *P*-values of <0.05 were considered significant.

Results

Body weight and blood sugar levels

The body weight and blood glucose values of the mice in the experimental groups are shown in Table 1. At the beginning of the study, the mean body weight and blood glucose levels were similar between the three groups ($P>0.05$). A statistically significant increase was observed in the D and D+M groups' body weights compared to the C group at week 4 ($P=0.006$, $P=0.006$, respectively). Mean body weight at the end of week 8 was significantly higher in the D+M when compared to the C and D groups ($P=0.001$ for both).

At the end of week 4, a significant increase was observed in mean blood glucose levels in groups D, and D+M fed with HFD compared to group C fed with standard mice food ($P<0.001$ for both). There was no significant difference in blood glucose levels between the D and D+M groups ($P>0.05$). After MTF treatment for 4 weeks, blood glucose levels in the D+M group were significantly lower compared to the untreated group D ($P<0.001$), while they were significantly higher than in group C ($P<0.001$).

Light microscopic results of sperm parameters

The results of light microscopic evaluation of sperm parameters are presented in Table 2. DM caused a significant decrease in all sperm parameters. Sperm density, percent motility, percent motility/immobility in situ, and percent of cells with normal morphology decreased significantly ($P<0.05$). These parameters were significantly decreased in the D group, and the mean values of the D+M group were close to those of the C group ($P<0.001$ for comparisons of all parameters).

Table 1: Body weights and blood glucose values of study groups at baseline, 4th and 8th weeks

Groups (n= 7)	Body weight (g) Mean(SD)			Blood sugar (mg/dL) Mean(SD)		
	Baseline	4th week	8th week	Baseline	4th week	8th week
C	16.57(0.34)	19.17(0.57)	22.35(0.40)	89.50(1.22)#	91.02(1.83)#	91.57(1.03)
D	16.44(0.28)	20.18(0.55)*	29.50(1.03)	230.28(17.21)	138.22(8.18)	271.31(9.08)
D+MTF	16.47(0.24)	22.52(0.47)**	17.20(0.36)**	181.37(68.02)	120.80(23.61)	140.72(2.95)**

C: Control, D: Diabetes, D+MTF: Diabetes and Metformin treatment group.SD:Standard deviation, *$P<0.05$ compared with C and D+MTF, **$P<0.001$ compared with C and D, # $P<0.001$ compared with DM and DM+MTF.

Table 2: Microscopic sperm parameters evaluation results in all groups

Parameters	C Mean(SD)	D Mean(SD)	D+MTF Mean(SD)	*P*-value
Sperm Count (millions)	29.14(3.89)	16.43(1.27)	26.57(1.51)	<0.001
Motility (%)	32.86(4.80)	17.57(2.51)	27.57(2.07)	<0.000
				0.024
On-site mobility (%)	17.142(4.80)	11.43(2.44)	13.57(2.44)	0.016
Immotile (%)	50(7.07)	71(4.51)	58.86(2.34)	<0.001
				0.011
				0.001
Morphology (%)	25(2.94)	14.43(3.10)	22.86(2.34)	<0.001
Johnsen Score	8.86(0.69)	6(0.82)	8.43(0.53)	<0.001

C: Control group, D: Diabetes group, D+MTF: Diabetes and Metformin treatment group, SD: Standard deviation

Histopathological findings and Johnsen score

Under the light microscope (Figure 1), the testicular tissue belonging to group C showed a normal seminiferous tubule and spermatogenic structure (Figure 1-A), and tight connective tissue. The tunica albuginea, and seminiferous tubules within the testicular lobules separated by septa extending interiorly from the capsule seemed normal. In the testes of group D (Figure 1-B), there was severe atrophy in most seminiferous tubules, decrease in the number and layer of spermatogenic cells, and separation of spermatogenic arrests, and intercellular junctions. Tissue sections of the testicles (Figure 1-C) taken from the D+M treated group had areas close to the healthy histological seminiferous tubule organizational structure similar to group C. Furthermore, spermatozoa accumulated in the spermatogenetic layers and seminiferous tubule lumen. Separations were less observed in the intercellular connections in the seminiferous tubules of these groups compared to group D (Figure 1). There was no significant difference in terms of the Johnsen scores between the C and D+M groups ($P>0.05$). The Johsen scores in

both groups were significantly higher than that of the D group. The p values were $P<0.001$ and $P=0.031$, respectively (Table 2).

Seminiferous tubules diameter

The diameters of seminiferous tubules in group D were significantly decreased compared to groups C and D+MTF ($P=0.004$, $P=0.006$, respectively). There was no significant difference between the D+MTF group and the C group (Figure 3).

Immunohistochemical results

VEGF and Ki-67 immune expression increased in C and D+M groups, and Caspase-3 expression decreased (Figure 2). In group D, on the contrary, Caspase-3 immune expression increased, while VEGF and Ki-67 decreased. VEGF and Ki-67 expression significantly increased in groups C and D+M, when compared with group D ($P=0.001$ and $P=0.002$, respectively). Caspase-3 expression was increased in group D compared to groups C and D+M ($P=0.002$). There was no difference between Caspase-3 expression in C and D+M groups ($P>0.05$). Although VEGF and Ki-67 expression increased after metformin treatment in the D+M group, statistical differences were observed compared to the C group. P values were $P=0.002$ and $P=0.001$, respectively.

Figure1: Seminiferous tubule preparations of the study groups, stained with H.E., 100X, 100 scale bar. Control group (C), diabetes group (D), and diabetes metformin treatment group (D+MTF). The typical testicular structure is seen in 1A. In 1B, seminiferous tubule structures are observed with reduced diameters. Distorted seminiferous tubule layers were remarkable in this group. In 1C, seminiferous tubules with increased diameters due to metformin effect are observed. In this group, the seminiferous tubule layers were prominent enough to distinguish.

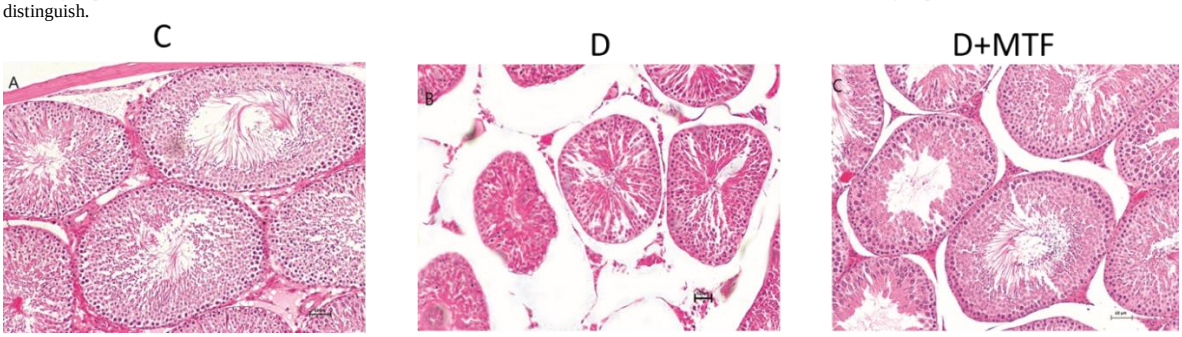


Figure 2: Seminiferous tubule tissue samples. 100X, 50 scale bar. VEGF, Ki-67 Caspase-3 immunoexpression in seminiferous tubule tissue samples belonging to C, D and D+MTF groups. Dark brown marked cells are considered positive. These cells indicate increased expression of the target protein Caspase-3. The black arrow heads in Figure 2-H show the Caspase-3 positive cell.

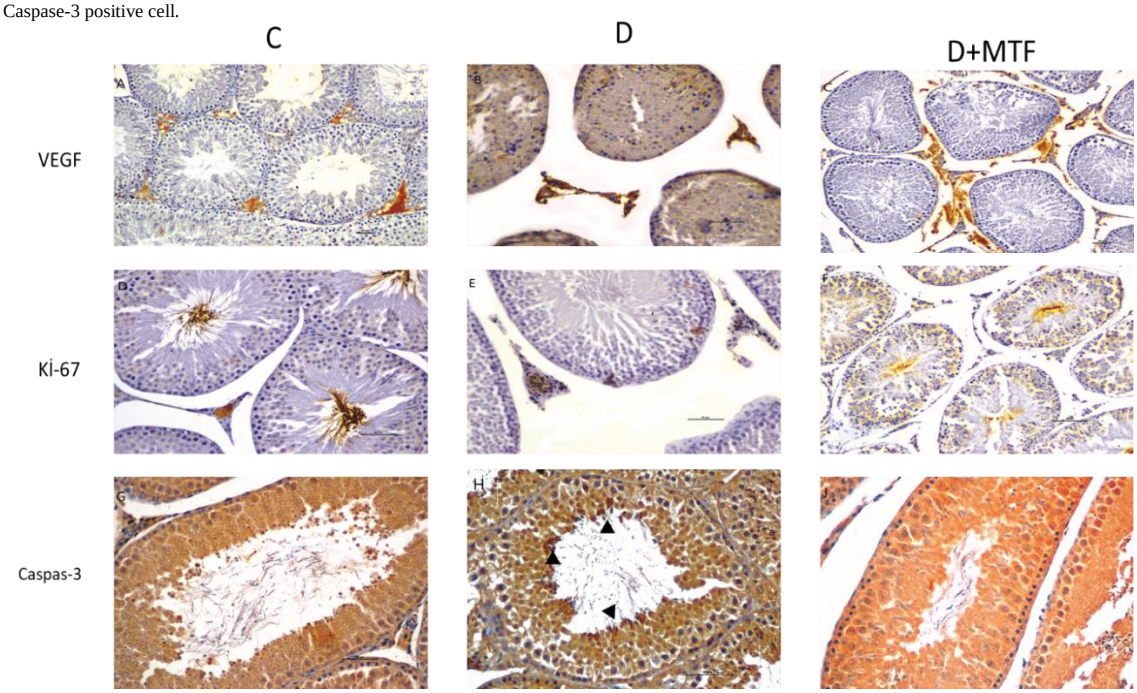
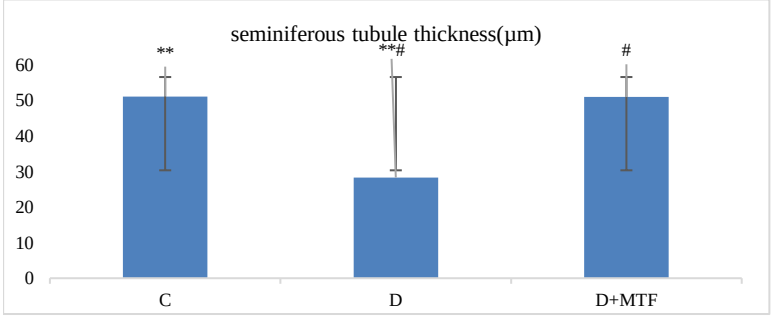


Figure 2: Comparison of seminiferous tubule (st) diameters of the experimental groups. Control group (C), diabetes group (D), and diabetes metformin treatment group (D+MTF). Kruskal Wallis, the continuation of the Mann-Whitney test. ** $P<0.05$ The st diameters of the C group were higher than those of the D group. # $P<0.05$ The st diameters of the D+MTF group were more significant than the D group. There was no statistical difference in ST diameters between the C and D+MTF groups.



Discussion

This study evaluated the protective effect of Metformin in HFD/STZ-induced diabetic testicular tissue and the histological changes using Caspase-3, Ki-67, VEGF immune expression staining and microscopic sperm parameters.

DM is a common health problem that impairs reproductive functions in men and women. In diabetic mice, high glucose levels can impair testicular function and cause infertility [22, 23]. A study stated that in diabetic mice, it also caused a decrease in the diameter of the seminiferous tubules, and damaged spermatogenic cell morphologies and epithelial layers [24].

Clinical studies point out that metformin provides satisfactory results in the treatment of patients with oligoasthenoteratospermia (OAT). It is thought that metformin has significant effects on decreasing insulin and globulin-dependent sex hormone levels and improving serum androgen levels and semen quality in OAT patients [25]. However, the mechanism by which metformin repairs spermatogenic function and the damage caused by obesity is still unknown. The functioning of a normal testis is determined by the cycle of spermatogenic cells formed by normal functioning Sertoli and Leydig cells. When we examined the preparations stained with HE, we observed that HFD-S caused not only obesity but also a decrease in the diameters of the seminiferous tubules. The results proved that the diameters of the seminiferous tubules and the Johnsen score were remarkably higher in the D+M group compared to the untreated D group. These values were significantly lower in group D, which was not treated in the same way, compared with group C. The same situation resulted in decreased sperm parameters and poor-quality sperm. Sperm parameters and in C and D+M groups were significantly higher in comparison with Group D. Studies are indicating that the sperm count, motility, and morphology of the DM groups are of lower quality when compared to the control groups, similar to the results of this study [26]. Niknamand and Mahmoudi [27], reported that sperm count and morphology were significantly disrupted and seminiferous tubule diameters decreased in diabetic rats.

Expression of the Ki67 protein is related to cell division. The interphase Ki67 protein is mainly located in the nucleus on the surface of most chromosomes [28]. In this study, Ki67-positive cell counts increased remarkably in the spermatid of groups C and D+M rats compared to group D. These results indicate the positive effects of Metformin treatment on the diabetic testis during oxidative stress. Previous studies indicated that the proliferative activity of germ cells decreased in the testicular tissues of diabetic mice due to STZ, whereas increases in cell apoptosis were observed [4, 24, 29]. Diabetes is associated with increased oxidative stress, which damages the nuclear DNA of sperm and oocytes. Antioxidant agents are known to help alleviate the oxidative damage associated with DM. In this study, the number of caspase-3-positive cells in the germinal epithelium increased remarkably in group D. On the other hand, the number of Caspase-3 positive cells markedly reduced after Metformin treatment in the D+M group. Similar to our study, in which the lowest caspase-3 levels were seen in group C, studies reported that hyperglycemia-induced apoptosis is regulated by activating the caspase-3 pathway [30] and that Caspase-3 expression is higher in the diabetes groups compared to the control groups [31].

The angiogenic factors, VEGF and VEGF receptors are produced in both the Sertoli and Leydig cells [32]. VEGF induces spermatogonia proliferation and is essential for the homeostasis of germ cells [33]. VEGF also stimulates microvascular permeability and affects the passage of spermatogonia through tight junctions in the Sertoli cells [34]. A study stated that the amount of testicular VEGF decreased in diabetic mice, and the decrease in VEGF level was associated with increased apoptosis and testicular damage [35]. In our study, we observed that VEGF expression was almost undetectable in the testicular tissues of the DM group compared to the control group, in line with the literature. These results suggest that the decrease in VEGF expression resulting from DM may cause decreased endothelial permeability and insufficient angiogenesis, resulting in vascular disorders.

Limitations

The diversity of antibodies used in the evaluation could be increased.

Conclusion

This study showed that type 2 DM induced by HFD and streptozotocin harms the spermatogenesis stage of mice, and causes quantitative, motility-related and morphological changes in semen quality. Deterioration of seminiferous tubule histology increased the apoptosis rate of testicular cells and the deterioration of the intratesticular vascular structure. We think that metformin administration probably regulates glucose metabolism, contributes to the restoration and repair of the damaged intratesticular vascular structure with its effect on weight loss and antioxidant support. We have the opinion that supporting the vascular structure improves semen parameters and reduces spermatogenic cell apoptosis.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2008 Jan;31(Supplement 1):S55-S60. doi: 10.2337/dc08-S055
2. Mealey BL, Ocampo GL. Diabetes mellitus and periodontal disease. Periodontol 2000. 2007;44:127-53.
3. Agbaje IM, Rogers DA, McVicar CM, McClure N, Atkinson AB, Mallidis CL, et al. Insulin dependant diabetes mellitus: implications for male reproductive function. Hum Reprod. 2007;22(7):1871-7.
4. Cai L, Chen S, Evans T, Deng, DX, Mukherjee K, Chakrabarti S. Apoptotic germ-cell death and testicular damage in experimental diabetes: prevention by endothelin antagonism. Urol Res. 2000;28(5):342-7.
5. Shrilatha B, Muralidhara. Early oxidative stress in testis and epididymal sperm in streptozotocin-induced diabetic mice: its progression and genotoxic consequences. Reprod Toxicol. 2007;23(4):578-87.
6. Kehler DS, Scott KD, Andrew NS, Shanel ES, Naomi CH, Dustin EK, et al. Cardiovascular complications of type 2 diabetes in youth. Biochem Cell Biol. 2015;93(5): 496-510.
7. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. 1989 December 8;246(4935):1306-9.
8. Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor (VEGF) and its receptors. Faseb J. 1999;13(1): 9-22.
9. Caires KC, De Avila J, McLean DJ. Vascular endothelial growth factor regulates germ cell survival during establishment of spermatogenesis in the bovine testis. Reprod. 2009;138(4):667-77.
10. Rashid K, Sil PC. Curcumin ameliorates testicular damage in diabetic rats by suppressing cellular stress-mediated mitochondria and endoplasmic reticulum-dependent apoptotic death. Biochim Biophys Acta. 2015;1852(1):70-82.
11. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-2251.
12. Esteghamati A, Eskandari D, Mirmiranpour H, Noshad S, Mousavizadeh M, Hedayati M, et al. Effects of metformin on markers of oxidative stress and antioxidant reserve in patients with newly diagnosed type 2 diabetes: a randomized clinical trial. Clin Nutr. 2013;32(2):179-85.
13. Attia SM, Helal GK, Alhaider AA. Assessment of genomic instability in normal and diabetic rats treated with metformin. Chem Biol Interact. 2009;180(2):296-304.
14. Rabbani SI, Devi K, Khanam S. Role of Pioglitazone with Metformin or Glimepiride on Oxidative Stress-induced Nuclear Damage and Reproductive Toxicity in Diabetic Rats. Malays J Med Sci. 2010;17(1):3-11.
15. Albasher G, Mona A, Mohamed M AD, Saad A, Rafa A. Protective effects of Artemisia judaica extract compared to metformin against hepatorenal injury in high-fat diet/streptozotocine-induced diabetic rats. Environ Sci Pollut Res Int. 2020;27(32):40525-36.

16. Rangel SR, Evelyn NGS, Edgar EIF, Karine LR, Adriana RS, Cassiano F GA, et al. High-fat diet-induced kidney alterations in rats with metabolic syndrome: endothelial dysfunction and decreased antioxidant defense. Diabetes Metab Syndr Obes. 2019;12:1773-81.
17. Zhang S, Huali X, XiaofengY, Yi W, Dayun S. Metformin ameliorates diabetic nephropathy in a rat model of low-dose streptozotocin-induced diabetes. Exp Ther Med. 2017;14(1):383-90.
18. Yokoi K, Uthus EO, Nielsen FH. Nickel deficiency diminishes sperm quantity and movement in rats. Biol Trace Elem Res. 2003;93(1-3):141-54.
19. Kruger TF, Menkveld R, Stander FS, Lombard CJ, Van der MJP, Van Zyl AJ, et al. Sperm morphologic features as a prognostic factor in in vitro fertilization. Fertil Steril. 1986;46(6):1118-23.
20. Johnsen SG. Testicular biopsy score count a method for registration of spermatogenesis in human testes: normal values and results in 335 hypogonadal males. Hormones. 1970;1(1):2-25.
21. Jalili C, Salahshoor M, Naderi T. The effect of hydroalcoholic extract of P. crispum on sperm parameters, testis tissue and serum nitric oxide levels in mice. Advanced Biomedical Research. 2015;4(1):40.
22. Cameron DF, Rountree J, Schultz RE, Repetta D, Murray FT. Sustained hyperglycemia results in testicular dysfunction and reduced fertility potential in BBWOR diabetic rats. Am J Physiol. 1990;259(6 Pt 1):E881-9.
23. Kushwaha S, Jena GB. Telmisartan ameliorates germ cell toxicity in the STZ-induced diabetic rat: studies on possible molecular mechanisms. Mutat Res. 2013;755(1):11-2.
24. Kanter M, Aktas C, Erboga M. Curcumin attenuates testicular damage, apoptotic germ cell death, and oxidative stress in streptozotocin-induced diabetic rats. Mol Nutr Food Res. 2013;57(9):1578-85.
25. Morgante G, Tosti C, Orvieto R, Musacchio MC, Piomboni P, De Leo V. Metformin improves semen characteristics of oligo-terato-asthenozoospermic men with metabolic syndrome. Fertil Steril. 2011;95(6):2150-2.
26. Salahshoor MR, Mojdeh H, Shiva R, Fatemeh M, Cyrus J. Effect of Thymoquinone on Reproductive Parameter in Morphine-treated Male Mice. Adv Biomed Res. 2018;7:18.
27. Zohreh N, Shahla R, Mahmoudi R. The Effect of Aloe Vera Extract on the Sperm Quality in Male Diabetic Rats. Bull. Env. Pharmacol. Life Sci. 2014;3:223-8.
28. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol. 2000;182(3):311-22.
29. Tsounapi P, Saito M, Fotios D, Koukos S, Shimizu S, Satoh K. et al. Antioxidant treatment with edaravone or taurine ameliorates diabetes-induced testicular dysfunction in the rat. Mol Cell Biochem. 2012;369(1-2):195-204.
30. Cai L, Li W, Guangwu W, Luping G, Youchun J, James YK. Hyperglycemia-induced apoptosis in mouse myocardium: mitochondrial cytochrome C-mediated caspase-3 activation pathway. Diabetes. 2002;51(6):1938-48.
31. Nna VU, AbuBakar AB, Azlina A, Mahaneem M. Diabetes-induced testicular oxidative stress, inflammation, and caspase-dependent apoptosis: the protective role of metformin. Arch Physiol Biochem. 2020;126(5):377-88.
32. Ebisch IM, Thomas CMG, Wetzels AMM, Willemsen NP, Sweep FCGJ, Steegers-Theunissen RPM. Review of the role of the plasminogen activator system and vascular endothelial growth factor in subfertility. Fertil Steril. 2008;90(6):2340-50.
33. Reddy N, Kasukurthi KB, Mahla RS, Pawar RM, Goelet S. Expression of vascular endothelial growth factor (VEGF) transcript and protein in the testis of several vertebrates, including endangered species. Theriogenology. 2012;77(3):608-14.
34. Yoshida A, Anand-Apte B, Zetter BR. Differential endothelial migration and proliferation to basic fibroblast growth factor and vascular endothelial growth factor. Growth Factors. 1996;13(1-2):57-64.
35. Sisman AR, Kiray M, Camsari UM, Evren M, Ates M, Baykara B, et al. Potential Novel Biomarkers for Diabetic Testicular Damage in Streptozotocin-Induced Diabetic Rats: Nerve Growth Factor Beta and Vascular Endothelial Growth Factor. Dis Markers. 2014;2014:108106. doi: 10.1155/2014/108106.

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Two-year outcomes in patients undergoing rotational atherectomy and drug coated balloon therapy for chronic total occluded peripheral arterial diseases: A retrospective cohort study

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Ethics committee approval was given by Istanbul Medipol University Non-Invasive Clinical Research Ethics Committee with a decision number of 361 at the date of 03.18.2021.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Atherectomy is a minimally invasive endovascular surgery technique for removing atherosclerotic plaques in stenosed arteries. It seems to increase the success of angioplasty in the treatment of peripheral artery disease. We aimed to evaluate the outcomes of patients who underwent rotational atherectomy and drug-coated balloon therapy.

Methods: In this retrospective cohort study, thirty-four patients who underwent rotational atherectomy and drug-coated balloon angioplasty between August 2016 and January 2019 were evaluated. The Rotablator System (Boston Scientific Corporation; Scimed, Plymouth, MN, USA) was used in all cases. Drug-coated balloons were used in the femoropopliteal section in all patients.

Results: The mean age of patients was 65.55 (8.36) years. Seventeen had diabetes mellitus, for which 12 were using oral antidiabetic drugs and 5 were using insulin. At the 3rd postprocedural month, 94.1% of patients (n=32) had no clinical symptoms ($P<0.01$), two patients needed additional procedures such as balloon angioplasty and stenting due to decreased blood flow and severe stenosis of the superficial femoral artery. At the 1-year follow-up, while 2 patients needed surgery, one needed stenting to the superficial femoral artery. Within 2 years, 27 patients (79.4%) were clinically stable without any symptoms and 2 patients had undergone surgery.

Conclusion: Atherectomy devices have become a major tool in the management of peripheral vascular disease. Opening the natural lumen of the arteries gives the patient more time before open vascular surgery.

Keywords: Rotational atherectomy, Balloon angioplasty, Peripheral arterial diseases

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Introduction

Peripheral arterial disease (PAD) is one of the most common diseases which increases with age. More than 20% of the >70-year-old population has a PAD. It also aggravates the risk of cardiovascular morbidity and mortality about 5 to 6 times [1].

Atherectomy is considered a minimally invasive endovascular surgery technique for removing atherosclerotic plaques in stenosed arteries. It seems to increase the success of angioplasty in the treatment of a PAD [2, 3].

When blood cannot pass through the arteries to nourish the peripheral tissues due to atheroma plaques, various symptoms, such as ischemia, pain, pulseless, claudication, coldness, loss of sensation, and motor dysfunction occur. The refinement and use of endovascular procedures in the treatment of PAD continue to grow at a rate of about 4.8% per year, hence, the rate of surgical procedures decreases at a rate of 6.6% [4, 5]. This study aimed to evaluate the 2-year follow-up results of 34 patients who underwent rotational atherectomy and drug-coated balloon therapy.

Materials and methods

Study design

Ethics committee approval was granted by the Ethics Committee of Istanbul Medipol University on 03.18.2021, with the decision number 361. All patients or their legal representatives signed informed consent forms before hospitalization.

The data of consecutive patients who underwent rotational atherectomy or drug-coated balloon angioplasty between August 2016-January 2019 were evaluated retrospectively. The findings of the patients were recorded from the hospital records and patients' files. All patients had symptoms of PAD and total occlusion was determined by CT angiography.

Our first choice in the treatment of patients with moderate renal insufficiency not on dialysis and previously occluded, stenotic arteries was open surgical repair for atherectomy. In three patients, the superficial femoral artery was occluded proximally, and the guidewire could not be passed antegrade or retrograde from the popliteal artery. In these patients, femora-popliteal bypass was the treatment of choice, and they were excluded from the study.

Procedures

Patients' lesions were preoperatively determined by CT angiography. All patients received acetylsalicylic acid, statin, and cilostazol if they had severe distal lesions [6]. Local anesthetics and midazolam were administered. The artery was punctured with the aid of ultrasonography. The femoral sheath was inserted, and 5000U of intra-arterial heparin was given for anticoagulation. In proximal lesions, the arterial puncture was performed contralaterally with the crossover technique or brachial access was achieved first, and after dilatation of common iliac arteries, the crossover technique was performed from other extremities, as in the case shown in Figure 1. We also used the ipsilateral antegrade approach in cases of mid and distal SFA lesions. Hydrophilic guidewires were preferred to pass through the arteries, but in totally occluded lesions, naviCross 0.018" support catheter (Terumo) was used. The Rotablator System (Boston Scientific Corporation; Scimed, Plymouth, MN, USA) was used in all cases, after which drug-coated balloons were used in the femoropopliteal section of arteries. In the infrapopliteal target vessels, lesser-sized guidewires of 0.014 were utilized.

Figure 1 shows the pre-procedural CT angiography of a patient and Figure 2 depicts the preoperative DSA angiography of the occluded SFA. The post procedural rotational atherectomy and recanalization of the SFA is shown in Figure 3. The distal pulses of this patient were palpable both after the procedure and during the follow-up period of 2 years. The patients were heparinized for 24 hours to ensure an aPTT level between 50-70. Then they were discharged with acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) [6]. In bilateral cases, the other side was intervened one week later.

Figure 1: Diagnostic CT Angiography of a patient with distal aorta, bilateral iliac and femoral arterial occlusion and multiple stenosis

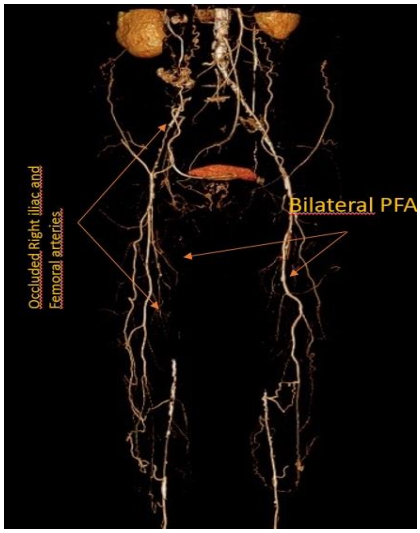


Figure 2: Preprocedural DSA angiography of an occluded right superficial femoral artery

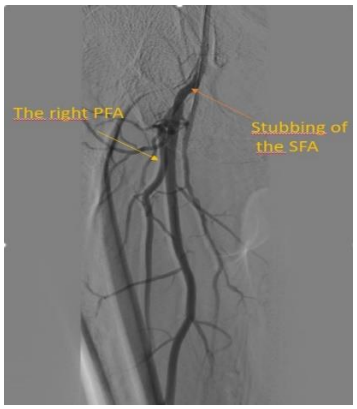
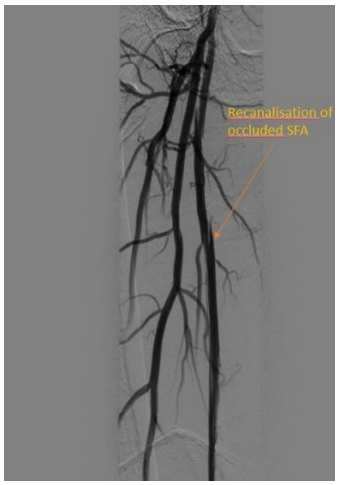


Figure 3: Postprocedural DSA angiography of the right superficial femoral artery



Statistical analysis

The analyses were performed with the Statistical Package for Social Sciences (SPSS) software. The variables were presented as percentages for categorical variables and mean and standard deviation. The Pearson correlation coefficients were used for correlation analysis. A *P* value of<0.05 was considered statistically significant.

Results

A total of 34 patients were enrolled in the study. There were 23 males (67.64%) and 11 females (32.35%). The mean age of patients was 65.55 (8.36) years. Seventeen patients had diabetes mellitus, 12 were using oral antidiabetic drugs and 5 were using insulin for diabetes mellitus. Ten of 17 diabetic patients were male (58.82%). Ten patients smoked one packet of cigarettes per day. Ten had hyperlipidemia, for which they were using antihyperlipidemia medications (Table 1).

Table 1: Patients' demographic findings

		Male	Female	Total (n)
Gender		23 (67.64%)	11 (32.35%)	34
Diabetes Mellitus	Oral Drugs use	7 (20.58%)	5 (14.70%)	
	Insulin	3 (8.82%)	2 (5.88)	17 (50%)
Smoking		8 (23.52%)	1 (2.94%)	9 (26.47%)
Hyperlipidemia		6 (26.47%)	4 (20.58%)	10 (29.41%)

The symptoms of patients included claudication in less than 50 meters, resting pain (n=15) and ischemic lesions or necrosis (n=7). The mean ABI was 0.57 (0.17). All patients' CT angiographies was investigated, based on which the atherectomy procedure was performed (Figure 1). In terms of Rutherford classification, 14 patients (41.17%) were grade 1, category 2 with moderate claudication, 6 (17.64%) were grade I, category 3 with severe claudication, 8 (23.52%) were grade II, category 4, 6 (14.70%) were grade III category 5 with non-healing ulcer (Table 2.). Regarding TASC (Trans-Atlantic Inter-Society Consensus classification, the Number of Type A, Type B, Type C, Type D patients were 3, 5, 11, and 15, respectively. Six cases had bilateral SFA lesions. While ten patients had iliac artery lesions, 4 had bilateral lesions. In the anatomical evaluation of lesions regarding the GLASS classification, the number of patients with SFA grade 1, grade 2, grade 3, and grade 4 were 3, 5, 11, and 15, respectively.

Urea and creatinine levels were evaluated before atherectomy. Moderate renal insufficiency of patients not on dialysis was treated by open surgery to prevent the risk of dialysis. All patients except one were discharged in 24 hours regarding clinical findings. In physical examination, 16 patients' (47.05%) ATP pulses and 6 patients' (17.64%) both ATP and ADP pulses were palpable. While 8 patients' (23.52%) both ATP and ADP pulses were bi-phasic positive by hand Doppler (Huntleigh Mini Dopplex Handheld Doppler System), 4 patients' only ATP pulses were positive by hand Doppler examination. The primary outcomes were mortality and amputation rates, while the secondary outcomes were perioperative complications, such as hematoma, infections, cost-effectivity, and duration of hospitalization. There was no mortality, and 2 patients' amputations were performed at the metatarsal necrotic region in a month due to previous necrotic lesions, saving their heels. In clinical findings, while only two patients had hematoma at the insertion site, there was swelling and hematoma in a patient's thigh region. He needed 600 ml of erythrocyte transfusion. Once his control CT angiography revealed no extravasation, he was discharged on the 3rd postprocedural day uneventfully. The other 33 patients were discharged in 24 hours without any complications.

The clinical and angiographic findings of patients improved. In outpatient follow-ups, Doppler USG was performed. In the 3rd postprocedural month, 94.1% of patients (n=32) had no clinical symptoms (P<0.01), 2 needed additional balloon angioplasty and stenting due to decreased blood flow and severe stenosis of the superficial femoral artery. At 1 year follow-up examinations, 2 patients needed a femora-popliteal 8 mm polypropylene synthetic graft bypass, and one needed stenting to the superficial femoral artery. In 2 years, 27 patients (79.4%) were clinically stable without any symptoms and 2 patients had undergone femora-popliteal 8 mm polypropylene synthetic graft bypass (Table 3). The ankle-brachial index increased significantly from 0.57 (0.17) at baseline to 0.85 (0.24), 0.82 (0.18), 0.80 (0.21) (P=0.02) at 3 months, 12 months, and 24 months respectively.

In follow-up, patients who had the re-interventional procedures or surgical bypass operation were clinically and radiologically (Doppler Ultrasonography) stable, without any complications.

Table 2: Rutherford classification of PAD

Grade	Category	Clinical Description	n (%)
I	2	Moderate claudication	14 (41.17)
I	3	Severe claudication	6 (17.64)
II	4	Ischemic rest pain	8 (23.52)
III	5	Minor tissue loss – non-healing ulcer, focal gangrene with diffuse pedal ischemia	6 (17.64)

Table 3: Reinterventions of patients in follow up of 3 months, 1 year and 2 years

	3 months	1 year	2 years
No symptoms	32 (91.1%)	29 (88.2%)	27 (79.4%)
PTA-Stenting	2 (5.88%)	1(2.94%)	0
Surgery	0	2 (5.88%)	2 (5.88%)

Discussion

Various atherectomy devices were developed by the manufacturers with the main aim of preserving the arterial structure and decreasing restenosis rate, as well as other complications such as dissection and distal embolization. The technology is developing mainly not to disturb or block the blood flow by the destruction of the smooth luminal wall or causing subintimal dissections [7]. In our study, we used the Rotablator System of Boston Scientific Corporation; Scimed, Plymouth, MN, USA). The leading edge has the capability to shave the plaque in 360 degrees [8, 9]. The principle of these devices is to cut the atheroma plaques by layers without destruction of the intimal layer of arteries.

The debris of atheroma plaques is small and can be digested by resident cells without causing embolization [10]. Rotational atherectomy devices significantly increase the luminal area and volume so the patients' comfort increases without using stents. Very short hospitalization duration and lack of general anesthesia administration also decrease mortality and morbidity in PAD patients, which increases the cost-effectivity. The advent of atherectomy devices also increases the effectiveness of drug-coated balloons by increasing the release of paclitaxel through the arterial wall to the media layer, so the compliance and volume of arteries increase. The need for metallic stents decreases more after atherectomy procedures compared to traditional angioplasty procedures [11]. The patients are saved from long-term stent-related complications like intimal hyperplasia, broken stent, occlusion by thrombus, and access difficulties in the branching point of arteries [12, 13].

The primary patency rates with directional atherectomy were 88% and 79% in one- and two-years of follow-up, respectively, in our study. The primary patency rate approaches 60% at 12 months with directional atherectomy as a stent-alone technique, whereas orbital atherectomy in conjunction with

balloon angioplasty and stenting achieved primary patency rates of 90% [14], as in our study. Some studies indicate that about 20% of patients have restenosis and need additional interventional procedures or may lose their extremities [15]. In our study, 32 patients (91%) had no symptoms in 3-month follow-ups. This ratio decreased to 79% in two years. While 7 patients required reintervention, only 4 of the patients needed a surgical approach (11.7%). The patients' limbs were salvaged from major amputation by invasive interventions. Only the previous necrotic sections were amputated in 2 patients.

Atherectomy offers the advantages of surgical endarterectomy by removing atherosclerotic plaques while remaining a minimally invasive and percutaneous method [16]. These devices are major treatment options for peripheral vascular disease. Peripheral arterial disease patients are generally diabetics and demonstrate a gradual, age-related impairment in vascular function, which causes multiple additional pathologies requiring surgery [17]. Additional lesions in the aorta or iliac artery increase the mortality and morbidity of the surgery. Lesion morphology is an important determinant of success and long-term patency. Balloon angioplasty is the procedure of choice for iliac artery occlusive lesions. Stent placement should be reserved for angioplasty failures [18] but in our cases, all iliac arterial lesions were severe and included long segments. The desired opening of the arterial lumen could not be achieved following balloon angioplasty without stent implantation. So, we preferred to implant stents in the narrowed or occluded long-segment iliac arteries. Postoperative antiaggregant treatment also should be aggressive in longer grafts, which increases postoperative drug-related risk for bleeding complications [19].

In our study, about 50% of patients were diabetic, and the mean age was 65 years. In this age group, widespread disease also increases the risk of surgery and general anesthesia. Interventional procedures pose lower risks regarding general anesthesia, the opening of the abdomen, and results in low hospitalization duration, and decreased wound infection and bleeding. Major complications of open vascular procedures are wound complications, graft infections, and poor runoff. Occlusion and anesthesia-related complications occur at a rate of 30%. Patients with PAD are generally elderly, and patient-related risks include increased age, cardiac and renal disease, high American Society of Anesthesiologists score, and those relating to the administration of general anesthesia. The mortality within the first month was about 5% (1% for claudication and 8% for acute ischemia) and the amputation rate was 7% [20]. In our study, there were no major complications, but one patient had thigh swelling. The other patients were discharged within 24 hours with cure. Amputation was performed in 2 patients in the previously necrotic metatarsal region. In two years of follow-up, only 3 patients required open surgery. In this study, the primary outcomes were mortality and amputation rates, while the secondary outcomes were perioperative complications, such as hematoma, infections, cost-effectivity, and duration of hospitalization. Rotational atherectomy provides decreased hospitalization duration and low complication risk, especially for high-risk patients. Also, the risk of redo interventions or need for primary open vascular surgery decrease.

Limitations

The limitation of the study is the relatively low number of patients.

Conclusion

Atherectomy devices have become the treatment of choice in the management of peripheral vascular disease. Opening the natural lumen of the arteries gives the patients time before open vascular surgery.

References

1. Cheanvechai V, Harthun NL, Graham LM, Julie A. Freischlag, Gahtan V. Incidence of peripheral vascular disease in women: is it different from that in men? J Thoracic and Cardiovasc Surg. 2004;127:314-7.
2. Yiğit G, Sarıcaoğlu MC, Çetinkaya F, Özen A, İşcan H.Z. Endovascular treatment of chronic total occlusion of iliac/femoral arteries: Mid-term follow-up. Turkish Journal of Vascular Surgery. 2020;29:7-12.
3. Singh T, Koul D, Szpunar S, et al. Tissue removal by ultrasound evaluation (the TRUE study): the Jetstream G2 system post-market peripheral vascular IVUS study. J Invasive Cardiol. 2011;23:269-73.
4. Robert S. Dieter, Raymond A. Dieter. Endovascular Interventions: A Case-Based Approach. Springer Science and Business Media Newyork. Kindle Edition. 2014;762-5.
5. Stavroulakis K, Bisdas T, Torsello G, Stachmann A2, Schwindt A. Combined Directional Atherectomy and Drug-Eluting Balloon Angioplasty for Isolated Popliteal Artery Lesions in Patients with Peripheral Artery Disease. J Endovasc. Ther. 2015;22:847-52.
6. Periferik Arter ve Ven Hastalıkları - Ulusal Tedavi Kılavuzu 2021;60-2.
7. Ahn SS, Concepcion BS. Current status of atherectomy for peripheral arterial occlusive disease. World J Surg. 1996;20:635–43.
8. Spencer B, Yeung AC. Rotational Atherectomy: Concepts and Practice. In: Interventional Cardiology. New York: McGraw-Hill; 2007;333–47.
9. Akkus NI, Abdulbaki A, Jimenez E, Tandon N. Atherectomy devices: technology update. Medical Devices: Evidence and Research. 2015;8:1–10.
10. Franzone A, Ferrone M, Carotenuto G, Carbone A, Scudiero L, Serino F, Scudiero F, Izzo R, Piccolo R, Saviano S, Amato B, Perrino C, Trimarco B, Esposito G. The role of atherectomy in the treatment of lower extremity peripheral artery disease. BMC Surg. 2012;12 Suppl 1(Suppl 1):S13. doi: 10.1186/1471-2482-12-S1-S13.
11. Maehara A, Mintz GS, Shimshak TM, et al. Intravascular ultrasound evaluation of JETSTREAM atherectomy removal of superficial calcium in peripheral arteries. Euro Intervention. 2015;11:96-103.
12. Bhat TM, Afari ME, Garcia LA. Atherectomy in Peripheral Artery Disease: A Review. J Invasive Cardiol. 2017 Apr;29(4):135-44.
13. Temizkan V, Uçak A, Alp İ, et al. Our experiences on endovascular and hybrid treatment of peripheral arterial diseases. Turk Gogus Kalp Damar Cerrahisi Derg. 2018;26:237-45. doi: 10.5606/tgkdc.dergisi.2018.13411
14. Quevedo HC, Arain SA, Ali G, Rafeh NA. A critical view of the peripheral atherectomy data in the treatment of infrainguinal arterial disease. J Invasive Cardiol. 2014;26:22-9.
15. Sussman M, Mallick R, Friedman M, et al. Failure of surgical and endovascular infrainguinal and iliac procedures in the management of peripheral arterial disease using data from electronic medical records. J Vasc Interv Radiol. 2013;24:378-91.
16. Katsanos K, Spiliopoulos S, Reppas L, et al. Debulking atherectomy in the peripheral arteries: is there a role and what is the evidence. Cardiovasc Intervent. Radiol 2017;40:964–77.
17. Thijssen DH, Carter SE, Green DJ. Arterial structure and function in vascular ageing: are you as old as your arteries? J Physiol. 2016;594:2275-84.
18. Brountzos EN, Kelekis DA. Iliac artery angioplasty: technique and results. Acta Chir Belg. 2004 Oct;104;5:532-9.
19. Rodoplu O, Oztas DM, Meric M, Beyaz MO, Ulukan MO, Yildiz CE, et.al. Efficacy of Rotational Atherectomy Followed by Drug-coated Balloon Angioplasty for the Treatment of Femoropopliteal Lesions-Comparison with Sole Drug-coated Balloon Revascularization: Two-year Outcomes. Ann Vasc Surg. 2021 May;73:222-33. doi: 10.1016/j.avsg.2020.10.051.
20. Kehlet M, Jensen LP, Schroeder TV. Risk Factors for Complications after Peripheral Vascular Surgery in 3,202 Patient Procedures. Ann Vasc Surg. 2016;36:13-21.

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The effect of recruitment maneuver on the development of expansion defect and atelectasis after lobectomy: A double-blind randomized controlled trial

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Abstract

Background/Aim: In pulmonary lobectomy operations, the operation is performed with one-lung ventilation by collapsing the related lung. Postoperative expansion failure on the deflated side is a critical issue. We aimed to correct the expansion failure and atelectasis with the recruitment maneuver performed at the end of the operation.

Methods: A total of 61 cases who underwent elective lobectomy under one-lung ventilation were included in this double-blind and prospective study. They were randomized into two groups comprising thirty and thirty-one cases. The first group included patients in whom the cycling recruitment maneuver (cRM) was performed, and the second group comprised patients who underwent the manual recruitment maneuver. Both groups were ventilated similarly during the one-lung ventilation period. After switching to double-lung ventilation, a standardized cycling recruitment maneuver was performed in the first group, and a high-volume manual recruitment maneuver with an anesthetic reservoir bag was used in the second group. Preoperative and postoperative inspiratory and hemodynamic parameters, wakefulness level, pain scores, developments of complications and durations of the hospitalization were noted. Expansion failure and atelectasis were evaluated both with chest radiography and thorax computerized tomography.

Results: There was no statistically significant difference among the two groups in terms of age, smoking, duration of operation, preoperative forced expiratory volume in 1 second (FEV1), SpO2 levels, respiratory and hemodynamic parameters noted during the operation, invasive arterial pressure monitoring results, electrocardiogram (ECG) findings, modified Aldrete score (MAS), and visual analogue scores (VAS) (P>0.05 for all). The gender distribution and types of operations performed were also similar. No complications were observed. Expansion failure was seen in 23.3% and 48.8% (P=0.042) of the patients in the cRM and mRM groups, respectively. Additional procedures were needed in 4 patients (13.3%) in the cRM group and in 11 patients (35.5%) in the mRM group. The duration of hospital stay was significantly shorter in the cRM group (P=0.045). Regression analysis revealed a 3.08-times increase in the incidence of expansion failure in the mRM group compared to group cRM.

Conclusion: In pulmonary lobectomy operations, we observed that with the utilization of the recruitment maneuver which is performed after switching to double-lung ventilation, the rate of expansion failure, the need for additional procedures and duration of hospital stay decreased.

Keywords: Atelectasis, Cycling recruitment management, Expansion defect, Lobectomy

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Introduction

Pulmonary complications are common after surgery and cause an increase in mortality and morbidity [1, 2]. The development of postoperative pulmonary complications depends on the anesthetic agents, surgical technique, and patient characteristics [3]. Major morbid complications may develop after lung resection operations, such as independently developing expansion defect and atelectasis along with prolonged air leak (PAL) [4-7]. The incidence of atelectasis and PAL varies depending on the underlying disease, lung structure and type of resection [5]. PAL is usually caused by the lung parenchyma after lobectomy [7]. Air leak usually ends in 2-3 days when the lung re-expands [8]. Prevention of the development of prolonged air leak requires a meticulous surgical technique. Naturally, the remaining lung can be filled by bringing the costae closer together, healing the mediastinum on the operative side, raising the diaphragm, or somehow ensuring that the lung on the operative side remains open [8-10]. In the postoperative period, negative intrapleural aspiration, chest tube insertion and respiratory physiotherapy contribute to the expansion of the lung and the prevention of atelectasis [9-11]. For the treatment of an expansion defect or residual air space, stapler use during surgery, suture line-support structures, fibrin adhesive use, decortication of the thickened pleura, separation of the inferior pulmonary ligament, pleural awning and pneumoperitonium can be considered [9, 12, 13]. The incidence of PAL in large series is 15.2%. The residual air gap ratio is between 10-30%. Eighty percent are usually reabsorbed within 4 weeks. Ninety percent may also be monitored for a year. Of these, 9% persist from 1 year to 10 years, and 5% of those with persistent air leaks are also infected [1, 8, 9].

These complications may be reduced thanks to the use of low tidal volume (Vt) during surgery, lower fractionated inspiratory oxygen (FiO_2) and end-expiratory positive pressure (PEEP), "Preventive Ventilation Strategy" [14, 15] and postoperative care including early mobilization, respiratory physiotherapy, and postoperative continuous positive airway pressure (CPAP) [1, 9, 16-19].

It is a routine practice to continue the operation by deflating the lung to be operated on, inserting a double lumen tube and performing single lung ventilation. Intrapulmonary shunting is observed in 15-40% due to complete deflation of the operated lung during single lung ventilation performed in the lateral position [12]. Atelectasis in the compressed zones of the lung is also shown by computed tomography (CT) [1, 12, 17]. Atelectatic zones and hypoventilated areas in the ventilated lung lead to ventilation/perfusion (V/Q) disorders and contribute to an increase in the shunt seen in the deflated lung [1, 12]. Atelectasis is a predisposing factor for ventilator-induced lung injury (VILI), the development of pneumonia, prolonged oxygen demand with hypoxemia, antibiotic treatment and even mechanical ventilation need [1, 14, 15]. For complete and uncomplicated recovery in the postoperative period, the remaining lung section after resection must completely fill the ipsilateral hemithorax as it re-expands. The necessity of additional procedures such as bronchoscopy, CPAP, respiratory physiotherapy performed to provide expansion after expansion defects and atelectasis in the postoperative period in both the deflated and ventilated lung increase the length of hospital stay and the treatment costs [1].

The recruitment maneuver is often used in the intensive care unit and in the peroperative period due to its positive contribution to gas exchange. In this study, a standardized cycling recruitment maneuver (cRM) and manual recruitment maneuver (mRM) were used. Mechanical ventilation began with 10 cmH_2O PEEP, 20 cmH2O PEEP-over pressure. After the PEEP value was increased to 15 and 20 cmH_2O at 1-minute intervals, it was waited for 1 minute at each step and decreased by 2 cmH_2O. This maneuver, which reduced PEEP to 8 cmH_2O, took a total of 9 minutes. With this prospective, randomized and double-blind study, the effects of these maneuvers on postoperative expansion defect, atelectasis development, the need for additional procedures and hospital stay were investigated.

Materials and methods

Patient characteristics

Sixty-one volunteers aged between 18-70 years in the ASA (American Society of Anesthesiologists) 1-2 category who underwent elective lobectomy were included in this double blind randomized controlled trial. The volunteers were randomly assigned numbers (RANDOM.ORG: True Random Number Service). Two groups consisting of 30 and 31 patients were created. Patients who required emergency operation, were uncooperative, had any contraindications for PEEP, those who received pleural awning, were given sub-diaphragmatic air, had contraindications to the drugs to be used, or were known to have atelectasis before elective lobectomy were excluded from the study. Group I consisted of patients who underwent cRM and Group II consisted of those who underwent high-volume uncontrolled mRM with an anesthetic reservoir bag.

Technique of anesthesia

No premedication was performed on the patients before surgery. A thoracic epidural catheter was inserted through T7 – T8 in all cases during preoperatively. The catheter was advanced epidurally about 6-8 cm and 10 mL of bolus bupivacaine (0.25%) was administered after a 2.5 mL-test dose (15 µg of adrenaline+20 mg of Lidocaine). Immediately afterwards, patient-controlled epidural analgesia was started in continuous mode with bupivacaine and fentanyl (1mg-2µg/ml). Before epidural catheterization, 500 mL of colloid solution, an intravascular volume extender (Voluven™), was administered, and fluid maintenance was continued with ringer lactate at 8 mL/kg/h. Epidural analgesia is the best pain relief method in thoracotomies. Using this method of analgesia, it was aimed to prevent the pain of patients with a low pain threshold from interfering with their mobilization and coughing in the postoperative period. After providing sedation with midazolam (0.03 mg/kg), 100% FiO_2 was given as an inhaler for 3 minutes. 2 µg/kg fentanyl, 1.5-2mg/kg propofol, 0.1 mg/kg vecuronium were administered as slow bolus during induction of anesthesia. A double-lumen endobronchial tube was inserted into the trachea of all patients. Anesthesia was maintained with a Draeger Primus® (Draeger AG, Lübeck, Germany) anesthesia device with sevoflurane (0.5-2%) and 50% N_2O. When it was clinically

necessary, a bolus dose of vecuronium (0.015 mg/kg) was administered.

All patients were given 0.5 FiO_2 in volume control mode, with a Vt of 6-8ml/kg, PEEP of 6cm H_2O, RR (respiratory rate) of 12/min, I/E (Inspiratory/Expiratory time ratio) of 1/2. When thoracotomy began, the lung to be operated on was deflated. Ventilation continued with a Vt of 3-4 ml/kg, a PEEP of 6 cmH2O, a RR of 12-15 to keep $EtCO_2$ between 30-40 during single-lung surgery.

Study plan

The following ventilatory settings were followed when switching to double lung ventilation in the cRM group: Pressure Controlled Ventilation (PCV) mode, FiO_2: 1, RR: 12/min, I/E: 1/1, PEEP-overpressure: 20 cmH_2O, PEEP: 10 cmH_2O, and target peak inspiratory pressure (PIP) was adjusted to a maximum of 40 cmH_2O. Ventilated was performed in these settings for 1 minute. PEEP was increased to 15 cmH_2O and 20 cmH_2O every 1 min. Afterwards, the PEEP value was reduced by 2 cmH_2O each minute until 8 cmH_2O. Finally, when PEEP reached 8 cmH_2O and PEEP-overpressure reached 20 cmH_2O, after waiting for 1 minute, the patient was ventilated with both lungs in PCV mode with PEEP: 8 cmH_2O, PIP: Vt 6-8 ml/kg, FiO_2: 0, 5, RR: 12/min, I/E: ½. Ventilation was continued with the same settings until extubation. During this procedure, the hemodynamic parameters of patients were monitored with GE B30 Patient Monitor (GE Healthcare, USA) or peripheral oxygen saturation (SpO_2). If deterioration was observed, the procedure was stopped, and normal ventilation was switched to, and the patient was removed from the study. The recruitment maneuver took a total of 9 minutes.

At the end of the resection, which was performed to the patients included in the mRM group, double lung ventilation began, and the anesthesia reservoir bag was used for about 2 min with FiO_2: 1, Vt: 10-15 ml/kg, RR: and $PaCO_2$: 40 mmHg for continuous and high-volume ventilation. The post-maneuver settings in volume control mode were as follows: FiO2: 0.5 Vt: 6-8 ml/kg, PEEP: 6 cmH2O, RR (respiratory frequency): 12/min, I/E (Inspiration/Expiration time ratio): ½. Ventilation continued at these settings until extubation.

Intraoperative follow-up

Invasive arterial pressure, electrocardiogram (ECG), SpO_2, and hourly urine output monitoring were performed. At the beginning and the end of each hour, arterial blood gas (ABG) was analyzed and partial O_2 and CO_2 pressures (PaO_2 and $PaCO_2$) and pH values were noted. Hemodynamic parameters and SpO_2 values were recorded continuously. High FiO_2 need due to hypoxemia and sudden SpO_2 decrease that may develop during single lung ventilation were taken note of, along with the type of lung resection performed on the patient.

Postoperative follow-up method

The physicians and health personnel who followed the patients were blinded to the study groups. All patients had the following parameters noted at the end of the operation: Alertness level (Modified Aldrete Score), heart rate (CAD), arterial pressure (TA), SpO, respiratory and hemodynamic parameters in the recovery unit. The patients were transferred to the wards once stable. Postoperative analgesia was provided at hours 0-1-2-4-12-24-48 with bupivacaine and dentanyl (1.25 mg/ml + 5 µg/ml) via patient-controlled epidural analgesia. Pain was evaluated with the Visual Analogue Scale (VAS) at the 1st postoperative hour. The VAS was intended to be kept ≤3.

PA lung X-ray and Thorax CT were obtained the same night, approximately 1 hour after being transferred to the ward as part of the routine follow-up, and expansion defect was evaluated as either present or absent. This assessment was routinely performed by the same experienced thoracic surgery specialist. The thoracic surgeon who performed the evaluation did not know which group the patient belonged to, both during and after the operation. In addition to the radiological evaluation, the patients were also evaluated in terms of complications. Nasotracheal aspiration, tube thoracostomy, CPAP-BiPAP (Bilevel Positive Airway Pressure) and bronchoscopy procedures performed on the patient from the postoperative period until discharge were noted as additional procedures. As long as the patient was in the operating room, the follow-up was performed by the same anesthesia technician and the same anesthesiologist. The follow-up in the ward was performed by the thoracic surgery team. The data of each patient were recorded in the follow-up form.

Statistical analysis

The design and data collection of our study follow the The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements. Power analysis was performed with the G power software, with an alpha value of 0.05 and a power of 80%. For 20% expansion failure in the group that underwent the cycling recruitment maneuver (cRM), and %40 expansion failure in the manual recruitment maneuver (cRM) group, at least 25 patients were needed. The data obtained in the study were evaluated with SPSS (Statistical Package for Social Sciences for Windows, Armonk, NY: IBM Corp.) v.22.0 with a 95% confidence interval and a significance level of $P<0.05$. Compliance with the normal distribution was assessed using the Kolmogorov Smirnov and Spiro-Wilk One-Sample tests. Since the data showed a normal distribution, parametric hypothesis tests were performed. Independent samples t-test was used for quantitative data among the independent groups, and Pearson chi-square test or Fisher's exact tests were used to assess qualitative data. To determine the effect of groups on the expression defect, logistic regression analysis was performed.

Results

The study included 61 lobectomy surgery patients who met the criteria for inclusion. According to the mode of double lung ventilation, the patients were divided into 2 groups. There was no significant difference between the groups in terms of age, duration of surgery, smoking, preoperative Forced expiratory volume in 1 second (FEV_1), SpO_2 values and the respiratory and hemodynamic parameters recorded during the preoperative period. The invasive arterial pressures and ECG monitoring findings were similar between the two groups. A decrease in the SpO_2 value was intervened with and brought to normal levels with FiO_2 increase. There was no significant difference between the groups in PaO_2 and $PaCO_2$ values in arterial blood gas analysis at the beginning of the operation and at the beginning of each hour. The groups were also similar in terms of pH values, alertness levels recorded with the Modified Aldrete Score in the

first 30 minutes postoperatively, VAS assessment, gender distribution and the type of operation performed (Tables 1 and 2).

Table 1: Quantitative data and significance levels

	Group	N	Mean	SD	*P*-value
Age, years	cRM	30	59.90	9.12	0.10
	mRM	31	55.71	10.53	
Use of tobacco, n	cRM	30	35.43	26.27	0.49
	mRM	31	31.29	19.49	
Duration of operation, minutes	cRM	30	174.33	80.97	0.97
	mRM	31	173.35	80.01	
Oxygen saturation, %	cRM	30	94.87	4.18	0.60
	mRM	31	95.42	4.10	
FEV1, L	cRM	30	2350.4	480.37	0.91
	mRM	31	2430.5	601.20	
VAS0	cRM	30	8.83	0.46	0.96
	mRM	31	8.84	0.45	
VAS4	cRM	30	5.52	1.15	0.48
	mRM	31	5.29	1.30	
VAS8	cRM	30	4.34	1.45	0.82
	mRM	31	4.26	1.44	
VAS15	cRM	30	3.72	0.92	0.64
	mRM	31	3.61	0.92	
VAS24	cRM	30	3.34	0.55	0.94
	mRM	31	3.35	0.55	
Postoperative hospitalization, days	cRM	30	5.83	2.59	0.02*
	mRM	31	9.03	6.51	

* *P*<0.05 Independent Samples T test, n: number, SD: Standard deviation, cRM: group of cycling recruitment maneuver, mRM: group of manual recruitment maneuver, FEV1: Forced expiratory volume in 1 second, VAS: visual analogue scores

Table 2: Comparison of gender and performed surgery according to group

n(%)		Group			
		cRM	mRM	Total	*P*-value
Gender	Male	24(80%)	25(80.6%)	49(80.3%)	
	Female	6(20%)	6(19.4%)	12(19.7%)	0.949
Surgery	RUL	14(46.7%)	15(48.4%)	29(47.5%)	
	Others	16(53.3%)	16(51.6%)	32(52.5%)	0.893

* *P*<0.05, Pearson Chi-Square Test, cRM: group of cycling recruitment maneuver, mRM: group of manual recruitment maneuver, RUL: Right upper lobectomy

When evaluated for additional procedures performed to treat the resulting expansion defect, additional procedures were required in 4 patients (13.3%) in the cRM group, and 11 patients (35.5%) in the mRM group (*P*<0.05) (Table 3). The length of hospitalization was significantly shorter in the cRM group (*P*<0.05). There were no complications associated with the recruitment process.

Regression analysis revealed that the MRM group was 3.08 times more likely to have an expansion defect than the cRM group (*P*<0.05) (Table 4).

Table 3: Distribution of expansion defects and additional procedures by groups

		cRM n(%)	mRM n(%)	Total	*P*-value
Expansion defect and atelectasis	None	23 (76.7%)	16 (51.6%)	39(63.9%)	0.042*
	Exist	7(23.3%)	15(%48.8%)	22(36.1%)	
Additional procedure	None	26 (86.7%)	20 (64.5%)	46(75.4%)	
	Exist	4(13.3%)	11(35.5%)	15(24.6%)	0.045*

**P*<0.05, Pearson Chi-Square Test, n: number, cRM: group of cycling recruitment maneuver, mRM: group of manual recruitment maneuver

Table 4: The logistic regression model

	B	*P*-value	O.R.	95.0% CI for Exp(B)	
				Lower	Upper
cRM	1.125	0.045*	3.080	1.024	9.262
Constant	0.065	0.857	1.067		

**P*<0.05, Logistic regression, B: beta coefficient, OR: Odds ratio, CI: confidence interval, cRM: group of cycling recruitment maneuver

Discussion

In subtotal lung resection operations, the recruitment maneuver positively affects arterial oxygenation by contributing to alveolar gas exchange during the peroperative period [12, 13, 16, 20, 21]. Although almost all rehabilitation studies in the literature aim to reduce the complications experienced during the peroperative period. This study was conducted to evaluate the re-expansion of the lung in the postoperative period and differs from other studies.

Expansion defects can be caused by poor lung compliance [8]. In this study, since the average FEV_1 between the groups was similar, it can be said that the lung compliance of both groups was equal. With preoperative values, it is seen how close both groups are to each other in terms of many variables. Some expansion defects seen after lobectomy are caused by small damages to the lung parenchyma, and when the lung re-expands, this air leak mostly ends in 2-3 days [8]. It is of great importance that the lung is expanded in case of air leak. With the applied recruitment maneuver, immediate expansion is provided after the procedure, which leads to the air leak terminating earlier. According to the results of this study, the 2-3-day period required for re-expansion in the postoperative period is significantly shortened by cRM, which is a standardized recruitment maneuver.

Compression atelectasis develops in the dependent areas of the lung during single-lung ventilation [12]. However, we observed no atelectasis in both groups in the dependent lung, possibly because an optimal PEEP value was given stably throughout the operation [15]. In addition, due to the complete deflation of the nondependent lung in the lateral position, atelectatic areas were formed during the re-ventilation period. For complete and uncomplicated recovery in the postoperative period, it is necessary that both the parenchyma remaining after resection in the independent lung completely fills the same side hemithorax with re-expansion, and the atelectatic areas in the dependent lung are fully re-expansed. In this study, a complete and uncomplicated recovery was achieved at a statistically significant level thanks to the cycling recruitment method.

The prevention of complications that may occur after thoracotomy surgery and early recovery of respiratory function are the most important factors in postoperative pain control. The superiority of the administration of analgesics in the epidural space to other methods is known [4]. In this study, postoperative pain control was achieved at the desired level by inserting a catheter into the epidural space before the operation. The fact that there is no significant difference between the two groups in the postoperative VAS assessment suggests that pain control was sufficient.

Our rate of expansion defects in the remaining lung after resection was 48% in the mRM group and 23.3% in the cRM group, which was significantly different. The rates may be relatively high as they were detected with postoperative thorax CT. In the light of the available data, it can be said that the used cycling recruitment maneuver reduces the expansion defect.

Additionally, fewer additional procedures were performed on the patients in the cRM group versus the mRM group, which also shows that the cRM group yielded positive results in terms of expansion defect.

Two known surgical methods are the application of pleural awning and creation of pneumoperitoneum to prevent postoperative expansion defects [9, 11, 22]. With these methods, the pleural cavity is reduced, allowing the remaining lung to fully fill the corresponding hemithorax. When applied during the operation, a recruitment maneuver is known to contribute to gas exchange [13, 15-17, 20, 23-25]. In addition, in the mRM group, logistic regression model revealed that the probability of an

expansion defect to be 3.08 times higher compared to the cRM group.

Its single-center design is the most prominent limitation of this study.

Conclusion

The cycling recruitment maneuver used when switching from single lung ventilation to double lung ventilation during the peroperative period results in significant reduction in expression defects, atelectasis development, the need for additional procedures. Also, hospitalization is significantly shorter, which lowers hospital costs.

References

1. Tusman G, Böhm SH, Warner DO, Sprung J. Atelectasis and perioperative pulmonary complications in high-risk patients. Curr Opin Anaesthesiol. 2012 Feb;25(1):1-10.
2. Handy JR Jr, Denniston K, Grunkemeier GL, Wu YX. What is the inpatient cost of hospital complications or death after lobectomy or pneumonectomy? Ann Thorac Surg. 2011 Jan;91(1):234-8.
3. Canet J, Gallart L, Gomar C, Paluzie G, Vallès J, Castillo J, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. Anesthesiology. 2010;113:1338-50.
4. Stolz AJ, Lischke R, Schutzner J, Petrik E, Harustiak T, Pafko P. Predisposing factors of atelectasis following pulmonary lobectomy. Acta Chir Belg. 2009 Jan-Feb;109(1):81-5.
5. Uramoto H, Nakanishi R, Fujino Y, Imoto H, Takenoyama M, Yoshimatsu T, et al. Prediction of pulmonary complications after a lobectomy in patients with non-small cell lung cancer. Thorax. 2001 Jan;56(1):59-61.
6. Uzieblo M, Welsh R, Pursel SE, Chmielewski GW. Incidence and significance of lobular atelectasis in thoracic surgical patients. Am Surg. 2000 May;66(5):476-80.
7. Abholda A, Liu D, Brooks A, Burt M. Prolonged air leak following radical upper lobectomy. Chest. 1998 Jun;113(6):1507-10.
8. Akkaş Y, Yazıcı Ü. Postoperative Complications In: Yüksel M, Balci AE, editors. Thoracic Surgery. Istanbul: Nobel Medical Bookstores; 2015. p. 203-11
9. Toker A, Dilege S, Bostancı K, Kalaycı G. Perioperative Pneumoperitoneum to Prevent Space and Air Leak after Lobectomy Operations. Thorac Cardiovasc Surg. 2003 Apr;51(2):93-6.
10. Rice TW, Kirby TJ. Prolonged air leak. Chest Surg Clin North Am 1992 Feb;23(2):803-11.
11. Handy JR, Judson MA, Zellner JL. Pneumoperitoneum to treat air leaks and spaces after lung volume reduction operations. Ann Thorac Surg. 1997 Dec;64(6):1803-5.
12. Tusman G, Böhm SH, Sipmann FS, Maisch S. Lung recruitment improves the efficiency of ventilation and gas exchange during one-lung ventilation anesthesia. Anesth Analg. 2004 Jun;98(6):1604-9.
13. Tusman G, Böhm SH, Suarez-Sipmann F, Turchetto E. Alveolar recruitment improves ventilatory efficiency of the lungs during anesthesia. Can J Anaesth. 2004 Aug-Sep;51(7):723-7.
14. Kilpatrick B, Slinger P. Lung protective strategies in anaesthesia. Br J Anaesth. 2010 Dec;105 Suppl 1:i108-16.
15. Inomata S, Nishikawa T, Saito S, Kihara S. "Best" PEEP during one-lung ventilation. Br J Anaesth. 1997 Jun;78(6):754-6.
16. Tusman G, Böhm SH, Vazquez de Anda GF, do Campo JL, Lachmann B. The 'alveolar recruitment strategy' improves arterial oxygenation during general anaesthesia. Br J Anaesth. 1999 Jan;82(1):8-13.
17. Lumb AB, Greenhill SJ, Simpson MP, Stewart J. Lung recruitment and positive airway pressure before extension does not improve oxygenation in the post-anaesthesia care unit: a randomized clinical trial. Br J Anaesth. 2010. May;104(5):643-7.
18. Stock MC, Downs JB, Gauer PK, Alster JM, Imrey PB. Prevention of postoperative pulmonary complications with CPAP, incentive spirometry, and conservative therapy. Chest. 1985 Feb;87(2):151-7.
19. Sentürk NM, Dilek A, Camci E, Senturk E, Orhan M, Tugrul M, et al. Effects of positive end-expiratory pressure on ventilatory and oxygenation parameters during pressure-controlled one-lung ventilation. J Cardiothorac Vasc Anaesth. 2005 Feb;19(1):71-5.
20. Hoftman N, Canales C, Leduc M, Mahajan A. Positive end expiratory pressure during one-lung ventilation: selecting ideal patients and ventilator settings with the aim of improving arterial oxygenation. Ann Card Anaesth. 2011 Sep-Dec;14(3):183-7.
21. Tusman G, Böhm SH, Melkun F, Staltari D, Quinzio C, Nador C, et al. Alveolar recruitment strategy increases arterial oxygenation during one-lung ventilation. Ann Thorac Surg. 2002 Apr;73(4):1204-9.
22. Carbognani P, Spaggiani L, Solli P, Rusca M. Pneumoperitoneum for prolonged air leaks after lower lobectomies. Ann Thorac Surg. 1998 Aug;66(2):604-5.
23. Jung JD, Kim SH, Yu BS, Kim HJ. Effects of a preemptive alveolar recruitment strategy on arterial oxygenation during one-lung ventilation with different tidal volumes in patients with normal pulmonary function test. Korean J Anesthesiol. 2014 Aug;67(2):96-102.
24. Unzueta C, Tusman G, Suarez-Sipmann F, Böhm S, Moral V. Alveolar recruitment improves ventilation during thoracic surgery: a randomized controlled trial. Br J Anaesth. 2012 Mar;108(3):517-24.
25. Park SH, Jeon YT, Hwang JW, Do SH, Kim JH, Park HP. A preemptive alveolar recruitment strategy before one-lung ventilation improves arterial oxygenation in patients undergoing thoracic surgery: a prospective randomised study. Eur J Anaesthesiol. 2011 Apr;28(4):298-302.

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The publication rate of presented abstracts at a congress and determining its publication factor

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All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Congresses, scientific fairs on an academic platform, are held in numerous disciplines all over the world and bring physicians together. Through these congresses, the physicians can follow the latest developments in their profession and present their work. Many researchers first present their work in a congress, then update their work in the light of the feedbacks and publish them in a peer-reviewed journal. Although many oral and poster presentations are made in scientific congresses, a small portion are finally published in a peer-reviewed journal. This may be because the effort spent in preparing an abstract is much less than that spent during the preparation of an entire manuscript. However, the publication of a presentation in a peer-reviewed journal is a gold standard factor showing the quality of research and that it is worthy of publication. More detailed congress abstract evaluation criteria and their proximity to the procedures involved during the journal acceptance stage will likely enhance the publication rate. The purpose of this study was to perform a detailed evaluation of presentations at congresses held by the European Society of Trauma and Emergency Surgery (ESTES) in 2013, 2014, 2015 and determine their rates of publication in peer-reviewed journals.

Methods: The booklets for three consecutive annual ESTES congresses (2013, 2014, 2015) containing presented papers were accessed online. All oral and poster presentations were analyzed, and published studies in peer-reviewed journals that are indexed in Google Scholar database until 2019 were identified. These published studies were then analyzed and used to determine the Publication Factor for Congress (PFC) for these congresses.

Results: The total number of presentations at ESTES congresses in 2013-2015 was 1746, of which 878 were oral (50.2%) and 868 (49.8%) were in poster form. 450 (25.7%) of these were subsequently published in peer-reviewed journals that are indexed in Google Scholar database. 148 of the published papers (32.9%) were based on poster presentations, and 302 (67.1%) were from oral presentations.

Conclusion: The publication rate of oral and poster presentations presented at the 2013-2015 ESTES congresses from the date of the congress to 2019 was 25.7%. Oral presentations were published more than poster presentations. It suggests that the papers with high publication potential have a high tendency to be presented as oral presentations by the authors. Determination of publication rates and publication factor for a congress at specific intervals may increase the motivation of authors at the participation and submission stages and strengthen the brand value.

Keywords: Congress, Publication factor, Trauma, Emergency, Publication

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Introduction

Congresses, scientific fairs on an academic platform, are held in numerous disciplines all over the world and bring physicians together. Through these congresses physicians can follow the latest developments in their profession, researchers share their experiences and present their work, and get to hear the experiences of other colleagues. This enables scientific findings to be used more widely in clinical practice. These organizations also lead up to novel studies and create new professional networks.

For reasons such as time and financial considerations, scientists cannot attend all these congresses. It is therefore more logical and practical for them to select from among these and attend only a few. Another problem for researchers is predatory conferences. In other words, they seek to be selective. It is increasingly difficult to determine which congress is the right address for sharing the work [1]. Since scientific organizations holding congresses have observed this reality in recent years, they started to demand descriptions that could be considered as the Publication Factor for Congress (PFC). Congress organizers attempt to give potential participants some idea about the quality of congresses by determining some parameters that will specify the PFC. They seek to emphasize parameters such as the identity of the speakers attending, and their H indices and their important studies. In addition, factors such as the number of congress participants and the number of research studies presented have also become important parameters in terms of the interest in and quality of a congress. Moreover, subsequent publication status of the studies presented at a congress is also indicative for the quality of the presentations submitted to it, and this ratio has become a significant parameter in determining the PFC. One systematic review showed that only 1/3 abstracts are subsequently published [2]. Congresses with a high publication rate may attract more participants. Although care is generally taken during the evaluation of submissions sent to scientific conferences, the extensive examination procedure required by several scientific journals is not available at congresses [3]. The fact that the presentations made at the congresses are now a condition for academic progress, as in our country, places important responsibilities on congress organizers and congress scientific committees.

The purpose of this study was to perform a detailed evaluation of presentations at congresses held by European Society of Trauma and Emergency Surgery (ESTES) in 2013, 2014 and 2015 and determine their rates of publication in peer-reviewed journals. The ESTES congress was chosen for this study because of its high international participation.

Materials and methods

The primary endpoint of this study was to determine the subsequent publication rates in peer-reviewed journals of oral and poster presentations at three ESTES congresses held in 2013, 2014 and 2015, together with the affecting factors. The secondary endpoint was to establish a PFC parameter.

Data collection

An average of 1500 surgeons and residents from different countries attend the annual ESTES congress. Up-to-date information is provided at these scientific assemblies in the form of oral and poster research presentations, panels, courses and lectures by invited speakers.

The booklets for three consecutive congresses (2013, 2014, and 2015) containing presented papers were accessed online (http://www.estesonline.org/past-congresses/). Oral and poster presentations appear in the online congress booklet including the study name, author names, and the country and city where the study was performed. Data obtained from the congress booklets were transferred to a computer database using Microsoft Excel (Microsoft Inc, Redmond, WA, USA) software. All presentations were analyzed and verbal and poster papers, author names and paper titles were recorded by years. After recording all presentations in these three ESTES congresses, the author scanned the author names and study titles of these presentations online on the Google Scholar database (https://scholar.google.com.tr/) in December 2019. Other popular databases such as Pubmed, and Web of Science was also scanned but most published articles were not detected in these databases. Since the database with the highest number of publications is the Google Scholar database, the data obtained from this platform were used in the study. When studies meeting the research criteria and published in peer-reviewed journals were identified, the journal name, year of publication, type of study, whether it was single- or multi-center, the country in which it was performed, index information for the publishing journal, the journal IF, and number of citations of the published paper since the time the record was made were investigated on Web of Science and recorded.

Statistical analysis

The Statistical Package for the Social Sciences software (SPSS, version 21, SPSS Inc, Chicago, IL, USA) was used for all statistical calculations. All data are presented as median with interquartile range values for continuous variables and as percentage values for categorical variables. The Kolmogorov-Smirnov test was used to identify the normal distribution of variables. The Chi-square test was used to compare categorical variables, whereas the Mann-Whitney U test and the Kruskal-Wallis test were used to compare continuous variables. Statistical significance was considered as $P<0.05$ using a confidence interval of 95%.

Results

The total number of presentations at these congresses in 2013-2015 was 1746, of which 878 were oral (50.2%) and 868 (49.8%) were in poster form. Four hundred fifty (25.7%) of these were subsequently published in peer-reviewed journals. One hundred forty-eight of the published papers (32.9%) were based on poster presentations, and 302 (67.1%) were from oral presentations (Table 1). Distributions of papers by years and publication rates are shown in Figure 1.

When subsequently published papers were classified in terms of study design, the most common were retrospective studies at a rate of 40.4% (n=182), followed by prospective studies at a rate of 32.4% (n=146), and experimental studies and case reports. Four hundred thirty-two published presentations (96%) were single-center, and 18 (4%) were multi-center. Ninety-six of the presentations (21.3%) were from the

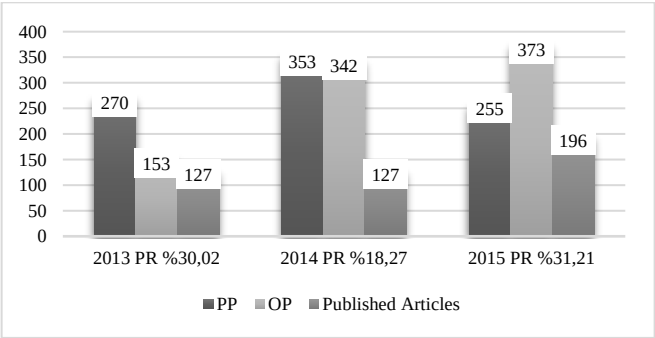
Netherlands, 76 (16.8%) were from Germany, and 48 (10.6%) were from the USA.

Table 1: Descriptive characteristics

	No.	%
Type of presentation		
Oral	302	67.1
Poster	148	32.9
Year of presentation		
2013	127	28.2
2014	127	28.2
2015	196	43.6
Type of study [a]		
Retrospective	182	40.4
Prospective	146	32.4
Experimental	48	10.6
Case report	41	9.1
Review	24	5.3
Multicenter	18	4.0
Meta-analysis	3	0.6
Study center		
Single-center	432	96.0
Multi-center	18	4.0
Country where the study was performed [b]		
The Netherlands	96	21.3
Germany	76	16.8
USA	48	10.6
Japan	23	5.1
France	20	4.4
United Kingdom	17	3.7
Turkey	13	2.8
Italy	10	2.2
Journal index		
SCI	94	20.9
SCI-E	236	52.4
Other	120	26.7
Journal IF (n=380) [c]		
<1	39	10.3
1-2	116	30.5
>2	225	59.2
Mean (SD) = 2.6 (0.2),		
Median (Min-Max) = 2.2(0.07-47.8)		
Number of citations (n=446) [d]		
0-9	276	61.3
10-19	99	22.0
>20	71	15.7
Mean (SD) = 12.3 (19.8), Median (Min-Max) = 6(0-164)		

[a] A study may be of more than one type and from more than one country. [b] Countries producing fewer than 10 studies are not shown in the table. [c] IF values of 70 journals cannot be found in database. [d] Citation information of 4 articles cannot be found

Figure 1: Percentages of abstracts published per year (OP – Oral presentation, PP – Poster presentation, PR – Publication rate)



Of the 450 articles published in 197 different internationally and nationally reviewed journals from various countries, 148 (40.8%) were clustered in 10 journals (Table 2). The largest number of papers was published in the journal 'Injury', (n= 51, 11.3%). Examination of the indices of the published presentations revealed that 52.4% were in Science Citation Index-Expanded (SCI-E), 20.9% were in Science Citation Index (SCI), and 26% were in other databases.

The mean IF of the journals in the time of publication of the presentations was 2.52 (2.79), and the median IF was 2.199 (min-max=0.07 - 47.8). When types of presentation were compared with the IFs of the publishing journals, oral presentations were published in journals with higher IFs than poster presentations (P=0.001, MWU). No statistically significant difference was determined between journals' IF and year of publication or number of centers in which a study was performed (P>0.05).

As this paper was being prepared, 15.8% (n = 71) of published presentations received 20 or more citations, 22% (n = 99) received 10-19 citations, and 61.3% (n = 276) received 0-9 citations. The 127 published abstracts in 2013 received a total of 1585 citations, with a mean value of 12.68 (20.91) (range 0 - 164). The 127 published abstracts in 2014 received 1751 citations, with a mean value of 14.01 (16.69) (range 0 – 111). The 196 published abstracts in 2015 received 2061 citations, with a mean value of 10.52 (20.097) (range 0 - 163). Citation rates of papers published from the presentations of 2015 congress were significantly lower than those presented in 2013 and 2014 (P<0.016 for both, Bonferroni adjustment).

Citation rates for publications derived from oral presentations in all years were higher than those from poster presentations (P<0.001 MWU), and multi-center publications attracted more citations that single-center publications (P=0.039 MWU).

The second endpoint was to develop a simple mathematical parameter as an indicator of the academic quality and scientific validity of a congress, called PFC. PFC values can be calculated by dividing the total PFC values in the years of publication of presentations published in journals through the study period by the total number of presentations submitted to the congress. The total PFC in 2013 was 279.317 for 423 presentations (270 oral presentations and 153 posters). The PFC was 0.660 in 2013, of 0.379 in 2014 with 695 presentations (353 oral presentations, 342 posters) (total PFC 263.507), and 0.665 in 2015 with 628 presentations (255 oral presentations, 373 posters) (total PFC 417.922) (Table 3).

Table 2: The 10 journals publishing the greatest numbers of presentations

Journal Name	Number and percentage of studies published (%)	IF (Impact Factor)	Journal index
1. Injury	51 (11.3%)	1.834	SCI-E
2. European Journal of Trauma and Emergency Surgery	35 (7.8%)	1.781	SCI-E
3. The Journal of Trauma and Acute Care Surgery	17 (3.8%)	3.377	SCI-E
4. World Journal of Surgery	14 (3.1%)	2.768	SCI-E
5. Scandinavian Journal of Trauma. Resuscitation and Emergency Medicine	13 (2.9%)	2.556	SCI-E
6. International Orthopaedics	12 (2.7%)	2.384	SCI-E
7. Journal of Orthopaedic Trauma	12 (2.7%)	1.826	SCI
8. World Journal of Emergency Surgery	12 (2.7%)	3.798	SCI-E
9. Archives of Orthopaedic and Trauma Surgery	11 (2.4%)	1.973	SCI-E
10. Plos One	7 (1.6%)	2.776	SCI-E

Table 3: Annual statistics for ESTES congresses

Parameter	2013	2014	2015
Publication Factor for Congress (PFC)	0.660	0.379	0.665
Mean PFC (SD)	2.56 (2.79) Min:0.230- Max:17.168	2.41(1.31) Min:0.070- Max:9.203	2.57 (3.768) Min:0.140- Max:47.831
Poster Presentation Number and mean (SD) PFC	28 1.76(1.474) Min:0.230- Max:6.630	36 2.05(1.187) Min:0.70-Max:4.840	84 1.92(0.696) Min:0.181- Max:3.198
Verbal Presentation Number and mean PFC	99 2.75(2.20) Min:0.330- Max:17.168	91 2.52(1.336) Min:0.108- Max:9.203	112 2.95 (4.66) Min:0.140- Max:47.831
Citation Number and Mean (SD)	1585 Mean:12.68(20.91) (Min 0-Max 164)	1751 Mean:14.01(16.69) (Min 0–Max 111)	2061 Mean:10.52(20.097) (Min 0–Max 163)
Publication Rate	30.02%	18.27%	31.21%

Discussion

Presentations at congresses are very important in terms of disseminating up-to-date research findings in all branches of medicine. The subsequent publication of these in peer-reviewed journals is a basic aim of research. Several studies have analyzed the publication rates of studies published at congresses in different branches. The branches with the highest publication rates in different studies are oncology (74%), orthopedics (64%) and anesthesia (50%) [4-6]. To date, 25.7% of presentations made at the three annual ESTES congresses held in 2013-2015 have been published in peer-reviewed journals. The publication of a presentation in a peer-reviewed journal is a gold standard factor showing the quality of research and that it is worthy of publication. More detailed the congress abstract screening committee evaluation criteria and their proximity to the procedures involved during the journal acceptance stage will likely enhance the publication rate. Factors such as the absence of explicit written acceptance criteria for a congress, a large number of presentations, and a short review time may cause many studies to be rejected by a journal even if they are accepted by the congress [7].

Problems such as the congress registration obligation, and author's transport, registration and accommodation costs can reduce authors' motivation to submit abstracts. One previous study of problems experienced during the abstract-to-manuscript stage revealed that the authors of abstracts submitted to the congresses and then got rejected are much more pessimistic regarding their work being published in peer-reviewed journals [8]. Another study cited insufficient time and low priority being attached to the abstract to manuscript stage as the main reasons for presentations not being published [9]. The effort expended in preparing an abstract is much less than that spent during the preparation of an entire manuscript. The conversion of abstracts into entire manuscripts is therefore a lengthy procedure, and author time limitations are the main reason for failure to be published [10]. Authors with academic affiliations have also been shown to be more successful at the publication stage [7].

Literature shows that a mean 50% of oral presentations and 35% of poster presentations are published [11]. However, other studies have determined no difference between oral and poster presentations [12-14]. It is generally believed that better designed presentations and those of greater scientific interest will be accepted as oral presentations by the congress committee, and that oral publications have a better chance of publication [15]. In the present study, too, oral posters were published at a higher rate than poster presentations. Oral presentations were also published in journals with higher IFs and attracted more citations. The principal reason for this may be that the authors who regard their papers as important in terms of effort and value will seek to submit these as oral presentations, while those regarded as less important may be submitted as poster presentations. The authors of oral presentations being exposed to direct questions, suggestions, and feedback from reviewers following submission may create an opportunity for them to revise and improve the manuscript, and this may also result in oral presentations having higher publication rates.

If a scientific publication attracts a large number of citations, this generally shows that it is regarded as high quality. A high number of citations also encourages the interest of other researchers in these publications and their contributions to the literature. The lowest mean citation number in this study was found in 2015, with 10.52 (20.097). The reason why this figure is lower than in the preceding two years, despite being quite high compared to the the rates previously reported in the literature, may be that less time had elapsed since publication compared to studies published earlier [16].

International databases show that papers which receive greater number of citations are published in journals with higher IFs. The presence of congress presentations in an international database is regarded as indicating that these are better prepared and of higher quality. Although the fact that national databases were not investigated in this study and that only the Google Scholar database was scanned might be regarded as a limitation, this is in fact a more suitable method for showing the quality of congresses.

Since they are more extensive, investigate large populations, and are more difficult to perform, multi-center studies are generally of greater scientific value than single-center research. Multi-center studies may therefore be published in journals with higher IFs and attract more citations. In this study, it was found that multi-center studies received more citation than single-center studies. Although the difference was statistically significant, the low number of multicenter studies may have prevented a more accurate comparison.

There is no universal PFC code for conference proceedings or conferences. IF is applicable for only journal rankings. However, there are a number of parameters by which conferences can be ranked, such as the Conference Proceeding Citation Index (http://wokinfo.com/products_tools/multidisciplinary/webofscience/cpci/), SCImago (through "H Index" measure) (http://www.scimagojr.com/journalsearch.php?q=conference&tip=jou), CORE Conference/Journal Ranking (http://core.edu.au/), Conference Proceedings Citation Index- Science (http://mjl.clarivate.com/scope/scope_cpci-s/) etc. Unfortunately, many of these ranking websites do not include medical sciences, and focus largely on computer science, electrical and electronic engineering, and communications. Of course, these web sites largely classify congresses on the basis of specific parameters and provide ranking lists for them. De Simone et al. used a mathematical calculation method to determine PFC values, although this was based on the proportions of lecturers' "mean H-index of lecturers normalized for the lecture topic" and "number of lectures on the topic at congress" [18]. Lecturers' H index values are not the sole factor bestowing high quality on a congress, and the quality of the presentations and future publication rates in peer-reviewed journals are also important parameters showing the scientific quality of congresses. Therefore, the IF value calculated in De Simone et al.'s study gives participants a prospective outcome, while the congress IF value calculated in the present study gives more of a retrospective outcome. The simultaneous evaluation of both parameters together will therefore elicit a more useful approach in selecting the best congress.

It may take up to three years for presentations to be published in peer-reviewed journals following their appearance

at congresses, and not all presentations from 2015 that would be eventually be published might have been determined by the time of this study, and some might not yet have been accepted by such journals. This may have resulted in both a lower number of published presentations and in a low citation count [7]. Although the publication rate was highest in 2015, there is a strong possibility that more studies will be published in the next 1-2 years.

Only the Google Scholar database was scanned in this study. The fact that other databases in addition to Google Scholar were not scanned may have led to other presentations recorded in other international or domestic databases being missed. Additionally, the congress booklets were scanned for a three-year period. Scanning over a longer period might have increased the chance of achieving a higher publication rate.

Although the rate of publication of ESTES congresses oral and poster presentations in peer reviewed journals in 2013, 2014 and 2015 was investigated in this study, it can be adapted to all congresses and become a universal evaluation parameter.

A publication rate of 25.7% was determined at the time of this study for ESTES congresses held between 2013-2015. Oral presentations were published more than poster presentations. It suggests that the papers with high publication potential have a high tendency to be presented as oral presentations by the authors. The mean IF of the journals in which papers were subsequently published was 2.52 (2.79), with a median value of 2.199 (min-max 0.07 - 47.8). This study investigated publication rates from the time of ESTES congresses in 2013, 2014 and 2015 to 2019, together with other factors impacting publication. Determination of congress publication rates or PFC at specific intervals may increase the motivation of the authors for participation and submission stages and strengthen the brand value.

References

1. Koçak Z. Precise and Immediate Action against Predatory Conferences. Balkan Med J. 2019 Dec 20;37(1):1-2. doi: 10.4274/balkanmedj.galenos.2020.2020.1.001
2. Von Elm E, Costanza MC, Walder B, Tramer MR. More insight into the fate of biomedical meeting abstracts: a systematic review. BMC Med Res Methodol. 2003 Jul 10; 3: 12. doi: 10.1186/1471-2288-3-12.
3. Bydder S, Marion K, Taylor M, Semmens J. Assessment of abstracts submitted to the annual scientific meeting of the Royal Australian and New Zealand College of Radiologists. Australas Radiol. 2006 Aug;50(4):355-9. doi: 10.1111/j.1440-1673.2006.01599.x
4. Krzyzanowska MK, Pintilie M, Tannock IF. Factors associated with failure to publish large randomized trials presented at an oncology meeting. JAMA. 2003 Jul 23;290(4):495-501. doi: 10. 1001/jama.290.4.495.
5. Nguyen V, Tornetta III P, Bkaric M. Publication rates for the scientific sessions of the OTA. Orthopaedic trauma association. J Orthop Traumatol. Sep-Oct 1998;12(7):457-9; discussion 456. doi: 10.1097/00005131- 199809000 -00004.
6. Yentis SM, Campbell FA, Lerman J. Publication of abstracts presented at anaesthesia meetings. Can J Anaesth. 1993 Jul;40(7):632-4. doi: 10. 1007/BF03009700.
7. De Meijer VE, Knops SP, van Dongen JA, Eyck BM, Vles WJ. The fate of research abstracts submitted to a national surgical conference: a cross-sectional study to assess scientific impact. Am J Surg. 2016 Jan;211(1):166-71. doi: 10. 1016/j.amjsurg.2015.06.017.
8. Weber EJ, Callaham ML, Wears RL, Barton C, Young G. Unpublished research from a medical specialty meeting: why investigators fail to publish. JAMA. 1998 Jul 15;280(3):257-9. doi: 10. 1001/jama.280.3.257.
9. Song F, Loke Y, Hooper L. Why are medical and health-related studies not being published? A systematic review of reasons given by investigators. PLoS One. 2014 Oct 15;9(10):e110418. doi: 10. 1371/journal. pone.0110418.
10. Dickersin K, Min Y, Meinert CL. Factors influencing publication of research results: follow-up of applications submitted to two institutional review boards. JAMA 1992;267:374–8. doi: 10. 1001/jama.1992. 03480030052036
11. Chalmers I. Underreporting research is scientific misconduct. JAMA. 1990 Mar 9;263(10):1405-8. doi: 10. 1001/jama.1990. 03440100121018
12. Scherer RW, Langenberg P, von Elm E. Full publication of results initially presented in abstracts. Cochrane Database Syst Rev. 2007:MR000005. doi: 10.1002/14651858.MR000005.pub3
13. Dahllöf G, Wondimu B, Maniere MC. Subsequent publication of abstracts presented at the International Association of Paediatric Dentistry meetings. Int J Paediatr Dent. 2008 Mar;18(2):91-7. doi: 10. 1111/j.1365-263X. 2007. 00898.x.
14. Lee DJ, Yuan JC, Prasad S, Ricardo Barao VA, Shyamsunder N, Sukotjo C. Analysis of abstracts presented at the prosthodontic research section of IADR General Sessions 2004-2005: demographics, publication rates, and factors contributing to publication. J Prosthodont. 2012 Apr;21(3):225-31. doi: 10.1111/j.1532-849X.2011.00792.x.
15. Ng L, Hersey K, Fleshner N. Publication rate of abstracts presented at the annual meeting of the American Urological Association. BJU Int. 2004 Jul;94(1):79-81. doi: 10.1111/j.1464-410X.2004.04905.x.
16. Oktay V, Çalpar Çıralı İ, Serin E, Sansoy V. A descriptive analysis of abstracts presented at the Turkish National Cardiology Congresses between 2011 and 2015. Anatol J Cardiol. 2018 Jul;20(1):16-20. doi: 10.14744/AnatolJCardiol.2018.94803.
17. Kalkan A, Kose O, Bilir O, Ersunan G, Ozel D, Guler F. Publication rate of abstracts presented at the emergency medicine congresses held by the European Society for Emergency Medicine (EUSEM) in 2011 and 2012. Emerg Med J. 2015 Sep;32(9):728-32. doi: 10.1136/emermed-2014-204063.
18. De Simone B, Ansaloni L, Kelly MD, Coccolini F, Sartelli M, Di Saverio S, Pisano M, Cervellin G, Baiocchi G, Catena F. The Congress Impact Factor: A proposal from board members of the World Society of Emergency Surgeons.it (WSES) and Academy of Emergency Medicine and Care (AcEMC). F1000Res. 2018 Aug 3;7:1185. doi: 10.12688/f1000research.15429.2.

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Investigation of the effect of anti-epileptic drugs on bone metabolism using osteoprotegerin and bone-specific alkaline phosphatase: The direct effects of antiepileptic drugs on bone metabolism

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Ethics Committee Approval
Approval for the study was granted by the Kahramanmaraş Sütçü Imam University Ethics Committee (Number: 2018-03/06).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Anti-epileptic drugs are long-term medications; thus, side-effects are frequently seen. An important but insufficiently known side-effect is the emergence of metabolic bone diseases. The mechanism of this entity is not clearly known, but it is usually seen with the use of cytochrome P450 enzyme-inducing anti-epileptics**.** However, recent studies demonstrated that non-enzyme-inducing molecules also cause bone mineral impairment. The aim of this study was to shed light on the pathogenesis of anti-epileptic metabolic bone disease using bone turnover markers.

Methods: This comparative, prospective case-control study included 37 patients followed-up in our outpatient clinic and 39 healthy control subjects. All the patients were female, aged over 18 years and in the premenopausal period, and had received the same anti-epileptic treatment for at least 3 months. Male patients, females who were <18 years old, pregnant, in the postmenopausal period, those with osteoporosis, gastrointestinal malabsorption, physical impairment that may prevent normal ambulation, endocrine and metabolic disease, musculoskeletal and joint disease or a history of medication use were excluded from the study. A healthy control group was formed of age-matched premenopausal women, with no disorders causing gastrointestinal malabsorption, no physical impairment preventing normal ambulation, no endocrine or metabolic disorder, or history of medication use that may affect bone turnover. The levels of serum calcium, alkaline phosphatase, 25-hydroxyvitamin D, osteoprotegerin and bone-specific alkaline phosphatase were assessed, and the results were recorded.

Results: Evaluation was made of 37 female epilepsy patients with a mean age of 30.8 (8.1) years and a healthy control group of 39 age- and body mass index-matched females (P=0.69, P=0.85, respectively). The mean duration of AED use was 6.1 (5.5) years. The calcium (P=0.09), phosphate (P=0.906) and alkaline phosphatase (P=0.22) levels were similar in both groups. The levels of 25-hydroxyvitamin D (P=0.049), osteoprotegerin (P=0.025), and bone- specific alkaline phosphatase (P=0.037) were significantly lower in the epilepsy group.

Conclusion: Our study showed that serum levels of osteoprotegerin and bone-specific alkaline phosphatase, which are markers of increased bone formation, were lower in epilepsy patients. Probably many factors cause the bone mineral disorder seen in epilepsy patients. Antiepileptic use is one of them. These results suggest that antiepileptics may not only affect enzyme induction but also bone turnover. Neurologists should be aware of this issue and monitor patients regularly with respect to bone mineralization to enable early treatment when necessary.

Keywords: Antiepileptic drugs, Metabolic bone disease, Osteoporosis, Osteoprotegerin, Bone-specific alkaline phosphatase

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Introduction

Epilepsy, one of the most common diseases at any age [1], is estimated to affect approximately 50 million people worldwide [2,3]. Most epilepsy patients use anti-epileptic drugs (AED). However, AEDs have many side effects which can cause patients to discontinue use, resulting in treatment failure. One of these is metabolic bone disease, which may range from bone mineral reduction to pathological fractures [4, 5]. However, the mechanism of this side effect is still unclear. Some authors advocated that enzyme-inducing anti-epileptic drugs (EIAED) cause secondary hypocalcemia and hyperparathyroidism by increasing vitamin D metabolism [6-8] and recent studies have shown that non-enzyme-inducing anti-epileptic drugs (NEIAED) can also lead to bone mineral deficiency [9, 10]. These recent outcomes suggest that factors other than enzyme induction play a role in the emergence of this side-effect, raising the question of whether anti-epileptic drugs have a direct impact on bone turnover.

The aim of this study was to investigate the effects of AEDs on bone mineralization using bone turnover markers and determine at which stage this side-effect occurs. To the best of our knowledge, this is the first study to have used bone-specific alkaline phosphatase (BALP) and osteoprotegerin (OPG) concurrently as two important bone turnover markers.

Materials and methods

This comparative, prospective case–control study included female patients aged >18 years who were being followed up in our outpatient clinic and had received the same anti-epileptic treatment for at least 3 months.

Male patients, and females aged <18 years, or who were pregnant or in the postmenopausal period were excluded from the study. Other exclusion criteria were the presence of osteoporosis, gastrointestinal malabsorption, physical impairment that may prevent normal ambulation, endocrine and metabolic disease (e.g., thyroid disorders, Cushing's Syndrome, hypogonadism, diabetes), musculoskeletal and joint disease (e.g., rheumatoid arthritis), or a history of medication use (e.g., corticosteroids, proton pump inhibitors).

A healthy control group was formed of age-matched premenopausal women, with no disorder causing gastrointestinal malabsorption, no physical impairment preventing normal ambulation, no endocrine or metabolic disorder, or history of medication use that may affect bone turnover.

A record was made for each patient of age, height, weight, body mass index (BMI), treatment duration, disease duration and type of antiepileptic medication prescribed. The levels of serum calcium (Ca), phosphate (P), alkaline phosphatase (ALP) and 25-hydroxyvitamin D [25(OH)D] were assessed and recorded. For the measurement of osteoprotegerin (OPG) and bone-specific alkaline phosphatase (BALP), fasting blood samples were withdrawn into anticoagulant-free tubes, and then centrifuged at 4000 rpm for 10 minutes after coagulation at room temperature. The serum BALP and OPG levels were determined using commercial ELISA kit procedures (201-12-1494; SunredBio, China, 201-12-1559; SunredBio, China).

This study was conducted in accordance with the Declaration of Helsinki. The ethical board approval was obtained from Kahramanmaraş Sütçü Imam University Ethics Committee (Number: 2018-03/06).

Sample size analysis

The sample size was determined using G*Power version 3.1 software. The minimum total sample size was calculated to be 68 (two groups, 34 per group) subjects with 90% power at a 95% confidence interval with a two-tailed alpha of <0.05 and a 0.80 effect size (f). A total of 76 participants, 37 in the patient group and 39 in the control group, were included in the study.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS for Windows v. 22 software (Statistical Package for the Social Sciences, IBM Corporation, Armonk, NY, USA). Continuous data were presented as mean (standard deviation (SD)) values and categorical variables were summarized as number (n) and percentage (%). The Kolmogorov Smirnov test was used for the evaluation of normal distribution. Comparisons between groups were made using Chi-square tests for categorical variables, Independent Samples Student's t-tests for normally distributed continuous variables and Mann-Whitney U-tests when the distribution was skewed. A *P*-value of <0.05 was considered statistically significant.

Results

Evaluation was made of 37 female epilepsy patients with a mean age of 30.8 (8.1) years and a healthy control group of 39 age and BMI-matched females (*P*=0.69, *P*=0.85, respectively). The mean duration of AED use was 6.1 (5.5) years. Monotherapy, most commonly levetiracetam, was found in 20 (54.05%) patients, and 17 (45.95%) patients were on multiple drug regimens. The Ca (*P*=0.09), P (*P*=0.906) and ALP (*P*=0.22) levels were similar in both groups. The levels of Vit D (*P*=0.049), OPG (*P*=0.025), and BALP (*P*=0.037) were significantly lower in the epilepsy group (Figures 1, 2, 3) (Table 1). In the correlation analysis of the study group data, OPG was positively correlated with vitamin D (rho = 0.479 / *P*=0.01) and BALP (rho = 0.571 / *P*=0.001), and negatively correlated with ALP (rho = -0.398 / *P*=0.036). The correlation analysis results are summarized in Table 2.

Table 1: Descriptive and analytical characteristics of the groups

	Epilepsy (n=37) Mean (SD) median (min-max)	Control (n=39) Mean (SD) median (min-max)	*P*-value
Age (years)	30.8 (8.1)	27.8 (5.9)	0.69
Duration of antiepileptic drug use (months)	6.1 (5.5)	-	
BMI (kg/m^2)	24.3 (3.6)	24.5 (5.5)	0.85
Ca^{++} (mg/dL)	9.1 (0.4)	9.2 (0.36)	0.09
Vit D (µg/L) *	6.9 (5)	8.0 (4.6)	0.049
ALP (U/L)	75.7 (26.7)	69.3 (18.1)	0.22
P (mg/dL)	3.4 (0.46)	3.4 (0.48)	0.906
Osteoprotegerin **	31 (13-751)	33.3 (12.7-725)	0.025
Bone-specific ALP **	28.5 (19.2-885.9)	49.4 (22.2-864.8)	0.037

BMI: body mass index, ALP: alkaline phosphatase, P: phosphorus, * Independent Samples t-test, ** Mann Whitney U-test, *P*<0.05, statistically significant difference

No correlation was found between the duration of drug use and Vit D level (rho=-0.229; *P*=0.173), OPG (rho= -0.311; *P*=0.108), and bsALP (rho= -0.125; *P*=0.512).

The levels of Ca (P=0.205), Vit D (P=0.95), ALP (P=0.36), OPG (P=0.46), and BALP (P=0.89) were similar in both the monotherapy and polytherapy groups.

Figure 1: Boxplot of osteoprotegerin according to the groups

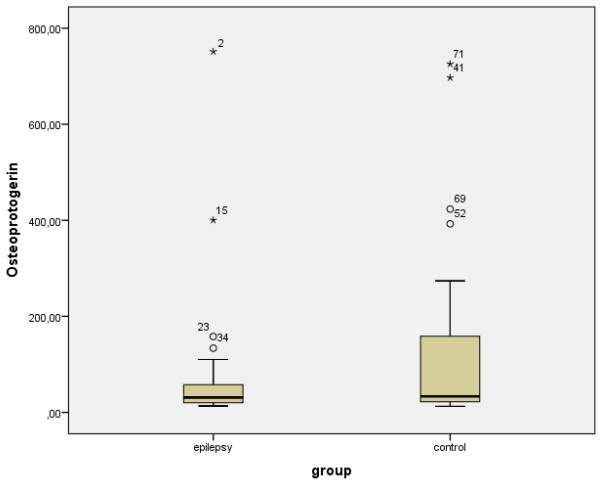

Figure 2: Boxplot of bone-specific alkaline phosphatase according to the groups

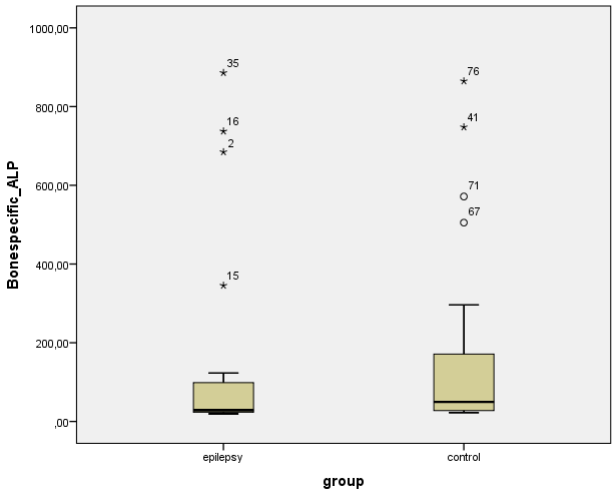

Figure 3: Boxplot of vitamin D according to the groups

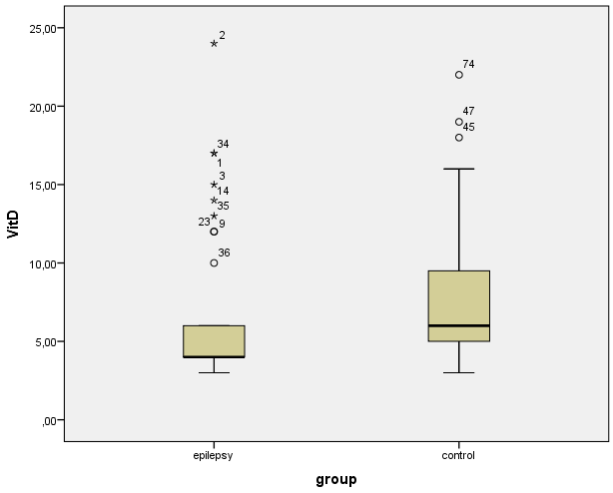

Table 2: Correlation analysis of the study group (epilepsy)

	Osteoprotegerin rho/*P*-value	Bone-specific ALP rho/*P*-value
Age (years)	0.233/0.232	-0.327/0.078
BMI (kg/m^2)	-0.194/0.323	-0.242/0.198
Duration (months)	-0.311/0.108	-0.125/0.512
Ca^{++}	0.178/0.366	0.324/0.081
VitD	0.479/0.01*	0.324/0.081
ALP	-0.398/0.036*	-0.155/0.414
P-value	0.092/0.641	0.228/0.226
Osteoprotegerin	-	0.571/0.001*

BMI: body mass index, ALP: alkaline phosphatase, P: phosphorus, * Spearman Correlation test, P<0.05: statistically significant difference

Discussion

The results of this study demonstrated that serum levels of OPG and BALP were lower in epilepsy patients compared to healthy control subjects. As both are markers of increased bone formation, the low levels in patients using AEDs suggests that anti-epileptics have a direct effect on bone mineralization.

AEDs are known to cause bone metabolism diseases, and although some studies have been carried out on this subject, no consensus has been reached and the pathogenesis is still a matter of debate.

Whereas earlier studies considered that the effects of AEDs on the cytochrome p450 enzyme system caused this side-effect, more recent studies have shown that NEIAED also cause bone mineral impairment.

Shen et al. [3] found that the use of both enzyme-inducing and non-enzyme inducing AEDs increased the risk of fractures, with a higher risk resulting from EIAED use.

Singla et al. [11] compared the levels of serum Ca, P, parathormone (PTH), vitamin D, ALP levels and DEXA scores of 25 AED users and 25 healthy control subjects. Serum Ca and protein levels were significantly decreased and serum PTH and ALP levels were significantly increased in AED users. In the comparisons between EIAED and NEIAED users, with the exception of ALP, no significant difference was found between the groups with respect to the changes in parameter levels. It was suggested that AEDs may affect the bone metabolism through some other mechanisms in addition to enzyme induction.

Although studies have been conducted using routine blood tests, Hamed et al. [8] used bone turnover makers as in the current study and found that epileptic patients had significantly lower serum Ca, 25OHD, OPG and higher Soluble Receptor Activator of Nuclear Factor-KappaB Ligand (RANKL) levels than the control subjects. It was concluded that low serum OPG and high RANKL levels indicated increased bone turnover. Although no correlation was found between serum parameters and the duration of treatment, a correlation was reported between the duration of treatment and bone mineral densities (BMD) measured using dual-energy X-ray absorptiometry (DEXA).

In an experimental animal model, Simko et al. [13] found a highly significant decrease in the OPG/RANKL* ratio in the phenytoin group. (*: Receptor Activator of Nuclear Factor-KappaB Ligand)

Although patients may have bone metabolism disorders due to anti-epileptics, these disorders may not be detected in the early stages on bone mineral densitometry or in routine blood tests such as Ca, P and ALP. In the current study, bone turnover markers were used to identify the effects of anti-epileptics on bone metabolism. There is known to be a balance of bone remodeling throughout life, and these events are mediated by osteoblasts producing bone matrix and osteoclasts that degrade it. OPG is a protein that inhibits osteoclastic bone resorption [14]. As in the study by Hamed et al. [8], OPG was used in the current study to investigate the effect of AEDs on bone turnover, and the results were consistent with those of Hamed et al. The OPG levels were significantly lower in the epilepsy group.

BALP, which is synthesized by osteoblasts and assumed to be involved in the calcification of the bone matrix, is considered a highly specific marker of the bone-forming activity of osteoblasts [15]. Different results have been reported in studies related to BALP.

Kir et al. [16] evaluated an epileptic patient group given carbamazepine and found no significant difference from the control group with respect to BALP levels. In the current study, serum BALP levels were lower in epilepsy patients than in the control group. These results demonstrate that AEDs impair bone mineralization by directly affecting bone turnover.

Limitations

Since the number of our patients was not high enough, we could not compare patients using AEDs as EIAED and NEIAED. In the future studies, by increasing the number of the patients, bone turnover markers can also be compared between patients who use EIAED and NEIAED.

Conclusion

Neurologists should be aware of this issue and monitor these patients regularly in terms of this complication. This situation is complicated by the presence of many factors which affect bone mineralization, a lack of studies on this subject, and the use of combined anti-epileptic treatments in some patients. There is a need for further studies of the pathogenesis of these side-effects to enable effective treatment planning.

References

1. Artemiadis AK, Lambrinoudaki I, Voskou P, Tsivgoulis G, Safouris A, Bougea A, et al. Preliminary evidence for gender effects of levetiracetam monotherapy duration on bone health of patients with epilepsy. Epilepsy Behav. 2016 Feb;55:84-6. doi: 10.1016/j.yebeh.2015.12.025. Epub 2016 Jan 13. PMID: 26773675.
2. Reynolds EH. Introduction: epilepsy in the world. Epilepsia. 2002;43 Suppl 6:1-3. doi: 10.1046/j.1528-1157.43.s.6.1.x. PMID: 12190964.
3. Shen C, Chen F, Zhang Y, Guo Y, Ding M. Association between use of antiepileptic drugs and fracture risk: a systematic review and meta-analysis. Bone. 2014 Jul;64:246-53. doi: 10.1016/j.bone.2014.04.018. Epub 2014 Apr 26. PMID: 24780876.
4. Andress DL, Ozuna J, Tirschwell D, Grande L, Johnson M, Jacobson AF, et al. Antiepileptic drug-induced bone loss in young male patients who have seizures. Arch Neurol. 2002 May;59(5):781-6. doi: 10.1001/archneur.59.5.781. PMID: 12020260.
5. Farhat G, Yamout B, Mikati MA, Demirjian S, Sawaya R, El-Hajj Fuleihan G. Effect of antiepileptic drugs on bone density in ambulatory patients. Neurology. 2002 May 14;58(9):1348-53. doi: 10.1212/wnl.58.9.1348. PMID: 12011279.
6. Verrotti A, Greco R, Latini G, Morgese G, Chiarelli F .Increased bone turn over in prepubertal, pubertal, and postpubertal patients receiving carbamazepine. Epilepsia 2002; 43:1488–92.doi:10.1046/j.1528-1157.2002.13002.x
7. Mattson RH, Gidal BE. Fractures, epilepsy, and antiepileptic drugs. Epilepsy Behav. 2004 Feb;5 Suppl 2:S36-40. doi: 10.1016/j.yebeh.2003.11.030. PMID: 15123010.
8. Hamed SA. Influences of bone and mineral metabolism in epilepsy. Expert Opin Drug Saf 2011; 10:265–80.doi:10.1517/14740338.2011.534455
9. Sato Y, Kondo I, Ishida S,Motooka H, Takayama K, Tomita Y,et al. Decreased bone mass and increased bone turn over with valproate therapy in adults with epilepsy. Neurology 2001; 57:445–9.doi:10.1212/WNL.57.3.445
10. Boluk A, Guzelipek M, Savli H, Temel I, Ozişik HI, Kaygusuz A. The effect of valproate on bone mineral density in adult epileptic patients. Pharmacol Res. 2004 Jul;50(1):93-7. doi: 10.1016/j.phrs.2003.11.011. PMID: 15082034.
11. Singla S, Kaushal S, Arora S, Singh G. Bone Health in Patients with Epilepsy: A Community-based Pilot Nested Case-control Study. Ann Indian Acad Neurol. 2017 Oct-Dec;20(4):367-71. doi: 10.4103/aian.AIAN_216_17. PMID: 29184339; PMCID: PMC5682740.
12. Hamed SA, Moussa MM, Youssef AH, El Hameed MAA and Nasr Eldin E. Bone status in patients with epilepsy: relationship to markers of bone remodeling. Frontiers in Neurology 2014 Aug;142(5):1-7. doi: 10.3389/fneur.2014.00142. PMID: 25136330
13. Simko J, Karesova I, Kremlacek J, Fekete S, Zimcikova E, Malakova J, et al. The effect of lamotrigine and phenytoin on bone turnover and bone strength: A prospective study in Wistar rats. Epilepsy research 2016;128:113-8. https:77doi.org/10.1111/j.1528-1167.2007.01176.x
14. Kostenuik PJ, Shalhoub V. Osteoprotegerin: a physiological and pharmacological inhibitor of bone resorption. Curr Pharm Des. 2001 May;7(8):613-35. doi: 10.2174/1381612013397807. PMID: 11375772.
15. Masrour Roudsari J, Mahjoub S. Quantification and comparison of bone-specific alkaline phosphatase with two methods in normal and Paget's specimens. Caspian J Intern Med. 2012 Summer;3(3):478-83. PMID: 24009918; PMCID: PMC3755844.
16. Kir HM, Garip S, Sahin D, Öztaş B. Effects of carbamazepine on serum parathormone, 25-hydroxyvitamin D, bone specific alkaline phosphatase, C-telopeptide, and osteocalcin levels in healthy rats. Bosn J Basic Med Sci. 2012 Nov;12(4):240-4. doi: 10.17305/bjbms.2012.2445. PMID: 23198939; PMCID: PMC4362499

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Increased mouse double minute X expression in human placental villous macrophages (Hofbauer cells) in gestational diabetes mellitus

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Ethics Committee Approval
Serial paraffin sections of human placental UC specimens were obtained from the University of South Florida with the protocol approved by the Ethics and Human Investigation Committees of the University of South Florida (approval number: 00015578).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Gestational diabetes mellitus is a common metabolic problem in pregnancy, and its prevalence ranges between 5-20%. Hofbauer cells are tissue macrophages of the feto-placental component that are raised in the villous tree of the placenta during pregnancy, but their quantity falls off with growing gestational age. We theorize that Hofbauer cells play a significant role in placental pathophysiology in GDM by controlling the MDMX (mouse double minute X/MDM4/HDMX) gene.
Methods: We performed immunohistochemistry on human placental specimens to determine cell-specific expression of MDMX in Hofbauer cells (HC) among the control and GDM (n=8 in each group) groups with matching gestational ages.
Results: Immunohistochemical analysis revealed that MDMXs were secreted by Hofbauer cells in the placental villous tree and compared to the placenta got from normal pregnancies, significantly higher MDMX HSCORE levels were detected in placenta Hofbauer cells (32.8 (24.52) vs. 190.1 (32.54), *P*=0.001) of the GDM group.
Conclusion: We revealed Hofbauer cells to be a source of MDMX secretion in human placenta. MDM2 levels in Hofbauer cells are also increased in GDM. This study found higher levels of MDMX in the Hofbauer cells from GDM placentas, suggesting an induction of MDMX secretion. GDM interaction in placental Hofbauer cells may contribute to GDM-associated feto-placental complications. Further studies are needed to define the significance of this relationship.

Keywords: Gestational diabetes mellitus, Mouse double minute X expression, Hofbauer cells, Placenta

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Introduction

Gestational diabetes mellitus GDM is defined as maternal hyperglycemia due to insulin resistance that develops during pregnancy, causing placental low-grade inflammation resulting in neonatal and maternal mortality and morbidity [1]. GDM prevalence is 11.5% among pregnant women [2], and it is associated with chronic low-grade inflammation of the placenta [2].

Fetal placental macrophages, or Hofbauer cells (HBCs), are present in the placental villous tree from the blastocyst implantation until delivery [2]. Hofbauer cells (HBCs) are characterized by high expression of the surface protein CD163 [3]. Hofbauer cells, located in the chorionic villi of the human placenta, are an essential part in controlling the pregnancy and providing homeostasis that is crucial for fetal growth [2]. It is not clearly explained how Hofbauer cell function varies in healthy pregnancy and specifically in pregnancies complicated by gestational diabetes, preeclampsia, and viral diseases [2].

We hypothesize that the human placenta bares functional, metabolic, and immunological cells in which Hofbauer cells play an essential role by altering many transcriptional gene expressions. MDMX (mouse double minute X/MDM4/HDMX) is the major negative regulator of p53, which regulates apoptosis in the villus tree. P53, the "guardian" of the human genome, is a tumor suppressor that is mutated in all cancers [4]. P53, the tumor suppressor gene, coordinates DNA repair, mitochondrial respiration, cellular metabolism, autophagy, and cellular responses to metabolic and environmental stress. In GDM, p53 is also upregulated in placental villi, in part due to hypoxia, metabolic and oxidative stress. The proteins MDM2, E3 ubiquitin ligase, and MDM4 coordinate the tumor suppressor gene p53 in proliferating cells. MDM2 and MDMX control p53 levels during growth [5]. Previous investigations demonstrate that p53 plays a significant role in the improvement of diabetes mellitus [4]. We hypothesize that the Hofbauer cells play a critical role in placental pathophysiology in GDM by regulating the MDMX gene.

Materials and methods

This prospective experimental laboratory study used placental samples collected from normal pregnant women who had never received steroid treatment, were suitable for their gestational age, and had no pathology, as well as those collected after delivery from patients diagnosed with gestational diabetes mellitus. Serial paraffin sections of human placental specimens were obtained from the University of South Florida per the protocol approved by the Ethics and Human Investigation Committees of the University of South Florida (approval number: 00015578) [6]. Written and verbal informed consent were obtained from each patient. Power Analysis was performed with G*Power 3.1.9.7 software with an α err prob of 0.05, and a power (1-β err prob) of 0.95. At 5% alpha error, 95% power (1-β), d=5.53 (large) and 95% confidence interval (CI), the sample size was calculated as 6. Due to case losses and possible negativities, the study was completed on 16 placental samples. All samples were grouped according to clinical diagnosis: Control (n=8) or GDM (n=8).

Immunohistochemistry

5-µm serial endometrial sections were incubated overnight at 56°C [5]. After deparaffinization, the slides were boiled in 10 mM citrate buffer (pH 6.0) for 15 min for antigen retrieval [5, 6]. The sections were then immersed in 3% hydrogen peroxide (in 1/1 methanol/distilled water) for 10 min to quench the endogenous peroxidase activity [6]. After washing with Tris-buffered saline (TBS; pH: 7.4) ×3 for 5 min, the slides were incubated in a humidified chamber with 5% blocking goat serum (Vector Laboratories, Burlingame, CA) in TBS for 30 min at room temperature [6]. Excess serum was then drained and the slides were incubated with a primary rabbit polyclonal MDMX (1:150; Cell Signaling Technology, Danvers, MA) in 1% normal goat serum overnight at 4°C [6]. The sections were washed ×3 for 5 min with TBS, and then biotinylated goat anti-rabbit IgG (Vector Laboratories) was added at 1:400 dilution for 30 min at RT. The antigen-antibody complex was detected using an avidin-biotin-peroxidase kit (Vector Laboratories) for 30 min at RT. DAB (3, 3-diaminobenzidine tetrahydrochloride dihydrate; Vector Laboratories) was used as the chromogen to visualize immunoreactivity, and sections were slightly counterstained with hematoxylin.

Immunoreactive MDMX levels were semi-quantitatively evaluated using the following intensity categories: 0, no staining; 1+, weak but detectable staining; 2+, moderate, or distinct staining; 3+, intense staining [6]. As defined already, a histological score value (HSCORE) was obtained for each tissue by summing the percentages of cells colored in each intensity group and multiplying this value by the weighted intensity of color, applying the formula HSCORE= Σ Pi (i + l), where i describes the intensity scores and Pi is the corresponding percentage of cells. In each slide, five randomly chosen sections were assessed under the light microscope (x40 magnification), and the percentage of cells for each intensity within these sections was established at various time points by two researchers who were blinded to the type and origin of tissues [7]. The intra-individual and inter-individual coefficients of variation were 10 and 12%, respectively, for the HSCORE evaluation. The average HSCORE of two examiners was used (Figure 1).

Statistical analysis

Results were analyzed using the Mann Whitney U test. Analyses were performed using SigmaPlot version 12.5 (Systat Software, Inc, San Jose, California, USA). A *P*-value of <0.05 was considered statistically significant in binary comparison.

Results

The mean gestational ages in the control and GDM groups were 39.1 (0.5) weeks and 38.8 (0.8) weeks, respectively. The two groups were similar in terms of mean gestational age (*P*=0.89). CA163 immunohistochemical staining revealed that MDMXs were produced by Hofbauer cells in a placental villous tree. MDMX immune activity was detected in high levels in the HBCs of GDM placental samples (Figure 2). This immune reaction was poor in the cytoplasmic region and intensive in the nuclear region of the HBCs. When the intensity of this immunostaining was quantified numerically, the following was found: The HSCORE of the control and GDM group HBCs were

132.8 (24.52), and 190.1 (32.54), respectively (P=0.001). MDMX immunostaining intensity was significantly higher in the GDM group (Figure 2).

Figure 1: Increased MDMX immune reactivity in the GDM placental villous tree. Picture symbolizes histological score (HSCORE) levels for Normal MDMX (n = 8) and GDM MDMX (n = 8) in placental villous tree samples. Bars represent (Mean (SD) •p < .001 compared to Normal and gestational age-matched GDM MDMX.

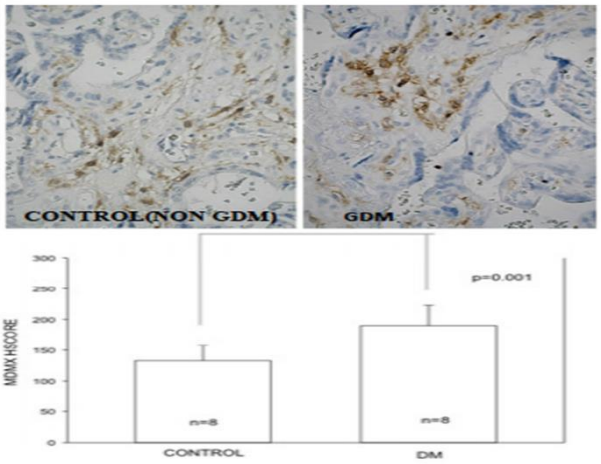
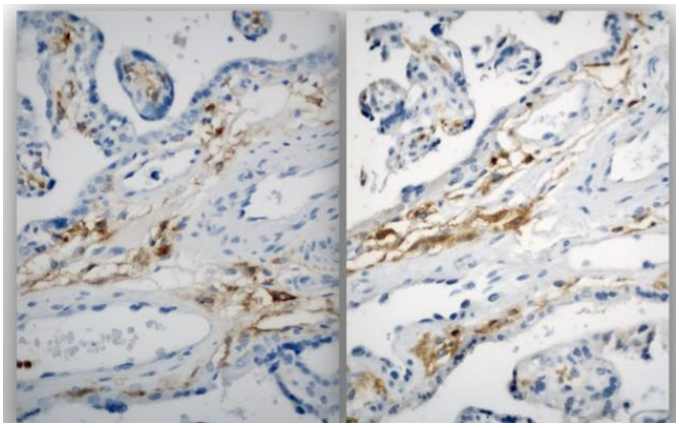


Figure 2: Association of CD 163 immunohistochemical staining with MDMX level in the placental villous tree. Demonstrative micrographs for the immunoreactivity of CD l63 and MDMX in placental villous tree serial sections



Discussion

GDM prevalence is 11.5% in the Asian pregnant population and creates a major obstetric problem, increasing mortality and morbidity in both the pregnant women and the offspring. Differences in diagnostic criteria, screening methods and work environment result in heterogeneity in the prevalence of Gestational Diabetes Mellitus (GDM) [8]. The human placental unit is sensitive to the high maternal glucose level and reacts to the adaptive variations in arrangement and function [9]. GDM is associated with high maternal and placental glucose levels, therefore resulting in a chronic low-grade inflammation of the placental villous tree [1]. An overproduction of pro-inflammatory mediators is found during blastocyst implantation and the developing embryo in the decidua and placenta from GDM. Maternal hyperglycemic environment-induced changes create pro-inflammatory and anti-inflammatory pathways that negatively affect the embryo and placental development in GDM [9–11].

Numerous studies have elucidated the possible role of regulator gene functions in the development and progression of GDM in the human placenta [12–14]. In this study, we researched whether placental villous tree MDMX levels vary in GDM. In addition, we posited that Hofbauer cells play a crucial role in placental pathophysiology in GDM, regulating the MDMX production, and found higher levels of MDMX in Hofbauer cells obtained from the GDM placenta, suggesting the induction of MDMX production by GDM [12]. To address this hypothesis, we identified phenotypic Hofbauer cells in the placental villous tree with surface markers of CD163 in immunohistochemical staining. Our immunohistochemical staining results reveal that MDMXs were mainly produced by the Hofbauer cells in the placental villous tree [15]. Moreover, significantly higher MDMX H scores were detected in the placentas of Hofbauer cells obtained from GDM patients [15]. During placental inflammation, Hofbauer cells produce different regulatory genes, proinflammatory cytokines or mediators that destroy or produce the villous cell boundary and trigger or destroy damaging responses as a continuity of chronic inflammation and anti-inflammatory balance [16].

Macrophages modulate tissue homeostasis and are widely distributed in the placenta during pregnancy, as the initial field of antimicrobial defense [2]. Placental macrophages, identified as Hofbauer cells (HBCs), are found in the villous tree [2]. HBCs are placed in the villous tree of the placenta in both healthy and pathological pregnancies such as those with GDM, preeclampsia and IUGR [2, 3].

Previous research shows that Hofbauer cells have a phenotype related with regulatory and anti-inflammatory reactions in the human placenta [2], and they are believed to play a critical role in regulating the pregnancy and maintaining a homeostatic environment important for fetal development [2, 17]. It is not yet clear how Hofbauer cell function changes in normal pregnancy and exceptionally in GDM, IUGR, preeclampsia, and viral infections [2]. New research recommends that diabetes/hyperglycemia impair the anti-inflammatory profile of the HBCs by arousing these cells to gain an inflammatory capacity [2, 3]. They are defined as anti-inflammatory M2 separated cells, stimulating tolerance and tissue remodeling [2]. They express surface markers such as CD163, CD206, and only intermediate or low levels of MHC-II proteins (MHC-II low). Their primary functions are tissue repair, wound healing and angiogenesis, as well as feto-maternal tolerance induction [3]. HBCs are present in all IUGR pregnancies and in 70% of GDM pregnancies [3].

Feng et al. [18] showed an increased infiltration of the chorionic villi by Hofbauer cells in GDM and inflammatory diseases of the placenta, such as villous inflammation of unknown etiology. Another study described a similar phenomenon in pregnancies complicated with GDM [19]. However, the role of Hofbauer cells is unclear under these conditions.

Previous studies have shown that MDMX are critical regulators of the tumor suppressor p53 and are overexpressed in many human malignancies [4]. It is two negative regulators – the E3 ubiquitin ligase MDM2 and its homologue, MDMX, which strongly regulate the tumor suppressor protein p53 in healthy cells [20]. Under stress conditions, such as DNA breakage, p53 escapes MDM2- and MDMX-induced functional inhibition and degradation and blocks proliferation of injured cells by promoting cell cycle delay, DNA repair, senescence, or apoptosis [20]. Considerable evidence points that stress signals promote phosphorylation of the MDM2 and MDMX, leading to the

activation of p53 [20]. Furthermore, MDMX and MDM2 are major negative regulators of p53 that control apoptosis in the placental villous tree. This regulator gene plays an important part in placental progress, consisting of vasculogenesis and angiogenesis [16]. The vasculogenesis and angiogenesis processes in the villous tree of the placenta are also administered by the expression of vascular endothelial growth factor (VEGF) by HBCs (villous macrophages) and trophoblast cells [16,17]. We investigate what is known about the main origin of this MDMX regulator gene [4]. MDMX is a negative regulator of p53 activity in vivo and in vitro [4]. A new research has established that control of p53 protein action is needed for healthy embryogenesis, tumor suppression, and cellular response to DNA damage [4]. Moreover, destruction of the p53-binding protein MDMX leads to embryo lethality in mid-gestation, a phenotype that is wholly protected by the lack of p53 [4]. Mice with homozygous MDMX and p53 null mutations develop normally [4]. These investigations confirm that MDMX behaves as a crucial negative regulator of p53 in vivo [4]. Recent studies show that increased p53 expression in the placental villi is associated with the placental dysfunction observed in pre-eclampsia and IUGR, suggesting that p53 plays a primary pathogenic role [21]. In contrast, the natural inhibitor of p53, MDMX, is expressed within the HBCs in term pregnancy, likely reflecting a change in the balance of p53 and MDMX with gestation. However, the structural basis of a stress-induced p53 activation remains inadequately known due to a lack of technical means to develop site-specifically phosphorylated MDM2 and MDMX proteins for biochemical and biophysical investigations [20]. Unfortunately, the role of MDMX does not describe the GDM pathophysiology in the human placental unit. Further molecular studies are required to understand the role of MDMX, which is produced by Hofbauer cells (HBCs), in the pathophysiology of GDM on the placenta.

Limitations

We are mindful of the limitations of our research. First, we designed our study on a particularly limited group of patients. In this research, we show that in vitro placenta immunostained HBCs had high MDMX levels. We first concentrated on the information that MDMX gene expression of HBCs has a key position in GDM. We observed that high glucose triggered increased expression of MDMX gene expression. Using immunohistochemical staining, we confirmed the increase in MDMX in response to high glucose in the villous tree of the placenta.

Conclusion

These immunohistochemical studies showed that the MDMX levels in HBCs is significantly lower than in uncomplicated term pregnancies. However, HBC MDMX density was found in all trials. So, there is an important variation in HBCs' MDMX density between GDM and normal gestations. HBCs were identified using immunohistochemistry, with the macrophage marker CD 163. Our investigation sheds light on the fields of molecular researchers on human placenta that can better describe these innate regulatory gene functions. Hofbauer cells are a source of MDMX secretion in the human placenta. Hofbauer cell levels of MDM2 are also increased in GDM. This study found higher levels of MDMX in the Hofbauer cells of the GDM placenta, suggesting the induction of MDMX secretion by GDM interaction. Further studies are needed to define the significance of this relationship.

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References

1. Pantham P, Aye ILMH, Powell TL. Inflammation in maternal obesity and gestational diabetes mellitus. Placenta. 2015 Jul 1;36(7):709–15.
2. Sisino G, Bouckenooghe T, Aurientis S, Fontaine P, Storme L, Vambergue A. Diabetes during pregnancy influences Hofbauer cells, a subtype of placental macrophages, to acquire a pro-inflammatory phenotype. Biochim Biophys Acta, Mol Basis Dis. 2013 Dec 1;1832(12):1959–68.
3. Grigoriadis C, Tympa A, Creatsa M, Bakas P, Liapis A, Kondi-Pafiti A, Creatsas G. Hofbauer cells morphology and density in placentas from normal and pathological gestations. Rev Bras Ginecol e Obstet [Internet]. 2013 Sep [cited 2021 Mar 20];35(9):407–12. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0100-72032013000900005&lng=en&nrm=iso&tlng=en
4. Finch RA, Donoviel DB, Potter D, Shi M, Fan A, Freed DD, Wang CY, Zambrowicz BP, Ramirez-Solis R, Sands AT, Zhang N. mdmx is a negative regulator of p53 activity in vivo. Cancer Res. 2002;62(11):3221–5.
5. Schonkeren D, Van Der Hoorn ML, Khedoe P, Swings G, Van Beelen E, Claas F, Van Kooten C, De Heer E, Scherjon S. Differential distribution and phenotype of decidual macrophages in preeclamptic versus control pregnancies. Am J Pathol. 2011 Feb 1;178(2):709–17.
6. Arlier S, Murk W, Guzeloglu-Kayisli O, Semerci N, Larsen K, Tabak MS, Arici A, Schatz F, Lockwood CJ, Kayisli UA. The extracellular signal-regulated kinase 1/2 triggers angiogenesis in human ectopic endometrial implants by inducing angioblast differentiation and proliferation. Am J Reprod Immunol. 2017;78(6).
7. Kim SH, Lee HW, Kim YH, Koo YH, Chae HD, Kim CH, Lee PR, Kang BM. Down-regulation of p21-activated kinase 1 by progestin and its increased expression in the eutopic endometrium of women with endometriosis. Hum Reprod [Internet]. 2009 [cited 2021 Mar 7];24(5):1133–41. Available from: https://academic.oup.com/humrep/article/24/5/1133/711053
8. Lee KW, Ching SM, Ramachandran V, Yee A, Hoo FK, Chia YC, Wan Sulaiman WA, Suppiah S, Mohamed MH, Veettil SK. Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis. BMC Pregnancy Childbirth [Internet]. 2018 Dec 14 [cited 2021 Mar 1];18(1):1–20. Available from: https://doi.org/10.1186/s12884-018-2131-4
9. Basmaeil YS, Al Subayyil AM, Khatlani T, Bahattab E, Al-Alwan M, Abomaray FM, Kalionis B, Alshabibi MA, Alaskar AS, Abumaree MH. Human chorionic villous mesenchymal stem/stromal cells protect endothelial cells from injury induced by high level of glucose. Stem Cell Res Ther [Internet]. 2018 Sep 21 [cited 2021 Mar 1];9(1):238. Available from: https://pubmed.ncbi.nlm.nih.gov/30241570/
10. Gonzalez E, Jawerbaum A. Diabetic Pregnancies: The Challenge of Developing in a Pro-Inflammatory Environment. Curr Med Chem [Internet]. 2006 Jul 24 [cited 2021 Mar 2];13(18):2127–38. Available from: https://pubmed.ncbi.nlm.nih.gov/16918343/
11. Radaelli T, Varastehpour A, Catalano P, Hauguel-De Mouzon S. Gestational Diabetes Induces Placental Genes for Chronic Stress and Inflammatory Pathways. Diabetes [Internet]. 2003 Dec [cited 2021 Mar 2];52(12):2951–8. Available from: https://pubmed.ncbi.nlm.nih.gov/14633856/
12. Chen B, Ge Y, Wang H, Zhu H, Xu J, Wu Z, Tang S. Expression of mitofusin 2 in placentae of women with gestational diabetes mellitus. J Genet [Internet]. 2018 Dec 1 [cited 2021 Mar 2];97(5):1289–94. Available from: https://link.springer.com/article/10.1007/s12041-018-1030-9
13. Barke TL, Goldstein JA, Sundermann AC, Reddy AP, Linder JE, Correa H, Velez-Edwards DR, Aronoff DM. Gestational diabetes mellitus is associated with increased CD163 expression and iron storage in the placenta. Am J Reprod Immunol [Internet]. 2018 Oct 1 [cited 2021 Mar 2];80(4):e13020. Available from: https://pubmed.ncbi.nlm.nih.gov/29984475/
14. Qi S, Wang X. Decreased expression of miR-185 in serum and placenta of patients with gestational diabetes mellitus. Clin Lab [Internet]. 2019 [cited 2021 Mar 2];65(12):2361–7. Available from: https://pubmed.ncbi.nlm.nih.gov/31850721/
15. Reyes L, Golos TG. Hofbauer cells: Their role in healthy and complicated pregnancy [Internet]. Vol. 9, Frontiers in Immunology. Frontiers Media S.A.; 2018 [cited 2021 Mar 1]. p. 2628. Available from: https://www.frontiersin.org/article/10.3389/fimmu.2018.02628/full
16. Chun CZ, Sood R, Ramchandran R. Vasculogenesis and Angiogenesis. In 2016. p. 77–99.
17. Regnault TRH, Galan HL, Parker TA, Anthony R V. Placental development in normal and compromised pregnancies - A review. Placenta. 2002;23(SUPPL. 1).
18. Zulu MZ, Martinez FO, Gordon S, Gray CM. The Elusive Role of Placental Macrophages: The Hofbauer Cell [Internet]. Vol. 11, Journal of Innate Immunity. S. Karger AG; 2019 [cited 2021 Mar 2]. p. 447–56. Available from: https://pubmed.ncbi.nlm.nih.gov/30970346/
19. Yu J, Zhou Y, Gui J, Li AZ, Su XL, Feng L. Assessment of the number and function of macrophages in the placenta of gestational diabetes mellitus patients. J Huazhong Univ Sci Technol - Med Sci [Internet]. 2013 Oct 1 [cited 2021 Mar 2];33(5):725–9. Available from: https://pubmed.ncbi.nlm.nih.gov/24142727/
20. Chen X, Gohain N, Zhan C, Lu WY, Pazgier M, Lu W. Structural basis of how stress-induced MDMX phosphorylation activates p53. Oncogene. 2016 Apr 14;35(15):1919–25.
21. Heazell AEP, Sumathi GM, Bhatti NR. What investigation is appropriate following maternal perception of reduced fetal movements? J Obstet Gynaecol (Lahore) [Internet]. 2005 Oct 1 [cited 2021 Mar 3];25(7):648–50. Available from: https://pubmed.ncbi.nlm.nih.gov/16263536

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Does vitamin D replacement therapy cause a regression in fatty liver disease? A case control study of comparison of vitamin D and other common therapy modalities

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Ethics Committee Approval
This study is approved by Clinical Ethical Committee of the Yeditepe University (Approval form number: 1267, Approval date: Oct. 27.2016).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Non-alcoholic fatty liver is quite common among modern populations, and simpler methods are researched for its early diagnosis and therapy. Studies are stating that vitamin D deficiency could play a role in the etiopathogenesis of fatty liver. This study aimed to compare the efficacy of metformin and vitamin D therapy in improving fatty liver disease.
Methods: A total of 86 patients with non-alcoholic fatty liver disease were included in this case control study and classified into four groups according to the treatment received. In the study group, 23 patients were using metformin only, and 21 patients were using both metformin and vitamin D. Twenty-one patients were using vitamin D only, and 21 patients were on a diet and an exercise regimen (control group). Weight, BMI, waist circumference, fatty liver index (FLI), HOMA-IR, AST, ALT, GGT, triglyceride parameters were evaluated before and after four weeks of therapy.
Results: There was a significant regression in the fatty liver disease of the patients who used both metformin and vitamin D (FLI-%5, 90 (11.1) P=0.025). Among patients who used only metformin and only vitamin D, the decrease in FLI was not significant (P>0.05); however, FLI was observed to significantly decrease in the control group (-7.30, P=0.018). The serum CRP levels were also observed to significantly decrease in the control, Met and Met-D vit groups (P=0.025, P=0.002, P=0.006, respectively).
Conclusions: The combination of vitamin D and metformin therapy could positively contribute to the improvement of NAFLD in patients with vitamin D deficiency.

Keywords: Fatty liver, Metformin, Vitamin D

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Introduction

Non-alcoholic fatty liver disease (NAFLD) describes the visceral adiposity of the liver without secondary causes (e.g., heavy alcohol use). NAFLD is the known leading cause of cryptogenic cirrhosis [1]. NAFL and nonalcoholic steatohepatitis (NASH) are the two subgroups of NAFLD. NAFL is the adiposis of the liver without significant inflammation signs, while NASH indicates inflammatory steatohepatitis [2].

The pathogenesis of NAFLD is still controversial. The dominant hypothesis is the "double-hit model" suggested by Day and James [3]. The first hit is made by free fatty acids in the liver, accumulation of the triglycerides (TG), insulin resistance (via lipolysis and hyperinsulinemia) and obesity (leptin resistance). Because of these mechanisms, proinflammatory cytokines are secreted and oxidative stress occurs, resulting in a chronic inflammatory state. Both mechanisms make the second hit, which is the progression of the liver damage to steatohepatitis and fibrosis. Insulin resistance is important in NAFLD pathogenesis. The fat content of the liver affects insulin sensitivity more than visceral adiposity [4]. This supports the hypothesis that fatty liver has a direct role in the insulin resistance pathogenesis.

Metformin was first used in the 1950s and is the first step therapy for type 2 diabetes mellitus patients today [5]. It reduces gluconeogenesis in the liver, stimulates glucose uptake at the muscles and increases fatty acid oxidation at the adipose tissue, causing decreased blood glucose [6]. As a result, peripheral insulin sensitivity increases. Metformin prevents adipose tissue growth not only by the direct inhibition of adipogenesis, but also with the modulation of the synthesis or secretion of adipokines [7]. Adiponectin, induced by metformin, stimulates AMPK (AMP-activated protein kinase) directly and prevents hepatic lipid accumulation by increasing free fatty acid oxidation and decreasing its synthesis. In a hepatic steatosis rat model, metformin was shown to downgrade hepatomegaly, hepatic fat accumulation, and cause a regression in elevated liver functions test by reducing hepatic tumor necrosis factor-α (TNF-α) expression [8].

Vitamin D receptors (VDR) are localized in the mononuclear cells in the peripheral blood and in various tissues containing activated T cells in the human body. There are epidemiologic proofs which show that vitamin D deficiency is an independent risk factor for NAFLD [9]. In healthy individuals with normal liver enzymes, low vitamin D levels were strongly and independently associated with NAFLD [10]. Another study shows that the severity of vitamin D deficiency is related with the histopathological severity of NAFLD and the patients with low vitamin D levels are at more advanced stages of liver steatosis and fibrosis [11]. According to the meta-analyses, the probability of an NAFLD patient having vitamin D deficiency is increased 1.26-fold [12].

This study aimed to research the effect of metformin and vitamin D monotherapies and combination therapies.

Materials and methods

This retrospective study was performed on the patients over 18 years of age who visited the Yeditepe University Internal Medicine outpatient clinic between 2015-2018. The ethics approval for the study was obtained from Yeditepe University Clinical Trials Ethical Committee (Approval form number: 1267 / Chairperson: Prof. Dr. T. CELIK) on 27 October 2016.

The study was conducted per the principles of the Declaration of Helsinki, and in compliance with all international and national laws and regulations. Patients gave their written informed consent before any procedures were performed.

The inclusion criteria were as follows:

- Being over 18 years old
- Having mild and moderately elevated levels of liver function tests and/or hepatosteatosis in ultrasonography
- >%50 FLI
- <30 ng/dl vitamin D levels
- Complete anthropometric and laboratory measurements

The exclusion criteria included having any of the following:

- Acute viral hepatitis
- Alcoholic hepatitis
- Autoimmune hepatitis
- Toxic ischemic hepatitis
- A liver mass
- Pancreatitis and/or cholangitis attack
- Steroid, antiepileptic, antiviral, antifungal drug use

The following parameters were evaluated at baseline and at the end of 6 months: Age (year), Height (cm), Weight (kg), waist circumference (cm), vitamin D level (ng/ml), HOMA-IR, CRP (mg/dl), AST (U/l), ALT (U/l), GGT (U/l), and TG (mg/dl). Fatty liver index (FLI) is calculated using waist circumference, triglyceride and GGT and shows the percentage of fat deposition of the liver. It is correlated with hepatosteatosis in ultrasonography. Values below 30% indicate no hepatosteatosis those>60% are significantly indicative of steatosis [13].

Calculation of FLI

$$FLI = \frac{e^{0{,}953*\log(TG)+0{,}139*BMI+0{,}718*\log(GGT)+0{,}053*waist\ circumference-15{,}745}}{1+e^{0{,}953*log(TG)+0{,}139*BMI+0{,}718*log(GGT)+0{,}053*waist\ circumference-15,}} * 100$$ [13]

Creation of study groups

- MetDvit Group: 21 patients using Metformin+ D vitamin
- Met Group: 23 patients using only Metformin
- Dvit Group: 21 patients using only D vitamin
- Control group: 21 patients using neither Metformin, nor D vitamin

Metformin was used at 1000-3000 mg/day for 6 months.

Vitamin D was used at 50000 Units/week for 4-6 weeks.

Statistical analysis

Minimum-maximum, mean and standard deviation values were included in descriptive statistics. The distribution of the variables was assessed by a coefficient of variation, Skewness – Kurtosis tests, histogram, detrended plot, and the normality test of Kolmogorov-Smirnov. The data were considered parametric if three or more tests mentioned above were positive.

The investigators used the Post Hoc test to identify if the sample size was sufficient. Then, the data were grouped into Control group ($G_{control}$), Dvit group (G_{Dvit}), Metformin group

(G_{Met}) and Metformin and Dvit groups ($G_{Met\text{-}Dvit}$) before and after the treatment. The groups were not compared with each other according to all treatment outcomes, because the study was retrospective. The groups were not randomized, and power analysis was not performed. Even the control group's outcomes were noted from the files of the patients examined in the Internal Medicine Department. Therefore, the investigators performed a One Way Anova test to all pre-treatment values. The non-differing data were selected, and their outcomes after the treatment were compared between the groups with a Mann Whitney U test.

The values obtained before and after the treatment were compared within the groups with a paired sample t-test or Wilcoxon test. The post-treatment data were evaluated for correlation with Pearson or Spearman Correlation Tests. $P<0.012$ was considered significant in the Post Hoc Bonferroni test, and $P<0.05$ was considered significant in others.

Results

Forty-four (51%) patients were male, and forty-two (49%) were female. The mean age and height of the participants were 41.2 (11.4) years, and 170.8 (9.3) cm, respectively.

The demographic data and the pre- and post-treatment values are shown in Table 1.

Table 1: Descriptive pre-treatment data

Pre-treatment data	Female Mean (SD) (n)	Male Mean (SD) (n)	Overall Mean (SD) (n)
Age (years)	41.5 (11.5)(42)	41.6 (11.6) (44)	41.2 (11.4) (86)
Height (cm)	163.7(5.1) (42)	177.7(5.7) (44)	170.8 (9.3) (86)
Weight (kg)	78.4(13.7) (42)	94.5(14.5) (44)	86.5 (16.2) (86)
BMI (kg/m2)	29.2 (4.9) (42)	30.0 (4.7) (44)	29.5(4.8) (86)
Waist C. (cm)	98.4(13.1) (42)	105.4(9.8) (44)	102.0 (12.0) (86)
D vit (ng/ml)	16.5(8.4) (42)	18.0 (7.7) (44)	17.8(7.5) (86)
FLI (%)	53.2(24.1) (42)	73.4(18.1) (44)	63.3(24.1) (86)
HOMA IR	4.0(2.3) (39)	4.5(2.5) (37)	4.2(2.3) (76)
CRP (mg/dl)	3.5(4.8) (34)	3.9(3.2) (40)	3.7(3.5) (74)
ALT (U/l)	22.1(9.3) (42)	54.2(41.6) (43)	38.1(36.1) (85)
AST (U/l)	21.9(6.9) (42)	33.2(20.6 (42)	27.6(16.5) (84)
GGT (U/l)	22.7(13.8) (42)	52.3(52.5) (44)	37.4(41.1) (86)
TG (mg/dl)	140.2(52.8) (42)	198.7(118.0)(44)	171.5(98.8) (86)

Within-group comparison

$G_{control}$: The decrease in TG and FLI and the increase in vitamin D following treatment were significant ($P=0.034$, $P=0.013$, and $P=0.01$). There were no significant differences between morphological (weight, BMI, waist circumference), or laboratory values (IR, CRP, AST, ALT, GGT) between the pre- and post-treatment periods.

G_{Dvit}: Vitamin D had significantly increased after the treatment ($P=0.001$). There were no significant differences between the morphological (weight, BMI, waist circumference), or laboratory values (IR, CRP, AST, ALT, GGT, TG) and FLI between the pre- and post-treatment periods.

G_{Met}: The decrease in morphological data (weight, BMI, waist circumference, $P=0.013$, $P=0.019$, and $P=0.008$, respectively), along with that in HOMA-IR values ($P=0.02$) was significant, while the increase of vitamin D and the decrease of CRP, AST, ALT, GGT, and TG, and FLI were not.

$G_{Met\text{-}Dvit}$: The decrease in morphological data (weight, BMI, waist circumference, $P=0.07$, $P=0.016$, and $P=0.011$, respectively), the increase in vitamin D, and the decrease in HOMA-IR ($P<0.001$, and $P=0.015$ respectively), and the decrease in FLI were significant ($P=0.025$). The decrease in CRP, AST, ALT, GGT, and TG were insignificant (Table 2).

Inter-group comparison

The groups were similar in terms of pre-treatment CRP, AST, ALT, GGT, TG values ($P>0.05$). Therefore, they were included in the intra-group comparison tests (Table 3).

Table 3: Inter-group comparison of post-treatment CRP, ALT, AST, GGT, and TG

Comparable Data	Group-Group (n-n) Mean(SD)	Z	*P*-value
CRP-at	$G_{control}$-$G_{Dvit\ (n:21-n:21)}$ (6.2(8.8) - 2.3(2.5))	-2.245	0.025*
	$G_{control}$-$G_{Met\ (n:21-n:23)}$ (6.2(8.8) - 5.1(3.9))	-0.554	0.579
	$G_{control}$-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (6.2(8.8) - 2.3(2.1))	-1.935	0.053
	G_{Dvit}-$G_{Met\ (n:21-n:23)}$ (2.3(2.5) - 5.1(3.9))	-3.039	0.002**
	G_{Dvit}-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (2.3(2.5) - 2.3(2.1))	-0.080	0.936
	G_{Met}-$G_{Met\text{-}Dvit\ (n:23-n:21)}$ (5.1(3.9) - 2.3(2.1))	-2.708	0.006**
ALT-at	$G_{control}$-$G_{Dvit\ (n:21-n:21)}$ (49.8(48.4) - 33.9(31))	-0.793	0.118
	$G_{control}$-$G_{Met(n:21-n:23)}$ (49.8(48.4) - 36.9(17.5))	-0.231	0.817
	$G_{control}$-$G_{Met\text{-}Dvit(n:21-n:21)}$ (49.8(48.4) - 31.2(22.2))	-0.849	0.396
	G_{Dvit}-$G_{Met\ (n:21-n:23)}$ (33.9(31) - 36.9(17.5))	-1.823	0.068
	G_{Dvit}-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (33.9(31) - 31.2(22.2))	-0.170	0.865
	G_{Met}-$G_{Met\text{-}Dvit\ (n:23-n:21)}$ (36.9(17.5) - 31.2(22.2))	-1.526	0.127
AST-at	$G_{control}$-$G_{Dvit\ (n:21-n:21)}$ (30.6(16.5) - 24(10.6))	-1.563	0.428
	$G_{control}$-$G_{Met\ (n:21-n:23)}$ (30.6(16.5) - 28.6(11.7))	-0.183	0.855
	$G_{control}$-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (30.6(16.5) - 34.5(44.7))	-0.862	0.389
	G_{Dvit}-$G_{Met\ (n:21-n:23)}$ (24(10.6) - 28.6(11.7))	-2.155	0.031*
	G_{Dvit}-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (24(10.6) - 34.58(44.7))	-0.562	0.574
	G_{Met}-$G_{Met\text{-}Dvit\ (n:23-n:21)}$ (28.6(11.7) - 34.5(44.7))	-1.174	0.240
GGT-at	$G_{control}$-$G_{Dvit\ (n:21-n:21)}$ (33.9(22.4) - 30.4(23.8))	-0.667	0.505
	$G_{control}$-$G_{Met\ (n:21-n:23)}$ (33.9(22.4) - 48.6(67.9))	-0.400	0.689
	$G_{control}$-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (33.9(22.4) - 28(24))	-1.007	0.314
	G_{Dvit}-$G_{Met\ (n:21-n:23)}$ (30.4(23.8) - 48.6(67.9))	-1.070	0.285
	G_{Dvit}-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (30.4(23.8) - 28(242))	-0.290	0.772
	G_{Met}-$G_{Met\text{-}Dvit\ (n:23-n:21)}$ (48.6(67.9)- 28(24))	-1.835	0.067
TG-at	$G_{control}$-$G_{Dvit\ (n:21-n:21)}$ (124.7(68.9) - 139.9(72.5))	-1.032	0.302
	$G_{control}$-$G_{Met\ (n:21-n:23)}$ (124.7(68.9) - 168(625))	-2.503	0.012*
	$G_{control}$-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (124.7(68.9) - 72.7(131.5))	-1.887	0.059
	G_{Dvit}-$G_{Met\ (n:21-n:23)}$ (139.9(72.5) - 168(62))	-1.821	0.069
	G_{Dvit}-$G_{Met\text{-}Dvit\ (n:21-n:21)}$ (139.9(72.5) - 172.7(131.5))	-1.120	0.263
	G_{Met}-$G_{Met\text{-}Dvit\ (n:23-n:21)}$ (168(62) - 172.7(131.5))	-0.729	0.466

* $P<0.05$, ** $P<0.01$, Mann Whitney U test

Table 2: Inter-group comparison

	$G_{control}$ (n:21)			G_{Dvit} (n:21)			G_{Met} (n:23)			$G_{Met\text{-}Dvit}$ (n:21)		
	Before Mean(SD)	After Mean(SD)	*P*-value	Before Mean(SD)	After Mean(SD)	*P*-value	Before Mean(SD)	After Mean(SD)	*P*-value	Before Mean(SD)	After Mean(SD)	*P*-value
Weight	81.1(10.5)	80.4(9.8)	0.4[p]	76.7(11.6)	76.8(11.2)	0.79[p]	91.2(16.1)	88.6(16.4)	0.012[*p]	95.6(18.7)	93(17.9)	0.007**[p]
BMI	27.95(2.8)	28.2(2.6)	0.37[w]	26.7(3.5)	26.8(3.5)	0.76[p]	30.7(4.5)	29.8(4.5)	0.009**[w]	32.3(6)	31.1(5.3)	0.010*[w]
Wcirc	100(9.9)	98.2(9.3)	0.06[p]	94.4(7.5)	94.5(7.7)	0.93[p]	106.1(11)	103.6(10.2)	0.034*[p]	107.2(14.3)	104.3(13.2)	0.010*[w]
Dvit	20.5(7.5)	24.8(9.4)	0.01*[w]	13.9(5.7)	29.1(13.8)	<0.001***[p]	18.8(6.3)	21.9(8.6)	0.08[w]	17.6(9)	27.8(9.5)	<0.001***[p]
FLI	57.4(23.4)	50.1(24.8)	0.018*[p]	50.6(21.9)	46(22.1)	0.18[p]	73.4(22.9)	68.9(22.9)	0.09[p]	72.2(22.5)	66.3(26.9)	0.025*[p]
HOMA-IR	3.4(1.1)	3.2(1.2)	0.38[w]	2.8(0.9)	2.7(0.9)	0.90[w]	5.6(3.1)	3.5(1.6)	0.020*[w]	5.2(2.8)	3.9(1.9)	0.02*[w]
CRP	4.0(4.2)	3.7(3.8)	0.66[w]	2.7(3.1)	2.3(2.7)	0.60[w]	4.8(3.5)	4.6(3.4)	0.90[w]	2.8(2.8)	1.9(1.6)	0.21[w]
ALT	46.4(31.8)	46.7(45)	0.84[w]	32.3(23.5)	33.9(31)	0.86[w]	40.5(21.2)	36.9(17.5)	0.58[w]	34.1(23.4)	31.2(22.2)	0.41[w]
AST	32.4(28.9)	29.3(16.9)	0.18[w]	23.2(7.8)	24(10.6)	0.89[w]	28.8(9.3)	29.1(11.8)	0.81[w]	25.9(11)	24.5(9.8)	0.36[w]
GGT	34.4(23.2)	33.1(24.2)	0.75[p]	33.9(23.8)	30.4(23.8)	0.25[p]	50.7(70)	48.6(67.9)	0.24[w]	28(24)	29.3(21.9)	0.71[w]
TG	150.8(114.1)	120(64.9)	0.034*[w]	166.3(72.7)	139.9(72.5)	0.14[w]	180.3(53.9)	168(62)	0.36[p]	172.7(131.5)	181.8(139)	0.40[w]

* $P<0.05$, ** $P<0.01$, *** $P<0.001$, p: Paired sample t test, w: Wilcoxon test

The post-treatment decrease in the CRP level of $\underline{G_{Dvit}}$ was significant (P=0.025) compared with that in the $G_{control}$, just as the post-treatment increase of TG in $\underline{G_{Met}}$ (P=0.012) compared to the $G_{control}$. The decrease in the CRP and TG levels of $G_{Met\text{-}Dvit}$ groups were insignificant (P=0.053, and P=0.059 respectively) compared with those in the $G_{control}$. The post-treatment decrease in the CRP and AST levels of $\underline{G_{Dvit}}$ were significant (P=0.002, and P=0.031, respectively) compared to those in $\underline{G_{Met}}$. The post-treatment data of $\underline{G_{Dvit}}$ and $\underline{G_{Met\text{-}Dvit}}$ were similar. The post-treatment decrease in the CRP level of $\underline{G_{Met\text{-}Dvit}}$ was significant (P=0.006) compared to that of $\underline{G_{Met}}$ (Table 4). The laboratory values not mentioned above yielded insignificant results in the intra-group analysis.

Table 4: Inter-group comparison of post-treatment CRP

CRP-at Groups(Mean (SD))	G_{Dvit}	G_{Met}	$G_{Met\text{-}Dvit}$ Mean (SD) 2.3(2.1)
	P-value	*P*-value	*P*-value
$G_{control}$ (6.2(8.8))	0.025*	0.579	0.053
G_{Dvit} (2.3(2.5))		0.002**	0.936
G_{Met} (5.1(3.9))			0.006**

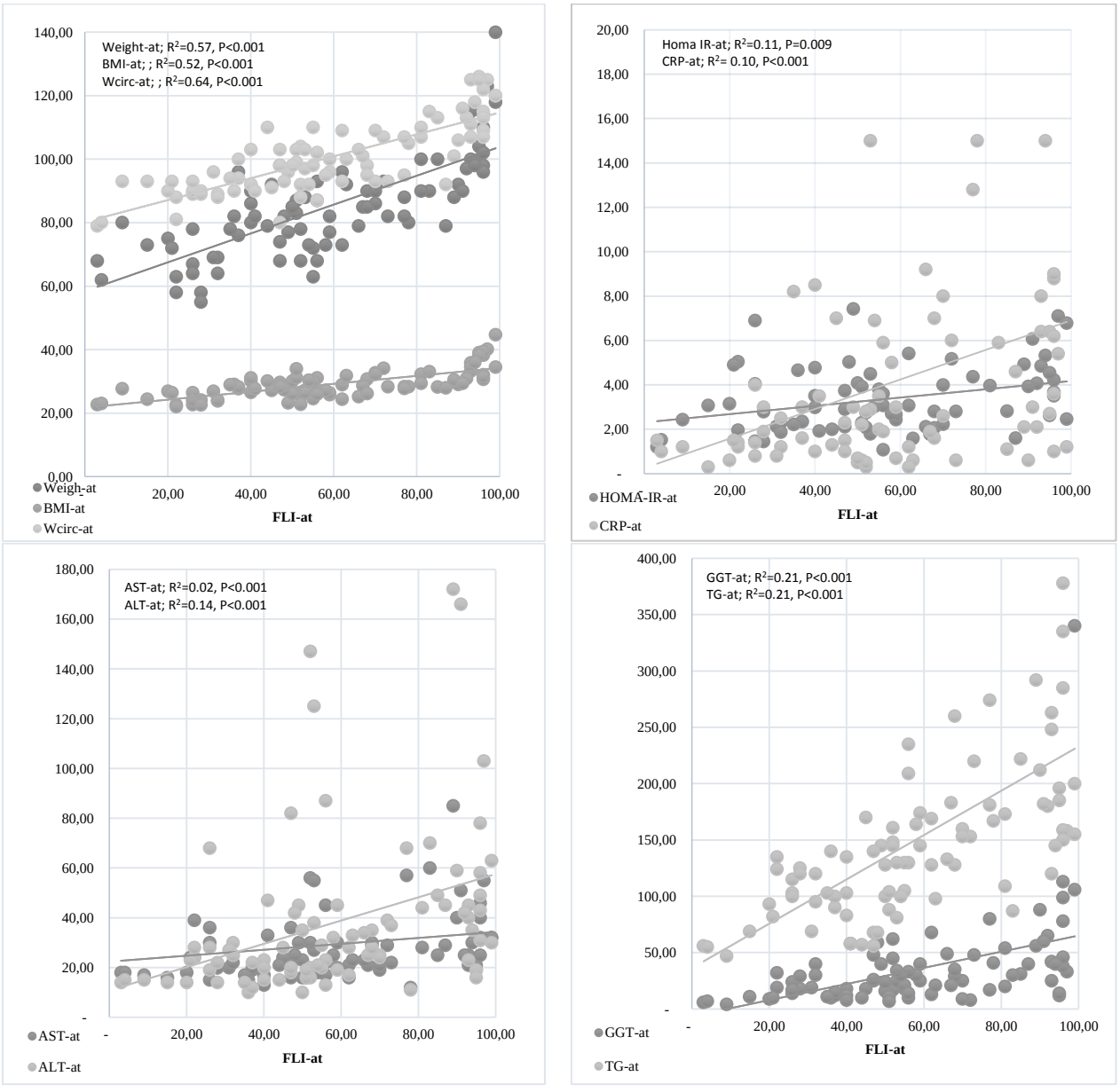
* P<0.05, **P<0.01, Mann Whitney U test

Correlations between post-treatment outcomes

A positive correlation was found between FLI, morphological outcomes (weight, BMI, waist circumference) and FLI (P<0.001, P<0.001, and P<0.001 respectively), and various post-treatment laboratory values (HOMA-IR, CRP, AST, ALT, GGT, TG) (P=0.009, P<0.001, P<0.001, P<0.001, P<0.001, and P<0.001 respectively). Post-treatment vitamin D was not correlated with FLI, while it was positively correlated with waist circumference (P=0.019) (Figure 1).

HOMA-IR was positively correlated with the morphological outcomes (weight, BMI, waist circumference) and the ALT level after treatment (P=0.005, P=0.013, P=0.007, and P=0.027, respectively). Post-treatment CRP was also positively correlated with the morphological outcomes (weight, BMI, waist circumference) (P=0.016, P=0.004, and P=0.062, respectively) and the ALT, AST, GGT, TG level after the treatment (P=0.012, P=0.029, P=0.026, and P=0.010, respectively).

Figure 1: Correlation of FLI with treatment outcomes



Discussion

This is the first study investigating the therapeutic efficacy of vitamin D alone and in combination with metformin in non-alcoholic liver fattening. We used the "Fatty Liver Index" for liver fattening and treatment outcomes were evaluated with FLI, laboratory and anthropometric parameters. The most interesting result of this study is that the FLI decrease was significant in the control group, which did not use metformin or vitamin D, and in the $G_{Met\text{-}Dvit}$. According to the rest of our results, it can be stated that vitamin D has a reductive pleotropic effect on the fatty liver when combined with Metformin.

CRP is an inflammation parameter, and it shows the pleotropic effect better than FLI, because the FLI is affected by TG, BMI and waist circumference. The decrease in CRP levels is another striking result of this study. In the Dvit and Met-Dvit Groups, CRP levels were significantly decreased after therapy.

The first study on the relationship between fatty liver and vitamin D was performed on 262 patients with metabolic syndrome at Sapienz University in 2011. Vitamin D deficiency was more common in fatty liver patients, and FLI and 25 (OH) vitamin D levels were negatively correlated [10]. In this study, there was no correlation between vitamin D and FLI, the probable reason being the inclusion of patients with low vitamin D levels only.

In another study conducted on 82 NAFLD cases, the changes in the fat parameters with exercise and diet were investigated, and despite the reduction in calories and vitamin D intake an increment was observed in serum 25-hydroxy vitamin D levels of the NAFLD patients. This resulted in an improvement in serum vitamin D levels and metabolic parameters without vitamin D supplementation in NAFLD patients [14].

Another study investigated the effects of different doses of Metformin on liver biochemistry (aminotransferases), histology and metabolic syndrome [15]. In 2001, Marchesini et al. [16] performed a non-randomized study using metformin (administered for 4 months, 1.5g/day) in 20 patients with non-diabetic NASH and found a significant improvement in insulin resistance, aminotransferase levels, liver morphology and volume in the treated group compared to the diet group. Histologic recovery could not be evaluated because biopsy was not performed. In another study on 17 non-diabetic patients who received metformin, the effect of metformin (twice a day 850 mg) vs. dieting on the fatty liver was investigated by biopsy and no histologic difference was detected. However, ALT, AST, BMI, and insulin resistance markers significantly improved when compared with the control group [17]. In this study, there was no change in liver enzymes or cholestasis tests but BMI, waist circumference and HOMA-IR results decreased in the Met group, while Vitamin D did not increase.

Metformin was compared with placebo among NAFLD patients in a meta-analysis including 417 cases evaluating 4-12 months of follow-up results. In the treated group, there were significant improvements in ALT (-8.12 U/I), AST (-4.52 U/I), HOMA-IR (-0.61), and BMI (-0.82 kg/m2), and insignificant improvements in histological response (steatosis, inflammation, hepatocellular ballooning, and fibrosis). Current information shows that metformin improves liver function, HOMA-IR, and BMI to some extent, but does not improve histological response in NAFLD patients [18].

In this study, HOMA-IR was significantly reduced by 2.10 in the Met group, by 1.30 in the MetDvit group, and insignificantly reduced by -0.121 in the Dvit group. In the control group, however, HOMA-IR did not change. Reduction in AST, ALT, GGT levels were significant in none of the groups. This might be due to the fact that initially, the baseline values were not high.

Although vitamin D was not administered to the control group, Fatty Liver Index and TG were decreased. These changes could be explained by doing more exercise, more sunbathing and adaptation to diet in the control group patients, who focused mostly on a lifestyle change.

All findings considered, it is safe to state that a combination of Metformin and vitamin D is more effective on liver fattening than single therapies. Also, various new peptide hormones, for example, preptin, can be associated with vitamin D and insulin resistance and cause NASH [19].

Limitations

The low number of cases prevented strong interpretations of the results. Also, due to the retrospective and single center nature of the study, no randomization could be performed. Further larger, prospective and randomized controlled trials evaluating histological outcomes are needed to shed light on the effect of metformin and vitamin D on fatty liver disease.

Conclusion

Our study showed that a combination of vitamin D and metformin could positively contribute to the regression of fatty liver. Clinical trials with metformin give hope in managing liver diseases by improving the metabolic features of fatty liver disease.

References

1. Caldwell SH, Oelsner DH, Iezzoni JC, Hespenheide EE, Battle EH, Driscoll CJ. Cryptogenic cirrhosis: clinical characterization and risk factors for underlying disease. Hepatology. 1999;29:664-9.
2. Ludwig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. Mayo Clin Proc. 1980;55:434-8.
3. Day CP, James OF. Steatohepatitis: a tale of two "hits"? Gastroenterology. 1998;114:842–5.
4. Stefan N, Kantartzis K, Machann J, Schick F, Thamer C, Rittig K, et al. Identification and characterization of metabolically benign obesity in humans. Arch Intern Med. 2008;168(15):1609–16
5. He L, Sabet A, Djedjos S, Miller R, Sun X, Hussain MA, et al. Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. Cell. 2009;137(4):635–46.
6. Turlin B, Mendler MH, Moirand R, Guyader D, Guillygomarc'h A, Deugnier Y. Histologic features of the liver in insulin resistance-associated iron overload. A study of 139 patients. Am J Clin Pathol. 2001;116:263.
7. Huypens P, Quartier E, Pipeleers D, Van De Casteele M. Metformin reduces adiponectin protein expression and release in 3T3- L1 adipocytes involving activation of AMP activated protein kinase. Eur J Pharmacol. 2005;518:90– 5.
8. Lin HZ, Yang SQ, Chuckaree C, Kuhajda F, Ronnet G, Diehl AM. Metformin reverses fatty liver disease in obese, leptin deficient mice. Nat Med. 2000;6:998-1003.
9. Dasarathy J, Periyalwar P, Allampati S, Bhinder V, Hawkins C, Brandt P, et al. Hypovitaminosis D is associated with increased whole-body fat mass and greater severity of non-alcoholic fatty liver disease. Liver Int. 2014;34:118–27. doi: 10.1111/liv.12312.
10. Barchetta I, Angelico F, Ben MD, Baroni MG, Pozzili P, Morini S, et al. Strong association between non-alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. BMC Med. 2011;9:85.
11. Targher G, Bertolini L, Scala L, et al Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis. 2007;17(7):517–24. doi: 10.1016/j.numecd.2006.04.002.
12. Eliades M, Spyrou E, Agrawal N, Lazo M, Brancati FL, Potter JJ, et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease Alimentary Pharmacology and Therapeutics. 2013;38:246-54.
13. Bedogni G, Bellentani S, Miglioli L, Massuti F, Passalaqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006;6:33.
14. Lee SM, Jun DW, Cho YK, Jang KS, Vitamin D deficiency in non-alcoholic fatty liver disease: The chicken or the egg? Clin Nutr. 2015 Epub ahead of print.
15. Cowin GJ, Jonsson JR, Bauer JD, Ash S, Ali A, Osland EJ, et.al. Magnetic resonance imaging and spectroscopy for monitoring liver steatosis. J Magn Reson Imaging. 2008;28(4):937–45.
16. Marchesini G, Brizi M, Bianchi G, Tomassetti S, Zoli M, Melchianda N. Metformin in non-alcoholic steatohepatitis. Lancet. 2001 Sep 15:358(9285):893-4. doi: 10.1016/s0140-6736(01)06042-1.

17. Abrams GA, Kunde SS, Lazenby AJ, Clements RH. Portal fibrosis and hepatic steatosis in morbidly obese subjects: A spectrum of non-alcoholic fatty liver disease. Hepatology. 2004;40:475– 83.
18. Li Y, Liu L, Wang B, Wang J, Chen D. Metformin in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Biomedical reports. 2013;1(1):57–64.
19. Arğun D, Basim P, Uysal BB, Argun F. Association of circulating preptin with non-alcoholic fatty liver disease: A case-control study. J Surg Med. 2021;5(6):628-32.

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The effects of capsular repair on quality of life after hip arthroplasty with the anterolateral approach

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Ethics Committee Approval
The scientific ethics committee of Ahi Evran University approved the study with the number 2018-07/68, dated 10.04.2018.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Hip fractures, commonly observed worldwide, cause severe functional problems and pose an economic burden. This study investigated the effects of different surgical approaches of joint capsule repair on morbidity and mortality and aimed to increase the quality of life after surgery with the most proper treatment option.

Methods: This prospective case-control study was conducted on 186 patients over 65 years of age admitted to our clinic from 2006 to 2012 for displaced femoral neck fracture. All patients were treated via a hemiarthroplasty. The patients (66 males, 110 females with an overall mean age of 80.43 years (70-90)) were followed up regularly. All patients were divided into two groups: Group 1 was treated with capsular repair, and Group 2 without. The groups were compared in terms of pre-and peri-operative data, demographics, concomitant diseases, post-operative complications, mortality rates, pain level, and hip scores. Hospitalization time, average surgical duration, and time from fracture to the operation were also noted.

Results: We found no significant differences between the groups in terms of surgery preferences ($P>0.05$). The survival of patients was significantly higher, blood loss was significantly less, and perioperative mortality rates were insignificantly lower in the noncapsular repair group ($P=0.005$, $P=0.015$, and $P=0.515$, respectively).

Conclusion: The use of capsule repair during hip hemiarthroplasty in patients over 65 years of age had no negative impact on mortality or morbidity. Surgical preference changes during hip arthroplasty procedures are essential.

Keywords: Gestational diabetes mellitus, Mouse double minute X expression, Hofbauer cells, Placenta

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Introduction

Hip fractures are a significant public health problem and can lead to disability, reduced quality of life, and increased mortality. In general, hip fractures affect around 1.5 million people per year worldwide and mainly occur in the elderly [1]. There are different treatment choices. Hip arthroplasty (HA) is one of the most preferred orthopaedic surgical operations due to its high success rate, early restoration, and low procedure-related morbidity. It contributes to early ambulation and good functional recovery. It can control the pain of patients and improve function and limb deformity. While reaching the hip joint in surgical treatment, approaches differ according to surgical experience. In this regard, the anterolateral and posterolateral approaches are frequently used to reach the hip joint. In addition to lower dislocation rates, the anterolateral approach provides particularly good acetabulum visualization. However, patients are more likely to have lameness due to the weakness of the gluteus medius.

HA with the posterior approach has the advantages of less soft tissue injury, shorter operation time, less bleeding volume, and faster recovery. At present, the posterior approach for hip arthroplasty is more commonly used than the anterior approach [2]. However, complications after the posterior approach are higher than those in the anterior approach, especially early post-operative dislocation.

Most of these patients have severe cardiovascular, respiratory, and hematopoietic system diseases. One of the most common complications in patients during the peri-operative period is anaemia treated primarily by blood transfusion. In the literature, many studies found that 30% to 70% of the elderly patients with hip fractures needed a peri-operative allogeneic blood transfusion [3, 4].

The hip joint capsule stabilizes the hip joint and the lower extremity; however, it is incised and frequently excised during hip arthroplasty. Depending on the surgical method, whether capsule repair is performed is an important technical detail. However, its effect on joint proprioception and other risk factors is still controversial [5].

The purpose of this controlled trial was to compare the results of arthroplasty using the anterior approach, investigate whether the rates of post-operative morbidity and mortality differ between the two groups, and whether the type of capsule repair affects the patient's activity scoring.

Materials and methods

Study population

A total of 186 hip fracture patients were treated with an arthroplasty from 2006 to 2012. The same surgeon group undertook all HA procedures in the anterolateral approach. Medical data were collected retrospectively. The patients participating in the study were divided into two groups based on the capsular repair. The first group comprised 95 hips, whose anterior capsule was excised during surgery, while the second group included 91 hips.

The surgical technique used for the two groups of patients, the standard anterolateral approach, was identical apart from the means of managing the anterior capsule. During this surgical procedure, the rectus femoris muscles and piriformis tendon were split in the insertion site on the trochanter and carefully separated from the posterior capsule. The demographic variables, used medications and comorbidities, types of fractures, hospitalization and surgery dates, time and cause of death, as well as the seniority levels of the operating surgeon and anesthesiologist were noted. In addition, patient age, sex, and pre-fracture ambulatory status, and their number of comorbidities were all retrieved. The general state of health was defined by the number of significant comorbidities, which are diabetes mellitus, congestive heart failure, cardiac arrhythmias, ischemic heart disease, previous cerebrovascular accidents, renal disease, Parkinson's disease, hypertension, chronic obstructive pulmonary disease, and anticoagulation therapy. Patients' ambulatory status was determined using the Barthel Index of Activities of Daily Living and the Harris Hip Score. Post-operative pain was assessed using the Likert pain score with responses ranging from 0 to 10. Additionally, peri-operative data and post-operative complications were noted. The regional scientific ethics committee of Ahi Evran University approved the study with the number 2018-07/68 on 10.04.2018.

Surgical technique

The same group of doctors performed all surgeries. The patients were divided into repair and dissection groups based on the articular capsule repair status during surgery. While the patient was lying in supine position on the edge of the large trochanter table, a Watson-Jones incision was performed. The muscles were separated by dissection, and the capsule was opened longitudinally along the femoral neck.

Using the "H" -shaped articular capsule incision, based on cutting the hip articular capsule throughout the direction of the femoral neck, the articular capsule was opened on both sides to reach the femoral head, femoral neck, and upper edge of the acetabulum. The stability of the hip joint was assessed in both groups, with the hip joint at 45 degrees of external rotation or internal rotation or 90 degrees of flexion. For repair, the articular capsule flaps were encircled to the front of the femoral neck and appropriately overlapped with a 2/0 vicryl suture. Smith and Nephew uncemented Hydroxyapatite-coated biotype total hip prostheses were used.

Postop care protocol

The patients were mobilized with two canes and allowed full weight-bearing immediately postoperatively, with no movement restrictions. They received the standard rehabilitation care of the department.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test quantitative variables for normality of distribution. Among the normally distributed quantitative variables, the differences between the groups were assessed with the independent t-test. Conversely, the analysis of non-normally distributed quantitative variables was performed with the Mann-Whitney U test. Qualitative variables were analyzed with the chi-square and Fisher's Exact tests. Descriptive statistics of normally distributed continuous data were presented as mean (SD), and descriptive statistics of non-normally distributed data, with median (min-max). Observation numbers (N) are given for qualitative variables. A *P*-value of 0.05 was considered

significant. Statistical analysis of the study was performed with the SPSS v21.0 software for Windows.

Results

A total of 1050 registry entries fulfilling the inclusion criteria were identified and included in the study. The study was conducted with 186 patients, of which 66 (35.5%) were male, and 120 (64.5%) were female (n = 120/186). The overall mean age was 80.43 (7.47) years. Their mean length of hospital stay after the operation was 3 (1-11) days.

In this study, capsule repair was performed in 95 patients, while 91 were repaired with the noncapsular method. Of the 186 patients included in the study, 87 were operated on the right and 99 on the left. Descriptive information of variables from the patients, classified based on their operation methods, is given in Table 1.

Table 1: Demographic features of the patients underwent hip arthroplasty

Variables	Capsule Repaired Group 1 (n=95) mean (SD)	Non-capsule Repaired Group 2 (n=91) mean (SD)	*P*-value
Gender			
male	36	30	0.687
female	59	61	
Age	81.46 (7.63)	79.36 (7.18)	0.055
Dementia			
Yes	4	3	0.919
No	91	86	
BMI	26.46 (4.24)	26.62 (4.50)	0.804
Fracture Type			
Collum	53	53	0.855
Trochanter	42	36	
Side			
Right	45	43	0.980
Left	50	48	

The effects of capsule repair on the variables during and after the surgery, such as intraoperative blood loss, transfusion, Likert pain scale, Harris hip score, and walking aid, were evaluated and statistically illustrated in Table 2.

Forty-one patients (22.04%) in Group 1, and 35 patients (18.81%) in Group 2 had died by the end of the follow-up period, and 13 (6.98%) of 186 patients died in the hospital. The mortality rates of the patients who had surgery are given below (Table 3).

Cox regression analysis revealed that among the patient's age, gender, the surgeon's experience, and surgical site, only the age of the patients was a significant risk factor for mortality. The HR ratio, which indicates the increased risk of mortality caused by a one-unit increase in the patient's age, was 1.07 (P<0.001). The HR ratio for gender was 1.528. Men were found at 1.528 times higher risk of periodic death (P=0.066). The side of the operated hip was not a significant parameter for mortality outcome (P=0.637). The HR ratio for the side of the operated hip was 1.117. Again, the surgeon's experience (HR: 1.016) was not a significant risk factor for survival (P=0.532). The result of the analysis is given in Table 4.

The mean survival of patients who did and did not undergo capsule repair were 34.50 (1-82) months, and 45 (1-86) months, respectively. According to these results, the survival of patients without capsule repair was higher than that of patients who underwent a capsule repair. However, based on the Wilcoxon (Gehan) value calculated for two different surgery preferences, the Kaplan-Meier test result, and the Log Rank (Mantel-Cox) value were insignificant (P=0.209 and P=0.532, respectively) (Figure 1).

Table 2: The comparison of surgery outcomes between the study groups

Variables	Capsule repaired (Group 1) (n=95) range	Non-capsule repaired (Group 2) (n=91) range	*P*-value
Intraoperative blood loss (cc)	450(200-700)	400(250-700)	0.015
transfusion (Unit)			
0	18	35	
1	18	25	0.000
2	36	27	
3	19	2	
4	4	2	
Mortality			
Yes	41	35	0.515
No	54	56	
Time-until-death (months)	34.5 (1-82)	45(1-86)	0.695
Likert pain scale			
0	12	7	
1	23	39	0.057
2	6	35	
3	14	10	
Harris hip score	78(0-94)	80(0-96)	0.005
Walking aid			
Yes	26	2	0.878
No	69	67	

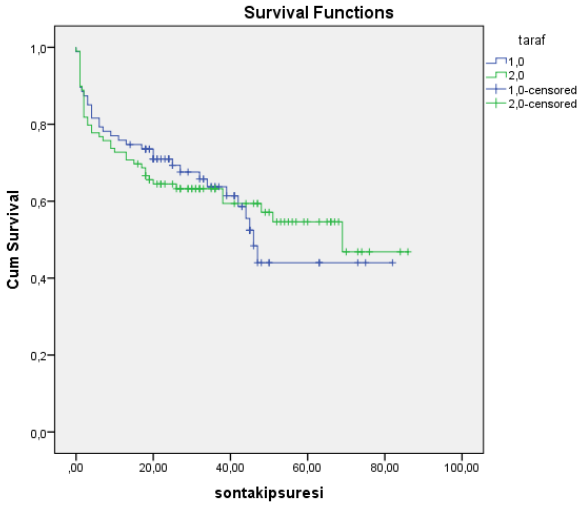
Table 3: The mortality rate after discharge

Time point (months)	Right	Left	Total
0-12	21	27	48
13-24	4	8	12
25-36	4	1	5
37-48	6	2	8
>49	0	3	3
Total	35	41	76

Table 4: Cox regression to analyze factors that impact survival after the surgery

	B	SE	Wald	P-value	HR	95.0% CI for HR	
						Lower	Upper
Gender	0.424	0.234	3.297	0.066	1.528	0.967	2.415
Age	0.075	0.018	17.889	<0.001	1.078	1.041	1.116
Side	0.111	0.235	0.222	0.637	1.117	0.705	1.770
Surgeon experience	0.016	0.026	0.390	0.532	1.016	0.966	1.069

Figure 1: Comparison the surgery techniques according to surival after the surgery (P=0.532) (Kaplan Meier curves)



Discussion

Fractures of the hip are common in older adults. Osteoporosis, comorbidities, and increased levels of minor trauma increase the incidence and complicate the treatment of such fractures [6]. Hip replacement surgery, total or partial arthroplasty, is a currently accomplished therapeutic modality that encourages repairing the damaged hips. In addition, under favorable conditions, surgical approaches for hip arthroplasty should attain capsule repairing as well. The HA method has recently gained popularity in improving the quality of capsule repair and assuring strength in the long term [5].

Many surgical approaches for total HA aim to maximize capsule preservation and/or repair capsule incisions, while others excise the capsule to improve exposure. Capsule preservation

and repair can help lower dislocation rates and maintain the defenses of the native hip against hypermobility [5, 7].

Capsule repair combined with HA allows the ligaments to wrap and stretch around the surface of the head of the repaired capsule's leash in a range of motion identical to the native hip. After follow-up, the combination of capsule repair and HA yields better short-term results than total HA despite the age of the patients, as is reported in the study of Zang et al. and Lu et al. Capsule protection and repair help prevent early post-operative hip joint dislocation and positively affect hip biomechanics [8, 9].

The most important result of the present study was elucidating the slight effects of HA on mortality and quality of life in treating hip fractures. This study also examined the impact of different surgical approaches on mid-term clinical results.

In this study conducted with 186 patients, blood loss was higher in patients who underwent capsule repair compared to those who did not.

Common causes of failure in surgical applications are the treatment of osteonecrosis and delayed hip arthroplasty. Owing to minimized muscle damage, decreased blood loss, and early functional recovery, the anterior approach is popularized and currently preferred by 10% of orthopedic surgeons performing HA [10]. It is known that older patients do not tolerate re-do surgery, therefore, the anterolateral approach is more convenient than posterolateral one [11]. Only patient age was a significant risk factor for the mortality. On the other hand, the survival of patients who did not undergo capsule repair was higher than the group.

Conclusion

The anterior or posterior capsular repair preference for primary HA procedure hardly affects post-operative long-term morbidity, hip quality and activity scores, and does not affect mortality.

The present study has enough sample size and presents long-term follow-up results. We evaluated various demographic features and their possible effect on the procedural outcomes; nevertheless, a more detailed evaluation of chronic diseases (such as osteoporosis) and their impact on procedural long-term success could be performed in further studies.

References

1. Corbett KL, Losina E, Nti AA, Prokopetz JJ, Katz JN. Population-based rates of revision of primary total hip arthroplasty: a systematic review. PloS one. 2010;5(10):e13520.
2. Ritter MA, Harty LD, Keating ME, Faris PM, Meding JB. A clinical comparison of the anterolateral and posterolateral approaches to the hip. Clinical Orthopaedics and Related Research®. 2001;385:95-9.
3. Smith G, Tsang J, Molyneux S, White T. The hidden blood loss after hip fracture. Injury. 2011;42(2):133-5.
4. Kumar D, Mbako A, Riddick A, Patil S, Williams P. On admission haemoglobin in patients with hip fracture. Injury. 2011;42(2):167-70.
5. Tomlinson J, Zwirner J, Ondruschka B, Prietzel T, Hammer N. Innervation of the hip joint capsular complex: A systematic review of histological and immunohistochemical studies and their clinical implications for contemporary treatment strategies in total hip arthroplasty. PloS one. 2020;15(2):e0229128.
6. Karaaslan F, Yurdakul E, Korkmaz M, Duygulu F, Baktır A. Is cemented bipolar hemiarthroplasty a safe treatment for femoral neck fracture in elderly patients? Clinical Interventions in Aging. 2015:1063. doi:10.2147/cia.s85039.
7. Post ZD, Orozco F, Diaz-Ledezma C, Hozack WJ, Ong A. Direct anterior approach for total hip arthroplasty: indications, technique, and results. JAAOS-Journal of the American Academy of Orthopaedic Surgeons. 2014;22(9):595-603.
8. Lu Y, Wu Z, Tang X, Gu M, Hou B. Effect of articular capsule repair on postoperative dislocation after primary total hip replacement by the anterolateral approach. Journal of International Medical Research. 2019;47(10):4787-97.
9. Zhang B, Wang F, Tian M, Yin W, You X, Li D et al. Articular capsule repair in initial artificial hip replacement via anterolateral approach to the hip joint. Journal of biological regulators and homeostatic agents. 2016;30(2):441-7.
10. Higgins BT, Barlow DR, Heagerty NE, Lin TJ. Anterior vs. posterior approach for total hip arthroplasty, a systematic review and meta-analysis. The Journal of arthroplasty. 2015;30(3):419-34.
11. Wang Z, Hou J-z, Wu C-h, Zhou Y-j, Gu X-m, Wang H-h, et al. A systematic review and meta-analysis of direct anterior approach versus posterior approach in total hip arthroplasty. Journal of orthopaedic surgery and research. 2018;13(1):1-11.

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Journal of Surgery and Medicine

Topical mitomycin C treatment in corneal and conjunctival intraepithelial neoplasia: A case report

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Abstract

Corneal and conjunctival intraepithelial neoplasia is a slowly progressive ocular surface lesion with low malignant potential. Owing to the high recurrence rates, cryotherapy or topical chemotherapy is used with surgical treatment. In this paper, we report the histopathologic findings and treatment of a case of intraepithelial neoplasia that began in the conjunctiva and progressed to the cornea. A 75-year-old woman presented with complaints of redness, irritation and lacrimation in her left eye for around 1 month. Slit-lamp examination revealed a papilliform mass on the nasal conjunctiva along with involvement of the adjacent corneal epithelium. Conjunctival excisional biopsy showed a moderate epithelial dysplasia. Topical 0.04% mitomycin C was administered 4 times daily for 3 weeks. No recurrence was observed in the following 18 months.

Keywords: Conjunctival intraepithelial neoplasia, Dysplasia, Mitomycin C

Introduction

Ocular surface squamous neoplasia (OSSN) encompasses the ocular surface epithelial tumor spectrum from intraepithelial dysplasia to invasive squamous cell carcinoma. Corneal and conjunctival intraepithelial neoplasia may spread in the cornea with conjunctival and limbal origin and are slowly progressing lesions with low malignancy potential. These lesions, which do not pass the basal membrane, are histopathologically mild, moderate, or severe dysplasia [1]. Factors such as smoking, exposure to ultraviolet light, ocular surface injury, vitamin A deficiency, human papilloma virus infection and acquired immunodeficiency syndrome play roles in disease development [2, 3]. Promoter mutations in the telomerase reverse transcriptase gene were identified as contributing factors by Scholz et al. [4] in patients with conjunctival OSSN.

The distinction between invasive and non-invasive conjunctival epithelial lesions is crucial for their treatment. Therefore, incisional and excisional biopsies, which may indicate the invasiveness of the lesion, are useful for obtaining a definitive diagnosis. Although surgical excision remains the first choice of treatment modality, the introduction of topical chemotherapy in recent years has rapidly changed the therapeutic approach [5]. Owing to the high recurrence rates, complementary treatments such as cryotherapy and topical chemotherapy are applied after surgical excision. Mitomycin C (MMC), 5-fluorouracil and interferon a2b are among the chemotherapeutic agents used for medical treatment [6, 7].

In this study, we aimed to assess the treatment and outcome of a patient with intraepithelial neoplasia beginning in the conjunctiva and progressing to the cornea.

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Case presentation

On ocular examination, her best-corrected visual acuity was 0.00 logMAR in the right eye and 0.5 in the left eye. Biomicroscopic examination revealed a grade 4 cataract in the left eye and papilliform mass in the nasal conjunctiva of nearly 3×4 mm (Figure 1). Neovascularization was not observed in the cornea. A grey opaque lesion and an epithelial defect were found in the area adjacent to the limbus in the nasal cornea. Split-lamp examination of the cornea revealed that the lesion did not reach the stroma. The anterior chamber and fundus examinations, as well as the anterior and posterior segment examinations of the right eye were normal. The patient was considered to have an intraepithelial neoplasia beginning from the conjunctiva, extending to the cornea. She was informed of the possible complications and asked to sign a consent form. The excisional biopsy from the lesion was performed with 2-mm clear margins. A 0.02% MMC solution (Mitomycin C Kyowa, Kyowa Hakko Kogyo Co Ltd., Tokyo, Japan) was administered for 30 seconds to the open tissue, which was then irrigated with physiologic serum. The conjunctival wound site was not sutured, and the sclera was left open. Corneal epithelial debridement was performed with a blunt spatula. Tissue excised from the conjunctiva was sent to the pathology department for histopathological assessment. After the patient's epithelium had fully healed, MMC (0.04%, 4×1) treatment was begun on the fifth postoperative day and continued for 3 weeks. Ocular irritation and conjunctival hyperemia were observed during the treatment but ceased after MMC drop treatment was stopped. The histopathological sections of the tissue showed moderate epithelial dysplasia (Figure 2, 3). Immunohistochemistry was human papilloma virus negative. Examination of the patient at 1 month did not reveal staining of the conjunctiva and cornea. No cloudiness was observed in the cornea. The patient had a cataract surgery on the same eye 2 months after the initiation of the topical MMC treatment. After the surgery, the visual acuity in the left eye increased to 0.00 logMAR. The patient was followed up with slit-lamp biomicroscopy for recurrence, with check-ups every month for 6 months and then every 3 months thereafter. Recurrence was not observed during the 18 month-follow-up (Figure 4). Written informed consent was obtained from the patient for the publication of this report and the accompanying images.

Figure 1: Papilliform mass in the nasal conjunctiva of the left eye

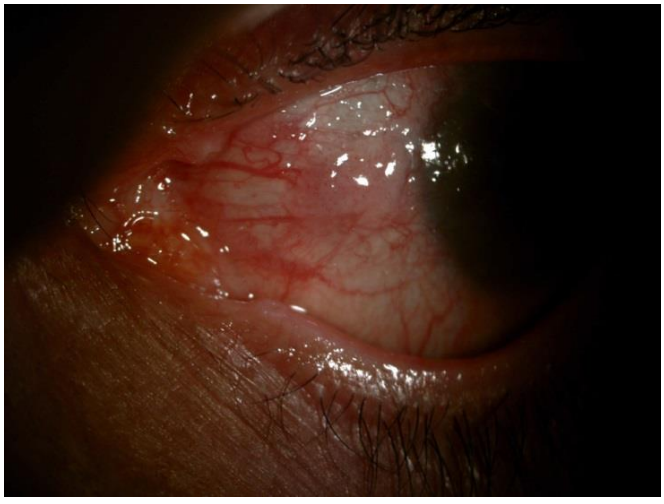


Figure 2: Histopathological picture showing acanthosis in the epithelium, increased cellularity and moderate dysplasia (Hematoxylin & Eosin x10)

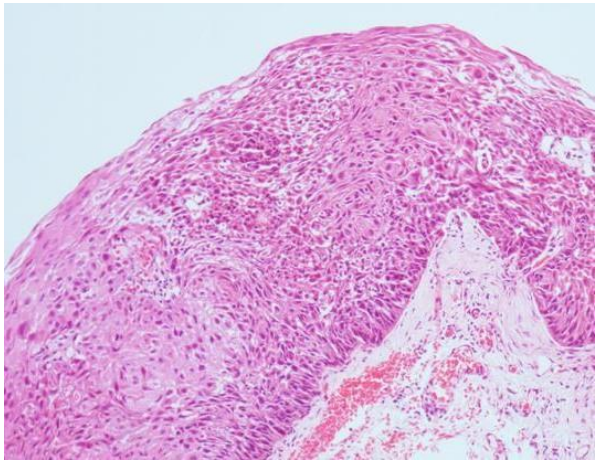


Figure 3: Increased ki-67 proliferation index in dysplastic epithelium (Ki-67x20)

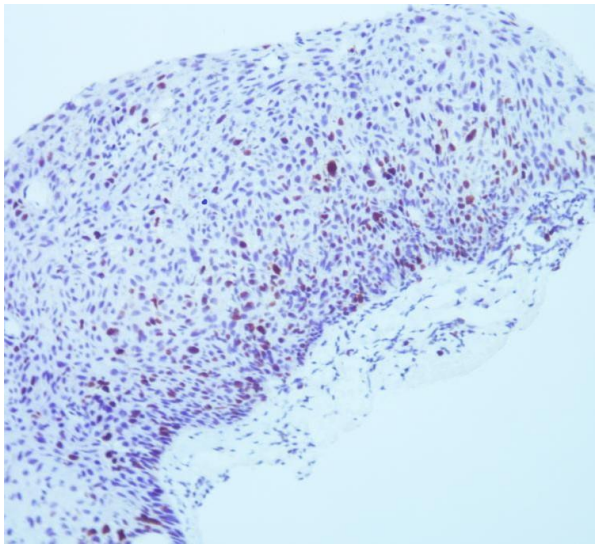
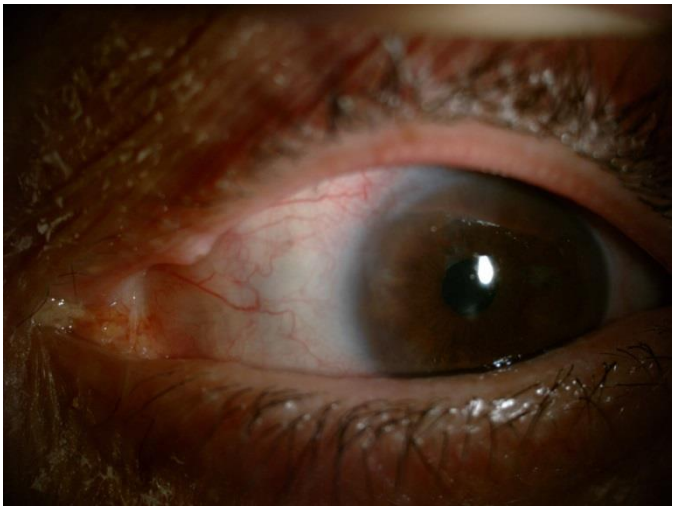


Figure 4: Postoperative image after excision of neoplasm and cataract surgery



Discussion

The aim of treatment for corneal and conjunctival intraepithelial neoplasia is to remove the neoplastic epithelium and prevent recurrence. The most important criterion for determining the recurrence rate is excision with positive surgical margins [8]. The recurrence rate after primary excision with pathologically clear margins is 33% [9]. Owing to the high recurrence rates, ocular surface damage such as limbal stem cell damage and corneal and conjunctival scarring may develop because of repeated surgery. Cryotherapy or topical

chemotherapy was used with surgical treatment to prevent recurrences and avoid risks. Adjuvant topical chemotherapy has several advantages, including targeting of the tumor cells, treatment of the entire ocular surface, simplicity of the treatment and reduced patient morbidity. As a topical chemotherapeutic agent, MMC was used for the treatment of microscopic disease and prevention of recurrence after surgical excision. MMC is used for both pigmented and non-pigmented epithelial tumors [5, 10].

MMC is an antibiotic isolated from *Streptomyces caespitosus* that affects the cell cycle as an alkylating agent. In topical application under aerobic conditions, MMC generates free radicals and has a cytotoxic effect. MMC-related changes in the ocular surface epithelium may persist for at least 8 months after topical treatment [11]. Before MMC was used for ocular surface neoplasia treatment, it was commonly used in glaucoma and pterygium surgery owing to its antiproliferative effect on subconjunctival fibroblasts. MMC was first shown to be effective against corneal intraepithelial neoplasia by Frucht-Pery and Rozenman [12] in 1994, and later studies supported its efficacy for ocular surface tumors [10, 13]. Currently, MMC is used as a complementary treatment for corneal and conjunctival intraepithelial neoplasia. Treatment uses 0.02% or 0.04% MMC doses after surgical excision [6, 13]. In topical use, MMC has a higher rate of adverse effect than 5-fluorouracil and interferon a2b. On the other hand, MMC as a monotherapy has high efficiency, and the conjunctival intraepithelial neoplasia resolution time is shorter [5]. We thought that our patient, who had a conjunctival mass removed from the same localization 1 year previously, had a recurrent conjunctival intraepithelial neoplasia. Owing to the corneal and conjunctival involvements in our case, we applied 0.02% MMC during surgery and topical 0.04% MMC treatment after surgery to prevent recurrence. During the follow-up examinations, no recurrence was found in the cornea or conjunctiva.

Although MMC is accepted as a safe chemotherapeutic agent for topical treatment of ocular surface neoplasia, temporary ocular side effects such as hyperemia, chemosis, corneal epitheliopathy and scleral thinning may be observed. These side effects usually regress with the addition of topical steroids or nonsteroidal anti-inflammatory drugs or interruption of MMC chemotherapy. Rarely observed but significant complications are limbal stem cell deficiency, scleromalacia, cataracts and corneal ulcers [14, 15]. Cornea and scleral melting can be prevented by waiting for epithelial healing before topical MMC application after surgical excision. Severe complications were not observed in our patient, and mild side effects such as conjunctival hyperemia and lacrimation resolved after MMC drop application was stopped. No sequelae developed.

Conclusion

Topical MMC administration after surgical excision and corneal debridement may be a highly effective and reliable adjuvant treatment choice for conjunctival and corneal intraepithelial neoplasia to reduce recurrence rates. The effectiveness of MMC for ocular surface neoplasia treatment can be better determined in further prospective studies.

References

1. Kao AA, Galor A, Karp CL, Abdelaziz A, Feuer WJ, Dubovy SR. Clinicopathologic correlation of ocular surface squamous neoplasms at Bascom Palmer Eye Institute: 2001 to 2010. Ophthalmology. 2012;119(9):1773-6. doi: 10.1016/j.ophtha.2012.02.049.
2. Gichuhi S, Ohnuma S, Sagoo MS, Burton MJ. Pathophysiology of ocular surface squamous neoplasia. Exp Eye Res. 2014;129:172-82. doi: 10.1016/j.exer.2014.10.015.
3. Hamam R, Bhat P, Foster CS. Conjunctival/corneal intraepithelial neoplasia. Int Ophthalmol Clin. 2009;49(1):63-70. doi: 10.1097/IIO.0b013e3181924ec3.
4. Scholz SL, Thomasen H, Reis H, Möller I, Darawsha R, Müller B, et al. Frequent TERT promoter mutations in ocular surface squamous neoplasia. Invest Ophthalmol Vis Sci. 2015;56(10):5854-61. doi: 10.1167/iovs.15-17469.
5. Pe'er J. Ocular surface squamous neoplasia: evidence for topical chemotherapy. Int Ophthalmol Clin. 2015;55(1):9-21. doi: 10.1097/IIO.0000000000000050.
6. Frucht-Pery J, Rozenman Y, Pe'er J. Topical mitomycin-C for partially excised conjunctival squamous cell carcinoma. Ophthalmology. 2002;109(3):548-52. doi: 10.1016/s0161-6420(01)00967-8.
7. Giaconi JA, Karp CL. Current treatment options for conjunctival and corneal intraepithelial neoplasia. Ocul Surf. 2003;1:66-73.
8. Galor A, Karp CL, Oellers P, Kao AA, Abdelaziz A, Feuer W, et al. Predictors of ocular surface squamous neoplasia recurrence after excisional surgery. Ophthalmology. 2012;119(10):1974-81. doi: 10.1016/j.ophtha.2012.04.022.
9. Tabin G, Levin S, Snibson G, Loughnan M, Taylor H. Late recurrences and the necessity for long-term follow-up in corneal and conjunctival intraepithelial neoplasia. Ophthalmology. 1997;104(3):485-92. doi: 10.1016/s0161-6420(97)30287-5.
10. Besley J, Pappalardo J, Lee GA, Hirst LW, Vincent SJ. Risk factors for ocular surface squamous neoplasia recurrence after treatment with topical mitomycin C and interferon alpha-2b. Am J Ophthalmol. 2014;157(2):287-93. doi: 10.1016/j.ajo.2013.10.012.
11. McKelvie PA, Daniell M. Impression cytology following mitomycin C therapy for ocular surface squamous neoplasia. Br J Ophthalmol. 2001;85(9):1115-9. doi: 10.1136/bjo.85.9.1115.
12. Frucht-Pery J, Rozenman Y. Mitomycin C therapy for corneal intraepithelial neoplasia. Am J Ophthalmol. 1994;117(2):164-8. doi: 10.1016/s0002-9394(14)73072-7.
13. Soysal HG, Yazar Z. The efficacy of postoperative topical mitomycin C in the treatment of conjunctival epithelial neoplasia. Turk J Ophthalmol. 2008;38(6):464-7.
14. Khong JJ, Muecke J. Complications of mitomycin C therapy in 100 eyes with ocular surface neoplasia. Br J Ophthalmol. 2006;90(7):819-22. doi: 10.1136/bjo.2005.086850.
15. Dudney BW, Malecha MA. Limbal stem cell deficiency following topical mitomycin C treatment of conjunctival-corneal intraepithelial neoplasia. Am J Ophthalmol. 2004;137(5):950-1. doi: 10.1016/j.ajo.2003.10.048.

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Giant retroperitoneal schwannoma removed with the laparoscopic approach: A case report

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Informed Consent
The authors stated that the written consent was obtained from the patient presented with images in the study.

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Abstract

Retroperitoneal tumors are extremely rare and the vast majority are malignant tumors. One of the least determined benign retroperitoneal tumors is schwannoma. We report the case of a 64-year-old male patient who had a solid mass in the left infrarenal space shown by computed tomography (CT). Percutaneous CT-guided biopsy of the mass was performed, and histopathological examination revealed a schwannoma. The mass was resected laparoscopically. Surgical resection of retroperitoneal tumors is difficult due to posterior deep location and adjacent major vessels and nerves. The laparoscopic approach for retroperitoneal tumors may allow better visualization of the surgical field, reduction of postoperative pain, and better cosmesis. Laparoscopy seems to be a safe and feasible method in the treatment of schwannomas and other retroperitoneal tumors.

Keywords: Schwannoma, Retroperitoneal tumors, Laparoscopy

Introduction

Primary retroperitoneal masses constitute a heterogeneous group of lesions that are categorized as solid and cystic. Solid lesions can be divided into four groups by origin: Mesenchymal, neural, germ-cell, and lymphoproliferative. Most cases are malignant tumors, of which approximately 75% are mesenchymal in origin [1]. Schwannomas are mostly benign tumors originating from the Schwann cells in the neural sheaths of peripheral nerves. Retroperitoneal schwannomas are rare, accounting for 0.5 to 3% of all schwannomas, and 1% of all retroperitoneal neoplasia [2, 3]. Schwannomas, which are most seen in the third to fifth decade of life, usually appear as a single lesion [4]. They are visualized in the form of a massive lesion with smooth contours, and benign radiological features that cannot be clearly distinguished from nerve fibers. They usually have a capsule that originates from the epineurium surrounding the nerve sheath. Although they mostly comprise a homogeneous internal structure and are solid, they may enlarge, and a heterogeneous radiological appearance of a cystic-necrotic nature may be observed since the retroperitoneal space is wide and suitable for tumor expansion. We would like to present our case of a retroperitoneal schwannoma treated laparoscopically. This case report followed the CARE guidelines for case reports.

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Case presentation

We report the case of a 63-year-old male patient who presented with left lower abdominal pain. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

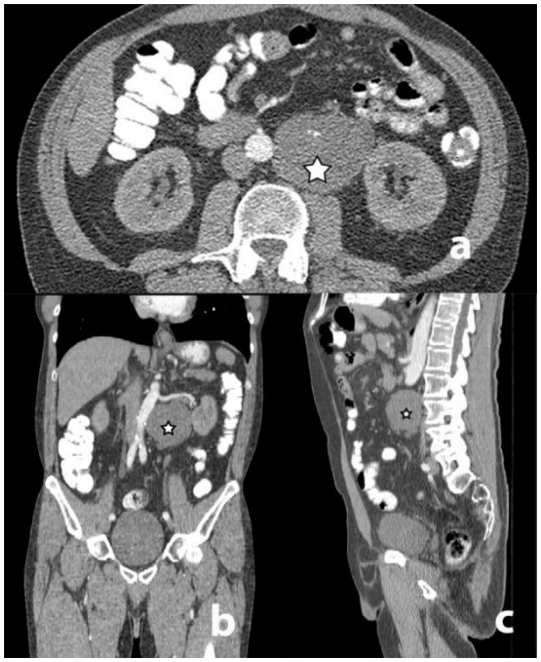
Clinical findings

A 63-year-old male with left lower abdominal pain presented to our general surgery outpatient clinic. He had no history of past abdominal surgery. He had mild hypertension and diabetes mellitus (DM), and he was using medication for the latter only. There were no complaints of nausea-vomiting, diarrhea, constipation, or fever. There were no significant features in physical examination or laboratory findings.

Diagnostic focus and assessment

A smoothly contoured iso-hypodense solid mass lesion sized 52x48x68 mm (APxTRxCC) was detected in the left retroperitoneal area at the level of L2-L3 vertebral corpora within the paravertebral-perirenal fatty plans on intravenous and oral contrast-enhanced abdominal CT examination (Figs.1a, 1b, 1c). After the contrast injection, the lesion did not show significant contrast enhancement. Nonspecific millimetric calcifications were observed within the internally homogenous lesion. The lesion showed a close relationship to the left renal vascular structures in its anterior segment, and abdominal aorta medially, but had no obvious invasion findings. In addition, the boundaries between the left kidney and the iliac muscle could be selected clearly. The lesion had no connection with intraabdominal formations but mildly extended towards the vertebral column in the anteromedial-inferior part. Neural foramen or spinal canal extension of the lesion could not be differentiated on CT in sagittal, coronal, and axial plans in multiplanar examinations. A percutaneous CT-guided biopsy of the mass was performed, and histopathological examination was consistent with a retroperitoneal schwannoma.

Figure 1: IV and oral contrasted abdominal CT examination of the patient a) On an axial section, solid mass lesion (star) with a smooth contour and millimetric calcifications is seen adjacent to the left iliac muscle and aorta in left pararenal fatty plans b) On the coronal section, the close relationship of the lobulated contoured lesion with the left kidney and renal vascular structures is observed (star) c) On the sagittal section, although the mass (star) was in the paravertebral area, its relationship with the nerve roots could not be visualized on CT.



Therapeutic focus and assessment

The surgical procedure was carried out with a transperitoneal approach with the patient in the supine position. Three trocars were used for a transperitoneal approach. First, an 11 mm trocar was inserted under the umbilicus. A 30-degree laparoscope was introduced through this trocar. Two 5 mm trocars were inserted at the lower midline and right upper quadrant (Figure 2). The tumor, which was exposed by mobilizing the descending colon from the retroperitoneum, was in the left pararenal area and had close contact with the aorta. It was widely dissected from the left ureter and gonadal vessels using LigaSure™ (Medtronic Parkway Minneapolis, USA) (Figure 3). The resected specimen was placed in a protected bag and extracted through a small incision that was created by extending the 11-mm umbilical port. After hemostasis and saline irrigation, a closed surgical drain was placed in the surgical bed. The total operation time was 120 min, the blood loss was about 100 mL. No perioperative complications were encountered. The resected specimen was 6.5x6.5 cm in size (Figure 4). The patient was discharged on the fourth postoperative day. The tumor was diagnosed as a benign schwannoma through histopathological examination. There were no postoperative complications.

Follow-up and outcomes

There was no recurrence during the 2-year follow-up.

Figure 2: Trocar incisions. The mass was removed in the bag by the expansion of the 10 mm trocar incision

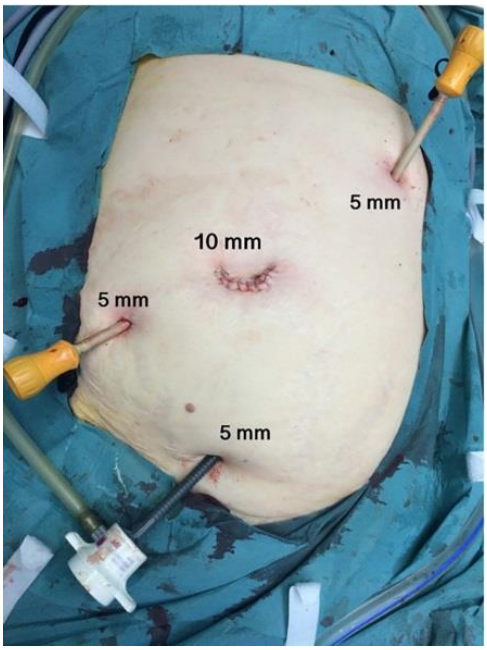


Figure 3: Preservation of ureter and gonadal vessels, which are released laterally, and the relationship of the mass with the sympathetic truncus

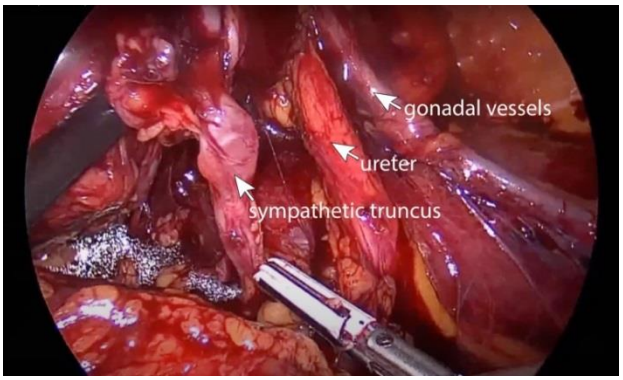
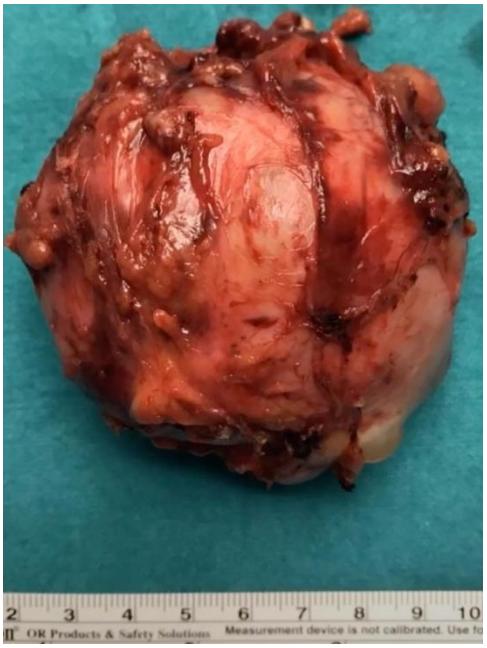


Figure 4: Benign schwannoma was 6.5x6.5 cm in size



Discussion

Schwannomas are benign neoplasms arising from the nerve sheath mostly in the cephalocervical region (44.8%) and limbs (32.6%) and are rarely situated in the retroperitoneal space (0.7%) [5]. Retroperitoneal schwannomas are mostly asymptomatic, slow-growing tumors. Although the tumor arises from the peripheral nerve sheath, they rarely cause clinically detectable neurological deficits. In our case, the mass was found incidentally, and the patient had nonspecific abdominal pain.

Complete surgical resection of the tumor is the ideal method of treatment [6], after which recurrence is rare. Only patients who undergo partial resection are reported to have recurrence. Schwannomas have a complete envelope, which is not tightly adhered to surrounding tissues. Therefore, they can be removed completely. Hemorrhage is a serious intraoperative risk in case of injury to major vessels [7]. Despite the controversy about the best approach, laparoscopic surgery was considered appropriate for the treatment of this tumor. Laparoscopic surgery permits the magnification of the retroperitoneal space and allows the best visualization of the surgical field in addition to the well-known other advantages [5]. This type of operation requires extensive experience in laparoscopic surgery because meticulous dissection is needed to preserve important vascular structures and nerves.

There are few reports on laparoscopic resection of nonadrenal retroperitoneal tumors and the majority are case reports. Ahn et al. [8] presented the largest case series to show the feasibility and safety of laparoscopic resection of nonadrenal retroperitoneal tumors. In this study, even when the tumors were large or near the vascular structures, laparoscopic resection of the tumors was performed easily by experienced hands. Using the laparoscopic approach to treat large tumors remains debatable and there is no established correlation between tumor size and malignant transformation. Advances in radiologic techniques allow the differentiation of benign and malignant lesions. Laparoscopic resection can be viewed as a first-line treatment option for tumors that are thought to be benign, even in large retroperitoneal tumors. In our case, a 68 mm retroperitoneal schwannoma that was adjacent to the aorta was resected without complications. However, patients with tumors larger than 10 cm are not deemed appropriate for laparoscopic resection because larger incisions would be needed to excise the specimens. Moreover, if malignancy is suspected in the preoperative radiologic studies or frozen section, laparotomy should be considered for wide dissection. Thus, there is no consensus on whether the laparoscopic approach can be used routinely for malignant lesions.

A retroperitoneal schwannoma is exceedingly rare and generally asymptomatic. Since the treatment of choice is complete excision to minimize the risk of recurrence, preoperative radiological evaluation is important. Moreover, the excision of retroperitoneal tumors is difficult and the laparoscopic approach requires extensive experience. This presented case demonstrates that laparoscopic resection of retroperitoneal tumors, even when tumors are large or adhered to adjacent vascular structures, is safe and feasible if there is no suspicion of malignancy on preoperative radiologic images.

References

1. Chaudhari A, Desai PD, Vadel MK, Kaptan K. Evaluation of primary retroperitoneal masses by computed tomography scan. Int J Public Health. 2016;5(7):1423-9. doi: 10.5455/ijmsph.2016.25062015442
2. Mastoraki A, Toska F, Tsiverdis I, Kyriazi M, Tsagkas A, Danias N, et al. Retroperitoneal schwannomas: dilemmas in diagnostic approach and therapeutic management. J Gastrointest Cancer. 2013;44(4):371-4. doi: 10.3892/ol.2016.4543
3. Sayin S, Gökdemir R, Bursalı B. Schwannoma as a rare cause of syncope: A case report. J Surg Med. 2018;2(2):184-6.
4. Singh M, Kumar L, Chejara R, Prasad OP, Kolhe Y, Saxena A. Diagnostic dilemma of a rare, giant retroperitoneal schwannoma: a case report and review of literature. Case Rep Oncol Med. 2014;2014:628538. doi: 10.1155/2014/628538
5. Funamizu N, Sasaki A, Matsumoto T, Inomata M, Shiraishi N, Kitano S. Laparoscopic resection of a retroperitoneal schwannoma behind the lesser omental sac. Surg Laparosc Endosc Percutan Tech. 2004;14(3):175-7. doi: 10.1097/01.sle.0000129379.96203.66
6. Chen H, QiangXu, Zhan P, Liu Y, Dai M, Zhang B. Giant paravertebral schwannoma near the lumbar nerve roots with bone destruction. Medicine (Baltimore) 2019;98(42):e17341. doi: 10.1097/MD.0000000000017341
7. Kang CM, Kim DH, Seok JY, Lee WJ. Laparoscopic resection of retroperitoneal benign schwannoma. J Laparoendosc Adv Surg Tech. 2008;18(3):411-6. doi: 10.1089/lap.2007.0098
8. Ahn KS, Han H-S, Yoon Y-S, Kim H-H, Lee T-S, Kang S-B, et al. Laparoscopic resection of nonadrenal retroperitoneal tumors. Arch Surg. 2011;146(2):162-7. doi: 10.1001/archsurg.2010.342.

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Anesthesia management in dystrophic epidermolysis bullosa: A case report

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Abstract

Epidermolysis bullosa (EB) is a rare hereditary disorder characterized by an abnormal increase in the fragility of the skin and mucosal surface and recurrent blistering. Blisters and scar formation can be seen in tissues even after a minor trauma. Due to the healing of this disease by leaving a contracted scar tissue, the findings, especially on the airway, may cause important anesthetic problems. In addition, the protection of the skin and the mucosa during the procedures to be performed, prevention of new bulla formation and prevention of infection constitute the main difficulty in anesthesia management. This case report describes the anesthesia management for the dental treatment of a patient diagnosed with dystrophic epidermolysis bullosa (DEB) and aims to review the current information.

Keywords: Epidermolysis Bullosa, Dystrophic Epidermolysis Bullosa, General anesthesia

Introduction

Dystrophic Epidermolysis Bullosa (DEB) is an autosomal recessive disease characterized by diffuse dystrophic scarring, deformities, and severe involvement of mucous membranes. Even a minimal trauma can cause massive separation of the skin and mucosa from the underlying tissue [1, 2]. The biggest challenge in anesthesia management in EBD cases is the protection of the skin and mucous membrane integrity and airway control.

In this case report, our anesthesia approach in an EBD patient scheduled for dental treatment under general anesthesia is presented and the current literature is reviewed.

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Informed Consent
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

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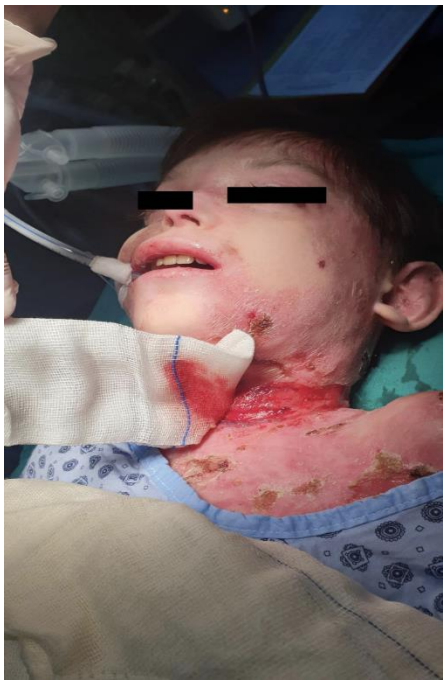
Case presentation

Dental treatment under general anesthesia was planned for a 17-year-old male patient with EBD weighing 20 kg. He had a history of surgery due to right knee joint contracture. On physical examination, there were extensive scar tissue and eroded lesions accompanied by hemorrhagic dryness on the extremities. Neck extension and mouth opening were limited due to contracted scars and ongoing hemorrhagic, drying lesions. Therefore, mallampati assessment could not be made. In indirect laryngoscopy, the vocal cords were bilaterally mobile, and the passage was open. In the laboratory examination, blood biochemistry, PT, PTT, INR, and hemogram values were within normal reference ranges.

In the preoperative unit, a tourniquet was applied, an intravenous (IV) line was opened with a 22-G cannula and fixed with vaseline gauze. Due to the expected difficult airway, various size masks, laryngoscope, endotracheal tube (ETT), flexible fiberoptic laryngoscope, flexible laryngoscope, and appropriately sized styles were prepared. Tracheotomy preparation was made.

The head of the patient, who was carefully placed on the operating table, the leg with flexion contracture, and the heel of the foot were supported with a silicone cushion. Oxygen saturation was monitored with a clip probe on different fingers instead of an adhesive finger probe. For electrocardiography (ECG) monitoring, the non-gel adhesive parts of the ECG electrodes were cut and fixed with a silk patch. Noninvasive blood pressure (NIBP) monitoring was planned before, after intubation, and when needed and was performed by placing wet cotton under the blood pressure cuff.

Figure 1: The endotracheal tube was fixed with a vaseline bandage.



Prophylactic intravenous ranitidine (1 mg/kg) and cefotaxime (50 mg/kg) were administered. Since difficult airway was considered, induction was performed with inhalation anesthetics. Using sterile gloves, the face mask was placed on the face with vaseline gauze without causing any damage to the skin, and anesthesia was induced with 4-8% sevoflurane and oxygen. Eyes were protected with moisturizing eye pomade and protective gauze. After securing the airway, muscle laxity was achieved with 0.5 mg/kg rocuronium bromide. A lubricated Macintosh was used to prevent mucosal trauma. Endotracheal intubation was performed with a no. 5 endotracheal tube, which was fixed with a vaseline bandage (Figure 1). Anesthesia was maintained with O2: N20 (40:60 ratio) and 1–1.5% sevoflurane. Methylprednisolone (1 mg/kg) was administered. Perioperative hemodynamic parameters were stable. Postoperative analgesia was provided with 10 mg/kg paracetamol. At the end of the operation, the neuromuscular blockade was antagonized with 2 mg/kg sugammadex. Extubation was performed when there was sufficient spontaneous breathing. There were no complications perioperatively, except for the development of fresh blisters on the buccal mucosa. The patient was observed in the postoperative recovery unit for 2 hours (Figure 2), then transferred to the ward, and was discharged after 24 hours. The parents were informed about the case report, and their written consent was obtained.

Figure 2: Observation of the patient in the postoperative recovery unit

Discussion

Epidermolysis bullosa is an autosomal dominant or recessive disease characterized by recurrent bullae and scar tissue formation due to increased fragility of the skin and mucosa. A bulla is formed as a result of mutations in genes encoding the proteins in the epidermis or the basement membrane (dermo epidermal junction). Repetitive bulla formation with minimal mechanical trauma is the characteristic finding in all types of EB. Four major types have been defined: EB simplex (EBS), Junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome. Other than cutaneous involvement, tracheolaryngeal complications, oral mucosal involvement, anemia, malnutrition, osteoporosis, growth and growth retardation, and cardiomyopathy may be observed [3]. Infection is common, and wound healing is delayed due to decreased immunity and long-term corticosteroid use. Recessive dystrophic EB is characterized by widespread dystrophic scarring, deformities, and severe involvement of mucous membranes, beginning at birth. Adhesion of the fingers and toes and limitation of movement due to pseudosyndactyly are frequently observed. Skin biopsy, tooth extraction, and care, eye surgery, contracture and adhesion surgery in the extremities, skin grafting, esophageal dilatation due to esophageal stricture are common surgical procedures. Anesthesia procedures can be extremely difficult due to airway distress, ankyloglossia, excessive skin sensitivity, deformities, and wounds. Because of oropharyngeal and esophageal lesions, patients have malnutrition, anemia, electrolyte disturbance, and decreased

immunity, which may change the pharmacokinetic effects of anesthetic agents.

The type of anesthesia technique is determined by the expected duration and type of surgery. In their study in which they reviewed the anesthesia records of patients with EB, Van Den Heuvel et al. reported that only patients requiring orofacial surgery were managed with standard general anesthesia, and deep sedation/analgesia technique was preferred in procedures such as wound dressings, esophageal dilatation, and syndactyly [4]. Regional anesthesia techniques can be preferred with or without general anesthesia in cooperative adult patients [5].

It is essential to know the EB subtype in EB patients. In autosomal recessive DEB, studies state that oropharyngeal bulla formation after endotracheal intubation, and postoperative stridor is less common, and dilated cardiomyopathy association is more frequent. Oral involvement, ankyloglossia, early tooth decay development, and imperfect tooth alignment are more common than other types. Subglottic stenosis, choanal and nasal stenosis, excessive paratracheal and intranasal granulation tissue, gastroesophageal reflux, and coexistence of renal and cardiac diseases are more common in JEB. EBS is more frequently associated with muscular dystrophy [5, 6].

The IV cannulation should be performed by a manual tourniquet procedure and fixed with non-adhesive silicone tapes in the preoperative preparation phase. Preoperative sedation may be beneficial in children with vascular access [6].

Atropine or glycopyrrolate, and antacid prophylaxis such as sodium citrate in case of a history of reflux or esophageal stricture, are useful to reduce excessive saliva release. Hydrocortisone treatment may be required in patients on long-term steroid therapy.

The biggest challenge in anesthesia management in EB patients is airway management and prevention of mucosal damage. In this patient group, detailed airway examination should be performed for anesthesia risk assessment. Decreased mouth opening due to contracture formation and development of temporomandibular joint motion limitation may cause position difficulties in laryngoscopy [7]. It is essential to prepare for tracheotomy considering the possibility of airway complications such as intubation difficulty, post-extubation edema, and obstruction. Lubricants should be applied to the laryngoscope blade before use. The endotracheal tube should be smaller than standard formulas suggest. ETT should be fixed with non-adhesive silicone bandages so as not to cause lip or skin damage. If nasal intubation is required in dental procedures, suturing can be used for tube fixation. Using a hard face mask, mandibular thrust, and oral airway can easily damage the skin, lips, tongue, and mucous membranes. For this reason, soft masks should be preferred, and gelled oral airways should be used. Silicone-based tape should be applied to the areas where the mask will contact the face. NgLY et al. suggested using high flow oxygen as a preferable method instead of a face mask in children with difficult airways since it does not harm the mucosa and the skin [8].

Fiberoptic intubation is less traumatic than direct laryngoscopy and should be the first choice for EB patients with difficult airway. A video laryngoscope can be helpful. Studies are suggesting that the use of a laryngeal mask (LMA) should be preferred in a difficult airway scenario because the cuff increases the formation of blisters by putting pressure on the pharynx wall. There are also publications showing that LMA, pre-lubricated with a water-based gel that is smaller than the customarily prescribed size, can be used safely [6, 9]. After difficult intubation, 0.25 mg/kg (maximum 8 mg) dexamethasone can be used to reduce postoperative airway edema. In our case, induction of anesthesia with an inhalation agent was preferred for the control of the airway, a mask with a soft air cushion was carefully used on a vaseline bandage in areas where it contacted the skin, and no complications occurred due to mask ventilation and intubation.

In EB patients, pressure and friction can cause new blisters and wounds to form. Therefore, avoiding friction and trauma during anesthesia, surgery and other procedures and preventing the formation of new blisters is the most important part of these patients' anesthesia management. The patients' transportation should be managed carefully, silicone pads should be placed on the required areas on the operating table, and it should be ensured that the bed sheet in contact with the patient's skin is appropriately placed. Self-adhesive tapes and wraps that are applied directly to the skin that may cause friction should be avoided. Instead, silicone adhesive tapes, gel, or vaseline dressings should be preferred. Minimal intervention and monitoring are recommended for EB patients [2]. ECG follow-up should be done by fixing the electrodes, whose adhesive part is cut and only the gel part is left, with silicone adhesive tapes. Pulse oximetry can be measured by using a 'clip probe' instead of an adhesive finger probe. NIBP tracking can be performed by placing cotton pads between the sleeve and the skin surface. Since no significant blood loss and hemodynamic deterioration were expected in our case, NIBP monitoring was used only when necessary. ECG electrodes were applied as recommended in the literature. Skin and mucosal damage were minimized by applying careful monitoring and handling.

Nasopharyngeal and rectal temperature probes should be used with caution and avoided if possible. Aspiration should be performed with lower pressure, protecting the mucosa.

EB patients are prone to ophthalmic complications. Especially in surgical procedures to be performed in the prone position, cornea and conjunctiva damage should be avoided, and adequate support should be provided with appropriate equipment and silicone pillows. It is important to cover the eyes with moisturizing eye pomade.

Anesthetic agents should be selected considering the accompanying systemic diseases, patient age, and difficulty in airway management. If there is IV access, intravenous induction is generally preferred. Propofol, thiopental and ketamine can be used safely in these patients [10, 11]. Induction with inhalation agents is safe in cases where a difficult airway is expected. In cases where the intravenous route cannot be provided, sevoflurane and isoflurane are the preferred agents. Inhalation anesthesia and TIVA can be used for the maintenance of anesthesia. In our case, after induction of anesthesia with sevoflurane, maintenance of anesthesia continued with inhalation anesthesia, and no complications developed. Suxamethonium, one of the muscle relaxants, should be used with caution due to its hyperkalemic potential. Muscle relaxants such as atracurium,

vecuronium, rocuronium bromide are frequently used. The duration of action of these drugs may be prolonged in the presence of hypoalbuminemia. However, it has been shown in some studies that this was not observed, and it can be used safely [11, 12].

Local anesthesia without a vasoconstrictor should be preferred for oral surgery. In postoperative analgesia, paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids can be used safely [13].

Conclusion

Preoperative and perioperative care and teamwork, minimal monitoring, and preparation for difficult airway scenarios are important in the anesthetic management of EB patients to prevent skin and mucosal damage and formation of new blisters.

References

1. Kelly L Crowley, Yuri O Shevchenko. Anesthetic management of a difficult airway in a patient with epidermolysis bullosa: a case report. AANA J. 2004 Aug;72(4):261-3.
2. Sujit V Saraf, Nishigandha J Mandawade, Sandeep K Gore, Usha D Padhye, Charissa S Pereira. Epidermolysis bullosa: Careful monitoring and no touch principle for anesthesia management. J Anaesthesiol Clin Pharmacol. 2013 Jul;29(3):390-3.
3. Karaduman A. Kalıtsal Büllü Hastalıklar. Türkderm 2011; 45 Özel Sayı 2: 81-6
4. I Van Den Heuvel, M. Boschin, M. Langer, M. Frosch, A. Gottschalk, B. Ellger, et al. Anesthetic management in pediatric patients with epidermolysis bullosa: a single center experience. Minerva Anestesiol. 2013 Jul;79(7):727-32.
5. Kenneth Goldschneider, Anne W. Lucky, Jemima E. Mellerio, Francis Palisson, Maria Del Carmen Vin, Uela Miranda, et al. Perioperative care of patients with epidermolysis bullosa: proceedings of the 5th international symposium on epidermolysis bullosa, Santiago Chile, December 4–6, 2008. Pediatric Anesthesia. 2010;20:797–804.
6. Reema Nandi, Richard Howard. Anesthesia and Epidermolysis Bullosa. Dermatol Clin. 2010;28:319–24.
7. Özkan A. Selim ,Kayhan E. Gülay, Akbaş S, Kaçmaz O, Durmuş M. Emergency Difficult Airway Management in a Patient with Severe Epidermolysis Bullosa. Turk J Anaesthesiol Reanim. 2016;44:270-2.
8. Ng LY, Chan AKM, Lam TWY. The use of high-flow nasal oxygen during airway management in a child with epidermolysis bullosa dystrophica and a difficult airway. Anaesth Rep. 2019 Dec 16;7(2):96-9.
9. Bethany C. Fitzmaurice & Barry G. Lambert. Failed fiberoptic intubation in a child with epidermolysis bullosa, rescued with combined use of the Glidescope. Pediatric Anesthesia. 2016;26: 455–6.
10. Griffin RP, Mayou BJ. The anaesthetic management of patients with dystrophic epidermolysis bullosa. A review of 44 patients over a 10 year period. Anaes- thesia. 1993;48:810–5.
11. Iohom G, Lyons B. Anaesthesia for children with epidermolysis bullosa: a review of 20 years' experience. Eur J Anaesthesiol. 2001;18:745–54.
12. Ames WA, Mayou BJ, Williams KN. Anaesthetic management of epidermolysis bullosa. Br J Anaesth. 1999;82:746–51.
13. Jane Herod, Jaqueline Denyer, Ann Goldman and Richard Howard. Epidermolysis bullosa in children: pathophysiology, anaesthesia and pain management. Paediatric Anaesthesia. 2002;12:388-97.

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