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Case Report	1000	200	15	No tables	10 or total of 20 images
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Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press; 2005.

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Computed Tomographic Assessment of Osteotomy with Respect to Open Roof in Patients Undergoing Primary Septorhinoplasty with Bilateral Osteotomy

Bilateral Osteotomi Yapılan Primer Septorinoplasti Olgularının Osteotomilerinin Open Roof Açısından Bilgisayarlı Tomografi ile Değerlendirilmesi

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ABSTRACT

Introduction: The objective of rhinoplasty is to provide predictable changes in the nasal contours and improve nasal functions. Nasal osteotomy is a frequently used correction technique in rhinoplasty. However, the optimal osteotomy technique and approach remain a matter of dispute.

Methods: In this study, 24 patients who underwent primary septorhinoplasty and 24 patients who underwent paranasal sinus computed tomography (CT) due to various causes were retrospectively assessed. Operated patients completing a minimum postoperative follow-up duration of 1 year were invited to the study center. Informed consent form was signed, and a CT of the nasal bone in the axial plane was performed. These recorded values were compared with their preoperative results and with non-surgical patients.

Results: Comparison of data between postoperative and non-surgical cases showed that there was a significant reduction in the ventral width of operated patients (p=0.022), whereas no significant difference was observed in the dorsal width despite bilateral spreader grafts (p=0.108).

Conclusion: Our results suggest that the dorsal width in patients undergoing bilateral osteotomy and bilateral spreader grafts was not significantly different from those in non-operated subjects. Also, contrary to what one may expect, spreader grafts are not associated with an increased dorsal width.

Keywords: Open roof, spreader graft, septorhinoplasty, rhinoplasty

ÖZ

Amaç: Rinoplastinin amacı, burun hatlarında öngörülebilir değişiklikleri sağlamak ve burun fonksiyonlarını iyileştirmektir. Nazal kemik osteotomisi, rinoplastide sıklıkla kullanılan bir tekniktir. Bununla birlikte, optimal osteotomi tekniği ve yaklaşımı bir tartışma konusu olmaya devam etmektedir.

Yöntemler: Bu çalışmada, primer septorinoplasti yapılan yirmi dört hasta ve çeşitli nedenlerle paranasal sinüs tomografisi çekilen diğer 24 hasta grubu retrospektif olarak değerlendirildi. En az bir yıllık postoperatif takip süresini tamamlayan opere edilen hastalar çalışma merkezine davet edildi, bilgilendirilmiş onam formu imzalatıldı ve aksiyal planda burun kemiği tomografisi çekildi. Kaydedilen bu değerler ameliyat öncesi sonuçları ve ameliyatsız hastalar ile karşılaştırıldı.

Bulgular: Ameliyat sonrası ve ameliyatsız olgular arasındaki verilerin karşılaştırılması, ameliyat edilen hastalarda ventral genişlikte anlamlı bir azalma olurken (p=0,022) dorsal genişlikte bilateral spreader greftlere rağmen anlamlı bir farklılık görülmedi (p=0,108).

Sonuç: Sonuçlarımız, bilateral osteotomi ve bilateral spreader greft uygulanan hastalarda dorsal genişliğin ameliyat edilmeyen hastalardan önemli ölçüde farklı olmadığını düşündürmektedir ve beklenenin aksine, spreader greftler artmış dorsal genişlik ile ilişkili değildir.

Anahtar Kelimeler: Open roof, spreader greft, septorinoplasti, rinoplasti

Introduction

The nose and its associated structures represent a common anatomical site subjected to physical trauma. Consequently, surgical correction procedures involving this site are performed very frequently. Among these, rhinoplasty is a common procedure performed by ear-nose-throat specialists (1). The objective of rhinoplasty is to provide predictable changes in nasal contours and improve nasal functions (2). Nasal surgery is classified into two major categories as follows: "Aesthetic rhinoplasty," which alters the appearance, and "functional rhinoplasty," which improves functions. Nasal osteotomy is a frequently used correction

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technique in rhinoplasty that is individualized according to the needs of specific patients. However, the optimal osteotomy technique and approach remain a matter of dispute. There has been a growing interest, particularly among the aesthetic surgeon community, toward the use of assistive imaging modalities such as computed tomography (CT) in planning and predicting the potential outcomes of such surgery (3).

Methods

The study was approved by the Ethics Committee of Kartal Lütfi Kırdar Training and Research Hospital (approval number: 8951337/1009/146).

A group of 24 patients who underwent primary septorhinoplasty due to breathing difficulties and nasal deformities and another 24 patients who underwent paranasal CT due to various causes between 2008 and 2013 at the Maltepe University Faculty of Medicine, Departments of Ear Nose and Throat Surgery and Head and Neck Surgery, were retrospectively assessed. All patients were operated by the same surgeon using the same surgical equipment and closed septorhinoplasty technique, with spreader grafts. Spreader grafts retrieved from the septal cartilage were placed in the submucoperichondrial area located between the upper laterals and septum and were then sutured to the septum and medial edges of the upper laterals, leading to the expansion of the internal nasal valve and provision of long-term support for the septum.

After the hump reduction, lateral osteotomies were performed using the internal continuous method in accordance with low-to-low technique and were merged with percutaneous transverse osteotomies. The nasal bones separated from the lateral side were approached to narrow the nasal dorsum and close the open roof. Excessive spreader graft parts were excised using a scalpel after the procedure.

Antibiotic-soaked intranasal packing was removed on postoperative day 3. The cast placed to provide stability to the nasal dorsum was removed on days 8 to 10, and steri-strips™ (İstanbul-Turkey) that were applied following the physical examination were removed on day 14. Follow-up visits were scheduled at increasing time intervals postoperatively.

Patients completing a minimum postoperative follow-up duration of 1 year were invited to the study center and went through a physical examination; the measurement of the dorsal width by palpation was recorded. After obtaining photographic records, informed consent form was signed, and a CT of the nasal bone in the axial plane was performed. When required, endoscopic imaging was also performed to assess the nasal passages. The ventral width crossing the lateral osteotomy lines and the dorsal width measured at the tip of the dorsum were recorded in millimeters (Figure 1). The recorded values were compared with those in non-surgical patients who had undergone a paranasal CT for various indications. In addition, the correlation between the dorsal width measurements and palpation findings was analyzed.

Statistical analysis

Statistical analysis was performed using SPSS 16.0 software. The distribution of variables was measured using the Kolmogorov-Simirnov test. Mann-Whitney U and chi-square tests were used to analyze quantitative and qualitative independent data, respectively. Fisher's test was used when chi-square test conditions were not met. A two-tailed $p<0.05$ was considered statistically significant.

Results

A total of 24 patients undergoing surgery (20 women and 4 men; age range: 19-51 years, mean age: 28.4 years) and 24 non-operated individuals (14 women and 10 men; age range: 17-88 years, mean age: 38.75 years) were examined (Table 1).

Closed septorhinoplasty was conducted in all patients who underwent primary surgical procedure, with placement of bilateral spreader grafts and low-to-low lateral osteotomy + percutaneous transverse osteotomy in all cases. No serious intraoperative or postoperative complications occurred. At the postoperative 1-year follow-up examination, photographic images of the patients were obtained, and the width of the nasal dorsum was graded according to open roof deformity. Of patients, 18 and 6 were negative and positive by palpation, respectively. In addition, a photographic examination corroborated the findings in two cases. The axial CT of the nasal bone performed at a mean of 30.4 months postoperatively was used to obtain the dorsal and ventral width measurements. The corresponding values in the 24 control patients enrolled in the study were also recorded and compared. The results are shown in Table 2 and 3 as mean and standard deviation, where a p-value of less than 0.05 was considered significant. A comparison of the data between postoperated and non-operated cases showed no significant difference in the dorsal width ($p=0.108$), but there was a significant reduction in the ventral width in operated patients ($p=0.022$; Table 2). In a within-group comparison among those who underwent primary septorhinoplasty, a significantly higher dorsal width was found in those with positive palpation than those with negative palpation ($p=0.045$). However, similar results were found between these two groups in terms of ventral width ($p=0.499$; Table 3).

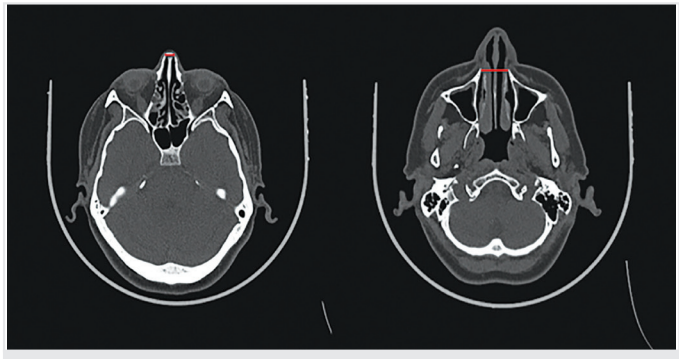

Figure 1. The short red line shows the dorsal width and long red line the ventral width

Table 1. Distribution of patients

Distribution of patients	Operated patients (50%)	Non-operated patients (50%)
Male	4 (8%)	10 (21%)
Female	20 (42%)	14 (29%)

Table 2. Dorsal and ventral widths in postoperated and non-operated patient groups

Measured value	Postoperated group median (IQR)	Non-operated group median (IQR)	p
Dorsal width (mm)	100±12	94±9	0.108
Ventral width (mm)	216±14	227±17	0.022

P<0.05 is considered significant, IQR: interquartile range

Table 3. Dorsal and ventral widths at postoperative 1-year in patients with palpable and non-palpable nasal dorsum

Measured value	Palpation (+) group median (IQR)	Palpation (-) group median (IQR)	p
Dorsal width (mm)	105±12	95±10	0.045
Ventral width (mm)	218±15	214±13	0.499

P<0.05 is considered significant, IQR: interquartile range

Discussion

Open roof deformity may arise from thickened or deviated dorsal septum and thickened bone in the radix or from greenstick fractures in non-mobilized nasal bones. Its surgical management involves correcting the septal deformity, displacing the medial triangular structure of the bone in the radix, and redoing the lateral osteotomy (4). Daniel described a symptomatic deformity due to the contact between the mucous membrane and open roof (5). However, this was not observed in the current study.

Similar to this study, Camirand et al. (6) reported that lateral osteotomy was very rarely associated with airway problems. The authors claimed that spreader grafts could correct the airway problems of patients who experienced such issues (6). However, lateral nasal osteotomy led to a significant narrowing of the nasal passage (7). In our study, despite low-to-low osteotomy, closed septorhinoplasty could prevent the collapse of the medial wall and preserve the structural integrity of the nasal valve, along with the placement of spreader grafts obviating the dorsal height loss and irregularity.

In the study by Egeli et al. (8) where nasal passage measurements were performed using CT, it was concluded that a reduction of the contralateral concha hypertrophy was necessary in subjects with septal deviation. In our study, the intervention involved the application of radiofrequency and lateralization of the lower concha hypertrophy.

Interventions involving the internal valve, that is, spreader grafts, have been recommended by authors such as Sheen (9) and Rohrich et al. (10) to relieve the airways. In our study, adequate airway passage was accomplished through septoplasty and nasal valve interventions.

In another study, Kortbus et al. (11) failed to observe a significant reduction in the dorsal width following osteotomy (p=0.24) while there was a statistically significant decrease in the ventral width postoperatively (p=0.003). Our osteotomy results were similar to Kortbus et al. (11) study; a significant ventral narrowing occurred in the osteotomy group (p=0.022), suggesting that osteotomy is not associated with a significant reduction in the nasal dorsal width when performed in conjunction with spreader graft while it was able to significantly reduce the ventral width.

Several previous studies have reported that the resolution of edema following rhinoplasty is a slow process requiring many months and that long-term assessment should be delayed until 1 to 2 years after surgery. In this regard, adequate time has been allowed for the postoperative evaluations in our study (mean: 30.4 months).

Gunter et al. (12) examined the analysis and classification of grafts and found that onlay grafts of the nasal dorsum could correct dorsal irregularity, provide dorsal augmentation, and obviate the "step off" deformity that may occur following osteotomy. For this purpose, we utilized various techniques such as the correction of such irregularities and augmentation and correction of dorsal asymmetry by spreader grafts.

Bottini et al. (13) concluded that composite grafts were more effective for opening the valves compared with spreader grafts, which were the preferred approach over composite grafts for the expansion of the nasal valve in our study.

Although nasal endoscopy is used for different purposes by rhinologists, in Lanfranchi et al.'s (14) study involving 96 patients, further interventions were required in 28 patients (30%) because of the use of preoperative endoscopy for several concomitant pathologies during surgery (e.g., Concha bullosa and choanal stenosis). Our patients also underwent endoscopic examination preoperatively and postoperatively and had the required interventions perioperatively (concha bullosaplasty).

Sam examined the effect of functional rhinoplasty on postoperative respiratory functions and determined that there were no statistically significant differences between the nasal obstruction symptom evaluation, a commonly utilized scale, and linear symptom scale, a subjective patient assessment tool (p<0.01) (15). In our patients, septoplasty, valve-relieving interventions, or spreader grafting were performed depending on the type of individual respiratory functional requirement. Linear symptom scale assessment was not performed in all patients, considering the reported similarity between these scales.

Study Limitations

Our study has several limitations. The most prominent limitation was the small study population. As a retrospective analysis, we are limited by what is documented in the electronic medical records. On the other hand, radiological evaluations are dependent on gender and age. Therefore, the number of women (14) and men (10) was similar to the control group patients. Also, the proportion of men (8%) included in the

study group did not make a significant difference. Future studies should include a larger number of patients.

Conclusion

Closed septorhinoplasty with good preoperative planning represents a viable alternative to classical rhinoplasty to correct septal, conchal, and nasal valve pathologies and to attain good cosmetic results. We believe that this approach may gain a more widespread popularity among surgeons with increasing numbers of patients undergoing such surgery, due to several advantages such as the efficacy in terms of respiratory functional outcomes, practicability, low postoperative complication risk, secondary surgery facilitation, and low propensity to damage the normal anatomy. Our results suggest that the dorsal width in patients undergoing bilateral osteotomy and bilateral spreader grafts was not significantly different from those in non-operated subjects. Furthermore, contrary to what one may expect, spreader grafts may not be associated with an increased dorsal width. However, this approach may lead to the occurrence of minimal increase in the width of the nasal dorsum that can be detected on palpation, although the difference in non-operated patients was not significant.

Ethics Committee Approval: The study was approved by the Ethics Committee of Kartal Lütfi Kırdar Training and Research Hospital (approval number: 8951337/1009/146).

Informed Consent: Informed consent form was signed.

Peer-review: Externally and internally peer-reviewed.

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C-Reactive Protein and Albumin Ratio Predicts Mortality in Elderly Patients Aged Eighty Years and Over with Non-ST-Segment Elevation Myocardial Infarction

C-Reaktif Protein/Albümin Oranı ST-Segment Yükselmesiz Miyokart Enfarktüsü Olan Seksen Yaş ve Üzerindeki Yaşlı Hastalarda Mortaliteyi Öngörür

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ABSTRACT

Introduction: To explore the prognostic importance for admission of C-reactive protein (CRP)/albumin ratio (CAR) in elderly patients aged 80 years over who presented with non-ST elevation myocardial infarction (non-STEMI).

Methods: This retrospective, observational research was related to the clinical data of 528 elderly non-STEMI patients. The study population was categorized based on CAR tertiles as T1, T2, and T3 groups. The CAR was obtained by dividing CRP to albumin level. The main outcome of the research was the in-hospital mortality.

Results: The in-hospital mortality rate during index hospitalization was 5% (n=27 patients). Cases included in the T3 tertile had significantly higher incidence of cardiopulmonary arrest, cardiac mortality, and all-cause mortality during the index hospitalization [(15% vs 4% vs 0.5%), (10% vs 1% vs 0%), and (13% vs 2% vs 0%), respectively, p<0.05 each]. In multivariate analysis, chronic renal failure, Killip class of >1 on admission, revascularization, and CAR (odds ratio: 1.47, 95% confidence intervals: 1.23-1.75, p<0.01) were independent parameters related with in-hospital mortality. A receiver operating characteristics curve analysis revealed that CAR >1.12 predicted in-hospital mortality with a sensitivity of 85% and specificity of 77% (area under the curve: 0.813, p<0.01).

Conclusion: In this clinical research, we observed that CAR may be a significant predictor of mortality in elderly patients who were aged 80 years and over with non-STEMI.

Keywords: C-reactive protein/albumin ratio, myocardial infarction, inflammation, acute coronary syndrome

ÖZ

Amaç: ST-segment yükselmesi olmayan miyokard enfarktüs (non-STYOME) ile başvuran 80 yaş üstü yaşlı hastalarda başvuru C-reaktif protein (CRP)/albümin oranının (CAO) prognostik önemini araştırmaktır.

Yöntemler: Bu geriye dönük, gözlemsel çalışma, STYOME'li 528 yaşlı hastanın klinik verileriyle ilgiliydi. Çalışma popülasyonu, CAO tertillerine göre T1, T2 ve T3 grupları olarak kategorize edildi. CAO'yu, CRP'nin albümin düzeyine bölünmesiyle elde edildi. Çalışmanın birincil ana sonlanımı, hastane içi mortaliteydi.

Bulgular: İndeks hastaneye yatışta, mortalite %5 (n=27 hasta) idi. T3 grubuna dahil edilen hastalarda, kardiyopulmoner arrest, kardiyak mortalite ve tüm nedenlere bağlı mortalite hastanede yatış sırasında önemli ölçüde daha yüksek saptandı [(%15 vs %4 vs %0,5), (%10 vs %1 vs %0) ve (%13 vs %2 vs %0), sırasıyla, her biri için p<0,05]. Çok değişkenli analizde; kronik böbrek yetmezliği, başvuru Killip sınıf >1, revaskülarizasyon ve CAO (olasılık oranı: 1,47, 95% güven aralığı: 1,23-1,75, p<0,01) hastane içi mortalitenin bağımsız prediktörleri ile ilişkiliydi. Alıcı işletim karakteristiği eğrisi analizi, CAO >1,12'nin %85 duyarlılık ve %77 özgüllük ile hastane içi mortaliteyi öngördüğünü ortaya koydu (eğri altındaki alan: 0,813, p<0,01).

Sonuç: Bu klinik araştırmada, STYOME'li 80 yaş ve üstü yaşlı hastalarda CAO'nun, mortalitenin önemli bir prediktörü olabileceğini gözlemledik.

Anahtar Kelimeler: C-reaktif protein/albümin oranı, miyokart enfarktüsü, enflamasyon, akut koroner sendrom

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Introduction

Acute coronary syndrome (ACS) is the main cause of deaths worldwide (1). As a consequence of increased life expectancy, the proportion of elderly patients in acute myocardial infarction (AMI) population is rising (2). Patients older than 80 years constitute 20% of AMI cases, and their mortality and morbidity are significantly elevated compared to younger patients with AMI (3). Thus, early risk stratification by clinical and laboratory parameters as well as patient specific treatment plans in this patient group is crucial to reduce mortality.

Inflammation, which is closely linked to atherosclerosis development, has a vital role in the onset, progression, and destabilization of atherosclerotic plaque that leads to myocardial ischemia due to plaque rupture and thrombosis (4-6). Inflammation can either increase or decrease acute phase proteins in the body. In particular, C-reactive protein (CRP), which is assumed to be a positive acute phase protein, is closely linked to atherosclerosis and cardiovascular disease in previous studies (7,8). In addition, serum albumin, which is accepted to be a negative acute phase protein and indicator of nutritional status, is related with the progression of atherosclerosis and poor cardiovascular events (9).

The CRP/albumin ratio (CAR) is a recently developed inflammation-based bioindex that showed to better predict outcome in a variety of disorders (malignancy, sepsis, and acute medical illness) than each parameters separately (10-13). Moreover, in a recent research, Çınar et al. (14) showed that an elevated CAR is associated with higher in-hospital and long-term mortality rates in patients with ST elevation myocardial infarction (STEMI) undergoing a primary percutaneous coronary intervention (PCI). However, the prognostic significance of this index has not been explored in predicting in-hospital death in elderly cases who were aged 80 years and over and diagnosed with non-STEMI. Hence, this study aimed to examine the prognostic significance of admission CAR in elderly subjects aged 80 years and over with non-STEMI.

Methods

Data Collection

This observational and retrospective research was conducted in elderly cases aged 80 years and over with non-STEMI admitted to a tertiary heart center. Exclusion criteria in the present study includes the following: Patients who had hepatobiliary disorder, acute inflammatory status, hematological disorder, end-stage renal disease, acute anemia, coagulopathy, cancer, venous graft-related infarcts, and those who presented with cardiogenic shock or cardiac arrest. Applying the exclusion criteria, a total of 528 non-STEMI elderly participants were enrolled in the present study. Clinical and laboratory data were retrieved from the hospital's electronic database. Non-STEMI was accepted according to the criteria of the European Society of Cardiology non-STEMI guideline (15). Informed consent form each case included in the study and an approval form the Haydarpaşa Numune Training and Research Hospital Local Ethics Committee was obtained (approval number: 2019/KK/157, date: 13.01.2020).

Laboratory Analysis and Echocardiographic Examination

In all cases, blood samples were obtained following admission to the emergency service. After sampling, complete blood count parameters were immediately analyzed by an ABX Pentra DX 120 hematology device. Biochemical parameters were analyzed by the Roche Cobas Integra 800 device. The CAR was obtained by dividing CRP to albumin level. In all cases, transthoracic echocardiography was performed before discharge using a commercially available machine. From the apical 4-chamber view, left ventricular ejection fraction (LVEF) of each case was estimated using the Simpson method.

Interventional Procedure

The attending physician decided for whom coronary angiography (CAG) will be performed according to hospital protocol. All cases were treated with two antiplatelet regimen, which was consisted of aspirin and either clopidogrel or ticagrelor loading dose. In all cases undergoing a PCI, intravenous unfractionated heparin (35-70 IU/kg) was used to achieve a periprocedural anticoagulation. A stent implantation during the PCI procedure was performed in accordance with the current myocardial revascularization guideline (15). The main aim of PCI procedure was to acquire a residual stenosis of <10% with thrombolysis in myocardial infarction-3 flow in the infarct-related artery by a visual evaluation.

Study Outcome and in-hospital Events

The main outcome of the research was the in-hospital death. In addition, data were collected regarding in-hospital events, such as ventricular tachycardia, ventricular fibrillation, and cardiac mortality, during index hospitalization.

Statistical Analysis

The International Business Machines SPSS software 21.0 was used to perform all statistical analyses. The number of cases and percentages were utilized for categorical parameters, whereas data was presented as mean ± standard deviation or median (25-75 intelligence quotients) for continuous variables. The Kolmogorov-Smirnov test was utilized to determine whether normal distribution assumption for continuous variables was provided or not. All categorical variables were analyzed with either a chi-square test or a Fisher's exact test. To evaluate the quantitative data, the Kruskal-Wallis test was used. Univariable and multivariable logistic regression analysis were applied to find out the independent parameters linked with in-hospital death. After performing univariable examination, parameters with $p<0.05$ were selected into a multivariable logistic regression examination. The odds ratio (OR) with 95% confidence intervals (CI) were used to present the findings of univariate and multivariate regression analyses. Cut-off value of CAR for in-hospital mortality with a highest sensitivity and specificity was calculated by nonparametric receiver operating characteristic (ROC) curve analysis. The model fit of multivariable analysis was assessed with Hosmer-Lemeshow test, which did not suggest a lack of fit ($X^2=8.19$, $p=0.41$). A p-value of <0.05 was accepted to be a statistically significant.

Results

The mean age of the study cohort was 85±4 years. In total, 314 (59%) cases were female. The in-hospital mortality rate during index hospitalization was 5% (n=27 patients). We categorized the study cohort based on CAR tertiles. Participants with CAR value of <0.24 (n=176) were stratified into T1 tertile, participants with CAR value of 0.24-0.73 (n=176)

were stratified into T2 tertile, and participants with CAR value of >0.73 (n=176) were stratified into T3 tertile.

The baseline demographic characteristics and laboratory findings of all cases are displayed in Table 1. T3 participants had a higher prevalence of diabetes, chronic renal failure (CRF) and active smoking compared to those in the other tertiles (p<0.05 for each). T3 tertile participants had an elevated Killip class and heart rate but a significantly decreased systolic and diastolic blood pressure upon admission compared to those stratified into T1 and T2 tertiles (p<0.05 for each). In terms of echocardiographic and laboratory findings, T3 tertile participants had a lower LVEF, albumin, and hemoglobin levels but higher CRP, white blood cell (WBC) counts, CAR, troponin, and creatinine kinase-myocardial band levels (p<0.05, for each). Both groups were indifferent in terms of premedication.

Both invasive CAG and PCI were significantly less performed in T3 tertile participants (p<0.05 for each). T3 tertile participants had significantly elevated incidence of cardiopulmonary arrest, cardiac mortality, and all-cause mortality during the index hospitalization [n=27 (15%) vs n=7 (4%) vs n=1 (0.5%), n=18 (10%) vs n=2 (1%) vs n=0 (0%) and n=23 (13%) vs n=4 (2%) vs n=0 (0%), respectively, p<0.05 for each) (Table 2).

Effects of different variables in in-hospital death were explored using univariable and multivariable logistic regression analysis, as shown in Table 3. Congestive heart failure, CRF, Killip class >1, WBC count, CRP, albumin, revascularization during index hospitalization, and CAR were predictors of in-hospital death based on a univariable analysis. According to a multivariable model that adjusted for the aforementioned parameters, CRF (OR: 3.53, 95% CI: 1.09-13.44, p=0.04), Killip class >1 (OR: 4.06, 95% CI: 1.72-9.55, p=0.013), revascularization during index hospitalization (OR: 0.25, 95% CI: 0.07-0.94, p=0.04) and CAR (OR: 1.47,

Table 1. Baseline properties and laboratory results of all patients according to CAR tertiles

	CAR with tertiles				
	Total (n=528)	**T1 <0.24 (n=176)**	**T2 0.24-0.73 (n=176)**	**T3 >0.73 (n=176)**	**p**
Age, years	85±4	84.8±3.9	84.8±3.8	85.2±4.2	0.52
Female gender, (n, %)	314 (59)	107 (60)	108 (61)	99 (56)	0.56
Hypertension, (n, %)	409 (77)	138 (78)	140 (79)	131 (74)	0.31
History of CAD, (n, %)	197 (37)	71 (40)	59 (33)	67 (38)	0.36
Diabetes mellitus (n, %)	203 (38)	75 (42)	56 (31)	72 (40)	0.08
History of HF, (n, %)	64 (12)	23 (13)	17 (10)	24 (14)	0.46
History of CRF, (n, %)	101 (19)	27 (15)	27 (15)	47 (27)	<0.01
Smoking, (n, %)	41 (7)	10 (5)	15 (8)	16 (9)	0.03
Heart rate, beat per min	91±26	87±23	91±27	95±26	0.02
DBP on admission, mmHg	80±19	81±18	82±20	77±18	0.02
SBP on admission, mmHg	146±30	151±29	150±30	138±30	<0.01
Killip class >1, (n, %)	86 (16)	19 (11)	22 (12)	45 (26)	<0.01
LVEF, (%)	47±11	48±10	47±11	44±12	<0.01
Laboratory results					
Hemoglobin, g/dL	12.4±1.9	12.6±1.8	12.6±1.9	11.9±1.8	<0.01
WBC count, 10^3 µ/L	9.1 (7.5-11.4)	8.8 (7.1-10.6)	8.7 (7.2-10.4)	10.1 (8-14.2)	<0.01
Baseline creatinine, mg/dL	1.19±0.72	1.13±0.65	1.14±0.64	1.31±0.85	0.06
Serum glucose level, mg/dL	155±78	156±85	148±73	163±77	0.26
Serum albumin, g/dL	3.6 (3.3-3.9)	3.7 (3.5-4.0)	3.7 (3.5-4.0)	3.4 (3.1-3.6)	<0.01
C-Reactive protein, mg/dL	1.5 (0.7-3.9)	0.4 (0.3-0.7)	1.5 (1.2-1.9)	6.2 (3.9-10.9)	<0.01
CAR	0.39 (0.20-1.20)	0.12 (0.07-0.20)	0.39 (0.31-0.50)	1.90 (1.20-3.30)	<0.01
Troponin I, ng/mL	0.40 (0.10-2.43)	0.3 (0.07-1.14)	0.3 (0.08-1.03)	1.5 (0.19-4.04)	<0.01
CK-MB level, IU/L	17 (11-31)	14 (10-22)	16 (10-29)	22 (12-47)	<0.01
Premedication					
Antiplatelet treatment, (n, %)	165 (31)	57 (32)	46 (26)	62 (35)	0.38
ACE/ARB, (n, %)	173 (33)	65 (37)	52 (29)	56 (32)	0.56
Beta blocker, (n, %)	142 (27)	47 (27)	46 (26)	49 (28)	0.85
Statin, (n, %)	91 (17)	27 (15)	35 (20)	29 (16)	0.48

CAR: C-reactive protein/albumin ratio, CAD: coronary arterial disease, HF: heart failure, CRF: chronic renal failure, DBP: diastolic blood pressure, SBP: systolic blood pressure, LVEF: left ventricular ejection fraction, WBC: white blood cell, CK-MB: creatinine kinase-myocardial band, ACE: angiotensinogen inhibitor, ARB: angiotensinogen receptor blocker

95% CI: 1.23-1.75, p=0.003) were independent predictors linked with in-hospital death.

An ROC analysis revealed that CAR >1.12 predicted in-hospital mortality with a sensitivity of 85% and specificity of 77% [area under the curve (AUC): 0.813, p<0.01]. AUC of CAR was significantly larger compared to AUC of CRP (AUC: 0.785) and albumin levels (AUC: 0.665), which indicates the discriminative power of CAR over CRP and albumin levels for prediction of in-hospital mortality (p=0.02 and p<0.01, respectively) (Figure 1).

Discussion

In this research, CAR was noted as a significant predictor of in-hospital death in elderly cases aged 80 years and over with non-STEMI. In addition, the combination of CRP and serum albumin into single bioindex, namely CAR, might predict poor outcomes better than either parameter alone.

Improved living condition and access to healthcare system lead to an increase in life expectancy, especially in elderly patients. As a result, an increase was noted in the proportion of participants presenting with ACS, including non-STEMI (16,17). However, age is an important predictor of poor clinical outcomes in AMI, and the potential benefit of reperfusion strategies in this patient group is controversial (18). Therefore, it is important to identify a prognostic biomarker to differentiate patients for whom an invasive strategy would be beneficial to better manage limited medical resources.

AMI causes a more severe inflammatory reaction particularly in patients with large infarction (19). This inflammatory reaction during AMI can

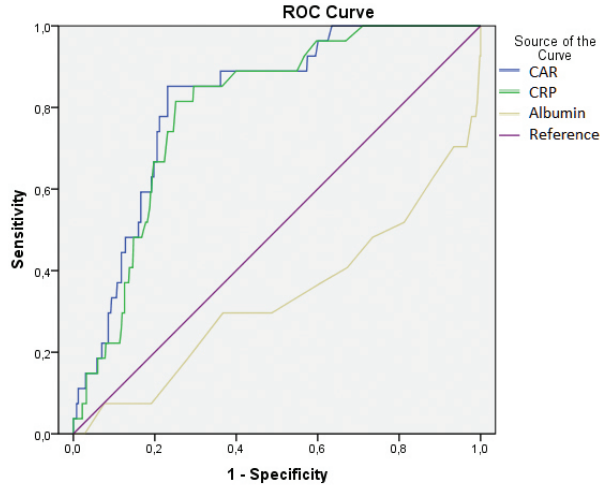

Figure 1. Receiver operating characteristics curve analysis of CAR, CRP, and albumin

CAR: C-reactive protein/albumin ratio, CRP: C-reactive protein, ROC: Receiver operating characteristics

Table 2. Coronary angiographic findings and in-hospital events of all patients according to CAR tertiles

	CAR with tertiles				
	Total (n=528)	T1 <0.24 (n=176)	T2 0.24-0.73 (n=176)	T3 >0.73 (n=176)	p
Revascularization					
ICA, (n, %)	298 (56)	109 (61)	111 (63)	78 (44)	<0.01
PCI, (n, %)	142 (27)	57 (32)	51 (29)	34 (19)	0.02
CABG, (n, %)	44 (8)	16 (9)	9 (5)	19 (11)	0.14
In-hospital events					
VT/VF, (n, %)	11 (2)	2 (1)	4 (2)	5 (3)	0.52
CPA, (n, %)	35 (6)	1 (0.5)	7 (4)	27 (15)	<0.01
Cardiac mortality, (n, %)	20 (3)	0 (0)	2 (1)	18 (10)	<0.01
All-cause mortality, (n, %)	27 (5)	0 (0)	4 (2)	23 (13)	<0.01

ICA: Invasive coronary angiography, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, VT: ventricular tachycardia, VF: ventricular fibrillation, CPA: cardiopulmonary arrest, CAR: C-reactive protein/albumin ratio

Table 3. Univariable and multivariable logistic regression analysis for prediction of in-hospital mortality

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% (CI)	p	Odds ratio	95% (CI)	p
CHF	2.66	(1.08-1.56)	0.034	-	-	-
CRF	3.05	(1.37-6.79)	0.006	3.53	(1.09-13.44)	0.04
Killip class >1	6.42	(2.89-14.21)	<0.01	4.06	(1.72-9.55)	<0.01
Revascularization	0.21	0.06-0.73	0.02	0.25	0.07-0.94	0.04
WBC count 10^3/µL	1.14	(1.04-1.25)	<0.01	-	-	-
CRP, mg/dL	1.12	(1.06-1.19)	<0.01	-	-	-
Albumin, g/dL	0.21	(0.09-0.41)	<0.01	-	-	-
CRP/albumin ratio (CAR)	1.47	(1.24-1.74)	<0.01	1.47	(1.23-1.75)	<0.01

CI: Confidence interval, CHF: congestive heart failure, CRP: C-reactive protein, WBC: white blood cell, CRF: chronic renal failure, CAR: C-reactive protein/albumin ratio

lead to elevation of CRP levels. In previous studies, high CRP levels have been found to be a poor predictor of cardiovascular events (20,21). The inflammatory process can cause a decrease in albumin in the body besides elevation CRP levels. Decreased albumin levels are closely related with an elevated morbidity and mortality risk in various forms of cardiovascular disease (22). Previous studies reported that higher CRP levels with lower albumin levels are linked with increases mortality rates in patients with chronic kidney disease (23,24). Moreover, Wada et al. (25) observed that both low serum albumin and high CRP levels had a synergistic adverse effect on the long-term risk of major adverse events in cases undergoing PCI. Thus, both CRP and serum albumin status can be used to identify patients with an exaggerated inflammatory condition.

The CAR is a newly defined systemic inflammatory bioindex that combines both CRP and albumin (4). Several researches have explored the prognostic value of CAR in participants with cardiovascular disease (14,26-28). In a recent research by Çınar et al. (14) an elevated CAR was observed to be independently linked with elevated in-hospital and long-term mortality in STEMI cases treated with a primary PCI. Moreover, Cağdaş et al. (27) observed that elevated CAR is related with a more severe form of coronary artery disease according to the Syntax score. In addition, Duman et al. (28) observed that CAR could be used as a useful and reliable marker in predicting coronary thrombus burden in cases with ACS. However, to our knowledge, the prognostic importance of the CAR has not been investigated in elderly non-STEMI cases. In our study, patients were classified from low to high (T1, T2, and T3) according to CAR values during index hospitalization. Both cardiac and all-cause mortality rates was found to be significantly higher in cases included the T3 tertile compared to those in the T2 and T1 tertiles. In addition, CAR was independently linked with in-hospital mortality according to our multivariable examination.

Our study results are considered to be clinically important regarding the follow-up and treatment plans for elderly patients with non-STEMI. Particularly, CAR may be a part of risk stratification in this high-risk patient group. In addition, it may be used to identify patients who need closely clinical follow-up and a more aggressive treatment approach if validated in large scale prospective trials.

Study Limitations

Our study had the following limitations. First, results of the study were based on retrospective design, which might be related with a selection bias. However, all consecutive elderly non-STEMI cases were included in this analysis. Second, our study was conducted in one geographical area, thus, restricting the generalizability of our results to other geographical areas. Third, we considered a possible presence of residual confounding from unmeasured variables, which might affect the final outcome of the study. Finally, further multi-center researches enrolling more patients are necessary to elucidate the exact relation between CAR values and in-hospital mortality in elderly patients with non-STEMI.

Conclusion

We have found that elevated CAR is a predictor of poor prognosis in elderly participants with Non-STEMI. Thus, as a simple and inexpensive inflammatory index, CAR might be used for early treatment plans to decrease in-hospital deaths in such patients.

Ethics Committee Approval: The approval form the Haydarpaşa Numune Training and Research Hospital Local Ethics Committee was obtained (approval number: 2019/KK/157, date: 13.01.2020).

Informed Consent: Informed consent was obtained form each case included in the study.

Peer-review: Externally and internally peer-reviewed.

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The Effect of Body Mass Index on Blood Pressure and Heart Rate Response During Treadmill Exercise Test in Non-diabetic Adults

Vücut Kitle İndeksinin Diyabeti Olmayan Yetişkinlerde Efor Testi Esnasında Gözlenen Kan Basıncı ve Kalp Hızına Olan Etkisi

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ABSTRACT

Introduction: Exaggerated blood pressure response to exercise is an independent risk of future hypertension (HT), and impaired heart rate (HR) response is a predictor of cardiovascular mortality and morbidity. Obesity is a risk factor for HT. This study aimed to evaluate the influence of body mass index (BMI) on systolic blood pressure (SBP) and HR during exercise treadmill test.
Methods: Data of 124 patients without diabetes who completed treadmill test with negative results were obtained from archives of the test unit. Patients were divided into three groups according to BMI; 18.5-24.9 (normal), 25-29.9 (overweight), and >30 (obese). Basal, 3rd and 6th minutes, peak exercise, 2nd minute of recovery phase SBP and HR values, and level changes (Δ) from the beginning were compared. A p-value of <0.05 was considered statistically significant.
Results: There was a difference in terms of mean SBP and ΔSBP among the three groups (p<0.05). The 6th minute and peak exercise difference was more apparent between the obese and normal groups (p<0.001). The overweight and obese group had significantly higher mean SBP and ΔSBP values than the normal group during the recovery phase (p=0.005 and <0.001, respectively). Analysis of HR revealed that the obese group had higher HR levels than the normal group in the 3rd and 6th minutes (p<0.001 and p=0.003, respectively) but no difference at the peak and recovery phases.
Conclusion: Office blood pressure measurements may underrecognize the hypertensive status during active daily life. Exercise tests can help identify particularly overweight or obese individuals with exaggerated blood pressure response to exercise and are, therefore, at risk of developing HT. In this way, these individuals can be directed to early exercise and diet programs.

Keywords: Body mass index, exercise test, blood pressure, heart rate

ÖZ

Amaç: Egzersize abartılı kan basıncı yanıtı, gelecekte hipertansiyon gelişimi için bağımsız bir risk oluştururken, bozulmuş kalp hızı (KH) yanıtı ise kardiyovasküler mortalite ve morbidite için bir belirleyici olarak kabul görmüştür. Obezite hipertansiyon için bir risk faktörüdür. Bu çalışmada vücut kitle indeksinin (VKİ) efor testi esnasında gözlenen sistolik kan basıncı (SKB) ve KH yanıtı üzerine etkisini değerlendirmeyi amaçladık.

Yöntemler: Efor testini negatif sonuçlarla tamamlayan 124 diyabetsiz hastanın verileri, test ünitesinin arşivlerinden elde edildi. Hastalar VKİ'ye göre üç gruba ayrıldı; 18,5-24,9 (normal), 25-29,9 (aşırı kilolu) ve >30 (obez). Bazal, 3., 6. dakika, zirve egzersiz, iyileşme fazı 2. dakika SKB ve KH değerleri ve başlangıca göre değişim miktarları (Δ) gruplar arasında karşılaştırıldı. P<0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Üç grup arasında ortalama SKB ve ΔSKB açısından istatistiksel olarak anlamlı fark mevcuttu (p<0,05). Altıncı dakika ve zirve egzersiz anında ortalama SKB ve ΔSKB açısından fark obez grupta daha belirgindi (p<0,001). Recovery fazında aşırı kilolu ve obez grubun normal gruba göre SKB ve ΔSKB ortalamaları normal gruba göre anlamlı olarak daha yüksekti (sırasıyla; p=0,005; p<0,001). KH analizinde obez grubun KH seviyeleri 3. ve 6. dakikalarda normal gruptan daha yüksekti (sırasıyla; p<0,001; p=0,003), ancak zirve ve iyileşme aşamasında fark bulunmadı.

Sonuç: Poliklinik kan basıncı ölçümleri, aktif günlük yaşam sırasında gelişen hipertansif durumu saptayamayabilir. Efor testi, egzersize aşırı hipertansif yanıt gösteren bu nedenle HT gelişme riski taşıyan aşırı kilolu veya obez bireylerin saptanmasında ayrıca bu bireylerin diyet ve egzersiz programlarına yönlendirilmesinde yardımcı olabilir.

Anahtar Kelimeler: Vücut kitle indeksi, efor testi, kan basıncı, kalp hızı

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Introduction

Hypertension (HT) is a leading risk factor for increased cardiovascular morbidity and mortality (1). In obesity, HT is three times more likely to be observed (2). Furthermore, according to the Framingham Heart study, body weight above 20% of the ideal weight increases HT probability by up to eight times (3). An exaggerated blood pressure response to moderate exercise is an indicator of cardiovascular risk and an independent risk of future HT (4,5). Increasing the heart rate (HR) is an immediate physiological response to exercise and after exercise cessation; HR is expected to return to resting values. HR response to a graded exercise test is a powerful predictor of cardiovascular mortality and morbidity (6,7). The standard graded exercise test is an easy and inexpensive tool that provides a wealth of information on the cardiovascular system (6). Bruce protocol treadmill test with increasing speed and level is a commonly used graded exercise test (8). Body mass index (BMI) is a historical strong predictor of metabolic risks and is used to differentiate between normal weight, overweight, and obese subjects by approximating adiposity and fat distribution in adults (9,10). The influence of BMI and obesity on blood pressure response and HR during and after exercise was demonstrated in various studies before (11-15).

Unlike previous studies, this retrospective study aimed to evaluate the changes in systolic blood pressure (SBP) and HR in acute exercise and exercise resting phase between non-diabetic normal weight, overweight, and obese adults whose treadmill testing was negative for ischemia.

Methods

In this retrospective study, patients who were referred to our center between September 2012 and February 2013 for a treadmill exercise test were searched from the records. Clinical properties and anthropometric measurements were obtained from the archives of the treadmill test unit and the hospital database. Patients with diabetes mellitus diagnosis or more than stage 1 HT [SBP >159 mmHg and diastolic blood pressure (DBP) >99 mmHg], according to JNC 7, were excluded (16). Treadmill exercise testing was initiated and reported based on the American College Cardiology/American Heart Association practice guidelines using a Bruce protocol modified by two warm-up stages (8,17). A total of 124 patients without diabetes who completed the test with negative results for ischemia were enrolled in the study. Patients were told to take their anti-hypertensive medications at their regular schedule. During the test, patients were questioned every 2 min for symptoms, and the HR, blood pressure, and 12-lead electrocardiogram were recorded at baseline, end of each stage, and peak exercise. All patients reached the target HR (85% of 220 age) without ischemic symptoms or electrocardiogram changes.

Patients were divided into three groups according to their BMI: normal group 1 (18.5-24.9), overweight group 2 (25-29.9), and obese group 3 (>30). SBP and HR values were obtained from our database program at the beginning, 3rd and 6th minutes, peak of exercise, and 2nd minute of recovery. The mean SBP and HR levels and level changes (delta: Δ) from the basal values were compared between the three groups.

The study protocol has been approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Hospital Ethics Committee (approval number: 237, date: 22.02.2013), and written informed consent was obtained from all patients.

Statistical Analysis

Numerical parameters were reported as mean ± standard deviation and categorical variables as percentage (%). In comparison, parametric or non-parametric statistical methods were used depending on whether the variable was normally distributed or not. One-Way analysis of variance and Tukey honest significant difference were used as a post-hoc test in comparison between the three groups in numerical parameters showing normal distribution. Chi-square statistics were used to compare categorical variables. Statistical analysis was performed using SPSS v.12.0. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics of patients are summarized in Table 1. All three groups were well matched with respect to age, gender, and mean HR and SBP at the beginning, and all groups reached the target HR percentage at peak exercise. The percentages of stage 1 HT among groups were similar

Table 1. Baseline characteristics of patients

	Total no of patients	Normal weight (group I)	Overweight (group II)	Obese (group III)	
Patient number, n (%)	**124 (100%)**	**39 (31.5%)**	**41 (33.1%)**	**44 (35.4%)**	**p**
Sex					
Female, n (%)	60 (48.4%)	18 (30%)	20 (33.3%)	22 (36.7%)	0.939
Male, n (%)	64 (51.6%)	21 (32.8%)	21 (32.8%)	22 (34.4%)	
Age (years), median (min-max)	49 (22-69)	49 (28-66)	47 (22-69)	49 (25-68)	0.437
BMI (kg/m^2), mean ± SD	28.5±5	23.2±1.6	27.8±1.3	33.9±3.3	-
Stage 1 HT, n (%)	45 (36.3%)	13 (33.3%)	15 (36.6%)	17 (38.6%)	0.881
Baseline SBP (mmHg), mean ± SD	124.2±16.1	122.8±15.8	121.9±16.6	127.7±15.6	0.204
Baseline HR (BPM), mean ± SD	96.1	97.2	94.3	96.9	0.633
Target HR (%)	93.2±6.1	91.6±6.3	94±6.4	93.9±5.6	0.155
Exercise time (minutes), mean (min-max)	7.9 (6-11.4)	8.5 (6-11.4)	8.1 (6.1-10.5)	7.5 (6-10.1)	0.013
MET, mean (min-max)	9.38 (7-12.8)	9.69 (7-12.8)	9.71 (7.3-12.8)	8.8 (7-11)	0.010

BMI: Body mass index, HR: heart rate, HT: hypertension, MET: metabolic equivalent, SBP: systolic blood pressure, SD: standard deviation, BPM: beat per minute, min: minimum, max: maximum

(p=0.881). There was a significant difference between the three groups in terms of exercise duration (p=0.013), and it was found that normal weight patients exercised longer than obese patients in the paired comparison (p=0.017). Correspondingly, the metabolic equivalent (MET) value achieved was significantly different between the groups (p=0.010); particularly, it was lower in the obese group than the normal and overweight groups (p=0.030 and 0.024, respectively). In all three groups, a significant increase was seen in SBP and HR during exercise and a significant decrease in the recovery phase as expected. However, there was a statistical difference in terms of mean SBP and average ΔSBP among the three groups (p<0.05; Table 2). In cross-group comparisons of mean SBP, a significant difference was observed between the normal and obese groups in the 3rd minute (p=0.004; Table 3). Obese patients had greater SBP responses. In the 6th minute and at peak exercise, the difference was more apparent between the normal and obese groups in terms of mean SBP and ΔSBP (p<0.001). The overweight and obese groups had significantly higher mean SBP and ΔSBP values than the normal group at the 2nd minute of recovery phase (p=0.005 and <0.001, respectively). In short, the SBP of the obese and overweight groups remained higher in the early recovery phase.

When average ΔSBP values were compared, statistical difference was observed between the normal and overweight groups and between the normal and obese groups at the 3rd minute, peak level, and at the 2nd minute of recovery. As the exercise duration is prolonged, ΔSBP observed during the 6th minute and peak exercise increased significantly more in the overweight and obese groups than in the normal group (p<0.001) and remained more hypertensive at the early phase of recovery.

Comparison of the mean HR and ΔHR is summarized in Table 4. There was a statistical difference in HR at the 3rd and 6th minutes of exercise with respect to mean HR and mean ΔHR among groups. Analysis revealed that the obese group had significantly higher HR levels in the 3rd and 6th minutes of exercise than the normal group (p<0.001 and 0.003, respectively; Table 5). No differences were found among groups in terms of peak exercise and recovery phase HR values.

Discussion

Dynamic exercise increases HR and blood pressure due to sympathetic tonus activation to provide adequate oxygen to fulfill the metabolic demand of exercising muscles and to guarantee metabolic end-products washout (18). Similarly, in our study, SBP and HR increased parallel to exercise duration in all groups.

The purpose of the exercise testing is to evaluate cardiovascular responses to exercise. In addition to the standard effort capacity and ischemia assessment, this test is also important in terms of blood pressure response (19). There are studies on the usability of exercise testing including indirectly evaluating endothelial dysfunction in both normotensive and hypertensive patients and determining the relationship between blood pressure response to exercise and HT development in the future. A study by Tsumura et al. (20) revealed that

Table 2. Systolic blood pressure changes among groups during exercise test

	Normal weight (Group I)	Overweight (Group II)	Obese (Group III)	p
SBP (mmHg) 3rd minute	138.0±16	147.4±22.7	152.4±20	0.005
SBP (mmHg) 6th minute	148.4±18.2	160.5±21.1	174.3±20.8	<0.001
SBP (mmHg) peak	165.4±21.8	177.0±19.1	186.8±19.7	<0.001
SBP (mmHg) recovery 2nd minute	135.9±20.9	151.0±22	164.8±21	<0.001
ΔSBP (mmHg) 3rd minute-baseline	15.2±10.5	25.5±15.8	24.7±15.3	0.002
ΔSBP (mmHg) 6th minute-baseline	25.6±14	38.6±14.4	46.6±17.4	<0.001
ΔSBP (mmHg) peak-baseline	42.6±16.8	55.1±15.6	59.1±16.3	<0.001
ΔSBP (mmHg) recovery 2nd minute-baseline	13.1±14.8	29.1±15.2	37.1±16.6	<0.001

Data are presented as mean ± standard deviation.
SBP: Systolic blood pressure, Δ: changes in levels (mmHg)

Table 3. Comparison of the systolic blood pressure responses among groups (p-values)

	Normal vs overweight	Normal vs obese	Overweight vs obese
SBP (mmHg) 3rd minute	0.089	**0.004**	0.488
SBP (mmHg) 6th minute	**0.022**	**<0.001**	**0.005**
SBP (mmHg) peak	**0.031**	**<0.001**	0.071
SBP (mmHg) recovery 2nd minute	**0.005**	**<0.001**	**0.010**
ΔSBP (mmHg) 3rd minute-baseline	**0.004**	**0.008**	0.958
ΔSBP (mmHg) 6th minute-baseline	**0.001**	**<0.001**	**0.045**
ΔSBP (mmHg) peak-baseline	**0.002**	**<0.001**	0.499
ΔSBP (mmHg) recovery 2nd minute-baseline	**<0.001**	**<0.001**	0.052

Mean SBP values were analyzed between binary groups. A p-value of <0.05 was considered statistically significant.
SBP: Systolic blood pressure, Δ: changes in levels (mmHg)

an exaggerated increase in blood pressure during exercise is associated with an elevated risk of developing HT.

Not only the exaggerated SBP but also DBP response to exercise was reported as associated with an increased risk of developing future HT in the Framingham Heart study (21).

There are also studies with different results that examine the prognostic significance of the increase in blood pressure during exercise stress testing. Gupta et al. (22) reported that the increase in SBP >44 mmHg, especially during peak exercise, was associated with better survival rates both in normotensive and hypertensive subjects (22). However, Kurl et al. (23) evaluated the increase of >19.7 mmHg every 1 min of exercise and found that exaggerated blood pressure increase was related to stroke. Obesity is a risk for developing HT, and the increase in body composition is linked to SBP response to exercise (24).

In our study, the mean SBP and ΔSBP from the beginning of exercise was significantly higher in the obese and overweight groups than in the normal group. Similar to our study, there are studies in the literature showing that ΔSBP during exercise tends to increase with obesity, mainly due to autonomic dysfunction by using methods such as isometric exercise, dynamic exercise, and cold pressor tests (11,13,25,26).

In the assessment of the mean SBP and ΔSBP from baseline to the 2nd minute of recovery, we observed that overweight and obese patients' blood pressure at the end of recovery remained significantly higher than the normal group.

Data on the importance of SBP, not decreasing properly in the recovery phase, were highlighted in the Framingham Heart study. It has been reported that the resistant high SBP, which continues up to the 4th minute in the recovery phase after exercise, is significant in terms of developing HT in the future. In middle-aged men, blood pressure in the recovery phase of the exercise testing and the risk of acute myocardial infarction were investigated, and patients with >195 mmHg SBP response after exercise have 1.69 times higher risk of acute myocardial infarction than patients with <170 mmHg blood pressure response (27).

We also evaluated HR and found that the mean HR and ΔHR were higher in the 3rd and 6th minutes of the exercise in the obese group than in the normal group. Impaired HR recovery after exercise was observed three times more prevalent in obese patients and twice in overweight patients than in those with normal BMI in a study by Barbosa Lins et al. (28). It is also broadly identified in the literature as a powerful and independent cardiovascular predictor and all-cause mortality in healthy adults and cardiovascular disease and diabetes patients (28,29).

However, our study is incompatible with the literature, and the groups' blood pressure responses and peak exercise HR or recovery phase HR values were similar.

The explanation of these unexpected results are as follows: Even in young male obese healthy subjects, a significant negative correlation between BMI and VO2 max was observed by Laxmi et al. (30), reflecting relationship between overweight and poor cardiorespiratory fitness status. Similarly, in our study, exercise capacity, especially in the obese group, was lower than in the normal group, based on exercise duration and achieved MET levels. As we observed more in the obese patient group, when the age-adjusted target HR was reached, the test was terminated if the patient described fatigue. So, the overweight and obese groups might have achieved submaximal peak exercise and had lower peak HR increase than expected compared with the normal group that performed better and longer and so has reached the maximal HR value. Therefore, a difference in the peak HR and early recovery phase HR might not be observed.

Additionally, negative chronotropic drug use could affect peak HR responses to exercise testing. Although HT frequency was similar between the groups, we do not know whether negative chronotropic drug usage was different among patients.

Table 4. Comparison of the heart rate changes between groups

	Normal weight (group I)	Overweight (group II)	Obese (group III)	p
HR (BPM) 3rd minute	118.5±17.3	120.8±18.1	129.2±18.3	**0.018**
HR (BPM) 6th minute	134.3±17	137.4±17.3	143.8±17.7	**0.044**
HR (BPM) peak	157.5±11.3	160.8±15.1	159.3±13.6	0.567
HR (BPM) recovery 2nd minute	112.3±12.8	114.8±18.5	116.8±13.6	0.486
ΔHR (BPM) 3rd minute-baseline	21.4±11.8	26.5±12	32.3±12.8	**<0.001**
ΔHR 6th minute-baseline	37.1±14	43.1±13,3	46.9±12.7	**0.005**
ΔHR peak-baseline	60.4±16.8	66.5±18.4	62.3±14.8	0.247
ΔHR recovery 2nd minute-baseline	15.1±12.6	20.5±14.4	19.8±12.7	0.145

Data are presented as mean ± standard deviation.
HR: Heart rate, BPM: beat per minute, Δ: changes in level (mmHg)

Table 5. Double group comparison results of heart rate responses (p-values)

	Normal vs overweight	Normal vs obese	Overweight vs obese
ΔHR (BPM) 3rd minute-baseline	0.153	**<0.001**	0.080
ΔHR (BPM) 6th minute-baseline	0.114	**0.003**	0.393

HR: Heart rate, BPM: beat per minute, Δ: changes in level (mmHg)

Study Limitations

The limitations of our study are as follows: because of the retrospective nature, we did not have detailed information about the subjects' stage 1 anti-hypertensive treatments or basal exercise capacity, smoking history, or regular exercise status, which might have influenced our results. Diabetes is considered the equivalent of cardiovascular disease today, and it is closely related to obesity. Therefore, patients with diabetes were excluded to minimize the effects of microvascular and macrovascular complications of diabetes on the study results, but in our study, prediabetes status could not be ruled out with the available data.

Conclusion

We observed that, especially in obese patients with BMI >30, SBP increased to higher values during exercise and showed greater level changes from baseline compared with normal patients. During the recovery period, SBP values remained higher in overweight and obese patients. HR increase was apparent in the obese group during the early phase of exercise and was unexpectedly similar at the peak and recovery phases between groups. The office blood pressure measurements may not uncover masked HT, especially in overweight and obese individuals with an active lifestyle. Thus, exercise testing can help detect individuals in this population with exaggerated blood pressure response to exercise who are at risk of developing HT and cardiovascular disease in the future and to direct them to early exercise and weight loss programs.

Ethics Committee Approval: The study protocol has been approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Local Hospital Ethics Committee (approval number: 237, date: 22.02.2013).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally and internally peer-reviewed.

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Colon Polyps with All Features: Third Step Center Experience in the Eastern Mediterranean

Tüm Özellikleri ile Kolon Polipleri: Doğu Akdeniz'de Üçüncü Basamak Merkez Deneyimi

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ABSTRACT

Introduction: Colon polyps are proliferative and neoplastic lesions which originate from the mucosa, submucosa and protrude into the lumen. With this study, we aimed to reveal the demographic data, histopathological features, malignant potential and characteristics of patients with colonic polyp in our region by evaluating the results of 4-year colononoscopic polypectomy in our tertiary university clinic.

Methods: The records of patients over 18 years of age with polyps detected during colonoscopy and removed by polypectomy between 2014 and 2019 in our hospital were retrospectively analyzed. The demographic characteristics of the patients, localization, size, number and histopathological features of the polyps, and control colonoscopy results were evaluated.

Results: During this period, data of 240 polyps of 180 patients who underwent polypectomy in our clinic were analyzed. 125 (69%) of the patients were male and 55 (31%) were female. The average age of men was 59.2±14.4, and the mean age of women was 57.2±11.3. One hundred and thirty-seven people had a single polyp, 43 people had multiple polyps. When polyps are examined according to their localization; 27% was in the sigmoid colon, 24% in the rectum and 15% in the ascending colon. 82% of polyps were adenomatous polyp, 10% hyperplastic polyps, 3% adenocarcinoma, 3% inflammatory polyp. 67% of adenomatous polyps were tubular adenoma, 27% tubulovillous adenoma, 0.5% villous adenoma. 71% of adenomatous polyps had low grade dysplasia, 23% had high grade dysplasia. Adenocarcinoma was detected in 8 of the cases and intramucosal carcinoma was detected in 6% of the patients with adenomatous polyp. Colonoscopy controls were performed periodically in the cases, and recurrent polyps were detected in 52% and adenocarcinoma development in 2 patients.

Conclusion: The colon polyps were observed in our study were more frequently in the 5th and 6th decades, and more frequently

ÖZ

Amaç: Kolon polipleri mukoza ve submukozadan köken alan ve lümen içine doğru çıkıntı yaparak kitle oluşturan proliferatif ve neoplastik olabilen lezyonlardır. Bu çalışma ile üçüncü basamak üniversite kliniğimizde 4 yıllık kolononoskopik polipektomi sonuçlarını değerlendirerek bölgemizde kolon polibi saptanan hastaların demografik verilerini, histopatolojik özelliklerini, malignite potansiyellerini ve özelliklerini ortaya koymayı amaçladık.

Yöntemler: Hastanemizde 2014-2019 yılları arasında kolonoskopide saptanmış ve polipektomi ile çıkarılmış polip olan 18 yaş üstü hastaların raporları geriye dönük olarak incelendi. Hastaların demografik özellikleri, poliplerin lokalizasyonları, büyüklükleri, sayıları ve histopatolojik özellikleri ve kontrol kolonoskopi sonuçları değerlendirildi.

Bulgular: Bu süre içinde kliniğimizde polipektomi yapılmış 180 hastanın 240 polibinin verileri incelendi. Hastaların 125'i (%69) erkek ve 55'i (%31) kadındı. Erkeklerin yaş ortalaması 59,2±14,4, kadınların yaş ortalaması ise 57,2±11,3 idi. Yüz otuz yedi kişide tek polip varken, 43 kişide birden çok polip vardı. Polipler lokalizasyonlarına göre incelendiğinde; %27 sigmoid kolonda, %24 rektumda ve %15'i çıkan kolonda idi. Poliplerin %82'si adenomatöz polip, %10 hiperplastik polip, %3 adenokarsinom, %3 enflamatuvar polipti. Adenomatöz poliplerin %67'si tübüler adenom, %27 tübülovillöz adenom, %0,5 villöz adenom idi. Adenomotöz poliplerin %71'inde düşük dereceli displazi, %23'ünde yüksek dereceli displazi vardı. Olguların 8'inde adenokarsinom, ayrıca adenomatöz polip saptanan hastaların %6'sında intramukozal karsinom tespit edilmişti. Olgularda kolonoskopi kontrolleri periyodik olarak yapılmış olup %52'sinde tekrar polipler ve 2 hastada adenokanser gelişimi saptanmıştı.

Sonuç: Bölgemizde saptadığımız kolon polipleri 5. ve 6. dekatta ve erkeklerde daha sık gördüğümüz, tek veya birden fazla sayıda olabilen sıklıkla neoplastik oluşumlardı. En sık

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ABSTRACT

in men, as single or multiple neoplastic formations. It is most commonly located in the left colon and were found to be malign at a rate of 9%. Detection of cancer precursor polyps and their removal by polypectomy show the importance of colon cancer screening programs and colonoscopy.

Keywords: Colon polyps, adenomatous polyps, colonoscopy

ÖZ

sol kolonda yerleşmektedir ve %9 oranında kanserleşmiş olarak saptanmıştır. Kanser öncüsü poliplerin saptanması ve polipektomi ile çıkarılması kolon kanseri tarama programlarının ve kolonoskopinin önemini göstermektedir.

Anahtar Kelimeler: Kolon polipleri, adenomatöz polipler, kolonoskopi

Introduction

Gastrointestinal polyps are proliferative and neoplastic lesions that originate from the mucosa and submucosa and form a mass by projecting into the gastrointestinal lumen. Gastrointestinal system polyps are most common in the colorectal region. The importance of colon polyps comes from its relationship with colon cancer. Colorectal carcinoma usually develops from an adenomatous polyp. Colorectal carcinoma is the second leading cause of cancer-related deaths in the western world (1). Colonic adenoma frequency increases with age and varies according to geography and ethnic origin (2,3). It is possible to detect and treat adenomatous polyps and early localized cancers that have not yet turned into cancer with screening programs. Colorectal cancer screening can reduce deaths from colorectal cancer with early detection. In this way, colorectal cancers are preventable and treatable diseases.

With this study, we aimed to reveal the demographic data, histopathological characteristics, malignancy potential and characteristics of patients with colonic polyp in our region by evaluating the 4-year colonoscopic polypectomy records.

Methods

The records of patients over the age of 18 who were diagnosed with colonoscopy, underwent polypectomy and diagnosed histopathologically between 2014-2019 in our hospital were retrospectively analyzed. Age and gender of all cases included in the study, histopathological type of colon polyps, location of polyps; the rectum, sigmoid colon, descending colon, transverse colon, ascending colon and cecum were divided into regions, and the number and size of polyps were recorded. In these patients, it was investigated whether malignancy developed according to the type of polyps and whether there was recurrence in the polyps. Patients with multiple polyp or recurrent polyp were included in the study as a different polyp. In this study, which was completed by retrospective file scanning, the consent of these patients was obtained during colonoscopy and the Mersin University Faculty of Medicine Local Clinical Trials Ethics Committee was obtained (approval number: 57, date: 22.01.2020).

Statistical Analysis

SPSS 21.0 for Windows program was used for statistical analysis. Descriptive statistical methods were used to evaluate the study.

Results

From the records, 12217 colonoscopy reports belonging to the range to be investigated were obtained. The data of 240 polypectomy materials obtained from 180 patients meeting the criteria were evaluated. 125 (69%) of these patients were male and 55 (31%) were female. The average age of men was 59.3±14.4, while that of women was 57.2±11.3. No serious complications developed in any of our patients who underwent polypectomy.

When we examined polyps according to their diameters, the diameter of 11 (4.6%) polyps was ≥2 cm, 84 polyps (35%) were 1-2 cm in diameter, and 45 (18.8%) polyps were 0.5-1 cm in diameter. The diameter of 100 (41.6%) polyps was ≤0.5 cm, that is, in the form of diminutive polyp (Table 1).

When we examined the polyps according to their localization in the colon, 64 (26.6%) of the polyps were in the sigmoid colon, 58 (24.2%) in the rectum, 36 (15%) in the ascending colon, 33 (13.3%) in the descending colon, and 27 (11.3%) in the transverse colon, 10 (4.1%) in the cecum, 4 (1.6%) in the entire colon, 4 (1.6%) in the anastomosis line, 2 (0.8%) in the hepatic flexure and 2 (0.8%) was observed in the splenic flexure (Table 2, Figure 1).

Table 1. Polyps by diameter

	Number (n)	Percentage (%)
≥2 cm	11	4.6
≥1 cm and <2 cm	84	35
>0.5 cm and <1 cm	45	18.8
≤0.5 cm	100	41.6

Table 2. Colon polyps by localization

	Number (n)	Percentage (%)
Sigmoid colon	64	26.6
Rectum	58	24.2
Ascending colon	36	15
Descending colon	33	13.3
Transverse colon	27	11.3
Cecum	10	4.1
All colon	4	1.6
Anastomosis line	4	1.6
Hepatic flexure	2	0.8
Splenic flexure	2	0.8

According to histopathological features, 196 (81.6%) of the sample were adenomatous polyps, 24 (10%) hyperplastic polyps, 8 (3.3%) adenocarcinomas, 7 (2.9%) inflammatory polyps, 2 (0.8%) mixed type (hyperplastic + adenomatous), 2 (0.8%) mild chronic non-specific inflammation and 1 (0.4%) focal erosive area (Table 3).

Of the adenomatous polyps, 132 (67.4%) were tubular adenoma, 54 (27.5%) tubulovillous adenoma, 1 (0.5%) villous adenoma, 5 (2.5%) sessile serrated adenomatous polyps and 4 (1.9%) in the form of adenomatous flat polyps (Table 4). Adenomatous polyps had low-grade dysplasia in 140 (71.4%), and high-grade dysplasia 44 (22.4%) out of 196 patients.

Adenocarcinoma was detected in 8 of the cases. 5 of them were men and 3 of them were women and the mean age was 64.8±9.5. In addition, intramucosal carcinoma was detected in 12/196 (6.1%) of the patients with adenomatous polyp. Three of the patients with adenocarcinoma died, 2 of them were male and 1 were female and all were over 80 years old. Although the polypoid masses of these patients were in the transverse colon and their diameter was greater than 5 cm, they had no metastases and were operated. However, they passed away due to other comorbidities. Polyp diameters of 3 patients were between 1-2 cm and one was located in the descending colon and two of them were located in the rectum. There were no signs of metastasis, only polypectomy was sufficient and the patients were still being followed up. Two of them were in 6th decade and women, with a polypoid mass in the sigmoid colon. The diameters were between 1 and 2 cm and had no signs of metastasis and were submitted to surgery. The patients were still being followed up. It was observed that seven polyps with intramucosal cancer were between 1-2 cm in diameter, four were smaller than 1 cm and one was larger than 2 cm. When we examined the patients with intramucosal carcinoma in terms of localization, eight were in the sigmoid colon, three were in the transverse colon and one was in the rectum.

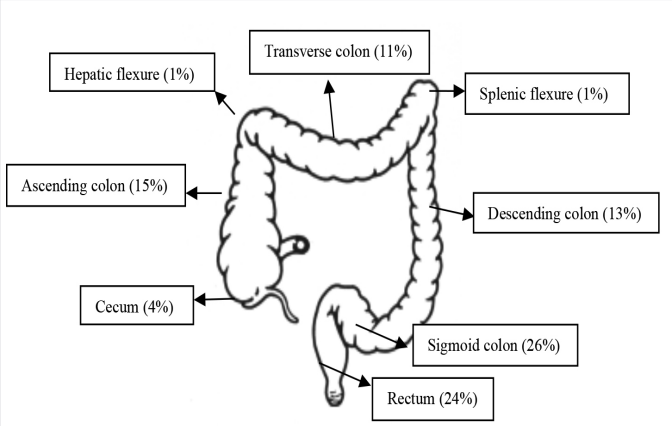

Figure 1. Polyp localizations

Table 3. Polyps according to histopathological features

	Number (n)	Percentage (%)
Adenomatous polyp	196	81.6
Hyperplastic polyp	24	10
Adenocarcinoma	8	3.3
Inflammatory polyp	7	2.9
Mixed type (hyperplastic + adenomatous)	2	0.8
Chronic non-specific inflammation	2	0.8
Focal erosive area	1	0.4

Table 4. Characteristics of adenomatous polyps

	Number (n)	Percentage (%)
Tubular adenoma	132	67.5
Tubulovillous adenoma	54	27.5
Villous adenoma	1	0.5
Sessile serrated adenoma	5	2.5
Flat adenomatous polyp	4	1.9

We also examined the control colonoscopies of the patients and any polyps or malignancies that recurred after colonoscopy. Colonoscopy was performed only once in 92 (51%) patients. 88 (49%) patients had control colonoscopy multiple times. No recurrent polyps were detected in 79 (48%) of these colonoscopies, and recurrent polyps were detected in 85 (52%). Of these, 61 (72%) had recurrent polyp in the same localization, and 14 (38%) had different localization. 58 (68%) of these patients had the same histopathological type and 27 (42%) had different histopathological types. While previous polyps were adenomatous, 16 of those with different histopathological types in control had chronic non-specific inflammation and eight had hyperplastic polyps. Tubular adenoma was found in the follow-up of 8 patients who were found to have tubulovillous type at their first colonoscopy. While there was tubulovillous adenoma in one colonoscopy, villous adenoma was detected on repeated colonoscopy. Adenocarcinoma was detected in 2 of the control colonoscopies (2.2% of the cases).

Discussion

Colon polyps can be single or multiple in multiple localizations, with or without a pedicle, neoplastic or non-neoplastic. Non-neoplastic polyps are hyperplastic polyps, inflammatory polyps, submucosal polyps (lipoma, lymphoid polyps), juvenile polyps. Adenomatous polyps are neoplastic polyps. Although polyps are clinically generally asymptomatic, rectal bleeding and iron deficiency anemia are sometimes observed; in large polyps located in the left colon, the patient can come with obstruction. Colon polyps are frequently seen in the left colon and rectum (4).

When we looked at the mean age and gender distribution of our patients in our study, we found that it is more common in males and between the ages of 50-60, consistent with other studies conducted in our country (5,6). According to localization, polyps were mostly localized in the sigmoid colon (26.6%) and rectum (24.2%) and were similar to the literature data (4).

Colorectal polyps are adenomatous polyps that are mostly neoplastic (81%). Adenomas are examined in three groups in size as those below 1 cm, between 1-2 cm and larger than 2 cm. Most adenomas are smaller than 1 cm. Those smaller than 0.5 cm are called diminutive polyps (4). Studies have reported that as the diameter of the polyp increases, the risk of dysplasia and malignancy increases, and the risk of malignancy is 10% higher in polyps that are 2 cm or larger (5). In our study, 41.6% of

the polyps were diminutive polyps, and 54% were between 0.5 and 2 cm. 4.6% of them were larger than 2 cm. In our cases, when the diameter of the polyp increased, the degree of dysplasia increased in accordance with the literature (4,5).

Adenomatous polyps according to their histopathology were tubular (65-80%), tubulovillous (10-25%) and villous (5-15%) adenoma (4,7,8). 67.4% of our cases were tubular adenoma, 27.5% were tubulovillous adenoma, which was consistent with the literature. Tubular adenomas can become malignant in 0-25%, tubulovillous adenomas in 25-75% and villous adenomas in 75-100%. Villous histology, increased polyp size, high-grade dysplasia, and an increase in the number of polyps are risk factors for cancer (3,4,9). Studies have reported that the rate of low-grade dysplasia in adenomatous polyp is 19-20.8%, and the rate of high-grade dysplasia is 6,7-8% (9,10). The low-grade dysplasia rate in adenomatous polyps in our study was 71.5% and the high-grade dysplasia rate was 22.5%. In our patients with high-grade dysplasia, polyps were found to recur on control colonoscopies, and 6.1% of them had progressed to intramucosal carcinoma. This finding may be due to the more aggressive course of lesions with high-grade dysplasia. In addition, 3.3% of all polyps had adenocarcinoma. This high rate indicates that polyps should be removed as soon as they detected and post-polyp follow-up colonoscopies are important.

Flat adenoma was detected in 1.9% of the cases. Typically, these lesions less than 1 cm in diameter can be easily overlooked on endoscopy. It is known that the progression of these adenomas to cancer is much faster than other types of adenomas (4). All of our cases were smaller than 1 cm and no malignancy was detected. There was also a 2.5% rate of sessile serrated adenoma. These adenomas, which have the characteristics of both adenomatous and hyperplastic polyps, rapidly lead to cancer development (4). In all of our cases, low-grade dysplasia was detected in sessile serrated adenomas, all of which were less than 1 cm in diameter.

Hyperplastic polyps consist of normal cellular components with normal structure and proliferative properties, do not show dysplasia, and have a characteristic “saw tooth” pattern. They are often 5 mm or less in size (4,11,12). 10% of our patients had hyperplastic polyp and 0.8% had mixed (adenomatous + hyperplastic) polyp. All of these polyps were under 1 cm and 61.5% of them were in the recto sigmoid region. None of them had dysplasia.

Inflammatory polyps are non-neoplastic intraluminal mucosa projections consisting of stromal and epithelial components and inflammatory cells. Inflammatory pseudo polyps are irregularly shaped islands of residual intact colonic mucosa that result from mucosal ulceration and regeneration in response to localized or widespread inflammation (e.g. ulcerative colitis or Crohn’s disease) (4). In 2.9% of our patients, there was inflammatory polyp, all of them larger than 1 cm in diameter and none of them had dysplasia. All of them had inflammatory bowel disease.

If adenomatous polyp is detected in the colon, control colonoscopy should be performed at certain intervals after polypectomy. Because if there is an adenoma in the colon, it means that the colon tends to develop malignancy and new adenomatous polyps may develop over time. Another reason for repeated colonoscopy is for the detection and treatment of polyps that may have been overlooked at the first colonoscopy (13-19). The timing of the next control colonoscopy is based on the findings of the initial colonoscopy. If no adenoma is found on the first surveillance colonoscopy, the next surveillance colonoscopy should be performed within five years (14,20). Patients with an advanced adenoma appear to be at high risk for colorectal at any examination and should have a short follow-up interval (1-3-5 years) for subsequent control colonoscopies (14,20). When we examined our repeated colonoscopies (49%), recurrent polyps were detected in 52% of them, and 72% were found to be in the same localization. It was observed that these were 42% different types compared to the previous histopathological type, 2 had adenocarcinoma and 1 had intramucosal cancer. All these results show that control colonoscopies should definitely be performed after the first colonoscopy.

Conclusion

It was determined that colon polyps in patients who underwent colonoscopy for various reasons in our region were more common in males and in the 5th and 6th decades, and most of them were neoplastic polyps. In the first colonoscopy, a high rate of early stage cancer (9%) was detected and treated. Detection of recurrent polyps and cancer in control colonoscopies once again demonstrated the importance of follow-up of these patients.

Ethics Committee Approval: The Mersin University Faculty of Medicine Local Clinical Trials Ethics Committee was obtained (approval number: 57, date: 22.01.2020).

Informed Consent: The consent of these patients was obtained during colonoscopy.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.Z.A., O.S., E.Ü., S.Y., O.Ö., F.A., F.Ay., H.R.B., E.A.; Concept - M.Z.A.; Design - M.Z.A., O.S.; Data Collection or Processing - M.Z.A., O.S., E.Ü., S.Y., O.Ö., F.A.; Analysis or Interpretation - M.Z.A., O.S., E.Ü., S.Y., O.Ö., E.A.; Literature Search - M.Z.A., O.S., E.Ü., S.Y., O.Ö., F.A., F.Ay., H.R.B., E.A.; Writing - M.Z.A., O.S., E.Ü.

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Association between Mean Platelet Volume and Bone Mineral Density in Rheumatoid Arthritis

Romatoid Artritte Ortalama Trombosit Hacmi ile Kemik Mineral Yoğunluğu Arasındaki İlişki

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ABSTRACT

Introduction: This study aimed to evaluate the mean platelet volume (MPV) levels in rheumatoid arthritis (RA) and determine whether there is a relationship between MPV and bone mineral density (BMD) measurement.

Methods: A total of 108 RA patients [31 osteopenia, 45 osteoporosis (OP), and 32 normal BMD] were included in the study. The age, gender, body weight, height, body mass index, MPV, calcium and vitamin D levels, and BMD scores were recorded.

Results: The mean age was 50.20±5.5 years. The mean levels of MPV were 10.70, 11.00, and 10.55 fL in the osteopenic, osteoporotic, and normal groups, respectively. The median weight and femoral neck T-score of the osteoporotic group were different from other groups. The median lumbar 1-4 T-score of all groups was different from each other. We found a negative correlation between MPV and femoral neck T-score.

Conclusion: Our study is the first to assess MPV levels in normal, osteopenic, and osteoporotic RA patients. However, we did not find similar results when the mean platelet levels of all three groups were compared. The correlation analysis showed that MPV elevation may be related to OP in the differential diagnosis for patients with RA.

Keywords: Bone mineral density, mean platelet volume, rheumatoid arthritis

ÖZ

Amaç: Bu çalışmada romatoid artritte (RA) ortalama trombosit hacmi (MPV) düzeylerini değerlendirmeyi ve MPV ile kemik mineral yoğunluğu (KMY) ölçümü arasında bir ilişki olup olmadığını belirlemeyi amaçladık.

Yöntemler: Çalışmamıza 108 RA hastası [31 osteopenik, 45 osteoporoz (OP), 32 normal KMY'ye sahip] dahil edildi. Hastaların yaş, cinsiyet, vücut ağırlığı, boy ölçüleri, vücut kitle indeksi, ortalama trombosit hacmi, kalsiyum ve D vitamini düzeyleri ve KMY skorları kaydedildi.

Bulgular: Yaş ortalaması 50,20±5,5 idi. MPV seviyesi osteopenik grupta 10,70 fL, osteoporotik grupta 11,00 fL ve normal grupta 10,55 fL idi. Osteoporotik grubun ortanca ağırlık ve femur boynu T-skoru diğer gruplardan farklıydı. Tüm grupların medyan lomber 1-4 T-skoru birbirinden farklıydı. MPV ile femur boynu T-skoru arasında negatif korelasyon bulduk.

Sonuç: Çalışmamız, normal, osteopenik ve osteoporotik RA hastalarında ortalama trombosit hacim düzeylerini değerlendiren ilk çalışmadır. Üç grupta ortalama trombosit düzeylerini karşılaştırdığımızda benzer sonuçlar bulamamış olsak da korelasyon analizi MPV yükselmesinin omatoid artritli hastalarda osteoporoz ile ilişkili olabileceğini göstermiştir.

Anahtar Kelimeler: Kemik mineral yoğunluğu, ortalama trombosit hacmi, romatoid artrit

Introduction

Rheumatoid arthritis (RA) is a chronic, symmetrical, and inflammatory autoimmune disease that affects the small joints, eyes, heart, kidneys, and lungs. The onset of this disease is usually from the age of 35 to 60 years (1). Management of RA includes conventional synthetic [disease-modifying antirheumatic drugs (DMARDs); methotrexate, leflunomide, and sulfasalazine], targeted DMARDs (tofacitinib and baricitinib), and biological DMARDs (biosimilar and biological originator) (2). Early onset, joint counts at diagnosis, rheumatoid factor/anti-citrullinated protein antibody positivity, radiographic erosion, extra-articular manifestations, comorbidities, and low bone mineral density (BMD) are reported as poor prognostic factors for RA. Osteoporosis (OP) has been reported twice as common in patients with RA than the controls (3). Also, low peak bone mass, hormonal factors, glucocorticoids, smoking, low physical activity,

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low calcium/vitamin D intake, small body size, and family history of fracture are risk factors associated with OP (4).

OP is a global health problem with an expected increase in fracture prevalence and public health burden with morbidity and mortality in the elderly population (5). It is defined as a BMD with 2.5 standard deviations (SD) or more and T-score below the average value for young healthy women (6). It occurs with the imbalance between bone resorption and bone formation. Local or systemic bone loss can occur in RA. Systemic bone loss in RA has a multifactorial etiology. It is related to the patients' disability, therapy, and risk factors such as advanced age, sex, postmenopausal period, genetic predisposition, low peak bone mass, low body weight, calcium and vitamin D deficiency, and smoking. Local (periarticular) bone loss is related to the release of cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, receptor activator of nuclear factor-κB (NF-κB), and macrophage-colony stimulating factor. The receptor activator of NF-κB ligand binds to the RANK receptor on osteoclast precursors and provokes osteoclast cell maturation (7). Pro-inflammatory cytokines such as IL-6 directly induce RANKL production through the Janus kinase/STAT pathway, STAT3 phosphorylation, and extracellular signal-regulated kinases (8).

Mean platelet volume (MPV) indicates the mean size of platelets and is widely used for platelet functions (9). There are numerous studies investigating the association between MPV and BMD (10-13). In a study, a negative correlation was found between MPV and femoral neck-lumbar spine BMD (11). Lower MPV and platelet distribution width (PDW) levels were found in OP than in the normal BMD group. Moreover, PDW was positively correlated with femur total and lumbar T-scores (12). In another study, a significantly positive correlation was found between MPV and femoral neck BMD in the normal weight osteoporotic group (13).

Megakaryocytes are responsible for platelet production and have increased osteoblast proliferation *in vivo* and *in vitro* (14). The role of platelets in bone remodeling has been investigated in Kim et al.'s (15) study. They analyzed the data of 5181 postmenopausal women and over 50 years of age men in the Korea National Health and Nutrition Examination Survey and data of 3,312 adults over 50 years of age in the Korean Genome and Epidemiology Study. The study found that the highest platelet counts were associated with osteopenia and OP in middle-aged and elderly individuals (15). D'Amelio et al. (16) reported that platelets have decreased vitamin D receptors in OP. The relationship between MPV and OP may be due to megakaryocytes' role in osteoblast proliferation (15) and decreased vitamin D receptors of platelets in OP (16). However, the exact mechanism of the relationship between MPV and BMD in RA patients is not yet known. It has been investigated in postmenopausal women (16).

Therefore, we aimed to evaluate MPV levels in RA patients and determine whether there is a relationship between MPV and BMD measurement.

Methods

A total of 108 patients with RA who were admitted to Adnan Menderes University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Division of Rheumatology were enrolled in the study. All RA patients were diagnosed according to the American College of Rheumatology/European League Against Rheumatism 2010 criteria (17). The patients were treated with bisphosphonates (alendronate, ibandronic acid, and zoledronic acid) for OP and DMARDs (methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide) for RA. Patients who were in the postmenopausal age, were pregnant and breastfeeding, have a spinal implant history, used drugs that cause OP, and have malignancies such as leukemia, lymphomas, and immune thrombocytopenic purpura were excluded from the study. Our study was conducted according to the criteria set by the Declaration of Helsinki, and the Aydın Adnan Menderes Faculty of Medicine Ethics Committee approved the study (approval no: 2017/1123, date: 23.03.2017). Written informed consent was obtained from all patients.

The age, gender, body weight, height, body mass index (BMI), MPV, calcium and vitamin D levels, and BMD scores were recorded for this retrospective study. BMI was calculated using the formula of weight/height^2, where height is expressed in meters and weight in kilograms. Dual-energy X-ray absorptiometry (Hologic, Inc., Waltham, MA, USA) was used to assess BMD in two bone sites of the femur (neck, intertrochanteric zone, and trochanter) and spinal lumbar vertebrae (Lumbar 1-4). OP was determined based on the World Health Organization criteria as follows: BMD T-score of -1.0 or more is normal, -2.5 and -1.0 is low bone mass (osteopenia), and -2.5 or less is OP. Compression fractures were evaluated using medical history, physical examination, and, if necessary, radiography in patients.

Statistical Analysis

The data were analyzed using the SPSS version 19.0. Descriptive statistics were presented as number, frequency (%), mean $\pm$ SD, and median (25th-75th percentile). The Kolmogorov-Smirnov test examined whether the variables were normally distributed or not. Mann-Whitney U test was used to compare not normally distributed differences between groups. Spearman's correlation test was used to determine the relationship between quantitative nonnormally distributed variables. A correlation coefficient r value of 0.00-0.19 is defined as "very weak," 0.20-0.39 as "weak," 0.40-0.59 as "moderate," 0.60-0.79 as "strong," and 0.81.0 as "very strong." The results were assessed at 95% confidence interval, and a p-value of less than 0.05 was considered significant.

Results

A total of 108 patients with RA were included in the study. The mean age of RA patients was 50.2$\pm$5.5 years. Of patients, 12% were men and 88% women. Patients were divided into three groups according to BMD results as follows: Normal, osteopenic, and osteoporotic patients. The demographic and laboratory features of the patients are shown in Table 1. No significant differences were found between the groups in terms of age, MPV, and calcium and vitamin D levels (Table 1). The median height and BMI of the osteoporotic and normal groups were different from each other ($p<0.001$ and $p=0.024$, respectively). The median weight and femoral neck T-score of the osteoporotic group were different from other groups ($p<0.001$ and $p<0.001$, respectively). The median lumbar 1-4 T-score of all groups was different from each other ($p<0.001$).

A negative correlation was found between MPV and femoral neck T-score ($p=0.011$, $r=0.314$). However, no significant correlation was found between MPV and lumbar 1-4 T-score (Table 2).

Table 1. Laboratory and demographic features of patients with rheumatoid arthritis

	Normal (n=32)	Osteopenic (n=31)	Osteoporotic (n=45)	p-value
Age (years)	49.00 (43.75-52.75)	52.00 (49.00-54.00)	51.00 (49.00-54.50)	0.051
Height (cm)	1.60 (1.57-1.67)	1.56 (1.52-1.61)	1.54* (1.47-1.60)	**<0.001**
Weight (kg)	78.50 (65.25-93.25)	77.00 (66.00-85.00)	63.00** (52.50-77.00)	**<0.001**
BMI (kg/m^2)	29.9 (25.37-34.17)	31.20 (26.80-34.50)	26.70* (22.60-32.85)	**0.024**
MPV (fL)	10.55 (9.72-11.75)	10.70 (9.90-11.50)	11.00 (9.60-11.15)	0.600
Calcium (mg/dL)	9.25 (9.00-9.67)	9.30 (9.00-9.60)	9.40 (8.90-9.70)	0.964
25(OH)D3 (ng/mL)	26.95 (21.62-32.87)	24.00 (19.90-28.90)	24.70 (18.10-34.10)	0.422
Lumbar 1-4 T-score	-0.55 (-1.12 to 0.55)	-1.70 (-1.90 to 1.30)	-3.10 (-3.70 to -2.50)***	**<0.001**
Femoral neck T-score	-0.40 (-0.77 to 0.12)	-0.90 (-1.40 to -0.20)	-2.50 (-2.80 to -1.60)	**<0.001**

*The osteoporotic and normal groups are different from each other, **The osteoporotic group is different from the other groups. ***All groups are different from each other, BMI: Body mass index, MPV: mean platelet volume

Table 2. The correlation analysis between mean platelet volume and bone mineral density

	L1-L4 T-score	Femoral neck T-score
MPV (fL)		
p	0.090	-0.314
r	0.421	0.011

MPV: Mean platelet volume

Discussion

OP occurs frequently in patients with endocrine, hepatic, nutritional, hematological, renal, autoimmune, and rheumatic diseases such as RA, systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS) (18). Local and systemic bone loss has been defined as hallmarks of RA (7). Meta-analyses showed higher fracture risk in RA patients compared with healthy controls (19). The low bone mass leads to fragility fractures. "Severe" or "established" OP was defined in the presence of one or more documented fragility fractures (6). In our study, we found 45 (41.6%) patients with OP. The median lumbar and femoral T-scores for osteoporotic patients were -3.1 and -2.5, respectively. There was no suspected compression fracture according to the medical history related to compression fractures such as sudden or gradual pain radiating to the lower parts of the body in patients included in our study. Moreover, compression fracture was not detected in the lumbar and dorsal direct radiographs of patients with suspicious symptoms.

In rheumatic diseases such as RA, proinflammatory cytokines such as IL-1, IL-6, and TNF-α play a critical role in osteoclast formation. These cytokines promote osteoclast differentiation, also termed as osteoclastogenesis (7). Therefore, inflammation was reported to decrease in BMD (7). The involvement of blood platelets and MPV in an inflammatory response is associated with the release of cytokines (20). The median MPV values were 10.55, 10.7, and 11.00 fL for the normal, osteopenic, and osteoporotic groups, respectively. Resorlu et al. (12) assessed the relationship between BMD and MPV in AS patients. The study found that MPV values were higher in the osteopenic group than in the normal group (8.4±0.81 vs 9.08±1.05). In our study, the median MPV value was higher in osteoporotic patients than in normal and osteopenic patients. There was no statistically significant difference between the three groups in terms of MPV values. A significant correlation was found between MPV and femoral neck T-score in Resorlu et al.'s (12) study. They reported that systemic effects underlie elevated MPV values in osteopenic patients. Also, Li et al. (10) found a significantly negative correlation between MPV and femoral neck-lumbar spine BMD. In this study, significant differences were found for the median femur and lumbar T-score between the control, osteopenic, and osteoporotic groups. In our study, the median femoral neck T-scores were -0.4, -0.9, and -2.5, and the lumbar T-scores were -0.55, -1.7, and -3.1 for the normal, osteopenic, and osteoporotic groups, respectively ($p<0.001$ for both). In contrast, a significantly positive correlation was reported between MPV and femoral neck BMD in the normal weight osteoporotic group (13). In addition, a significant negative correlation was found in the overweight-obese osteoporotic group in the same study (13). In our study, we found higher MPV levels in osteoporotic RA patients than in osteopenic RA patients. However, we did not find higher MPV levels in patients with normal BMD when we compared them with osteopenic RA patients. Also, we found a significant negative correlation between MPV and femoral neck T-scores. Although aging affects MPV, it has been stated previously that MPV may be affected by different cytokines and factors (9). Our results can also be explained with the differences in the storage time of the blood or with the use of different devices and kits for MPV measurement (21,22).

Patients with higher BMI values have a lower OP prevalence (23,24). Higher body weight imposes a greater mechanical load on the bone, which results in an increase in bone mass (25). Body fat seems to be a protective factor for fractures. Adipocytes induce estrogen production, which increases leptin, insulin, preptin, and amylin. These hormones have roles in osteoblast and osteoclast activities, and they increase the bone mass (26). In Li et al.'s (10) study, the median BMIs were 24.2, 23.4, and 21.6 for the control, osteopenic, and osteoporotic groups, respectively. In this study, there were significant differences between

groups and significant association with lumbar spine L2-L4 BMD (10). In our study, the median BMI was 29.95 for the normal group, 31.2 for the osteopenic group, and 26.7 for the osteoporotic group. BMI was lower in the osteoporotic group than the other groups. Also, we found a significant correlation between the groups in terms of BMI (p=0.02). However, no correlation was found between BMI and femur/lumbar T-scores.

Study Limitations

The limitation of the study is that this was a retrospective and cross-sectional study without any control group. Also, we have no data on the parathormone level, inflammation markers, and disease activity.

Conclusion

To the best of our knowledge, our study is the first to assess the association between MPV and BMD in RA. In conclusion, this study has demonstrated that MPV levels are higher in osteoporotic RA patients and are correlated with femur neck BMD.

Ethics Committee Approval: Our study was conducted according to the criteria set by the Declaration of Helsinki, and the Aydın Adnan Menderes Faculty of Medicine Ethics Committee approved the study (approval no: 2017/1123, date: 23.03.2017).

Informed Consent: Written informed consent was obtained from all patients.

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The Clinicopathological Findings of 121 Patients Presenting with Spontaneous Nipple Discharge

Meme Başından Spontan Akıntı Şikayeti ile Başvuran 121 Olguya Ait Klinikopatolojik Bulgular

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ABSTRACT

Introduction: This study aimed to investigate the cytopathological findings of patients who presented to our hospital with spontaneous nipple discharge. A cytological smear examination was performed to evaluate the correlation between cytology and biopsy in patients whose complementary biopsy or excision sampling was performed.

Methods: The nipple discharge smears of 121 patients sent to us over six years were retrospectively reviewed. Acellular smears without any cells were considered "insufficient", and smears that contained ductal cells, inflammatory cells, and foamy histiocytes were considered "sufficient". Smears considered sufficient for microscopic evaluation were classified and reported as "benign cytology", "compatible with papillary lesion", "suspicious for malignancy", and "malignant cytology".

Results: When the first smear samples of 121 patients were examined, "malignant cytology" was observed in one patient, "suspicious for malignancy" in two patients, "ductal ectasia" in one hundred and two patients, and "papillary lesion" in fourteen patients. The material was "acellular" in two patients. Nineteen patients were histopathologically diagnosed with malignancy (n=7), ductal ectasia (n=6), intraductal papilloma accompanied by florid-type intraductal hyperplasia without atypia (n=2), intraductal papilloma (n=2), complex sclerosing lesion (n=1), and sclerosing papilloma (n=1).

Conclusion: In cases where nipple discharge is persistent, repeated smear samples may contribute to the diagnosis if they contain epithelial components. In cases with histopathologically confirmed breast carcinoma, it should be kept in mind that the tumor may often show neuroendocrine features.

Keywords: Breast cancer, neuroendocrine features, ductal ectasia

ÖZ

Amaç: Bu çalışmada, hastanemize spontan meme başı akıntısı şikayeti ile başvuran ve akıntıdan yayma yapılan hastaların sitopatolojik bulgularını araştırmak ve tamamlayıcı biyopsi ve eksizyon spesmeni olan hastalarda sitoloji ve biyopsi korelasyonunun değerlendirilmesi amaçlanmıştır.

Yöntemler: Altı yıl süresince tarafımıza gönderilen, 121 hastaya ait meme başı akıntısı yaymaları retrospektif olarak incelendi. Hiç hücre içermeyen aselüler yaymalar "yetersiz", köpüksü histiosit, enflamatuvar hücre ve duktal hücrelerin izlendiği yaymalar "yeterli" olarak kabul edildi. Mikroskopik inceleme için yeterli kabul edilen yaymalar, "benign sitoloji", "papiller lezyon ile uyumlu", "malignite şüphesi" ve "malign sitoloji" olarak sınıflandırıldı ve raporlandı.

Bulgular: Yüz yirmi bir hastaya ait ilk smear örnekleri incelendiğinde, hastalardan 1'inde "malign sitoloji", 2'sinde "malignite şüphesi", 14'ünde "papiller lezyon" ve 102'sinde "duktal ektazi" saptandı. İki olguya ait materyal aselüler idi. Histopatolojik inceleme yapılabilen 19 olgudan 7'sinde malignite (n=7), 6'sında duktal ektazi (n=6), 2'sinde atipisiz florid tip intraduktal hiperplazinin (n=2), eşlik ettiği intraduktal papillom (n=2), 2'sinde intraduktal papillom, 1'inde kompleks sklerozan lezyon (n=1) ve 1'inde sklerozan papillom (n=1) tespit edildi.

Sonuç: Kalıcı meme başı akıntısı olan olgulara ait tekrarlanan yayma preparatlarında epitelyal içerik görülmesi tanıya katkıda bulunabilir. Histopatolojik olarak meme kanseri olduğu kesinleşmiş olgularda tümörde sıklıkla nöroendokrin değişikliklerin olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: Meme kanseri, nöroendokrin özellikler, duktal ektazi

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Introduction

Breast-related diseases are one of the most common health problems in women. Nipple discharge generally constitutes 3%-5% of breast-related symptoms in all women. However, 80% of women of reproductive age may encounter nipple discharge at least once in their lives (1,2). The underlying causes of nipple discharge may be physiological or pathological. Most of the pathological causes develop due to benign lesions (intraductal papilloma, ductal ectasia, galactorrhea, trauma, use of some antipsychotics, and anti-hypertensive and antidepressant drugs) or at a lesser extent to malignant lesions (ductal/lobular/papillary breast carcinoma) (3,4).

Nipple discharge may be clinically spontaneous/non-spontaneous or unilateral/bilateral or arise from a single duct or multiple ducts. The discharge can be bloody, milky, serous, or purulent. Among these, spontaneous, unilateral, bloody, and single-duct discharges particularly raise suspicion for malignancy (5-7). Breast ultrasonography (USG), mammography, and ductography are among the radiological examination methods that can be used for diagnostic purposes for patients presenting with nipple discharge. If an abnormality is detected on mammography or the lesion is palpable, fine needle aspiration biopsy (FNAB), tru-cut needle biopsy, or excisional biopsy is performed. However, in cases where there is no palpable lesion and no mammographic abnormality is detected, a direct smear from the discharge can be used to distinguish between malignant and benign lesions and for further diagnostic examination (6,8,9).

In patients with nipple discharge, the diagnostic value of cytopathological examination depends on the amount and quality of the material. Some studies have reported that cytological examinations of nipple discharge are more useful in the diagnosis of malignant and "suspicious for malignancy" lesions rather than benign lesions (10).

In this study, we reviewed the cytopathological findings and clinicopathological features in patients who presented to our center with spontaneous nipple discharge and investigate the correlation of cytology/biopsy after excision/biopsy in patients with recurrent nipple discharge.

Methods

A total of 121 patients who applied to the İstanbul Training and Research Hospital, Clinic of Surgical within a period of six years between January 2011 and June 2017 and whose smears of nipple discharge were sent to the pathology laboratory were included in this study. This study was approved by the Ethical Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1220, date: 06.04.2018). Patients' consent was not obtained because the study was retrospective. The smear of each patient was retrieved from the archives of the pathology clinic and reevaluated. Of these 121 patients, 41 patients with continuing complaints who had recurrent admissions to our clinic and were sampled were identified. Two or more consecutive cytology-biopsy samples of these patients were reevaluated in combination. Information on the demographic characteristics, laterality of the lesion, and color/nature of the discharge was obtained through the intranet system of our hospital.

During the preparation of the smear, the material was obtained using the installation method in patients with spontaneous discharge after cleaning the nipple and applying gentle pressure to the breast with no discharge at that time. The collected samples were spread with the help of a second slide: Half of them were fixed in alcohol and stained by the Papanicolaou method, and the other half were air-dried and stained by May-Grünweld Giemsa method. FNAB materials were also prepared with the protocol applied to smears.

A pathologist specialized in breast pathology examined the smear preparations. Acellular smears, without any cells, are considered "insufficient" for microscopic examination. Smears with varying levels and contents of ductal epithelial cells, inflammatory cells, blood components, and foamy cells were considered "as sufficient" for microscopic examination. Smears that did not contain epithelial cells that could represent the lesion but contained inflammatory cells were also included in the adequate category. Accordingly, smears deemed sufficient for microscopic evaluation were classified as follows: (i) benign cytology (inflammatory nipple discharge, compatible with ductal ectasia), (ii) compatible with papillary lesion, (iii) suspicious for malignancy, and (iv) malignant cytology.

Synaptophysin and chromogranin immunostainings were performed on paraffin blocks containing the tumor tissue to reveal possible neuroendocrine differentiation (synaptophysin, rabbit monoclonal antibody MRQ-40, dilution: 1/250, Cell Marque Sigma-Aldrich Co., Rocklin, CA, and chromogranin A, mouse monoclonal antibody LK2H10, dilution: 1/250, Cell Marque Sigma-Aldrich Co., Rocklin, CA).

Statistical Analysis

Statistical analyses were performed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) package program. All data is presented as mean for parametric variables, and as percentage for categorical variables as descriptive statistics.

Results

One hundred and twenty patients were female (99.2%), and one patient was male (0.8%). The ages of the patients ranged between two and eighty-eight years (mean age: 47.4; median: 46). The youngest patient was a two-year old boy with a unilateral bloody nipple discharge. Smears of the nipple discharge from both breasts (n=8; 6.6%), left breast (n=52; 43%), and right breast (n=61; 50.4%) were prepared and examined. The nipple discharge was bloody in 104 (85.9%) and serous in 17 (14.1%) patients.

The first cytopathology samples of the cases were examined and reported as compatible with "malignant cytology" in one patient (0.8%), "suspicious for malignancy" in two patients (1.6%), "ductal ectasia" in 102 patients (84.3%), and "papillary lesion" in 14 patients (11.6%). The material of the two patients was "acellular" (1.6%) (Figure 1).

Eighty of 121 patients who presented with the complaint of spontaneous nipple discharge were sampled only once, while 41 patients underwent two or more cytology or biopsy samplings. In 19 of these 41 patients (15.7%), the final diagnosis was made by performing a biopsy or surgical excision. Accordingly, nipple discharge smears of seven patients (36.8%)

were marked as "malignancy"; smears of six patients (31.6%), "ductal ectasia"; smears of two patients (10.5%), "intraductal papilloma" accompanied by florid-type intraductal hyperplasia without atypia; smears of two patients (10.5%), "intraductal papilloma"; smears of one patient (5.3%), "complex sclerosing lesion"; smears of one patient (5.3%), "sclerosing papilloma" (Table 1).

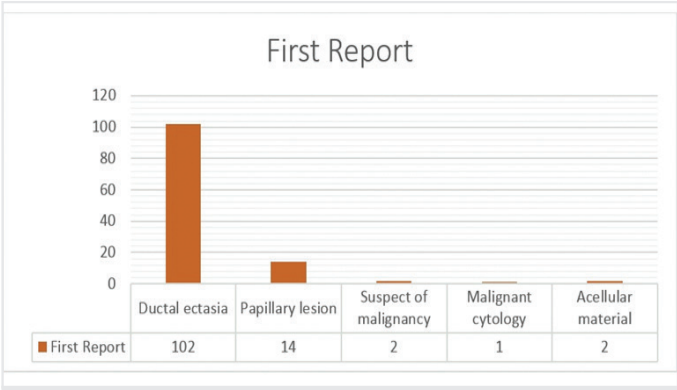

Figure 1. Initial pathology reports of 121 patients with nipple discharge

On the first sampling, the nipple discharge smears of seven patients were marked as "malignancy"; smears of four patients, "ductal ectasia"; smears of two patients, "papillary lesion/neoplasia"; smears of one patient "malignant cytology" (Table 2) When the first radiological images (USG/mammography) of all seven patients, whose smears were marked as "malignancy" in the pathology report, were examined, it was found that two of the seven patients were reported as Birads-3 (probably benign), one patient as Birads-4 (suspicious), and four patients as Birads-5 (highly suggestive of malignancy). The nipple discharge originated from the right breast in four patients and from the left breast in three of these seven cases. In six patients, the discharge was bloody, and in one patient, it was serous. The age of the patients diagnosed with malignancy ranged from 30 to 71 years, with a mean age of 52.8 years.

Table 1. Patients with histopathological biopsy or excision materials (n=19)

	(n)	(%)
Malignancy	7	36.8%
Ductal ectasia	6	31.6%
"Intraductal papilloma" accompanied by florid-type intraductal hyperplasia without atypia	2	10.5%
Intraductal papilloma	2	10.5%
Complex sclerosing lesion	1	5.3%
Sclerosing papilloma	1	5.3%
	19	**100%**

Table 2. Analysis of patients whose tissue biopsy/excision is reported as "malignant"

Patient	Accurate diagnosis	Age and symptoms	Pathology report
1	Invasive tubular carcinoma	30 years old; Unilateral, non-bloody discharge	1. Right nipple smear: compatible with intraductal papilloma (2012), 2. Right breast tru-cut biopsy: intraductal proliferative lesion (2012), 3. Right breast quadrantectomy: invasive tubular carcinoma, NG: 2 (2012).
2	Invasive ductal carcinoma	71 years old; Unilateral, bloody discharge	1. Right nipple smear: compatible with ductal ectasia (2012), 2. Right breast BCS: invasive ductalcarcinoma, NG: 2 (2012).
3	Invasive ductal carcinoma with marked DCIS component	45 years old; Unilateral, bloody discharge	1. Left nipple smear: papillary neoplasia (2013), 2. Left breast tru-cut biopsy: DCIS, NG: 2 (2013), 3. Left breast MRM: invasive ductal carcinoma with marked DCIS component (2013).
4	Invasive ductal carcinoma	54 years old; Unilateral, bloody discharge	1. Left nipple smear: malignant cytology (2015), 2. Left breast tru-cut biopsy: invasive ductal carcinoma, NG: 3 (2015), 3. Left breast MRM: invasive ductal carcinoma, NG: 3 (2015).
5	Invasive breast carcinoma	39 years old; Unilateral, bloody discharge	1. Right nipple smear: compatible with ductal ectasia (2015), 2. Right breast tru-cut biopsy: invasive breast carcinoma, NG: 2 (2015).
6	Invasive ductal carcinoma	64 years old; Unilateral, bloody discharge	1. Left nipple smear: compatible with ductal ectasia (2017), 2. Left beast tru-cut biopsy: invasive ductal carcinoma, NG:2 (2017), 3. Left breast BCS: invasive ductal carcinoma, NG: 2 (2017).
7	DCIS papillary/solid/ neuroendocrine pattern	67 years old; Unilateral, bloody discharge	1.Right nipple smear: compatible with ductal ectasia (2015), 2.Right breast FNAB: suspicious for malignancy (2015), 3.Right breast excisional biopsy: DCIS papillary/solid/neuroendocrine pattern, NG: 2 (2015).

DCIS: Ductal carcinoma *in situ*, NG: nuclear grade, BCS: breast-conservative surgery, MRM: modified radical mastectomy, FNAB: fine needle aspiration biopsy

Synaptophysin and chromogranin immunostainings were performed on paraffin blocks containing the tumor tissue of two patients, except for the patient with ductal carcinoma *in situ* (DCIS). In one of these patients, cytoplasmic immunostaining for both markers was identified in more than 90% of tumor cells, while neuroendocrine markers were negative in another patient. Estrogen receptor, progesterone receptor, human epidermal growth factor receptor-2, Ki-67, chromogranin, and synaptophysin status of the seven patients diagnosed with malignancy are shown in Table 3.

While the first nipple discharge of a 50-year-old female patient, who presented with the complaint of bloody discharge from the right nipple, was reported as "compatible with ductal ectasia," the FNAB sample made upon the continuation of her complaint was reported as "malignant cytology." The definitive diagnosis could not be achieved as the patient did not undergo biopsy/excision in our hospital.

Seven of eight patients with bilateral nipple discharge also had a bloody nipple discharge. Direct smear samples from the nipple discharge of these patients were reported as "compatible with ductal ectasia," and repeated hospital admissions with the same complaint were not detected.

Discussion

Niple discharge is the one of the challenging situation in breast lesions. Although nipple discharge is frequently associated with an underlying benign disease, it is related to malignancy in 1.2%-15% of patients (11). For this reason, accurate, fast, and non-invasive diagnostic methods are needed. Although direct cytological examination of the smear prepared from the nipple discharge is a non-invasive and easily applicable method, its place in routine practice is unfortunately limited. Many studies have indicated that the cytological method in nipple discharge samples has low sensitivity but higher specificity rates and an inadequate diagnostic value (12-15).

In studies conducted in the literature on the nipple discharge, varying specificity and sensitivity rates have been reported. These specificity and sensitivity rates were, respectively, 66.1% and 16.7% in the study by Kooistra et al. (12) (n=618), 100% and 55.6% in the study by Lee (14) (n=174), and 97.4% and 31.2% in the study by Dinkell et al. (16) (n=384). In the study by Castellano et al. (17) on 139 patients, the specificity, sensitivity, and positive and negative predictive values were found to be 100%, 58%, 100%, and 63%, respectively, and a significant relationship was reported between the cytological examination of malignant nipple discharge and lesion size.

To clarify the debates made for the importance of cytological examination of nipple discharge for diagnosis, Li et al. (18) conducted a meta-analysis study on 12 articles (1,476 patients), which met the inclusion criteria, of 286 articles. Accordingly, the sensitivity and specificity of nipple discharge cytology in predicting breast cancer were 63% and 95%, respectively. According to this meta-analysis, it was stated that the cytological examination of the samples prepared from the nipple discharges was a useful method that had a moderate sensitivity and high specificity in predicting breast malignancies in patients with a pathological nipple discharge (18).

In our study, the specificity, sensitivity, and positive and negative predictive values of the cytological examination of nipple discharge were 97.1%, 14.3%, 50%, and 65%. In this study, most of the initial smears did not contain epithelial components that could represent the lesion, and additional samples could not be obtained for all patients. Therefore, the sensitivity rate was low. However, more accurate results were obtained in cases where the cytological samplings were repeated or tissue biopsy samples were taken due to the complaint of ongoing discharge. In our series, the first diagnosis of cytological materials of four of seven patients, whose histological diagnosis was malignant, was reported as "compatible with ductal ectasia," and there were no epithelial cells or groups of cells in their samples of smears. The first cytological samples of the other two malignant cases suggested the presence of a papillary lesion. Whereas the subsequent tru-cut biopsy specimen of one of these patients was compatible with DCIS, the specimen of another patient was compatible with an intraductal proliferative lesion. However, in the latter patient, a small focus of invasive tubular carcinoma was detected in the ipsilateral breast, simultaneously (patient 1 in Table 2). Another patient whose first cytological diagnosis was reported as "ductal ectasia" and whose nipple discharge sampling was repeated due to the persistence of her complaints was found to be suspicious for malignancy because of the presence of a small amount of monotonous epithelial population with cytonuclear atypia. This patient was diagnosed with DCIS (pattern: papillary, solid, neuroendocrine type, nuclear grade 2) in the subsequent examination of the excision material (patient 7 in Table 2). Patient 7 is the only patient diagnosed with DCIS in our series, and it is interesting as it shows diffuse cytoplasmic staining with synaptophysin, a neuroendocrine marker (patient 7 in Table 3). In a study of 89 patients, who presented with symptomatic nipple

Table 3. ER, PR HER2, Ki-67, synaptophysin, and choromogranin status of patients diagnosed with malignancy

	ER	PR	HER-2	Ki-67	Synaptophysin	Chromogranin
Patient 1	80%, MP	90%, SP	Score 0 (negative)	15%	NP	NP
Patient 2	30%-40%, L-MP	40%-50%, MP	Score 0 (negative)	10%	NP	NP
Patient 3	7%, L-MP	Negative	Score 3 (positive)	30%-35%	NP	NP
Patient 4	Negative	Negative	Score 0 (negative)	50%	NP	NP
Patient 5	80%, SP	90%, SP	Score 0 (negative)	10%	Diffuse positive	Diffuse positive
Patient 6	100%, SP	98%, SP	Score 0 (negative)	15%	Negative	Negative
Patient 7	Diffuse nuclear positive	Diffuse nuclear positive	NP	NP	Diffuse cytoplasmic positive	Negative

ER: Estrogen receptor, PR: progesterone receptor, HER-2: human epidermal growth factor receptor-2, MP: medium positive, L-MP: low-medium positive, SP: strong positive, NP: not performed

discharge and in which samples were examined histologically, breast carcinoma was observed in 55 patients (61.8%). Of these 55 patients, 24 patients (43.6%) showed expression with neuroendocrine markers (synaptophysin or chromogranin) in more than 50% of tumor cells and were diagnosed with neuroendocrine breast tumor. While the samples of nine of these 24 patients showed foci of DCIS, the samples of the rest of the patients showed both invasive and *in situ* components. Interestingly, immunohistochemical staining at varying levels with neuroendocrine markers was detected in all patients with breast carcinoma (31 patients), except these 24 patients, and it was mentioned that neuroendocrine features were detected at a high rate in patients with breast carcinoma presenting with nipple discharge (19). In our series, apart from the patient with DCIS, two more patients who have paraffin blocks containing the tumor tissue were determined, and synaptophysin and chromogranin immunostainings were used to reveal possible neuroendocrine differentiation (patients 5 and 6, Table 3). In one of these patients, invasive breast carcinoma with neuroendocrine features was detected, which showed cytoplasmic immunostaining for both markers in more than 90% of tumor cells (patient 5). In our series, it is remarkable that two of three patients, where immunostaining was applied, had breast tumors with neuroendocrine features. In this respect, immunohistochemical staining and investigation of neuroendocrine features in patients presenting with nipple discharge and diagnosed with breast cancer may provide important data. Neuroendocrine tumors of the breast are uncommon, and their relationship with a bloody nipple discharge is important and new information (19,20). They were first defined as a separate entity in the World Health Organization breast booklet in 2003 and have been increasingly described in the last two decades (20,21).

The clinical features of nipple discharge can also aid in the diagnosis. In many studies, where the patient's age was ≥50, the fact that nipple discharge is unilateral, spontaneous, and bloody was defined as a probable sign of malignancy (5,22). In a study by Kan et al. (23) on 102 patients, it was reported that if the nipple discharge was not bloody, the underlying pathology was often benign, and negative radiological imaging methods supported their findings. In our study, bloody nipple discharge was observed in six of seven patients diagnosed with malignancy, and all patients had a unilateral nipple discharge. Additionally, on radiological examination, five of seven patients were reported as "suspicious" or "highly suggestive of malignancy." These findings support the previous study's results. Although the mean age of the patients in this study was 52.4 years, four patients were 50 years and older, and three patients were under 50 years of age.

Study Limitations

The limitations of our study are as follows: the retrospective character of our study, the absence of biopsy or excision specimens of all patients, and the inability to perform histopathological examination.

Conclusion

Smears of patients who presented to the clinic with nipple discharge may have low sensitivity and medium-high specificity in the identification of lesions. Smears in which cytological examination suggests "ductal ectasia" (presence of histiocyte based on proteinaceous material) and with no epithelial component representing the lesion may indicate an underlying malignancy in patients with persistent nipple discharge. In such cases, resampling of nipple discharge as a smear or tissue biopsy of the lesion may increase the chance of detecting malignancy. It should also be kept in mind that breast tumors with neuroendocrine features may be seen in patients presenting with nipple discharge.

Ethics Committee Approval: This study was approved by the Ethical Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1220, date: 06.04.2018).

Informed Consent: Patients' consent was not obtained because the study was retrospective.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - D.C.T.; Concept - B.B.S.; Design - B.B.S., C.K.T.; Data Collection or Processing - B.B.S., Y.Ç.; Analysis or Interpretation - C.K.T., Y.Ç., C.L.; Literature Search - Y.Ç., C.L.; Writing - B.B.S.

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Cochlear Nerve Dimensions in Asymetrical Sensorineural Hearing Loss: A Morphometric Study

Asimetrik Sensörinöral İşitme Kaybında Koklear Sinir Boyutları: Morfometrik Çalışma

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ABSTRACT

Introduction: To investigate the relationship between morphometric variants of the cochlear nerve (CN) and the hearing level. To investigate the confounding effects of age, sex, and audiometric variables on the relationship between CN morphometrics and hearing loss, if present.

Methods: Audiological data and magnetic resonance imaging findings of 127 patients with asymmetrical sensorineural hearing loss (ASNHL) were reviewed retrospectively. According to pure tone average (PTA) frequencies of each ear, difference above 25 dB were accepted as ASNHL. The vertical (Vd) and horizontal diameters (Hd) and the cross-sectional area (CSA) of the CN were measured.

Results: The difference in CSA and Vd between ears showed a negative correlation with age. The mean CSA was 1.57 in AE and 1.60 in NE. Mean Hd was 1.00 in AE and 1.00 NE. Mean Vd was 1.40 in AE and 1.50 in NE. There was no correlation between the difference ratios of thresholds and CN diameter parameters. There was no significant correlation of CSA, Vd, and Hd with PTA thresholds at each frequency.

Conclusion: Aging is associated with losses in Vd diameter and CSA. The degree of hearing loss was not correlated with the morphometric features of the CN. The morphometry of the CN should be interpreted together with the etiology of hearing loss.

Keywords: Hearing loss, unilateral, deafness, ear, inner, cochlear nerve

ÖZ

Amaç: Koklear sinirin morfometrik özellikleri ile işitme seviyesi arasında ilişki varlığını araştırmaktır. Yaş, cinsiyet ve odyometrik özelliklerin, koklear sinir morfometrisi ve işitme kaybı ilişkisine etkisi olup olmadığını araştırmaktır.

Yöntemler: Asimetrik sensörinöral işitme kaybı (ASNİK) nedeniyle başvuran 127 olgunun odyolojik verileri ve manyetik rezonans görüntüleme bulguları retrospektif olarak tarandı. Saf ses ortalamasına göre kulaklar arasında 25 dB ve üzeri fark olması ASNİK olarak kabul edildi. Koklear sinirin vertikal çapı (Vd), horizontal çapı (Hd) ve kesitsel alanı (CSA) ölçüldü.

Bulgular: Kesit yüzey alanı ve Vd yaş ile negatif korelasyon gösterdi. Ortalama CSA etkilenen kulaklarda 1,57 iken etkilenmeyen kulaklarda 1,60 idi. Ortalama Hd'yi etkilenen ve etkilenmeyen kulakta aynı idi. Ortalama Vd etkilenen kulakta 1,40 etkilenmeyen kulakta 1,50 idi. İşitme eşiklerindeki değişim oranları ile koklear sinir çapları arasında ilişki gözlenmemiştir. CSA, Vd, Hd ile saf ses ortalaması arasında ilişki gözlenmemiştir.

Sonuç: Yaşlanma ile sinir Vd'den kaybeder ve toplam CSA azalır. İşitme kaybının derecesi ile sinirin morfometrik özellikleri arasında ilişki yoktur. Koklear sinir morfometrisi incelenirken işitme kaybının etiyolojisi göz önünde bulundurulmalıdır.

Anahtar Kelimeler: İşitme kaybı, tek taraflı, sağırlık, kulak, iç, koklear sinir

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Introduction

Asymmetrical sensorineural hearing loss (ASNHL) is defined as a difference in hearing loss greater than 15 decibels (dB) between ears at 0.5, 1, and 2 kHz, or greater than 20 dB at 3, 4, and 6 kHz on a bone conducted pure tone average (PTA) audiogram that interrupts binaural hearing (1-3). ASNHL demonstrates a wide spectrum of PTA threshold from mild sensorineural hearing loss to single-sided deafness (1). ASNHL is estimated to influence 7.9%-13.3% of the general population (4).

The causes of ASNHL can be listed as inner ear anomalies, cochlear nerve (CN) agenesis, mumps, congenital cytomegalovirus infection, meningitis, vestibular schwannoma, and idiopathic (2). ASNHL causes disruption of both temporal and spatial localization of sound in space. Patients experience difficulty understanding speech in the presence of noise (5). Rehabilitation of ASNHL is very important to provide balanced binaural hearing.

Management of ASNHL includes conventional hearing aids, cross devices, bone conduction hearing aids, and cochlear implantation. Cochlear implantation is indicated in ASNHL especially with down-sloping audiogram and single-sided deafness (6). Treatment success of ASNHL depends on several factors such as the age of the patient, duration of hearing loss, etiology of hearing loss, and cognitive capacity of the patient. However, the most important factor related to a satisfactory auditory outcome is a functioning CN (7). Sensorineural hearing loss can be caused by damage to either cochlear or retro- cochlear structures. If cochlear damage exists, retrograde axonal degeneration may cause neuronal degeneration, which eventually presents as a decrease in the cross-sectional area (CSA) of the CN (8-11).

The morphologic features of the CN have prognostic importance in determining the candidacy of a patient for cochlear implantation and for side preference. CN size is accepted as an important parameter in the estimation of postoperative auditory verbal abilities after CI (12). In the literature, some studies reveal a relationship between the function and size of the CN (13).

Magnetic resonance imaging (MRI) is a reliable method of measuring the diameter and CSA of the CN (14). The objective of our study is to investigate whether there is a relationship between the hearing level and the CN diameter.

Methods

This is a retrospective review of the audiological charts and MRI findings of the patients with ASNHL diagnosed between 2014 and 2017 at a tertiary referral center. Medical records of 127 patients were enrolled in this study. Informed consent was not taken because of its retrospective nature. Cases with acquired etiology such as trauma or labyrinthitis and those who display conductive components of hearing loss were excluded.

Patients' demographics, PTA averages at frequencies of 250, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz were recorded. University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital by Institutional Ethics Committee approval was obtained (approval number: 2017/12).

Audiological Evaluation

PTA averages for frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz were evaluated. A difference in PTA average between the affected and unaffected ears of more than 25 dB HL (dB hearing level) was accepted as ASNHL. Patients with insufficient audiological documentation were not included in the study.

Temporal MRI Protocol and Measurement of Nerve Sizes

CN diameters of the affected and unaffected ear were measured and compared by using MRI. All MRI procedures were performed using a 3T MR unit (Verio; Siemens Medical Solutions, Erlangen, Germany) with an 8-channel head-array coil and parallel imaging techniques. All images were evaluated with an oblique-sagittal 3D-driven equilibrium sequence perpendicular to the internal auditory canal (IAC) (repetition time/echo time: 1000/132 msec; 3.48 min acquisition time; 20 cm field of view; 0.5 mm section thickness; 0.75 mm overlap; and number of acquisitions: 2) The sequences used for procedure were axial T2W, axial T1W, post-contrast axial and coronal T1W, and axial heavily T2W sequence [constructive interference in steady state, (CISS) sequence]. Oblique-sagittal images of the IAC were further evaluated, since the visualization of the CN is optimal at that section. Selected reconstructed images were then transferred to a specialized workstation where CSA measurements could be performed (Figure 1).

All MRI scans were reviewed by two independent observers (OY2 and EI2) who were blinded to patients' data (sensorineural deafness) as well as each other's measurements. The vertical, (Vd) horizontal diameters (Hd) and the cross-sectional area (CSA) of the CN was measured on the parasagittal image of the middle of the IAC.

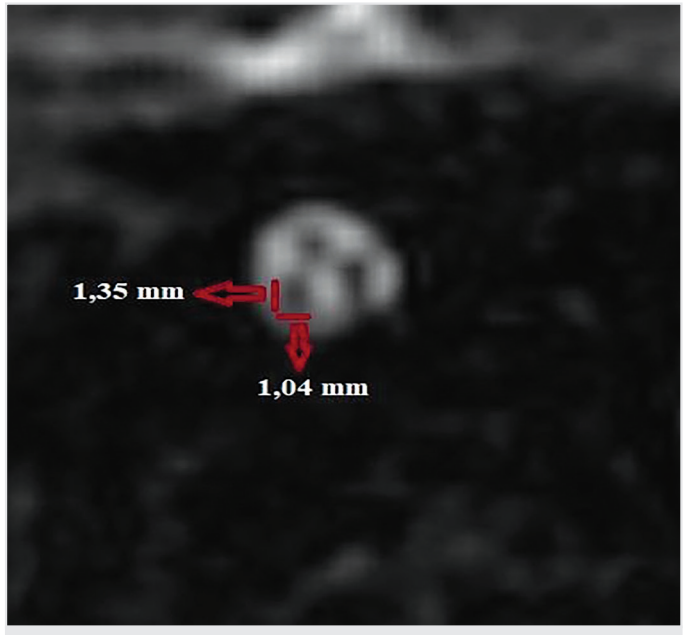

Figure 1. Parasagittal CISS MRI parasagittal images perpendicular to the nerve course at the internal auditory meatus. Measurement of the cochlear nerve (antero-inferior) diameter is demonstrated with the region of interest outlined, and cross-sectional area was calculated

CISS: Constructive interference in steady state, MRI: magnetic resonance imaging

Statistical Analysis

Mean, standard deviation, median, min and maximum, frequency and ratio values were used for descriptive statistics. The one-sample Kolmogorov-Smirnov test was used to test for the normal distribution.

We analyzed the relationship between dependent variables on a frequency basis, and for 250 Hz, speech frequencies and 8000 Hz. We used the intra-class correlation coefficient to determine the inter-observer reliability.

For independent quantitative variables a Mann-Whitney U test and for dependent quantitative variables a Wilcoxon signed-rank test was performed. Correlation was tested with a Spearman correlation test. The interclass correlation coefficient (ICC) was performed to examine inter-rater reliability (15). Results were considered statistically significant at $p<0.05$, and all statistical analyses were performed using SPSS Statistics for Windows, Version 22.0 (IBM Inc., Armonk, NY).

Results

Thirty-six female and 31 male participants were enrolled in the study. Their mean age was 16.9 (minimum: 13; maximum: 84) years. Two cases with higher displacement of non-dehiscent jugular bulbus but neither inner ear nor intracranial anomaly, including the intracranial path of the CN, were diagnosed.

We studied the difference between the PTA thresholds of the two ears. The mean PTA threshold was 58.14 dB for AE and 26.16 for NE. The median difference between the affected and non-affected ear [ΔAE-NE (%)] in the PTA averages of each frequency were 31%, 38%, 29%, 34%, 31%, and 32% for 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, and 8000 Hz, respectively. The AE has significantly worse thresholds than the NE. Correlations between variations of Vd, Hd, CSA, and ΔAE-NE (%) were calculated. The ICC was calculated as 78%, which indicates good reliability.

There was no significant association of CSA, Vd, and Hd with PTA thresholds at each frequency (Spearman's correlation p for Vd: 0.828, p for horizontal: 0.947, p for CSA: 0.930) (Table 1).

The difference in CSA and Vd between affected and non-affected ears showed a negative correlation with age for speech frequencies. As age increased, the difference in the Vd and CSA of the affected ear decreased by more than that of the non-affected ear at speech frequencies (p=0.008 Vd; p=0.006 for CSA) (Table 2). The difference in CSA, Vd, and Hd between the affected and non-affected ears did not demonstrate any significant relationship with gender (p for Vd: 0.229, p for horizontal diameter: 0 885, p for CSA: 0.274) (Table 3).

The differences in frequency between the affected and non-affected ears were analyzed for a relationship with the difference ratio of CSA, Vd, and Hd. Mean CSA was 1.57 (±0.62) in AE and 1.60 (±0.50) in NE. Mean Hd was 1.00 (±0.99) in AE and 1.00 (±0.17) in NE. Mean Vd was 1.40 (±0.24) in AE and 1.50 (±0.21) in NE. There was no correlation between the difference ratios of thresholds and CN diameter parameters (p-values for 250, 500, 1000, 4000, 8000 Hz = 0.623; 0.305; 0.361; 0.056; 0.065; 0.176, respectively).

Table 1. There was no correlation between age and the difference in pure tone average averages with cross-sectional area, vertical diameter, and horizontal diameter at each frequency

		AE-NE Difference dB		
		Vertical	**Horizontal**	**CSA**
250 Hz	r	-0.041	-0.107	0.046
	p	0.743	0.389	0.714
500 Hz	r	0.049	-0.101	-0.001
	p	0.691	0.416	0.992
1 kHz	r	0.023	-0.075	0.060
	p	0.856	0.547	0.628
2 kHz	r	0.146	-0.069	0.140
	p	0.237	0.579	0.259
4 kHz	r	-0.006	-0.064	-0.033
	p	0.961	0.605	0.793
8 kHz	r	-0.010	-0.083	0.033
	p	0.938	0.506	0.788

Spearman correlation.
PTA: Pure tone average, CSA: cross-sectional area, AE: affected ear, NE: non-affected ear

Table 2. Negative correlation between age and cross-sectional area, vertical diameter, and horizontal diameter at speech frequencies

		AE-NE Difference		
		Vertical	**Horizontal**	**CSA**
Age	r	-0.320	-0.120	-0.329
	p	0.008	0.332	**0.006**

Spearman Correlation.
AE: affected ear, NE: non-affected ear, CSA: cross-sectional area

Table 3. There was no correlation between the difference between the affected ear and non-affected earaccording to pure tone average averages of 500-4000 Hz and sex

	Female		Male		p	
	Mean ± SD	Median	Mean ± SD	Median		
Difference AE-NE						
Vertical	-3.8±14.7	-7.1	-0.4±17.9	0.0	0.229	[m]
Horizontal	-1.5±16.6	0.0	1.1±23.2	0.0	0.885	[m]
CSA	-5.2±24.6	-7.8	0.1±31.2	4.0	0.274	[m]

[m]: Mann-Whitney U test, SD: standard deviation, AE: affected ear, NE: non-affected ear, CSA: cross-sectional area

Discussion

The dimensions of inner ear structures are valuable prognostic parameters for beneficial estimation of future interventions in patients with sensorineural hearing loss. According to Kang et al. (7), in normal-hearing ears, there is no relation between CN size and age. The CN is ovoid rather than round, i.e., its vertical and horizontal diameters are not equal (16,17). CN morphometry is well measured by MRI with CISS sequence) on parasagittal images of the IAC, in which the CN is optimally visualized (18-20). In the present study, two-dimensional measurements were performed for the vertical and horizontal diameters. Nadol et al. (23) reported that the diameter of the CN was smaller in the deaf population, compared with that of normal-hearing controls, but wide variability of diameters of the CN in hearing and deaf subjects complicates its usefulness (21,22). In our study, the difference ratios between the affected and non-affected ear for each frequency threshold were analyzed for a relationship with the difference ratio of CSA, Vd, and Hd of the affected and non-affected ear, and no correlation was found ($p>0.05$).

Aging is an important parameter in the volume decrease of neuronal structures either due to cell death or atrophy. Age-related cell loss in the spiral ganglion was studied many times (21). Nadol et al. (23) demonstrated that spiral ganglion cell count is lower in older deaf individuals (22). In our study, Vd and CSA of the affected ear decreased with age more than non-affected ear did ($p=0.008$ for vertical, $p=0.006$ for CSA). Kim et al. (12) stated such relevance although they did not observe statistical significance. It is known that development and regeneration of both neural structures and their supporting cells have receptors of sex hormones. Kempster et al. (25) reported the presence of sexual dimorphism in favor of females exhibiting more abundant electrosensory axons, especially via ERβ receptors (24). In the present study, difference ratio of CSA, Vd, and horizontal diameter between the affected and non-affected ear did not show a correlation with sex ($p>0.05$). Russo et al. (19) reported on a genetic study in which they compared a Connexin 26 (Cx26)-mutated sensorineural hearing loss group and a non-mutated sensorineural hearing loss group with a normal-hearing control group. Although there was no difference in nerve size between the Cx26 mutated group and non-mutated group, both groups with profound hearing loss had smaller CNs, in comparison with the normal-hearing group (19).

In an analysis of the correlation between CN dimensions and the degree of hearing loss, patients were divided in to five groups: mild, moderate, severe, and profound hearing loss and normal hearing. There was no correlation between the severity of hearing loss and CN size for 250 Hz, speech frequencies, and 8000 Hz. For the affected ear, no relationship was observed between the level of hearing loss and CN size for 250 Hz, speech frequencies, and 8000 Hz.

Etiological evaluation of SNHL is of great importance. Henneberger et al. (26) reported that if the etiology of SNHL is Meniere's disease, a swelling may be observed in the cranial nerves, especially in the CN. A major limitation of our study is the lack of etiological analysis of hearing losses and the duration of hearing loss, which both may affect the size of the CN (12). However, absent correlation of CN size between affected and non-affected ears may be due to the confusing effect of such swelling of CNs in SNHL with Meniere's disease (26).

The literature provides data about how CN sizes differ between the hearing and non-hearing population. However, this is the first study that compares the CN sizes of the good hearing ear with the bad hearing ear in the same person. If a hazardous insult is present on a patient this will affect the CNs of both ears. Therefore, each patient should be evaluated in their own.

Study Limitations

The lack of previous audiologic history, including the etiology of hearing loss and follow-up, were the major limitations of the study.

Conclusion

There is a negative correlation between Vd and CSA with aging. However, because the severity of hearing loss lacks correlation with nerve size, we concluded that the more affected ear does not necessarily have the smaller nerve. A smaller nerve might be more vulnerable to hazardous effects, which results in hearing loss. Prospective studies should be performed to identify the relationship between size and function in detail. The morphometry of the CN should be interpreted together with the etiology of hearing loss.

Ethics Committee Approval: University of Health Sciences Turkey, Bakırköy Dr. Sadi Konuk Training and Research Hospital by Institutional Ethics Committee approval was obtained (approval number: 2017/12).

Informed Consent: Informed consent was not taken because of its retrospective nature.

Peer-review: Externally and internally peer-reviewed.

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Design - A.P.Y., Ö.Y., L.K., H.A., F.T.K., E.İ.; Data Collection or Processing - A.P.Y., Ö.Y., L.K., H.E.K., E.İ.; Analysis or Interpretation - A.P.Y., Ö.Y., H.E.K., F.T.K., E.İ.; Literature Search - A.P.Y., Ö.Y., L.K., H.A.; Writing - A.P.Y., Ö.Y., L.K., H.E.K., H.A., F.T.K., E.İ.

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Tramadol for Early Postoperative Analgesia in Abdominal Hysterectomy: Comparison of Different Administration Techniques

Abdominal Histerektomide Erken Postoperatif Analjezi için Tramadol: Farklı Uygulama Tekniklerinin Karşılaştırılması

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ABSTRACT

Introduction: Tramadol is a centrally acting analgesic for control of postoperative pain. This study aimed to compare three different routes of administration of tramadol for early postoperative analgesia in abdominal hysterectomy.

Methods: Patients who were scheduled for abdominal hysterectomy with Pfannenstiel incision were divided into three groups according to the routes of administration of tramadol: incisional subcutaneous infiltration (group 1), subcutaneous infiltration plus intravenous administration (group 2), and slow intravenous administration (group 3), by sequential randomization. The analgesic effect was assessed using the revised face pain scale, and side effects such as nausea or hypotension were evaluated at 1, 2, 3, and 4 hours after surgery.

Results: A total of 90 cases were evaluated, including 30 cases in each group. In group 3, the pain score at the 1st hour was lower than the others (4.1±2.1 vs.5.2±1.9 and 5.6±2.3; p=0.040). Nausea more often occurred in group 2 at the second hour (33% vs 13% and 13%; p=0.017) and in group 1 at the fourth hour (20% vs 7% and 0; p=0.022). The mean arterial pressure in group 3 was lower at the first and second hours than those in the other groups at the same time points. The mean pulse rates of the groups were similar for each hour.

Conclusion: The results of this study showed that intravenous administration of tramadol is more effective for pain control in the first hour.

Keywords: Hysterectomy, postoperative, analgesia, tramadol

ÖZ

Amaç: Tramadol, postoperatif ağrının kontrolü için merkezi olarak etkili bir analjeziktir. Bu çalışmanın amacı, erken postoperatif analjezi için abdominal histerektomide tramadolün üç farklı uygulama yolunu karşılaştırmaktır.

Yöntemler: Pfannenstiel insizyonu ile abdominal histerektomi yapılacak olgular sıralı randomizasyon yöntemi ile insizyonel subkutan infiltrasyon (grup 1), infiltrasyon artı intravenöz (grup 2) ve intravenöz (grup 3) olmak üzere 3 gruba ayrıldı. Face pain skalası-revize ile analjezik etki ve mide bulantısı veya hipotansiyon gibi yan etkiler postoperatif 1., 2., 3. ve 4. saatlerde değerlendirildi.

Bulgular: Her grupta 30 hasta olmak üzere toplam 90 hasta değerlendirildi. Grup 3'ün ağrı skoru ilk saatte diğerlerinden daha düşüktü (4,1±2,1'e karşı 5,2±1,9 ve 5,6±2,3; p=0,040). Bulantı; grup 2'de 2. saatte (%33'e karşı %13 ve %13; p=0,017), grup 1'de 4. saatte (%20'ye karşı %7 ve 0; p=0,022) daha sıktı. Grup 3'te ortalama arter basıncı birinci ve ikinci saatte diğerlerine göre daha düşüktü. Grupların ortalama nabız hızı her saat için benzerdi.

Sonuç: Abdominal histerektomide postoperatif ilk saatte ağrı kontrolü için i.v. tramadol uygulaması, sc infiltrasyon ve sc infiltrasyon artı i.v. infüzyondan daha etkilidir ve tercih edilebilir.

Anahtar Kelimeler: Histerektomi, postop ağrı, tramadol, bulantı

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Introduction

Total abdominal hysterectomy (TAH) is the most common major non-obstetric surgical procedure for women and causes postoperative pain and discomfort. Tramadol, a centrally acting analgesic, consists of two enantiomers, both of which contribute to analgesic activity through different mechanisms (1,2). These two enantiomers act synergistically to provide analgesia. In addition to the weak opioid receptor agonist effect, tramadol inhibits presynaptic reuptake of noradrenaline and serotonin (5-HT), as well as stimulates 5-HT release. Thus, tramadol potentiates the endogenous analgesia system with both opioid agonist mechanism and monoaminergic effect (3). Tramadol is a synthetic medication that is structurally related to codeine and morphine (4).

For approximately 30 years, tramadol drug has been used for the control of postoperative pain. Its efficacy for the treatment of moderate to severe postoperative pain has been demonstrated in patients who underwent surgery. Tramadol may be administered orally, rectally, intravenously (IV), intramuscularly, or subcutaneously (SC) (5,6).

In this study, different routes of administration of tramadol were compared in terms of pain control and side effects in the early postoperative period in patients who underwent abdominal hysterectomy with a Pfannenstiel incision for benign diseases.

Methods

This prospective, randomized, patient-blinded, evaluator-blinded, observational trial study included 90 female patients (mean age: 49 years) with American Society of Anesthesiologists (ASA) physical status I/II scheduled to undergo elective TAH with or without bilateral salpingo-oophorectomy through Pfannensteil incision under general anesthesia for benign diseases. The exclusion criteria were presence of giant fibroids, severe intra-abdominal adhesion, and malignancy, history of chronic pain, history of regular analgesic drug use, and contraindications to tramadol. In addition, those who had undergone abdominal surgery, those using narcotic analgesics or psychotropic drugs, and those with alcohol dependence were excluded.

For postoperative analgesia, patients were randomly allocated into one of the three groups according to the routes of administration of tramadol: incisional SC infiltration (group 1), SC infiltration plus IV administration (group 2), and slow IV administration (group 3) by sequential randomization. In all three groups, tramadol was administered immediately following the closure of the Pfannenstiel incision.

In group 1, 2 mg/kg tramadol was diluted with 20 mL of sterile saline and applied equally to the SC tissue on both sides of the incision. In group 2, half of the tramadol dose calculated as 2 mg/kg was diluted with 20 mL of sterile saline and applied SC; the other half was administered by slow IV infusion. In group 3, 2 mg/kg tramadol was administered by slow IV infusion.

All cases were either ASA I or ASA II. In all patients, procedures were performed under general anesthesia. During the induction period, pentothal 6 mg/kg, rocuronium 0.6 mg/kg, and midazolam 2 mg were also administered. Following orotracheal intubation, anesthesia was continued with 1%-2% sevoflurane and NO_2%50 + O_2%50 mixture.

Patients' pain was evaluated using the revised face pain scale (FPS-R) on the first, second, third, and fourth hours after surgery. The FPS-R is commonly used for measuring pain intensity in pediatric and adult populations (7). The FPS-R consists of six face pictures that depict different degrees of pain from "no pain" to "most pain possible." A numerical value ranging from 0 to 10 (i.e., 0, 2, 4, 6, 8, 10) is assigned to each face [visual analog scale, (VAS)].

Blood pressure and pulse values were measured. The mean blood pressure was taken into consideration while analyzing blood pressure values. Occurrences of nausea and vomiting were recorded. The study was double-blind. The physician who evaluated using FPS-R did not know which group the patient belonged to. The patients did not know which drug was used for analgesia. The operation time was defined as the time period from skin incision to closure of the incision. In patients who had a pain score ≥4 or could not tolerate pain, an additional 75 mg diclofenac sodium was administered IV.

The study was approved by the Local Ethics Committee University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1175/2018). Informed consent form was obtained from all patients for the inclusion and publication of their data.

Statistical Analysis

Data were analyzed using SPSS 22.0 program. Mean and standard deviation, median and minimum-maximum values, frequencies, and ratios were used for descriptive analysis. The Shapiro-Wilk test was used to analyze normality distribution of data. The Kruskal-Wallis test was used in the analysis of quantitative independent data. The chi-square test was used for the analysis of qualitative independent data. A p-value <0.05 was considered to indicate significance.

Results

A total of 90 patients were evaluated, with 30 patients in each group. The mean age, body mass index, gravidity, and parity of the groups were comparable (Table 1).

In the first hour, the VAS score was lower in group 3 than in other groups ($p=0.040$) (Figure 1). Nausea tended to improve in later hours, especially in group 3 (Figure 2). No vomiting was observed in group 3 at the fourth hour postoperatively. Additionally, group 3 showed significance in the binary comparisons (Table 2 and Figure 3). The pain scores in the second hour postoperatively in group 3 were acceptable, although not significant ($p=0.069$). The pain scores of the other groups at the third and fourth hours postoperatively were comparable. The mean arterial pressures in group 3 were lower at the first and second hours postoperatively than those in the other groups at the same time points ($p=0.013$, $p=0.023$, respectively). The pulse rates of the three groups were comparable. Nausea more often occurred in group 2 at the second hour and in group 1 at fourth hour postoperatively (respectively, $p=0.017$, $p=0.022$).

Table 1. Characteristics of patients according to the method of tramadol administration

	Group 1 (SC) (n=30)	Group 2 (SC + IV) (n=30)	Group 3 (IV) (n=30)	p
Age (mean ± SD)	49.3±6.2	50.4±6.9	49.9±6.0	0.825
BMI* (mean ± SD)	29.5±5.2	30.6±5.7	30.5±6.7	0.899
Gravida [median (min-max)]	3 (0-6)	3 (1-6)	4 (2-10)	0.128
Parity [median (min-max)]	2 (0-6)	2 (1-4)	3 (2-6)	0.052
OD* [minute (mean ± SD)]	135±50	119±31	133±34	0.782
Pulse rate (mean ± SD)				
Postoperative 1st hour	78±10	75±14	77±8	0.982
2nd hour	80±12	77±12	79±8	0.897
3rd hour	79±8	80±14	77±6	0.620
4th hour	80±10	79±16	78±5	0.892
MAP* (median, 95% CI)				
Postoperative 1st hour	100 (93.0-103.0)	95.0 (91.6-98.2)	83.3 (83.3-93.3)	**0.013**
2nd hour	99.3 (90.8-99.7)	93.3 (86.6-100.0)	90 (86.6-96.0)	**0.023**
3rd hour	96.6 (88.6-103.0)	93.3 (91.6-96.6)	86.6 (84.1-90.3)	0.061
4th hour	96.6 (90.0-101.6)	93.3 (90.3-96.6)	93.3 (87.3-95.8)	0.288
VAS* scores (median, 95% CI)				
Postoperative 1st hour	6.0 (4.0-8.0)	6.0 (4.0-6.0)	4.0 (4.0-6.0)	**0.040**
2nd hour	4.8 (2.4-7.2)	5.0 (2.8-6.9)	3.6 (2.1-5.7)	0.069
3rd hour	4.1 (2.1-6.0)	4.0 (2.0-6.0)	3.2 (1.2-4.0)	0.250
4th hour	3.0 (1.0-4.1)	2.5 (1.5-3.9)	2.5 (1.0-3.0)	0.570
Nausea [n (%)]				
Postoperative 1st hour	6 (20%)	14 (47%)	12 (40%)	0.083
2nd hour	4 (13%)	10 (33%)	4 (13%)	**0.017**
3rd hour	4 (13%)	8 (27%)	2 (7%)	0.096
4th hour	6 (20%)	2 (7%)	0	**0.022**
Vomiting (n)				
Postoperative 1st hour	4 (13.3%)	2 (6.6%)	0	0.120
2nd hour	0	0	0	-
3rd hour	0	0	0	-
4th hour	2 (6.6%)	0	0	-

To calculate the mean arterial pressure, double the diastolic blood pressure and add the sum to the systolic blood pressure, and then divide by 3.

SC: Subcutaneously, IV: intravenously, SD: standard deviation, BMI: body mass index, min: minimum, max: maximum, OD*: operation duration, MAP: mean arterial pressure, CI: confidence interval, VAS: visual analog scale

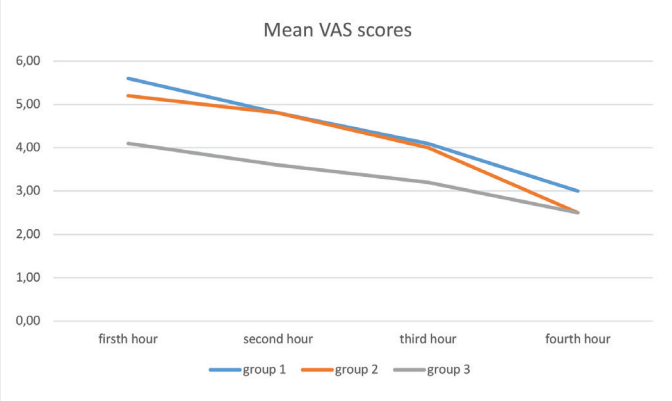

Figure 1. Graph of the mean visual analog scale scores of the patients by groups

VAS: Visual analog scale

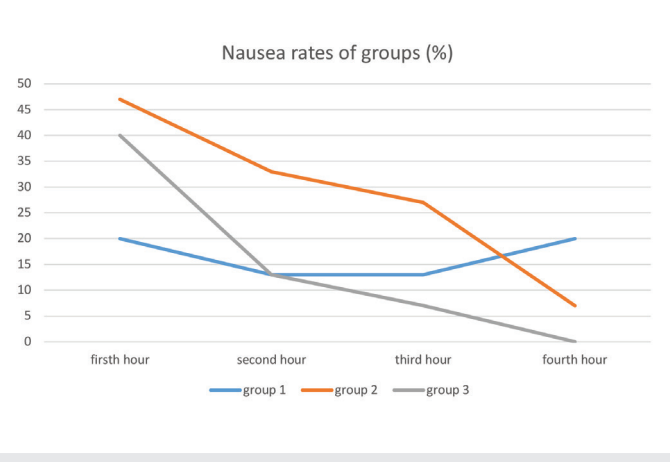

Figure 2. Graph of percent rates of nausea of the patients by groups

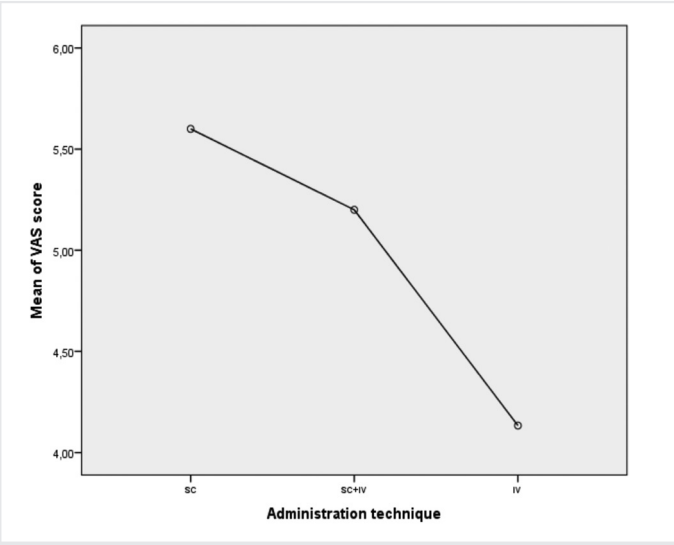

Figure 3. Graph of the visual analog scale scores for the first-hour postoperatively

Table 2. Binary comparisons for first-hour VAS scores

Groups	p
Subcutaneous and subcutaneous plus intravenous	0.480
Subcutaneous and intravenous	**0.040**
Subcutaneous plus intravenous and intravenous	0.070

VAS: Visual analog scale

Discussion

In this randomized trial, the effectiveness of different routes of tramadol administration to control pain in the early postoperative period of abdominal hysterectomy was compared. At the first-hour postoperatively, the analgesic effect of IV administration was significantly higher than those of other routes of administration. The results of this study imply that IV administration of tramadol was more advantageous for the control of postoperative pain. However, when tramadol was given IV, patients should be monitored carefully for low blood pressure. Blood pressure was significantly lower in the IV group, especially during the first-hour postoperatively. In addition, nausea more often occurred with IV intravenous administration than with SC infiltration, especially in the first-hour postoperatively. Side effects such as low blood pressure and nausea were less common with SC administration. However, the pain score was higher with SC administration than with IV administration of tramadol.

Several studies have reported on the postoperative effects of tramadol on obstetrics and gynecologic surgery. In patients who underwent cesarean section, Haliloglu et al. (8) and Sahmeddini et al. (9) have reported that SC infiltration of tramadol may be a useful technique to reduce postoperative pain (8). Altunkaya et al. (10) suggested that tramadol can be used as a local anesthetic agent (11). However, in these studies, SC infiltration was not compared with the IV administration. In our study, both SC infiltration and SC plus IV administration of tramadol were not as effective as IV administration in early postoperative analgesia. These patients may need additional analgesics in the early postoperative period.

Study limitation

A potential limitation of this study was the lack of a placebo group. However, a placebo group is unlikely in patients who underwent surgery. This study showed that IV administration of tramadol was more advantageous in controlling early postoperative pain. However, in this application, low blood pressure and nausea in the first-hour postoperatively appeared to be a disadvantage.

Conclusion

This study showed that IV administration of tramadol is more effective than SC infiltration or SC infiltration plus IV infusion to control pain in the first hour after abdominal hysterectomy. However, the mean arterial pressure of patients who received tramadol via the IV route becomes lower for the first 2 hours postoperatively; thus, patients should be closely monitored for hypotension.

Ethics Committee Approval: The study was approved by the Local Ethics Committee University of Health Sciences Turkey, İstanbul Training and Research Hospital (approval number: 1175/2018).

Informed Consent: Informed consent form was obtained from all patients for the inclusion and publication of their data.

Peer-review: Externally and internally peer-reviewed.

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

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Cardiac Hydatid Disease and Extracardiac Organ Involvement: A Tertiary Single-Center Experience

Kardiyak Hidatik Kist Hastalığı ve Ekstrakardiyak Organ Tutulumu: Üçüncül Tek Merkezli Deneyim

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ABSTRACT

Introduction: Cardiac involvement is rare in hydatid cyst disease, which accounted for 0.5%-2% of all hydatidosis cases. Cardiac cysts usually occur as part of a wider infestation with extracardiac involvement. This study aimed to describe the general characteristics, imaging findings, and range of organ involvement in cases of cardiac hydatid disease.

Methods: Retrospective assessment of cardiac hydatid disease records, between 2007 and 2019, was undertaken to identify patients with cardiac hydatidosis. Hydatid cysts were assessed by transthoracic echocardiography, magnetic resonance imaging, and computed tomography. Clinical symptoms, treatment modalities, and follow-up were also evaluated.

Results: Over the study period, 22 (13 males: 59.1%; mean age: 43.1 years; range: 12-63 years) patients with 24 cardiac hydatid cysts were identified. The most common symptom was chest pain, which occurred in 13 (59.1%) patients. Cardiac cysts were located in the left ventricle (n=10, 41.7%), right ventricle (n=5, 20.8%), interventricular septum (n=5, 20.8%), and pericardium (n=4, 16.7%). Extracardiac involvement was present in 14 (63.6%) patients, most commonly affecting the liver (n=10, 45.4%), but in 8 (36.3%) patients, there was no extracardiac organ involvement. Cardiac hydatid cysts were surgically removed in 20 (90.9%) patients.

Conclusion: Cardiac hydatid disease is very uncommon, with the left ventricle as the most commonly affected structure in this series. Chest pain was the most common presenting symptom. Extracardiac involvement is common, so patients with cardiac hydatid cysts should be investigated for involvement of other organs.

Keywords: Hydatid disease, cardiac hydatid cyst, cardiac echinococcosis, multiple organ involvement, cystectomy, cardiac MRI, transthoracic echocardiography

ÖZ

Amaç: Hidatik kist hastalarında kardiyak tutulum nadirdir ve tüm hidatidoz olgularının sadece %0,5-2'sinde bulunur. Kardiyak hidatik kistler genellikle ekstrakardiyak tutulum ile beraber ortaya çıkar. Bu makalenin amacı, kardiyak hidatik hastalığın genel özellikleri, görüntüleme bulgularını ve ekstrakardiyak organ tutulum oranlarını tanımlamaktır.

Yöntemler: Kardiyak hidatidoz'lu hastaları belirlemek için 2007 ile 2019 yılları arasında kardiyak hidatik hastalık kayıtlarının retrospektif değerlendirmesi yapılmıştır. Hidatik kist değerlendirmesi, transtorasik ekokardiyografi, manyetik rezonans görüntüleme ve bilgisayarlı tomografi kullanılarak yapıldı. Klinik semptomlar, tedavi yöntemleri ve takipleri değerlendirildi.

Bulgular: Çalışma süresi boyunca ortalama yaş 43,1 (dağılım: 12-63) olan 24 kardiyak hidatik kisti olan 22 (13 erkek: %59,1) hasta belirlendi. En sık görülen semptom 13 hastada (%59,1) göğüs ağrısı idi. Kalp hidatik kistlerinin lokalizasyonları şu şekildeydi; sol ventrikül n=10 (%41,7); sağ ventrikül n=5 (%20,8); interventriküler septum n=5 (%20,8); ve perikardiyum n=4 (%16,7). Ekstra kardiyak tutulum 14 (%63,6) olguda mevcuttu, en sık karaciğerde saptandı (n=10, %45,4), ancak sekiz (%36,3) olguda kalp dışı organ tutulumu yoktu. Kalp kist hidatiğinin cerrahi olarak çıkarılması 20/22'de (%90,9) hastada yapıldı.

Sonuç: Kardiyak hidatik hastalığı çok nadirdir ve en sık tutulan yapı bu çalışmada sol ventriküldür. Göğüs ağrısı en sık görülen semptomdu. Ekstra kardiyak tutulum yaygındır, bu nedenle kardiyak hidatik kistleri olan hastalar başka organ tutulumu açısından araştırılmalıdır.

Anahtar Kelimeler: Hidatik kist hastalığı, kardiyak hidatik kist, kardiyak ekinokokus, çoklu organ tutulumu, kistektomi, kardiyak MRG, kardiyak BT, transtorasik ekokardiyografi

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Introduction

Hydatid cyst disease results from a parasitic infection with *Echinococcus granulosus*. Hydatidosis is still endemic in some countries, including Turkey. Although domestic dogs and cats are the most commonly affected species, humans may become infected after ingestion of viable *E. granulosus* ova because of poor food hygiene (1). Hydatid cysts may occur in many organ systems; however, in humans, they are most commonly found in the liver (55%-70%) and lungs (20%-30%) (1). Cardiac involvement is rare, presenting in only 0.5%-2% of all cases of hydatidosis, and can occur either as a part of a broader systemic infection or more rarely as the only organ system affected. The most commonly affected cardiac structures are the left ventricle (LV) in 50%-60%, interventricular septum in 10%-20%, and right ventricle (RV) in 5%-15% of patients with cardiac hydatidosis. Less commonly, cysts have been reported in the pericardium (7%), pulmonary artery (6%), and right or left atrium (5%-8%) (2-5). Most patients with cardiac hydatid cyst disease develop symptoms very late, because cardiac cysts grow very slowly. Symptoms of cardiac hydatid cyst include chest pain, dyspnea, syncope, and palpitation, and symptom severity correlates with the size of the cyst and the affected cardiac structures (2-6). On diagnosis of a cardiac hydatid disease cyst, because of the likely involvement of other organ systems, whole body screening should be performed. The main treatment of hydatid disease is surgery with complete removal of the cyst (7). Medical therapies may include albendazole or mebendazole, given before and after surgery (2). This study aimed to present a single tertiary center experience of cardiac hydatid cyst disease and describe the general characteristics, management, imaging findings, range of organ involvement, and follow-up in cases of cardiac hydatid disease.

Methods

Patients diagnosed with cardiac hydatid cyst with extracardiac organ involvement and presented to the cardiology and radiology departments between December 2007 and December 2019 were enrolled retrospectively in this study. Patient data were extracted from a detailed clinical database of all patients diagnosed with hydatid cyst disease. Details extracted included demographic information, such as age and sex, and other relevant medical history. Clinical symptoms on admission including chest pain, dyspnea, palpitation, syncope, and headache were also evaluated. From each patient, other information obtained included cardiac structures affected by the hydatid cysts, all extracardiac organ system involvement, surgical and medical treatment, preoperative complications, and postoperative follow-up of at least 12 months.

All patients underwent basal electrocardiography, chest X-ray imaging, and echocardiography. Transthoracic echocardiography (TTE) images were obtained for each patient using a Vivid 7 ultrasound system (GE Medical System, Horten, Norway). When hydatid cysts were found in the heart, patients underwent cranial, thoracic, and abdominal computed tomography (CT) and/or magnetic resonance imaging (MRI) to detect the involvement of other organ systems. Cardiac MRI was performed in selected cases using a 3-T Philips MRI unit (Philips Achieva Intera Release, Eindhoven, Netherlands). Non-contrast and contrast-enhanced CT was performed with a 64-channel multidetector CT scanner (Aquilion 64; Toshiba Medical Systems, Tokyo, Japan). Survival and disease status was obtained from the hospital records or, if necessary, by direct communication with the patient or their families.

The study was approved by the Kocaeli University Faculty of Medicine Ethic Committee (approval number: KU-GOKAEK-2020/37). Given the retrospective nature of the study, no specific individual informed consent was required. All patients had given informed consent for the treatment procedure.

Statistical Analysis

Statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Continuous data are shown as mean ± standard deviation and categorical variables as numbers and percentages.

Results

In 12 years, 22 (13 males: 59.1%) patients were diagnosed with cardiac hydatid cyst after cardiac examination, and these patients were initially admitted for various cardiac symptoms, including chest pain, dyspnea, palpitation, syncope, and headache. The mean age was 43.1±18.2 years. The baseline demographic, clinical, treatment, follow-up characteristics and imaging findings of patients with hydatid cyst disease are shown in Table 1.

All patients underwent non-contrast and contrast-enhanced CT, while 14 (63.6%) patients underwent cardiac MRI. Twenty (90.9%) patients had a single cardiac hydatid cyst, while the remaining two (9.1%) had two cardiac cysts. Cardiac hydatid cysts were found in the following cardiac regions: LV (n=10, 41.7%), RV (n=5, 20.8%), interventricular septum (n=5, 20.8%), and pericardium (n=4, 16.7%). Common symptoms at admission included chest pain (n=13, 59.1%), dyspnea (n=7, 31.8%), and palpitations (n=5, 22.7%). In addition, one patient (4.5%) presented with syncope due to a complete atrioventricular (AV) block and one (4.5%) was admitted for complaint of headache due to brain hydatid cysts. Finally, one patient presented without symptoms, and the cyst was found incidentally at checkup with chest X-ray imaging.

Lesions were assessed according to Gharbi classification (1). This revealed that 8/24 (33.3%) cases were type 1, 5/24 (20.8%) were type 2, 1/4 (4.2%) was type 3, 3/24 (12.5%) were type 4, and 7/24 (29.2%) were type 5. MRI was performed in 14 patients. In patients who underwent MRI, 4 lesions were hyperintense and 10 lesions were hypointense on T1-weighted images, and 10 lesions were hyperintense and 4 lesions were hypointense in T2-weighted images. CT and TTE were performed in all 22 patients. On CT, 9/24 (37.5%) lesions were mildly hypodense and 14/24 (58.3%) lesions were hypodense. A calcification component was observed on CT examination in seven patients, all with Gharbi type 5 cardiac hydatid cyst. On TTE, 5/24 (20.8%) lesions were hyperechoic, 7/24 (29.1%) lesions were anechoic, and 11/24 (45.8%) lesions were hypoechoic. In patient 2, CT, MRI, and TTE showed LV aneurysmatic dilatation due to a ruptured cardiac hydatid cyst. Imaging findings of cardiac hydatid cysts are shown in Figure 1-7.

There was no extracardiac hydatid disease organ involvement in 8/22 (36.4%) patients. The remaining 14 patients had hydatid organ system involvement, as follows: Liver in 10/22 (45.4%), lung in 5/22 (22.7%), brain in 2/22 (9.09%), and spleen hydatid cysts in 2/22 (9.09%) patients.

Table 1. Demographic, clinical, diagnostic, therapeutic characteristics and imaging findings in 22 patients with cardiac hydatid cyst disease

Case	Age, sex	Location	Size (mm)	Gharbi classification	MRI	CT	TTE	Admission symptom	Extracardiac involvement	Treatment	Preoperative complication	Postoperative complication
Patient 1	49, F	LV lateral (intraventricular and extraventricular extension)	59x45	Type 2	T1 heterogeneous and hyperintense; T2 heterogeneous and hyperintense	Heterogeneous and hypodense	Heterogeneous and hypoechoic	Chest pain	No	Cardiac surgery	-	-
Patient 2	12, M	LV inferolateral	42x34	Type 1	Aneurysmatic dilatation	Aneurysmatic dilatation	Aneurysmatic dilatation	Headache	Brain	Cardiac and brain surgery	Vascular embolism	-
Patient 3	63, M	1. interventricular septum	70x30	Type 4	-	Hypodense	Hyperechoic	Palpitation, dyspnea, chest pain	Lung	-	Pulmonary embolism, exitus	-
		2. RV (intraventricular)	46x28	Type 5	-	Hypodense + peripheral calcification	Hypoechoic					
Patient 4	60, M	LV lateral	35x30	Type 5	T1 heterogeneous and hypointense; T2 heterogeneous and hypointense	Mildly hypodense + peripheral calcification	Hyperechoic	Chest pain	No	Cardiac surgery	-	-
Patient 5	17, F	Interventricular septum	54x35	Type 2	T1 heterogeneous and hyperintense; T2 heterogeneous and hyperintense	Hypodense	Anechoic	Chest pain, palpitation,	No	Cardiac surgery	-	Intraoperative exitus and anaphylaxis
Patient 6	55, F	Interventricular septum	44x38	Type 4	-	Mildly hypodense	Hyperechoic	Dyspnea, chest pain, palpitation,	Lung, liver	Surgery for all	-	-
Patient 7	22, M	LV apex	49x45	Type 1	T1 hypointense; T2 hyperintense	Hypodense	Heterogeneous and hypoechoic	Dyspnea, palpitation.	No	Cardiac surgery	-	-
Patient 8	43, M	Pericardial	78x65	Type 2	-	Hypodense	Hypoechoic	Chest pain	No	Cardiac surgery	-	Pulmonary atelectasis
Patient 9	39, F	LV inferior	98x76	Type 3	T1 heterogeneous and hypointense; T2 heterogeneous and hyperintense	Hypodense	Heterogeneous and hypoechoic	Chest pain	No	Cardiac surgery	-	-
Patient 10	24, M	LV inferior	26x24	Type 1	T1 hypointense; T2 hyperintense	Hypodense	Anechoic	Dyspnea	Liver	Cardiac surgery, PAIR for liver	-	-
Patient 11	48, F	LV anterolateral	48x34	Type 2	-	Hypodense	Hypoechoic	Chest pain	Liver	Cardiac and liver surgery	-	-

Table 1. Continued

Case	Age, sex	Location	Size (mm)	Gharbi classification	MRI	CT	TTE	Admission symptom	Extracardiac involvement	Treatment	Preoperative complication	Postoperative complication
Patient 12	33, M	RV lateral	37x33	Type 1	T1 hypointense; T2 hyperintense	Hypodense	Anechoic	Chest pain	Lung	Cardiac and lung surgery	-	Pulmonary atelectasis
Patient 13	48, M	RV lateral	42x24	Type 1	-	Hypodense	Anechoic	Dyspnea	Liver, spleen	Cardiac and spleen surgery, PAIR for liver	-	-
Patient 14	21, F	LV apex	63x45	Type 1	T1 hypointense; T2 hyperintense	Hypodense	Anechoic	Palpitation	Liver, brain	Cardiac and brain surgery, PAIR for liver	-	-
Patient 15	58, M	RV lateral	26x32	Type 1	-	Hypodense	Anechoic	Chest pain	Liver	Cardiac surgery, PAIR for liver	-	-
Patient 16	32, M	RV lateral	35x19	Type 1	T1 hypointense; T2 hyperintense	Hypodense	Anechoic	Chest pain	Lung, spleen	Cardiac, lung, and spleen surgery	-	-
Patient 17	15, M	LV lateral	42x51	Type 2	T1 hypointense; T2 hyperintense	Heterogeneous and hypodense	Heterogeneous and hypoechoic	Chest pain	Lung, liver	Cardiac surgery, lung surgery, PAIR for liver	-	-
Patient 18	69, F	Interventricular septum	21x19	Type 5	T1 hyperintense; T2 heterogeneous hypointense	Mildly hypodense + peripheral calcification	Hyperechoic	Syncope	Liver	Medical treatment	-	-
Patient 19	63, F	L pericardial	53x31	Type 4	T1 hyperintense; T2 heterogeneous and hyperintense	Heterogeneous and hypodense	Heterogeneous and hypoechoic	Chest pain	Liver	Cardiac surgery, liver surgery	-	-
Patient 20	58, M	Interventricular septum	54x42	Type 5	T1 hypodense; T2 heterogeneous and hypointense	Mildly hypodense + peripheral calcification	Hyperechoic	Dyspnea	No	Cardiac Surgery	-	-
Patient 21	59, F	L pericardial	93x41	Type 5	-	Mildly hypodense + peripheral calcification	Hypoechoic	Dyspnea	Liver	Cardiac and liver surgery	-	-
		R pericardial	52x14	Type 5								
Patient 22	60, M	LV apex	35x24	Type 5	T1 hypodense; T2 heterogeneous and hypointense	Mildly hypodense + peripheral calcification	Hypoechoic	Asymptomatic	No	Medical treatment	-	-

MRI: Magnetic resonance imaging, CT: computed tomography, TTE: transthoracic echocardiography, F: female, M: male, L: left, R: right, LV: left ventricle, RV: right ventricle, PAIR: puncture, aspiration, injection, and reaspiration for treatment of cysts

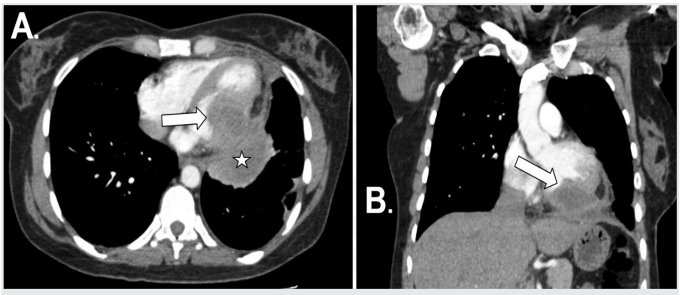

Figure 1. (Patient 1*) A 49 year-old female patient with Gharbi type 2 hydatid cyst of the left ventricular lateral wall. The cyst is heterogeneous and hypodense on the post-contrast axial and coronal computed tomography image (arrow, A and B). Extraventricular involvement of cyst is also seen (star, A)

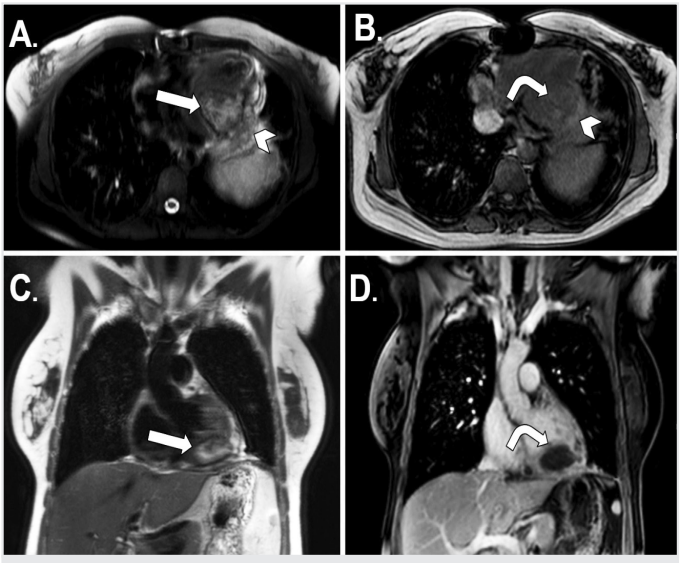

Figure 2. (Patient 1*) The cyst is heterogeneous and hyperintense on the axial and coronal T2-weighted images (arrow, A and C) and heterogeneous and hyperintense on precontrast axial T2-weighted image (curved arrow, B). On coronal T1-weighted, delayed-phase cardiac images after contrast injection, peripheral rim enhancement (curved arrow, D) is seen around the cyst. Extraventricular involvement of the cyst is also seen on the axial T1- and T2-weighted images (arrowheads, A, B)

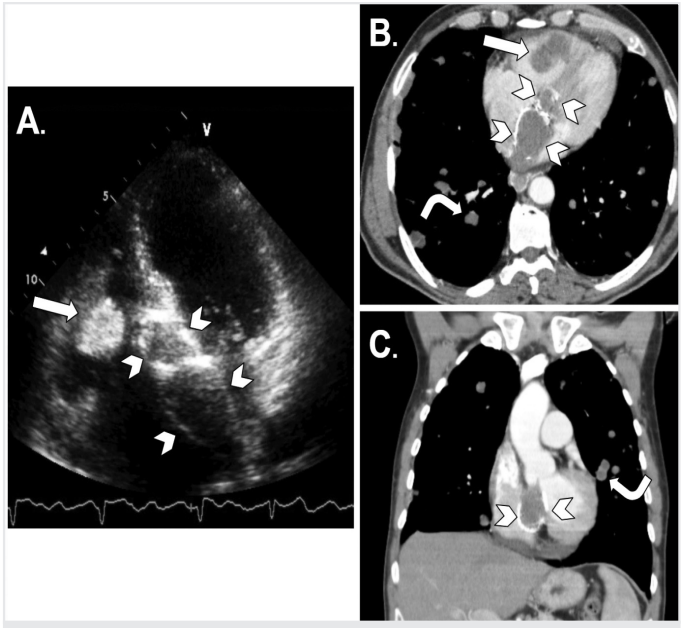

Figure 3. (Patient 3*) A 63 year-old male patient with two cardiac hydatid cysts: one Gharbi type 4 and one type 5. The right intraventricular cyst is hyperechoic on TTE (arrow, A) and hypodense on CT (arrow, B). The interventricular septum cyst is hypoechoic and has hyperechoic peripheral calcification (arrowheads, A). The interventricular septum cyst is hypodense with hyperdense peripheral calcification on axial (arrowheads, B) and coronal (arrowheads, C) CT images. Pulmonary hydatid cysts are also seen on axial (curved arrow, B) and coronal (curved arrow, C) CT images

CT: Computed tomography, TTE: transthoracic echocardiography

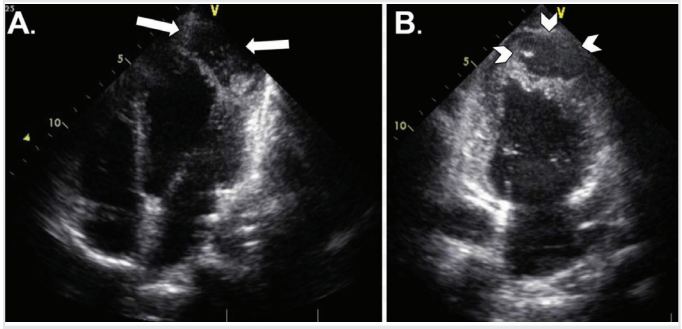

Figure 4. (Patient 7*) A 22 year-old male patient with Gharbi type 1 cyst of the left ventricular apex. The cyst is heterogeneous and hypoechoic on transthoracic echocardiography (arrows, A: arrowheads, B)

Of the 8 patients with hydatid disease only affecting the heart, 7/8 (87.5%) underwent open-heart surgery and the eighth patient had medical therapy only. Of those undergoing open-heart surgery, one died intraoperatively because of generalized anaphylaxis (patient 5), while another patient (patient 3) died of pulmonary embolism due to hydatid cyst rupture while being prepared for surgery. A 12 year old male patient (patient 2) had concomitant cardiac and brain surgery for hydatid cyst disease without any postoperative complication. Open-heart surgery and puncture, aspiration, injection, and reaspiration (PAIR) for treatment of cysts in the liver were performed in 5 of 10 patients with cardiac and liver cysts, without any complication, while 4 more of them (18.1%) underwent successful open-heart and liver surgery for cysts. Complete removal of lung hydatid cysts were successfully achieved in four of the five patients with concomitant lung and cardiac involvement, in addition to surgical removal of cardiac cysts. Surgical removal of spleen cysts was successful in two patients. A 21 year old female patient (patient 14) had successful open cardiac and brain surgery with PAIR for the liver. Two patients did not undergo surgery because of comorbidities (patients 18 and 22), which included pulmonary embolism, pulmonary atelectasis, and vascular embolism that occurred preoperatively. Preoperative treatment of 400 mg albendazole or mebendazole was given to all patients and continued for 12 months after surgery. On follow-up, the remaining 20 patients continued to have good health status, without any further complications. In addition, there was no cardiac reinfestation in 18 patients, while in the two patients who were on medical therapy alone, cardiac cysts were stable at 1 year follow-up.

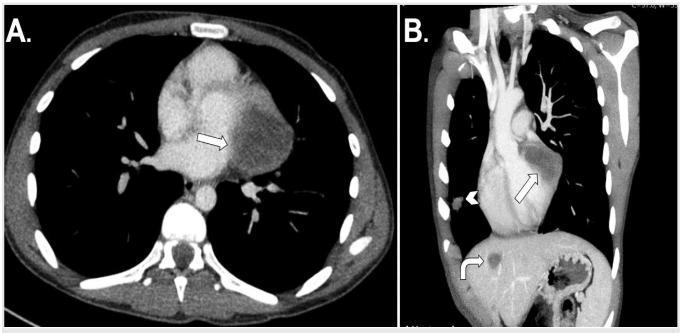

Figure 5. (Patient 17*) A 15 year-old male patient with Gharbi type 2 cyst of the left ventricular lateral wall. The cyst is heterogeneous and hypodense on post-contrast axial and coronal CT (arrow, A and B) images. Pulmonary (arrowhead, B) and hepatic (curved arrow, B) hydatid cysts are also seen on the coronal CT image

CT: Computed tomography

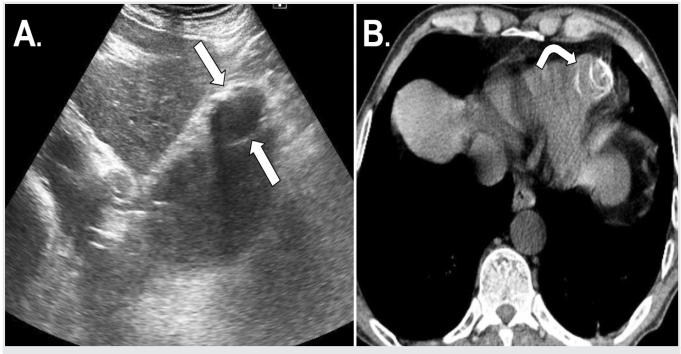

Figure 6. (Patient 22*) A 60-year-old male patient with Gharbi type 5 cyst of the left ventricular apex. The cyst is hypoechoic on TTE and has hyperechoic peripheral calcification (arrows, A). On the axial CT image, the cyst is hypodense with hyperdense peripheral calcification (curved arrow, B)

CT: Computed tomography, TTE: transthoracic echocardiography

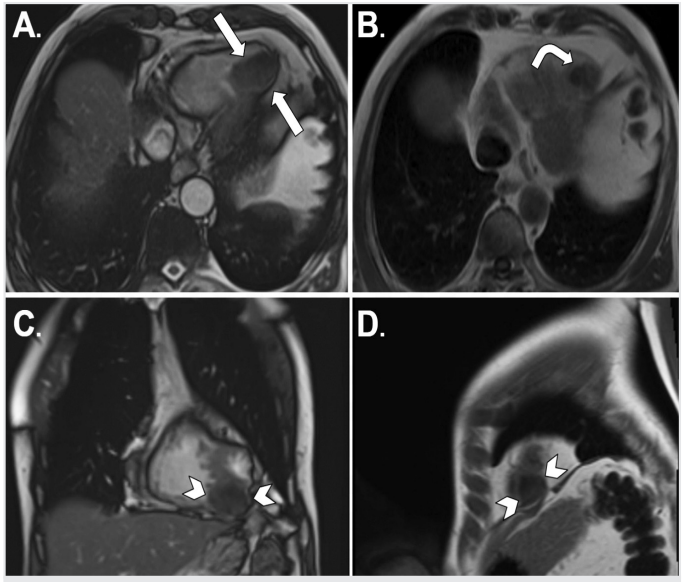

Figure 7. (Patient 22*) The cyst is hypointense on precontrast axial T1-weighted image (arrows, A) and heterogeneous and hypointense on precontrast axial (curved arrow, B) and coronal T2-weighted image (arrowheads, C). On sagittal T1-weighted, delayed-phase cardiac images after contrast injection, peripheral rim enhancement (arrowheads, D) is seen around the cyst

Discussion

Cardiac hydatid cysts are rare and account for 0.5%-2% of all cases of hydatidosis. When cardiac hydatid cysts are present, extracardiac organ system involvement is reported to range from 38% to 100% of cases (7-9). In hydatid cyst disease with extracardiac involvement, cardiac hydatid cyst may occur as single or multiple cysts and affect a single or multiple organ systems (10). Cardiac involvement has several possible mechanisms: 1) Infection of the myocardium via coronary arterial supply, 2) infestation as a result of echinococcal cyst rupture into a pulmonary vein, and 3) direct tissue-to-tissue contact with cysts in the liver or lungs (11).

The most common symptom in patients with cardiac hydatid cyst disease is chest pain. However, patients may present with dyspnea, palpitations, and/or syncope, depending on the location and size of the cyst. Angina pectoris may occur if the cyst impedes coronary artery function (2-4). Cardiac conduction impairment, such as AV block or nodal rhythm abnormality, may occur if the cysts compress the AV node or bundle of His (6).

Complications of cardiac hydatid cysts can be severe and fatal, so prompt and accurate diagnosis is important. Cyst rupture is the most dangerous complication, which may cause cardiac tamponade, anaphylactic shock, systemic embolism or combined pulmonary and systemic embolisms, and arrhythmias (11-14). In the present series, one patient died from anaphylactic shock and the other from pulmonary embolism.

Diagnostic methods for cardiac cysts include non-invasive imaging techniques such as those used in this series (TTE, CT, and MRI) and serological tests (15). Serologic tests are more sensitive and specific for liver involvement than for cardiac hydatid disease, although these tests are not capable of positively identifying the organ(s) involved (11). Serological testing, using an enzyme-linked immunosorbent assay, is the most sensitive (94%) and specific (90%) test for most hydatid cyst locations (11). TTE is the first-line imaging modality of choice being widely available, easy to use, and with good sensitivity for cardiac hydatid cyst diagnosis (16). CT is a good second-line modality for cardiac cysts and shows cyst wall calcification well in type 5 cysts. However, cardiac motion artifacts are an important limitation of CT. MRI is excellent at identifying the exact anatomic location of cysts and provides information concerning cystic internal and external structures, thus allowing cysts to be differentiated from other masses and tumors. Hydatid cysts have a characteristic appearance on MRI, usually as a hypointense and hyperintense oval lesion on T1- and T2-weighted images, respectively. In addition, T2-weighted images may show a hypointense peripheral ring caused by the formation of a pericyst consisting of host tissues deposited as a result of the inflammatory response to the cyst (5,15). On suspicion of a hydatid cyst, positive identification of the cystic wall and peripheral contrast enhancement are crucial to distinguishing the cyst from other cardiac masses. Cardiac hydatid disease occurs more often in the LV because of its large myocardial mass and abundant blood supply (2,15). Thus, the LV was the most commonly affected cardiac region in our series.

The definite treatment for hydatid cyst disease is surgery, and an open-heart surgery for cardiac cysts is known as cystopericystectomy. Rarely,

partial pericystectomy can be performed to preserve organ function (11). In our study, majority (19/22) of the patients underwent total cystopericystectomy during open-heart surgery with cardiopulmonary bypass. Different approaches for cystectomy during open-heart surgery have been described. Birincioğlu et al. (17) suggested that subepicardial cysts can be resected without cardiopulmonary bypass. By contrast, Abhishek and Avinash (11) suggested that cardiopulmonary bypass is still required for optimal safety. Gentle handling of the heart during cardiopulmonary bypass minimizes operative risks and complications, such as cyst rupture (18). Unfortunately, cyst rupture occurred in a 17-year-old female patient (patient 5) in our series, resulting in intraoperative anaphylaxis and death.

Previous reports from small series have indicated extracardiac organ involvement in approximately one-third of all patients (7-9). In our series, an incidence of 63.7% falls at the middle of this range. Thus, given the high likelihood of extracardiac involvement in patients initially diagnosed with cardiac hydatid cyst, we suggest that all patients undergo systemic screening to identify other affected organ systems. In patients with hepatic involvement, the gold standard treatment is complete removal with open surgery, such as through percutaneous, minimally invasive surgery and PAIR (19). In our series, PAIR was successfully performed in four patients with liver hydatid cysts. The two remaining patients with liver disease underwent open surgery without any postoperative complication. For all patients with cardiac hydatid disease, medical therapy with albendazole or mebendazole should be implemented to reduce repeated infections and minimize perioperative complications. This treatment should be started 14 days before surgery and continued for at least 1 year following surgery (6,11,14,20).

Study Limitations

This study has some limitations. First, this is a single-center retrospective study, with inherent biases. Second, the sample size was small; however, cardiac hydatid cyst is a very rare disease, which also led to the long duration of the study period, a further limitation. This led to some missing data and inevitable variation in clinical management and treatment strategy because of the lack of standard guidelines. Prospective, randomized, and multicenter study is the ideal study design for collection of data concerning cardiac hydatid cyst disease, but this is difficult, given the rarity of the condition.

Conclusion

Cardiac hydatid cyst is a very rare condition, and majority of the cases have left ventricular involvement. The most common presenting symptom is chest pain. TTE is the first-line imaging modality of choice, while CT and MRI provide valuable additional findings for the diagnosis of cardiac hydatid disease, including the exact anatomic location. In our cohort, more than two-thirds of patients had extracardiac organ system involvement; thus, all patients should be screened for other cyst locations, especially the liver, lung, and brain. In addition, multisystem involvement is common, so patients presenting with non-cardiac hydatid disease should also undergo cardiac imaging. Surgery is the main treatment modality with adjunctive medical therapy using either albendazole or mebendazole therapy. Given the rarity of the condition, there is little data about the clinical course and outcomes in patients with cardiac hydatid cyst, so further studies are necessary.

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Ethics Committee Approval: The study was approved by the Kocaeli University Faculty of Medicine Ethic Committee (approval number: KÜ-GOKAEK-2020/37).

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Authorship Contributions: Surgical and Medical Practices - K.K., İ.K., O.O., E.Ç.; Concept - İ.Ç., K.K., İ.K., A.Y., Ö.Ç., O.O., E.Ç., Y.A.; Design - İ.Ç., K.K., T.Ö., Ö.Ç., O.O., E.Ç., T.Ş.; Data Collection or Processing - İ.Ç., K.K., İ.K., T.Ö., Ö.Ç., O.O.; Analysis or Interpretation - İ.Ç., K.K., İ.K., A.Y., H.C., B.E.G., E.Ç., T.Ş., Y.A.; Literature Search - İ.Ç., T.Ö., A.Y., H.C., B.E.G., Y.A.; Writing - İ.Ç., K.K., A.Y., H.C., B.E.G., E.Ç., Y.A.

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The Efficacy and Safety of Busulfan-Etoposide-Melphalan Regimen in Autologous Stem Cell Transplantation in Relapsed/Refractory Hodgkin and Non-Hodgkin Lymphoma Patients: "A Single-Center Experience"

Nüks Dirençli Hodgkin ve Hodgkin Dışı Lenfoma Hastalarında Otolog Kök Hücre Nakli Hazırlama Rejiminde Busulfan-Etoposid-Melfalan Rejiminin Etkinlik ve Güvenirliliği: "Tek Merkez Deneyimi"

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ABSTRACT

Introduction: High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the standard treatment for relapsed and refractory lymphoma patients. The difficulties in accessing and high cost of carmustine have led to the increased use of alternative regimen before ASCT for the treatment of lymphoma, including busulfan-based busulfan-etoposide-melphalan (BuEM) regimens.

Methods: Data of 16 Hodgkin's lymphoma and non-Hodgkin's lymphoma patients who underwent ASCT following BuEM conditioning regimen were retrospectively analyzed within the scope of the study.

Results: The median overall survival and progression-free survival during the 188 day follow-up period were found to be 93.8% and 87.1%, respectively. Neutrophil and platelet engraftment times were found to be 11 and 17 days, respectively, and the median duration of hospitalization was determined to be at 22.5 days. The prevalence of grade 3-4 mucositis was found to be at 37.6% (81.3% in total), whereas that of grade 1-4 infection was 87.5%, and grade 1-3 gastrointestinal system toxicity was found to be at 68.3%. No obvious liver and kidney toxicity were observed. Transplantation-related mortality was detected in 1 (6.25%) patient.

Conclusion: Our results suggest that a prospective study on the BuEM regimen involving a large number of cases is required.

Keywords: Autologous stem cell transplantation, Hodgkin's lymphoma, non-Hodgkin's lymphoma, conditioning regimens, BuEM

ÖZ

Amaç: Yüksek doz kemoterapi ve ardından otolog kök hücre nakli (OKHN), dirençli ve nükseden lenfoma hastaları için standart tedavidir. Karmustine ulaşımdaki zorluklar ve yüksek maliyet, Busulfan bazlı busulfan-etoposid-melfalan (BuEM) dahil olmak üzere lenfoma tedavisi için OKHN öncesinde alternatif hazırlama rejimlerinin kullanımının artmasına neden olmuştur.

Yöntemler: BuEM konsolidasyon rejimi ile OKHN uygulanan 16 Hodgkin lenfoma ve Hodgkin dışı lenfoma hastasının verileri retrospektif olarak incelendi.

Bulgular: Medyan 188 günlük takipte OS %93,8 ve PFS %87,1 olarak saptandı. Nötrofil ve trombosit engrfatman süreleri sırasıyla medyan 11 ve 17 gün oldu. Medyan hastanede kalış süresi 22,5 gün olarak belirlendi. Grade 3-4 mukozit %37,6 (total: %81,3), grade 1-4 enfeksiyon %87,5, grade 1-3 gastrointestinal sistem toksisitesi %68,3 oranında görüldü. Belirgin karaciğer ve böbrek toksisitesi görülmedi. Transplant ilişkili mortalite sadece bir hastada (%6,25) oranında görüldü.

Sonuç: Sonuçlarımız BuEM rejimi ile çok sayıda olgu içeren prospektif bir çalışmanın gerektiğini düşündürmektedir.

Anahtar Kelimeler: Otolog kök hücre nakli, Hodgkin lenfoma, Hodgkin dışı lenfoma, hazırlama rejmi, BuEM

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Introduction

Autologous stem cell transplantation (ASCT) is considered the standard treatment in patients with chemosensitive relapsed non-Hodgkin lymphoma (NHL) and relapsed/refractory (R/R) Hodgkin lymphoma (HL) following high-dose chemotherapy (1,2). In 1986, an international group called PARMA was organized involving bone marrow transplant centers from around the world. PARMA study is the first randomized study that showed the advantages of ASCT over the salvage regimen in relapsed NHL (3). Carmustine-etoposide-cytarabine-melphalan (BEAM) is the most commonly used conditioning regimen for R/R HL and NHL (4,5). Severe mucositis, gastrointestinal symptoms, and varying degrees of lung, liver, and kidney toxicities have been reported following the conditioning regimen (6-9).

Researchers have revealed that the high-dose conditioning regimen is effective and have acceptable hematological and non-hematological toxicity in ASCT in R/R lymphomas. It is clear that new treatment regimens need to be developed in several countries, including Turkey, due to the high cost of carmustine and its unavailability. Therefore, it is recommended to develop new and more effective and accessible treatment regimens with lower incidence of side effects.

The most common drug combinations such as carmustine, cyclophosphamide, etoposide, melphalan, busulfan, cytarabine, and thiotepa are used in conditioning regimens. Thus, comparative studies to BEAM have been conducted with regimens such as bendamustine-etoposide-cytarabine-melphalan (BEAM) (10,11), thiotepa-etoposide-cyclophosphamide-cytarabine-melphalan (12), lomustine-etoposide-cytarabine-melphalan (13), lomustine-cytarabine-cyclophosphamide-etoposide (14), cyclophosphamide-carmustine-etoposide (15), carmustine-etoposide-cytarabine-cyclophosphamide (BEAC) (15), busulfan-cyclophosphamide-etoposide (16,17), fotemustine-etoposide-cytarabine-melphalan (18), and mitoxantrone-etoposide-cytarabine-melphalan (19); no regimen has demonstrated significant superiority over the other.

In a study, Sakellari et al. (20) compared the effects between BEAM and busulfan-etoposide-melphalan (BuEM) regimens in patients with R/R lymphoma. BuEM regimen was well tolerated, with acceptable toxicity and without mortality, and was found to be equally effective like BEAM in NHL. In HL, it was reported that overall survival (OS) and progression-free survival (PFS) were significantly better than BEAM (20).

In this retrospective study, we aimed to report our observations regarding BuEM conditioning regimen in ASCT conducted in our center.

Methods

Sixteen patients diagnosed with R/R HL and NHL and treated with BuEM regimen as conditioning in ASCT were retrospectively analyzed. Patient characteristics included the patient's age and gender, subtype of the disease, and time period between diagnosis and transplantation; whether plerixafor was used during stem cell collection; the number of stem cells given, duration of febrile status, time to neutrophil and thrombocyte engraftment (TE), and drug-related renal, liver, and gastrointestinal toxicity and mucositis degrees; and final status in positron emission tomography/computed tomography (PET/CT) 100 days after ASCT. Neutrophil >1000/mm^3 and thrombocyte >50.000/mm^3 were accepted as engraftment levels.

The study design was approved by the Bezmialem Vakıf University Non-Interventional Research Ethics Committee (approval number: 11/230, date: 07.07.2020); however, informed consent was waived because it was a retrospective study.

Treatment Protocol

BUEM regimen was applied to all patients as conditioning before ASCT: Busulfan 9.6 mg/kg (1.6 mg/kg/12 hours per day, days -6, -5, -4), etoposide 800 mg/m^2 (400 mg/m^2/day, days -3 and -2) and melphalan 140 mg/m^2 (day, -1). Stem cells were administered at least 24 hours after the melphalan dose.

Response Criteria

Response was assessed 3 months after ASCT using the widely accepted International Working Group response criteria. Complete remission (CR) was defined as the complete regression of all detectable clinical diseases and disease-related symptoms. Response evaluation was performed by CT or PET/CT scanning in all patients 100 days after transplantation (21).

Toxicity Assessment

Regimen-related toxicities were recorded in the first 100 days. The severity and duration of oral mucositis were recorded according to the "World Health Organization" toxicity criteria (22). The other toxicities were recorded according to the Common Terminology Criteria (Version 3.0).

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median lowest and highest, frequency, and ratio values were used. The Kaplan-Meier method was used in survival analysis and SPSS 26.0 program in the analyses.

Results

Sixteen adult patients who underwent ASCT after BuEM conditioning regimen and diagnosed with R/R HL and NHL between January 2018 and January 2020 were included in the study. Among these patients, 5 (33.3%) were females and 11 (68.7%) were males. The median age was 61 (range: 23-75) years. Four (25%) patients were diagnosed with diffuse large B cell lymphoma, four (25%) with grade 3 follicular lymphoma, four (25%) mantle cell lymphoma, two (12.5%) HL, one marginal zone lymphoma, and one primary effusion lymphoma. The median duration from diagnosis to transplantation was 194 (range: 126-385) days (Table 1). Plerixafor was applied to four of the patients (25%) for stem cell collection due to insufficient stem cell collection with lenograstim. Stem cells were collected using only lenograstim in the other 12 (75%) patients. The characteristics of the patients before HSCT are summarized in Table 1.

The median time until neutrophil engraftment (NE) was 11 (range: 10-15) days and median time until TE was 17 (range: 13-77) days. The median number of stem cells transfused to the patients was 6.3

(range: 3.6-13) x10^6/kg. The median usage time of granulocyte colony-stimulating factor (G-CSF) (lenograstim) was 7.5 (range: 5-14) days.

All patients were in CR before transplantation. Remission control was performed with PET/CT 100 days after the transplant, except for one patient who died of post-transplant-related mortality. According to PET/CT results, 14 patients (87.25%) had CR and one patient (6.25%) had recurrence. One patient relapsed 200 days after ASCT. The median follow-up period after ASCT was 188 days (range: 14-775 days, 95% CI).

Four patients had grade 1, five grade 2 (31.3%), two grade 3 (12.5%), and five grade 4 (31.3%) pneumonia and sepsis. Only one patient had septic shock due to deep neutropenia. Transient grade 1 renal and liver toxicity developed in only two (12.5%) patients. The remaining 14 (87.5%) patients did not exhibit liver and renal toxicities. Moreover, patients were followed up for mucositis. Seven (43.8%) patients had grade 1, five grade 2 (31.3%), and one (6.3%) grade 3 mucositis. Grade 4 mucositis was not observed in any of the patients, and mucositis was not detected in three (18.8%) patients. No gastrointestinal toxicity was observed in five patients (31.3%); however, four patients had grade 1 (25%), five patients (31.3%) grade 2, and two patients grade 3 (12.5%) gastrointestinal toxicity such as nausea, vomiting, and diarrhea. Grade 4 GI side effects were not observed in any patient. The median duration of hospitalization of the patients was 22.5 (range: 19-27) days. Post-transplant response status and non-hematological toxicities are shown in Table 2.

Discussion

The BEAC conditioning regimen was preferred in the PARMA study, which was the first randomized study to show the superiority of ASCT over salvage chemotherapy in relapsed NHL patients following high-dose chemotherapy. In this study, the 5-year event-free survival and OS were 12% and 32% in the salvage chemotherapy group and 46% and 53% in the ASCT group, respectively (3). Furthermore, in various studies, the superiority of ASCT over conventional chemotherapy was confirmed (4,23,24). Researchers agree that a conditioning regimen with a high response rate and acceptable hematologic and non-hematologic toxicity should be determined.

However, commonly used conditioning regimens have their pros and cons, and the available literature provides limited data demonstrating the superiority of any regimen for lymphomas. Among these factors, BEAM regimen has been the leading and most widely used regimen in both HL and NHL. Moreover, its superiority has been shown in various studies (25-28). However, severe chemotherapy-induced mucositis, gastrointestinal symptoms, and varying degrees of lung, liver, and renal toxicities result in the need for new conditioning regimens (6-9). Experimental data show that the combination of busulfan and nucleoside activates a DNA damage response in lymphoma cell lines (29). Busulfan is one of the oldest alkylating agents, which is highly lipophilic and active in various malignancies such as multiple myeloma and lymphomas (30).

Table 1. The characteristics of the patients before ASCT

		Min-Max	Median	Mean ± SD/(n, %)
Age		23.0-75.0	61.5	54.3±16.9
Gender	Female	-	-	5 (31.3%)
	Male	-	-	11 (68.7%)
Histology; n (%)				
Diffuse large B cell lymphoma		-	-	4 (25.0%)
Follicular lymphoma		-	-	4 (25.0%)
Hodgkin's lymphoma		-	-	2 (12.5%)
Mantle cell lymphoma		-	-	4 (25.0%)
Marginal zone lymphoma		-	-	1 (6.25%)
Primary effusion lymphoma		-	-	1 (6.25%)
Usage of plerixafor	(-)	-	-	12 (75.0%)
	(+)	-	-	4 (25.0%)
Stage at the time of diagnosis	Stage 2	-	-	3 (18.7%)
	Stage 3	-	-	1 (6.3%)
	Stage 4	-	-	12 (75.0%)
Stage of disease before salvage regimen	Stage 2	-	-	3 (18.8%)
	Stage 3	-	-	4 (25.0%)
	Stage 4	-	-	9 (56.2%)
Status before ASCT	CR	-	-	16 (100.0%)
N of pretransplant line of chemotherapy				
1st line		-	-	5 (31.3%)
>1st line		-	-	11 (68.7%)

ASCT: Autologous stem cell transplantation, CR: complete remission, Min: minimum, Max: maximum, SD: standard deviation

Table 2. Post-transplant response status and non-hematological toxicities

		Min-Max	Median	Mean ± SD/(n,%)
Status after 3 months after ASCT	CR	-	-	14 (87.25%)
	Relapsed	-	-	1 (6.25%)
	Exitus	-	-	1 (6.25%)
Follow-up duration after ASCT (days)		14.0-775.0	188.0	229.0±150.0
Time to neutrophil engraftment		10.0-15.0	11.0	11.3±1.3
Time to platelet engraftment		13.0-77.0	17.0	23.7±21.2
Number of stem cells (x10^6/kg)		3.6-13.0	6.3	7.0±2.5
Usage of G-CSF (days)		5.0-14.0	7.5	8.3±3.1
Duration of febrile status (days)		2.0-11.0	4.5	5.8±3.1
Infection	Grade 1	-	-	4 (25.0%)
	Grade 2	-	-	5 (31.25%)
	Grade 3	-	-	2 (12.5%)
	Grade 4	-	-	5 (31.25%)
Renal toxicity	(-)	-	-	14 (87.5%)
	(+) (grade 1)	-	-	2 (12.5%)
Mucositis	Grade 0	-	-	3 (18.75%)
	Grade 1	-	-	7 (43.75%)
	Grade 2	-	-	5 (31.25%)
	Grade 3	-	-	1 (6.25%)
Liver toxicity	(-)	-	-	14 (87.5%)
	(+)	-	-	2 (12.5%)
Gastrointestinal toxicity	Grade 0	-	-	5 (31.25%)
	Grade 1	-		4 (25.0%)
	Grade 2	-	-	5 (31.25%)
	Grade 3	-	-	2 (12.5%)
Hospitalization (days)		19.0-27.0	22.5	22.8±2.7
Last status	CR	-	-	13 (81.25%)
	Exitus	-	-	1 (6.25%)
	Relapsed	-	-	2 (12.5%)

ASCT: Autologous stem cell transplantation, G-CSF: granulocyte colony-stimulating factor, CR: complete remission, Min: minimum, Max: maximum, SD: standard deviation

Since BEAM is the most commonly used conditioning regimen in ASCT, comparative studies in the literature were conducted with BEAM regimen. In our study, BuEM protocol was used as conditioning in ASCT. The median follow-up period after ASCT was 188 days, and the median PFS and OS have not yet been obtained. PFS in month six was 87.1%, and the OS was 93.8% (Figure 1, 2).

As studied by Sakellari et al. (20) in a comparative study of BEAM and BuEM regimens, the 2 year OS with the BEAM regimen was 82.4% in HL and 77.6% (p=0.3) in NHL patients. The 2 year PFS was 64.8% in HL and 57.8% (p=0.5) in NHL. With the BuEM regimen, the 2 year OS in HL patients was 96.2% and PFS was 85.1%, whereas in NHL patients, it was 56.6% and 41%, respectively. OS was superior in HL patients compared to the BEAM arm in the BuEM cohort (2 year OS of 96.2% versus 77.3%, p=0.05). In particular, reduced risk of relapse was reported in HL patients receiving BuEM compared to NHL patients. It was observed that the same significant difference in PFS was reached in patients with chemoresistant HL (HL, 55.6%, and NHL, 9.1%; p=0.0005) (20).

In our study, the patients were transfused with CD34 + cells at a median number of 6.3x10^6 kg. In the study of Sakellari et al. (20), median numbers of 4.3 and 5.7x10^6 of CD34 + cells (p=0.054) were administered in the BEAM and BuEM arms, respectively. The BuEM regimen was generally well tolerated and engraftment was rapid and permanent in the majority of patients.

The importance of time to NE findings is widely accepted. In our study, the median time to NE was 11 days and time to TE was 17 days. In the study of Sakellari et al. (20), the median times to NE for the BuEM and BEAM regimen were 10 and 9 days and median times to TE were 13 and 11 days, respectively. In this study, a faster NE was found in BEAM cohort; however, the real difference was a 1 day delay in the BuEM arm (BEAM, 9.0, vs BuEM, 10.0 days; p=0.05). Additionally, platelet engraftment was

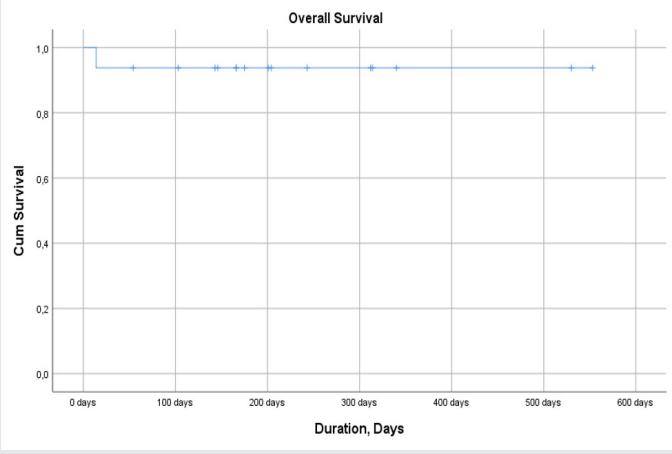

Figure 1. Overall survival (93.8%)

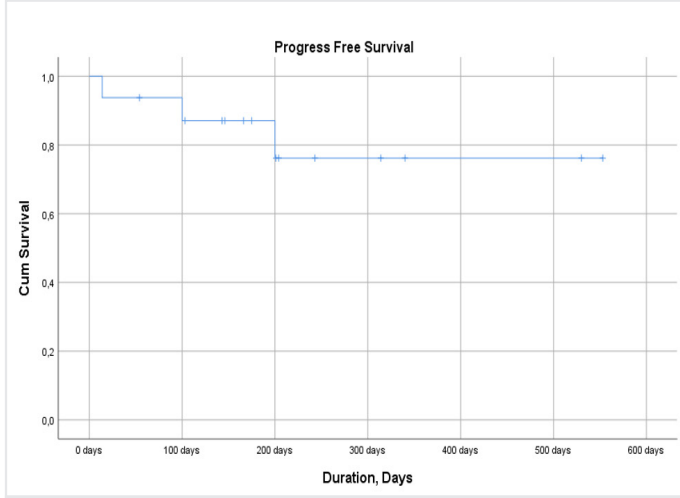

Figure 2. Progression-free survival (87.1%)

2 days earlier in the BEAM cohort (11.0 vs 13.0 days; p=0.025) (20). In studies comparative with BEAM, times to NE and TE were found to be similar (10-19). Times to engraftment, OS, and PFS in various studies are summarized in Table 3.

In our study, median G-CSF administration time was 7.5 days. Paradoxically, in Sakellari et al.'s (20) study, there was a significantly less need for G-CSF (11.0 vs 9.0 days) in the BuEM arm, although time to NE was longer in the BuEM arm than in the BEAM arm (p<0.001). In the present study, the median hospitalization duration was 22.5 days. In the study of Sakellari et al. (20), patients were hospitalized for 21 (BEAM) and 22 (BuEM) days (p=0.074). These results were consistent with those of our study. In several studies, comparative with BEAM, duration of hospitalization ranged from 19 to 23 days in the BEAM arm (10-19).

In our study, infection was not observed in two patients. However, 14 patients developed an infection (87.5%); 56.3% of them had grade 1-2 and 43.8% had grade 3-4 infection. In the study of Sakellari et al. (20), the BEAM regimen was associated with a low infection incidence (p=0.006); however, grade 3-4 infection was not observed in the groups. In our study, our infection rates were found to be higher. In comparative studies with BEAM regimen, the lowest rate for infection was 47.2%, whereas the highest rate was 100% (15,16).

In our study, the total GIS toxicity (vomiting and diarrhea) was 68.8%, whereas it was 12.5% in grade 3 toxicity. Different GIS toxicities were seen in comparative studies with the BEAM regimen. In various studies, GIS toxicity rates ranged from 39% to 97.7% with the BEAM regimen (10-19). In these studies, only lomustine had an effect on prolonged GIS symptoms, and similar rates of GIS toxicity were observed in others (13).

In the present study, grade 1 renal and liver toxicity such as mild transaminase and creatinine elevation was observed in only two patients. Sinusoidal obstruction syndrome (SOS) cases were not observed. In the study of Sakellari et al. (20), a total of 6% and 15.9% kidney toxicity was observed in BuEM and BEAM arms, respectively, whereas 72% and

Table 3. Times to engraftment, OS and PFS in various studies

Name of study	Time to NE (median, range)	Time to PE (median, range)	OS (2 years)	PFS (2 years)
Our study	11 (10-15)	17 (13-77)	93.8	87.1
BeEAM[10,11]	10 (0-98)	11 (0-210)	NR (30)	72 (30)
TECAM (NHL/HL)[12]	12 (9-72)	17 (8-935)	61.8/82.8	50/49
LEAM[13]	11 (10.4-11.2)	12 (1.5-14)	86	69
LACE[14]	10 (7-28)	13 (6-34)	46	37
BEAC[15]	11 (8-14)	12 (7-26)	81.8	67.6
CBV[15]	10.5 (9-12)	11.5 (9-18)	68.8	43.8
BuCyE[16,17]	12 (8-14)	14.5 (10-32)	72.1	70.1
FEAM[18]	10 (6-NR)	13 (7-NR)	86.1	73.1
NEAM[19]	12.3 (3-50)	13.5 (0-175)	64.2	NR
BuEM[20]	10 (8-31)	13 (6-150)	79.8	65.6
BEAM[20]	9 (6-20)	11 (3-25)	76.7	63.2

BEAM: BCNU (carmustine)-etoposide-cyatarabine- melphalan, TECAM: thiotepa-etoposide, cyclophosphamide-cytarabine-melphalan, LEAM: lomustin-etoposide-cytarabine-melfalan, LACE: lomustine-cytarabine-cyclophosphamide-etoposide, BEAC: BCNU (carmustine)-etoposide-cytarabine-cyclophosphamide, CBV: cyclophosphamide-carmustine-etoposide, BuCyE: busulfan-cyclophosphamide-etoposide, FEAM: fotemustine-etoposide-cytarabine-melfalan, NEAM: mitoxantrone-etoposide-cytarabine-melphalan, BuEM: busulfan-etoposide-melphalan, OS: overall survival, PFS: progresion free survival, NR: not reached

Table 4. Non-hematological toxicities in our and various studies

Name of study	Infection (%)	GIS toxicity (%)	Renal toxicity (%)	Liver toxicity (%)	Mucositis (%)	TRM (%)
Our study	87.5	68.8	12.5	12.5	81.3	6.25
BeEAM[10,11]	78.2	54	27.9	15	87	3.3
TECAM[12]	74	*	16	*	85.7	2.8
LEAM[13]	*	50	5	8	30	4
LACE[14]	*	39	*	*	53	9
BEAC[15]	31.2	62.3	*	61	22.1	0
CBV[15]	56.2	50	*	81.5	25	0
BuCyE[16,17]	77.4	54.8	*	*	38.7	6.5
FEAM[18]	71.3	28.3	0.7	3	76.8	3.8
NEAM[19]	23.2	*	20.3	66.7	100	2.9
BuEM[20]	89.6	60	6	72	98	0
BEAM[20]	65.1	97.7	15.9	52.3	93.2	3.4

*No data, BEAM: BCNU (carmustine)-etoposide-cyatarabine-melphalan, TECAM: thiotepa-etoposide, cyclophosphamide-cytarabine-melphalan, LEAM: lomustin-etoposide-cytarabine-melfalan, LACE: lomustine-cytarabine-cyclophosphamide-etoposide, BEAC: BCNU (carmustine)-etoposide-cytarabine-cyclophosphamide, CBV: cyclophosphamide-carmustine-etoposide, BuCyE: busulfan-cyclophosphamide-etoposide, FEAM: fotemustine-etoposide-cytarabine-melfalan, NEAM: mitoxantrone-etoposide-cytarabine-melphalan, BuEM: busulfan-etoposide-melphalan, GIS: gastrointestinal system, TRM: transplant related mortality

53% liver toxicity were observed at the same time. In the BEAM group, grade 3 liver toxicity was 3.4% and 18.0% in the BuEM group. A moderate case of SOS was observed in the BuEM cohort, which was resolved with defibrotide (20).

Significant cardiac toxicity was not reported in our study and in thatzof Sakellari et al. (20) In our study, all degrees of mucositis were seen in 81.2% of our patients. Only 6.3% of them were grade 3. Grade 4 mucositis was not noted. In Sakellari et al.'s (20) study, the BEAM arm was associated with significantly less severe (grade 3-4) mucositis ($p<0.001$). It was noted that only 2% of patients receiving BuEM had grade 4 mucositis. Sakellari et al. (20) recorded no mortality in the BuEM cohort. In our study, one patient (6.25%) died due to post-transplant septic shock.

Information obtained from studies comparing the toxicity and efficacy profiles of different high-dose regimens applied in NHL and HL treatment is limited. All of these studies were done comparatively with the BEAM regimen. Although the results were not homogeneous, it was observed that the side-effect profile was generally similar. Grade 1-4 non-hematological toxicities seen in our study and in various studies are summarized in Table 4.

Study Limitations

The limitations of our study were the small number of cases and the short follow-up period.

Conclusion

Within the limitations of a retrospective analysis, we concluded that the BuEM conditioning regimen exhibited a similar efficacy and toxicity profile with the commonly used BEAM and other new protocols, with neither regimen significantly superior to the other. Although the median follow-up time of 24.2 months was relatively short in our study, our results appear comparable to those of previous studies. Our results recommend considering BuEM as an alternative ASCT conditioning regimen in high-risk lymphoma patients. Large, prospective clinical studies should be conducted to validate our results. The fact that Busulfan, which is an effective agent in lymphoma treatment, is more accessible and low cost compared to carmustine stands out as another reason for preference. BuEM conditioning regimen is promising for patients with refractory and recurrent aggressive lymphomas.

Ethics Committee Approval: The study design was approved by the Bezmialem Vakıf University Non-Interventional Research Ethics Committee (approval number: 11/230, date: 07.07.2020).

Informed Consent: Informed consent was waived because it was a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - A.E., A.T.; Concept - A.E.; Design - A.E.; Data Collection or Processing - A.E.; Analysis or Interpretation - A.E., A.T.; Literature Search - A.E., A.T.; Writing - A.E.

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

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A Simple Technique to Close Peritoneal Tears in Laparoscopic Totally Extraperitoneal Hernioplasty: Extracorporeal Peritoneal Knotting

Laparoskopik Ekstraperitoneal Herni Tamirinde Periton Defektlerinin Kapatılmasında Kolay Bir Teknik: Ekstrakorporeal Periton Düğümleme

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ABSTRACT

Introduction: Peritoneal tear (PT) is a common surgical challenge in laparoscopic totally extraperitoneal (TEP) hernioplasty and the most common reason for conversion surgery. It prolongs the operation time and may cause serious complications. Therefore, rapid closure of PTs is essential.

Methods: This is a retrospective study of patients with PTs during TEP hernioplasty and PT closure using the extracorporeal peritoneal knotting (ECPK) technique. Patient demographics, operative findings, and the success of the technique were evaluated.

Results: The technique was successful in eight of the 10 patients. In two patients with a high body mass index (MRI), the technique failed, so an additional closure technique was required. No complications occurred, and conversion surgery was not required.

Conclusion: ECPK is an easy technique and does not require wide surgical experience and additional laparoscopic surgical devices. The success rate is high in patients with low MRI and may reduce the operation time compared with other peritoneal closure techniques.

Keywords: Extracorporeal peritoneal knotting, inguinal hernia, TEP, peritoneal tear, laparoscopy

ÖZ

Amaç: Periton defektleri (PD), laparoskopik total ekstraperitoneal (TEP) herni onarım cerrahisinde yaygın görülen problemlerdir ve açık cerrahiye geçişin en sık nedenidir. Ameliyat süresinin uzamasına ve ciddi komplikasyonların oluşmasına neden olabilirler. Bu nedenle PD'lerin hızlı bir şekilde kapatılması önemlidir.

Yöntemler: Bu çalışma TEP herni onarımı prosedürü sırasında oluşan PD'leri ekstrakorporeal peritoneal düğüm (EKPD) ile onarılan hastaları içeren retrospektif bir çalışmadır. Hastaların demografik özellikleri, peroperatif bulguları ve yöntemin başarısı değerlendirilmiştir.

Bulgular: EKPD tekniği 10 hastanın 8'inde başarılı olmuştur. Yüksek vücut kitle indeksi (VKİ) olan 2 hastada teknik başarısız olmuştur ve defektin kapatılması için ek yöntem gerekmiştir. Hiçbir hastada komplikasyon ve açık cerrahiye dönüş gözlemlenmemiştir.

Sonuç: EKPD tekniği ciddi bir cerrahi deneyim gerektirmeyen ve ek laparoskopik cerrahi aletlere ihtiyaç duyulmayan basit bir tekniktir. Düşük VKİ olan hastalarda daha başarılıdır ve diğer periton kapatma teknikleriyle karşılaştırıldığında ameliyat süresini kısaltabilir.

Anahtar Kelimeler: Ekstrakorporeal peritoneal düğümleme, inguinal herni, TEP, peritoneal defekt, laparoskopi

Introduction

Peritoneal tear (PT) is a frequent surgical problem, with an incidence of 47% in patients undergoing laparoscopic totally extraperitoneal (TEP) inguinal hernioplasty. Large scrotal hernias, history of inguinal region surgery, and surgical inexperience are risk factors (1). PT may result in pneumoperitoneum. The loss of the surgical view prevents extensive peritoneal mobilization, which is the primary technical step of TEP inguinal hernioplasty (2). It is the most common reason for the conversion of TEP inguinal hernioplasty to other hernioplasty procedures (3). Most surgeons consistently have recommended the routine closure of

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PTs whenever feasible to prevent potential postoperative complications, such as bowel herniation and obstruction (1). However, there has not been a consensus about the location or size of peritoneal defects that require repair. Pretied suturing, loop ligation, endoscopic stapling, and endoscopic suturing are techniques for closing PTs. All methods are equally successful without complication. However, they prolong the operation time and require surgical experience. Thus, it is fundamental to initiate PT management with a laparoscopic approach to complete TEP inguinal hernioplasty successfully (3). In this study, we aimed to describe a new extracorporeal peritoneal knotting (ECPK) technique to close PTs during TEP inguinal hernioplasty.

Methods

This retrospective study enrolled patients who underwent elective TEP inguinal hernioplasty at the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Surgery between 2015 and 2019. The study included patients who developed PTs during surgery that were closed with the ECPK technique. Patient demographics, body mass index (BMI), perioperative findings, PT size, and procedure success were documented. Hernia types were identified intraoperatively according to the European Hernia Society (EHS) groin hernia classification system (4).

The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital and was performed in accordance with the Declaration of Helsinki (approval number: 2569, date: 30.10.2020). Written informed consent was obtained from all patients.

Surgical technique

A standard technique of laparoscopic TEP procedure was performed, as previously described by Bittner et al. (1). Routine urinary catheterization was not performed, as the patients were asked to urinate before the surgery to empty the bladder. Moreover, 1 gram of cefazolin was given intravenously on the induction of general anesthesia. A 10 mm trocar was inserted into the preperitoneal space with a direct open access technique. Blunt dissection was performed with a 30° telescope to create an extraperitoneal space. Two 5 mm trocars were inserted at the midline between the first trocar and pubis under direct vision. Extensive preperitoneal dissection was performed by a combination of blunt stripping and dissection using sharp scissors. In female patients, the round ligament was preserved routinely.

When a peritoneal defect occurred, the defect site was clamped by a laparoscopic grasper (Figure 1a, b). The dissection was continued to provide adequate free space around it. If there was progressive loss of the working space, a Veress needle was inserted through the subumbilical incision into the peritoneal cavity to decrease the intraperitoneal pressure. Nevertheless, the whole pelvic floor dissection was as meticulously completed as possible. After sufficient free space was provided around the defect, gas insufflation was stopped and the preperitoneal area was desufflated. While the preperitoneal space was closing, the grasper holding the PT has removed gently into the skin from the nearest trocar incision (Figure 1c). The peritoneum was held under the defect with a mosquito forceps and knotted with 3-0 vicryl stitch (Figure 1d). While the preperitoneal space was insufflated, the repaired peritoneum was pushed back into the operation field with a grasper (Figure 1e, f). Endoscopic stapling or suturing was performed when the ECPK technique failed. A polypropylene 12x15 cm mesh was placed and stapled with tacker clips to Chooper's ligament and the anterior abdominal wall. Suction drains were not used routinely.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, lowest value, highest value, frequency, and ratios were used. Statistical analyses were performed using SPSS Statistics for Windows (version 21.0, IBM Corp., Armonk, NY).

Results

The ECPK technique was performed on 10 patients (male: 7, female: 3). The mean age and BMI of the patients were 43.9±3.3 years and 26.4±1.6 kg/m^2, respectively. None of the patients had a history of inguinal hernia surgery. All had a unilateral inguinal hernia, with five on the right and five on the left side. The x groin hernia classification system was LII in three patients, LIII in four patients, and McIII in three patients. The median peritoneal defect size was 1 cm, which ranged from 1 cm to 3 cm. PT occurred during the dissection of the hernia sac from the spermatic cord or the round ligament. The technique was successful in eight patients. In two patients with BMI >30 kg/m^2, the peritoneal defect did not reach the extracorporeal area (Table 1). However, none of them required conversion to either transabdominal preperitoneal hernioplasty or open hernioplasty, in which PTs could be repaired with the endoscopic stapling technique. No significant postoperative surgical complications were recorded. All patients were discharged the day after the surgery.

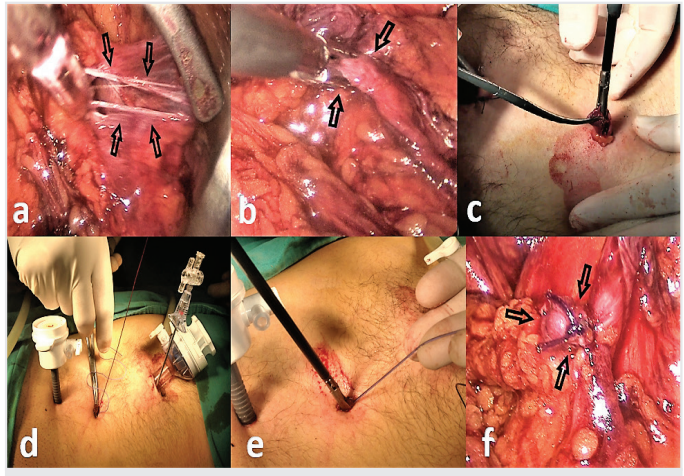

Figure 1. Surgical stages of the extracorporeal peritoneal knotting technique. a) Black arrows indicate a peritoneal defect. b) The peritoneal defect site was clamped by a laparoscopic grasper (black arrows). c) The peritoneal tear was removed gently into the skin from the nearest trocar incision. d) The peritoneum was held under the defect with a mosquito forceps and knotted with 3-0 vicryl stitch. e) While the preperitoneal space was insufflated, the repaired peritoneum was pushed back into the operation field with a grasper. f) Peritoneal tear after closing with extracorporeal peritoneal knotting technique

Discussion

Although reported rarely, PT is not a rare condition during hernioplasty procedures. Its incidence ranged from 0.4% to 67% and considered intraoperative complication, especially in TEP. It is the only disadvantage of the TEP procedures relative to open surgery (5) and is the most common reason for the conversion (3). It is two times more common in recurrent inguinal hernia surgery (2).

Three types of PTs are defined: Type I is a large tear that occurred early at the start of surgery and caused by balloon insufflation. Type II, which is the most common, is a small tear caused by blunt dissection of the hernia sac and peritoneum from the spermatic cord. Type III is created intentionally in congenital hernias. Conversion surgery is necessary for type I defects. More often, a type II defect does not affect the operative course, and the procedure is mostly completed with/without peritoneal decompression and closure of the PT (2). In a randomized multicenter trial, pneumoperitoneum developed in 7% of the patients with PT (1).

No consensus about the routine closure of PT that does not affect the operative course has been established. Some surgeons have reported that routine closure of PT is technically challenging and significantly prolonged the operation time. They believe that after desufflation, the redundant peritoneum folds upon itself and seals the PT quickly. In addition, they had not observed any intraoperative or postoperative complications during the early and long-term follow-up when they left it open in their series (2,6-8). By contrast, current guidelines (1) recommended closure of PTs whenever feasible to prevent potential complications such as adhesion and internal herniation. Meyer et al. (9) reported a laparoscopic pelvic exploration to repair a suspected PT (8).

Performing meticulous blunt traction and counter-traction with minimal use of sharp dissectors is the most crucial point to prevent PTs, especially during dissection of the hernial sac from the spermatic cord. Balloon dissection is considered during the learning period. However, the balloon is placed away from the scar tissue and distended with much less than the standard air volume or with saline in patients with the history of inguinal region surgery (1,10).

Surgical techniques for the closure of PTs are pretied suturing, loop ligation, endoscopic stapling, and endoscopic suturing. Lau et al. (3) found that all these techniques were equally successful without complication. Pretied suturing and loop ligation are safer than endoscopic suturing. However, it may be inadequate to close large defects and may need repeated interventions or an additional closure method (3). Endoscopic stapling is the fastest technique, but it is not suitable for large defects. Protrusion of staples into the peritoneal cavity may lead to visceral complications. Endoscopic suturing is the slowest to perform but the most effective method in patients with large defects. Nevertheless, laparoscopic suturing in a limited surgical space needs surgical experience and poses a minimal intraoperative complication such as vascular and visceral injury. Although an Endo stitch is a useful device for suturing within a minimal extraperitoneal space, it needs an additional 10 mm trocar and has a high cost (8) (Table 2).

The ECPK is a straightforward technique for repairing PTs and does not require surgical experience. In this technique, the PT is pulled out into the extracorporeal area and tied with simple knotting or per string method and then pushed into the preperitoneal area again. It did not have any complications. By contrast, it was more secure due to the removal of the peritoneal region with tears from visceral and vascular

Table 1. Patients with intraoperative peritoneal tear closed with the extracorporeal peritoneal knotting technique

Case	Age/sex	BMI	Side of hernia	Type of hernia*	Defect size (cm)	Success of technique
1	34/M	24	R	L2	1	+
2	36/M	26	L	Mc3	1	+
3	42/M	36	R	L3	1	–
4	26/M	34	R	L3	2	–
5	46/M	30	L	Mc3	1	+
6	56/M	24	L	Mc3	1	+
7	60/M	22	R	L2	2	+
8	41/F	20	L	L3	1	+
9	44/F	23	R	L2	1	+
10	54/F	25	L	L3	3	+

*European Hernia Society groin hernia classification, BMI: body mass index, M: male, F: female

Table 2. Comparison of peritoneal closing techniques during totally extraperitoneal hernioplasty

	Endoscopic stapling	Pretied suturing	Endoscopic suturing	Endo stitch suturing	ECPK
Easy	Yes	Yes	No	Yes	Yes
Quick	Yes	Yes	No	Yes	Yes
Cost-effective	No	No	Yes	No	Yes
Complication	Yes	No	Yes	No	No
Obesity	Yes	Yes	Yes	Yes	No

ECPK: Extracorporeal peritoneal knotting

structures during the repairing procedure. Moreover, there is no need for any additional expensive surgical tools. However, this technique has a low success rate among obese patients. The thickness of subcutaneous adipose tissues prevents adequate peritoneal displacement into the extracorporeal area (Table 2).

Conclusion

ECPK is a useful peritoneal closing technique, especially in patients with low BMI and minimal abdominal subcutaneous adipose tissue thickness. Surgeons even without experience can efficiently perform it without complications. The rapid application of the technique and non-requirement of additional surgical devices may provide a cost-effective solution to PTs during TEP procedures without increasing the operation time.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital and was performed in accordance with the Declaration of Helsinki (approval number: 2569, date: 30.10.2020).

Informed Consent: Written informed consent was obtained from all patients.

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Relationship between Mode of Delivery and Frequency and Treatment Outcomes of Congenital Nasolacrimal Dacryostenosis

Doğum Şeklinin Konjenital Nazolakrimal Dakriostenoz Görülme Sıklığı ve Tedavi Sonuçları ile İlişkisi

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ABSTRACT

Introduction: The present study evaluates the relationship between the mode of delivery and the frequency and treatment outcomes of congenital nasolacrimal duct obstruction (CNDO).

Methods: The medical records of children who were referred to oculoplasty outpatient clinics due to epiphora and diagnosed with CNDO following ophthalmological examination were reviewed retrospectively. The patients' demographic characteristics, history of pregnancy and delivery, clinical characteristics of CNDO, and treatment outcomes were evaluated.

Results: The study included 167 eyes of 136 patients. The mode of delivery was vaginal in 61 patients (45%) and cesarean section in 75 patients (55%). The patients delivered by cesarean section were assigned to group 1, and those delivered via the vaginal route were assigned to group 2. The mean age (p=0.554), gender distribution (p=0.661), laterality (p=0.075) and mean birth weight (p=0.918) did not differ significantly between the two groups. The success rate of probing did not differ significantly between the two groups (p=0.146).

Conclusion: The present study found that the mode of delivery did not affect the frequency of CNDO in babies born at term, and there was also no significant difference in the success rate of probing between the two groups. Although the difference was not statistically significant, the authors found cesarean section to be associated with a higher risk of CNDO.

Keywords: Cesarean section, vaginal delivery, CNDO, probing, Hasner's valve

ÖZ

Amaç: Term bebeklerde doğum şeklinin konjenital nazolakrimal dakriostenoz (CNDO) görülme sıklığı ve tedavi sonuçları ile ilişkisini saptamaktır.

Yöntemler: Oküloplasti polikliniklerine epifora nedeniyle refere edilen ve oftalmolojik muayeneleri sonucunda CNDO tanısı alan çocukların tıbbi kayıtları retrospektif olarak incelendi. Hasta demografisi, hamilelik, doğum öyküsü, CNDO'nun klinik özellikleri ve tedavi sonuçları değerlendirildi.

Bulgular: Çalışmaya 136 hastanın 167 gözü dahil edildi. Olguların %55'i (75) kız, %45'i (61) erkek idi. Olguların yaşları 1-3 (ortalama: 1,8 yaş) idi. Olguların 61'i (%45) vaginal yolla, 75'i (%55) sezaryenle dünyaya gelmişti. Sezaryenle doğanlar birinci grup, vajinal yolla doğanlar da ikinci grup olarak değerlendirildi. Vaginal doğum ve sezaryen doğum gruplarının yaş ortalamaları (p=0,554), cinsiyet dağılımları (p=0,661), taraf dağılımları (p=0,075), doğum ağırlığı (p=0,918) ortalamaları arasında istatistiksel olarak anlamlı farklılık gözlenmemiştir. Vajinal doğum ve sezaryen doğum gruplarının probing başarı dağılımları arasında da istatistiksel olarak anlamlı farklılık gözlenmemiştir (p=0,146).

Sonuç: Bu çalışmada doğum şeklinin term bebeklerde CNDO sıklığını değiştirmediğini saptadık. Vajinal doğum ve sezaryen doğum gruplarının probing başarı dağılımları arasında da istatistiksel olarak anlamlı bir farklılık gözlenmemiştir. Ancak istatistik olarak anlamlılık oluşturmasa da sezaryen doğumun daha fazla risk oluşturduğunu saptadık.

Anahtar Kelimeler: Sezaryen doğum, vajinal doğum, CNDO, probing, Hasner valvi

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Introduction

Congenital nasolacrimal duct obstruction (CNDO) is the most common ocular disorder in the pediatric population, with a reported prevalence of approximately 20%. The condition is caused by a failure in the drainage system of the nasolacrimal duct. A persistent membrane at Hasner's valve is the most common etiologic factor related to the development of CNDO. The condition often becomes symptomatic a few weeks after birth, and epiphora is the most common presenting symptom, although matting of the eyelashes, swelling of the lacrimal sac, and discharge from the lacrimal punctum upon the application of pressure on the lacrimal sac can also be observed (1-3).

First-line therapy includes massaging the lacrimal sac [Crigler (4) massage] and administering antibacterial drops to avoid bacterial superinfections. It is reported that 90% of CNDOs resolve spontaneously in the first year of life without requiring surgical intervention. Other treatment options include probing, silicone intubation, balloon dacryoplasty, and dacryocystorhinostomy (DCR) in patients who fail to respond to massage therapy. Most surgeons follow a conservative approach, involving massage, and topical therapy in the first year of life. Probing is the first-line therapy in epiphora that persists beyond the first year of life, followed by silicone intubation and balloon DCR after failed probing, whereas DCR is reserved as the last option for cases in which all other treatment options have failed (5,6).

The nasolacrimal duct starts to develop during the fifth week of embryogenesis. CNDO occurs as a result of a canalization fault in the columnar epithelial cells that form the nasolacrimal duct. Canalization of the nasolacrimal duct normally takes place at the end of the sixth month of intrauterine life, although it may be delayed for several weeks after birth (7,8). In a retrospective case series involving facial imaging of normal children, a 4.6-fold increase was noted in nasolacrimal duct volume during the first 34 months of life, and this volume expansion is associated with the increased intracanal hydrostatic pressure necessary to open the distal canal. For this reason, the incidence of CNDO is believed to be higher in premature infants than in term infants. The incidence of cesarean section (CS) is higher in premature infants than in term infants, and although there are many studies in the literature investigating the effect of the mode of delivery on the development of CNDO in premature and term infants, there have been few similar studies to date in term infants (2,9,10).

The World Health Organization (WHO) recommends that the rate of CS should not exceed 15%, taking countries with a low perinatal mortality rate in 1985 as a reference, although the WHO reported CS rates of 30.2% in the United States, 22% in the United Kingdom, 37.4% in Italy, and 41.3% in Brazil in 2010. The CS rate in Turkey was 6.9% in 1993 but had increased to 51.2% by 2017, and this upward trend in the prevalence rate elevated Turkey to one of the highest CS rates (11-13).

Due to this rapid increase in the popularity of CS, even in infants born at term, the present study investigates the effect of the mode of delivery on the development of CNDO in term infants.

Methods

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki, and approval for the study was granted by the Bezmialem Vakıf University Non-Invasive Clinical Research Ethics Committee (approval number: 06/83, date: 19.03.2019). All patients provided written informed consent for their participation.

The medical records of patients who were referred to oculoplasty outpatient clinics due to epiphora, were diagnosed with CNDO after examination, had not undergone surgery previously, and were to undergo probing for the first time were reviewed retrospectively. Included in the study were patients diagnosed with CMDO after 12 months of age, those born after 36 weeks of gestation (term), those who underwent probing after 12 months of age, and those followed up for longer than 6 months.

Infants with a history of maternal drug use, infections, and X-ray exposure during pregnancy; those with a history of complicated vaginal delivery; those with a past history of trauma; those with anatomical abnormalities in the nasolacrimal duct; those born before 36 weeks of gestation; those who underwent surgery before the age of 12 months; and those with a patent nasolacrimal duct, as evidenced by duct lavage prior to surgery (functional epiphora), were excluded from the study.

The demographic characteristics of the patients, mode of delivery, gestational age, birth weight, age at presentation, mode of therapy, efficacy of therapy, and recurrences were all evaluated.

Diagnosis was based on history, an ophthalmological examination, and a fluorescein dye disappearance test (FDT) (14). The ophthalmological examination was performed to rule out ocular allergy, glaucoma, conjunctivitis, and eyelid anomalies (entropion, trichiasis, etc). For the FDT, a proparacaine HCl drop was dripped onto fluorescein paper and applied bilaterally to the patient's inferior fornix. The level of fluorescein on the lower eyelid was checked five minutes later and graded.

0: No fluorescence in the conjunctival sac,

1: Thin fluorescing marginal tear strip persists,

2: More fluorescein persists, between 1 and 3,

3: Wide, brightly fluorescing tear strip.

Those who scored 2 or 3 in the fluorescein disappearance test were diagnosed with CNDO, and surgery was planned. All of the patients also underwent an otorhinolaryngological examination, and those identified with allergic rhinitis were first treated in the otorhinolaryngology clinic.

All surgeries were performed under general anesthesia. The patients first underwent lacrimal irrigation with a fluid lavage of rifampicin and saline (rifampicin diluted with saline at a ratio of 1:3). The patients found to have a patent duct during lacrimal irrigation were considered to have functional dacryostenosis. The superior and inferior lacrimal puncta were dilated before the probing procedure, after which the probe was advanced vertically until the ampulla, and then at an angle of 90° to the horizontal plane. The probe was advanced up to the nasal wall of the lacrimal sac (until the bone was reached) and then directed 90° downward until the membrane was felt to rupture. The same procedure was performed through the inferior punctum. Lavage fluid prepared with rifampicin [1 mL rifampicin, 125 mg/3 mL (the toxic dose of rifampicin in children is 600 mg)] was administered into the nasolacrimal system to check for patency, and the fluid was aspirated

from the nasal cavity. The procedure was considered to be successful upon observation of discharge of the rifampicin solution. The lacrimal system was then irrigated with a dexamethasone solution, and topical antibiotics (tobramycin four times daily), a fluorometholone steroid (four times daily) for two postoperative weeks and a nasal xylometazoline spray (twice daily) were applied.

The patients attended control visits on postoperative day 1, at week 1, week 2, month 1, and months 3, and then every 3 months thereafter. Complaints of epiphora were questioned during the control visits, and a fluorescein disappearance test was performed. Cases without epiphora and those that scored 0 or 1 points on the fluorescein disappearance test were considered successful. Intraoperative and postoperative complications were evaluated. Patients in whom probing failed underwent repetitive probing 2 months later, and silicone intubation was performed in the same session. Those in whom silicon tube intubation failed were scheduled for external DCR.

The patients were divided into two groups on the basis of their mode of delivery, as group 1 (CS) and group 2 (vaginal delivery). The two groups were compared with respect to the prevalence of CNDO, gender, birth weight, gestational age at birth, and probing success.

Statistical Analysis

The Number Cruncher Statistical System 2007 Statistical Software (Utah, USA) was used for data analysis. Aside from the application of descriptive statistics (mean, standard deviation), a Shapiro-Wilk normality test was conducted to evaluate the distribution of variables, and an independent-samples t-test was used for paired comparisons of normally distributed variables. Univariate and multivariate logistic regression analyses were used to identify the factors affected by the mode of delivery. The level of significance was α=0.05.

Results

The study included 167 eyes of 136 patients, of which 75 (55%) were female and 61 (45%) were male, with a mean age of 1.8 years (range: 1-3 years). The mode of delivery was vaginal in 61 patients (45%) and CS in 75 patients (55%). Those delivered by CS were assigned to group 1, and those delivered via the vaginal route were assigned to group 2. Mean age (p=0.554), gender distribution (p=0.661), laterality (p=0.075), and mean birth weight (p=0.918) did not differ significantly between the two groups. The mean gestational age at birth was significantly higher in group 1 than in group 2 (p=0.007). The probing success rate not differ significantly between the two groups (p=0.146) (Table 1). Age, gender, laterality, gestational age at birth, birth weight, and mode of delivery were found to be significantly insignificant in a univariate logistic regression analysis (p>0.05). The risk of failure was 2.09 times higher (0.76-3.74) in group 1 than in group 2. The probing success was significantly higher in those with a high gestational age (p=0.096).

Recurrence occurred in six patients (8%) in group 2 following the first probing attempt, and these patients underwent a repeat probing and silicone intubation 2 months later. Recurrence occurred in one patient after a mean follow-up of 7.1 months following silicone tube intubation, and this patient was then scheduled for external DCR. Recurrence occurred in 14 patients (15) after CS, and of these, 12 underwent repeat probing and silicone tube intubation, while two patients rejected therapy and were lost to follow-up. Recurrence occurred in 3 out 12 patients during a mean follow-up of 6.3 months, and these three patients were scheduled for external DSR. The epiphora resolved after external DSR.

Discussion

There is a limited body of knowledge regarding the etiopathogenesis of CNDO, although there have been many studies to date investigating treatment methods. Among these, there have been studies investigating the relationship between the development of CNDO and maternal age, maternal X-ray exposure, drug use during pregnancy, geographic and environmental characteristics, smoking status, parental education level, and gender of the infant, although no such relationships have been identified (15).

The marked increase in the prevalence of CS in recent years has prompted researchers to investigate the positive and negative effects of this mode of delivery on both the mother and the infant (16). As a common ocular disorder in newborns in ophthalmology outpatient clinics, the possible relationship between CNDO and the mode of delivery has attracted the attention of ophthalmologists and has prompted investigations into the effect of vaginal and CS deliveries on the nasolacrimal duct.

The uterine contractions required for the successful advancement of the infant along the birth canal during a vaginal delivery increases intrauterine hydrostatic pressure, which has been measured as high

Table 1. Relationship between mode of delivery and demographic characteristics of the patients and probing success

		Vaginal delivery (n=75)		Cesarean Section (n=91)		p
Age (months)		19.59±10.18		20.51±9.75		0.554*
Gender	Girl	38	50.67%	43	47.25%	0.661+
	Male	37	49.33%	48	52.75%	
Side	Left	30	40.00%	49	53.85%	0.075+
	Right	45	60.00%	42	46.15%	
Week of birth		38.27±1.93		38.99±1.45		0.007*
Birth weight		3212.13±490.39		3204.84±420.46		0.918*
Probing success	Successful	69	92.00%	77	84.62%	0.146+
	Unsuccessful	6	8.00%	14	15.38%	

*: Independent t-test, +: chi-square test

as 100 mmHg. While some studies suggest that increased intrauterine pressure may lead to complications in the infant, others report that such pressure may act to open the nasolacrimal duct, particularly Hasner's valve, in the infant. It is reported that various collagenolytic enzymes are released from the uterus into the amniotic fluid due to uterine contractions during vaginal delivery, and this fluid is mostly directed into the nasolacrimal duct during a vaginal delivery. The increased activity of collagenolytic enzymes in amniotic fluid may cause early lysis of Hasner's valve and perforation of the membrane. It has been further reported that levels of collagenolytic enzymes are lower in the amniotic fluid in CS deliveries than in vaginal deliveries (17-20).

Studies in the literature have also reported an increased incidence of autoimmune and allergic disorders in recent years, in parallel to the increased rate of CS deliveries (21,22). The authors of the present study suggest that this increase may be associated with increased inflammation in the lacrimal duct, which may prevent opening of the nasolacrimal duct, thus negatively affecting probing success.

In 2015, Zhang et al. (23) reported an expansion in the bony part of the nasolacrimal duct on the obstructed side in patients with CNDO, and a significant expansion of the affected bony nasolacrimal duct areas with transverse and vertical diameters has been demonstrated on the computed tomography (CT) scans of patients with unilateral CNDO, when compared with the unaffected side. The bony part of the lacrimal duct is soft in childhood, and the increased pressure resulting from a blockage of the nasolacrimal duct may lead to enlargement of the intraosseous portion of the ipsilateral lasolacrimal duct. This is caused by the constant increase in hydrostatic pressure within the lacrimal duct that occurs with age, and this may play a role in the recovery of the blockage with advancing age (2,23). In practice, CT scans are not routinely requested in patients with CNDO in the ophthalmology clinic, although eight patients in the present study underwent a CT scan for various reasons, and a review of these CT scans revealed an expanded nasolacrimal duct on the affected side when compared with that of the contralateral duct. Probing was performed after 12 months of age in all patients in the present study in an attempt to open the nasolacrimal duct naturally.

In a study by Tavakoli et al. (24) involving 106 patients, a significantly higher percentage of patients with CNDO (61%) were delivered via CS ($p=0.0001$). Among full-term infants, there was a 55% greater risk [odds ratio (OR): 5 1.55; 95% confidence interval (CI), 0.98-2.43; $p=0.067$] of CNDO in those born by CS, when compared with other babies. Among preterm babies, there was no significantly greater likelihood of CNLDO in those born by CS when compared with those born vaginally ($p=0.575$). CNDO did not resolve spontaneously in 50 patients, including the 37 patients delivered by CS (74%) and the 13 patients delivered via the vaginal route (26%) ($p=0.007$). Among the patients in whom first-line probing failed, 86.2% were born via CS and 13.8% via the vaginal route (24).

Spaniol et al. (25) also reported no statistically significant association between the overall CS rate and incidence of CNDO, although primary CS was significantly more frequent among patients with CNDO (73.15%, $p<0.05$). The difference was significant in both genders for the 2000-2008 period ($p<0.05$%). The relative risk for CNLDO was 17-fold higher in children delivered by primary CS (25).

In a study by Dolar Bilge (26) conducted in Turkey, the gestational age of babies who were born via CS was lower than that of babies who born via spontaneous vaginal delivery (NSVD; $p=0.002$). Babies born via CS were found to be at a 3.75-fold greater risk of developing CNLDO, when compared with those born via the vaginal route (OR: 3.754) (26).

Palo et al. (27) reported no significant relationship between CNDO and the mode of delivery but reported complex CNDOs to be more frequent in CS deliveries.

The present study found the mode of delivery to have no effect on the frequency of CNDO in babies born at term. CNDO was noted to be more common in infants with a low birth weight, and the success rate of probing was higher in patients delivered via the vaginal route.

Study Limitations

As a limitation of the present study, the study group comprised only patients who were referred to oculoplasty outpatient clinics with a diagnosis of CNDO for surgical treatment. As such, no patients with spontaneously resolved CNDO or with resolved CNDO after massage therapy were included in the study.

Conclusion

The present study found that the mode of delivery did not affect the frequency of CNDO in babies born at term, and there was also no significant difference in the success rate of probing between the two groups. Although the difference was statistically insignificant, the authors found CS to be associated with a higher risk of CNDO. We believe that a wider range of studies including these groups is needed.

Ethics Committee Approval: This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki, and approval for the study was granted by the Bezmialem Vakıf University Non-Invasive Clinical Research Ethics Committee (approval number: 06/83, date: 19.03.2019).

Informed Consent: All patients provided written informed consent for their participation.

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Changing Trends over the Years in Pregnancy Termination due to Fetal Anomalies

Fetal Anomalilere Bağlı Gebelik Terminasyonunda Yıllar İçerisinde Değişen Eğilimler

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ABSTRACT

Introduction: To examine the indications for termination due to fetal anomalies performed in our clinic between January 2015 and October 2020 and to determine the differences between years.

Methods: This study is a retrospective, observational study involving 385 patients who underwent termination before the 24th week due to fetal anomalies at Karadeniz Technical University, Farabi Hospital, Clinic of Perinatology. Termination data were analyzed by dividing the sample into two groups: terminations performed between 11 and 14 weeks (first trimester) and those between 15 and 24 weeks (second trimester) of gestation.

Results: Structural malformations constituted 81.3% of termination of pregnancy (TOP) cases, chromosomal anomalies 14.5%, and genetic diseases 4.2%. Central nervous system (CNS) anomalies, at 43.4%, were the most common cause of termination. Aneuploidy was present in 56 (34.8%) of 161 cases for which karyotype analysis was available. The number of terminations that took place in both the first and the second trimesters was the highest in 2019. A continuous increase was observed in the number of terminations over the years evaluated. When the systems were evaluated individually, it was observed that the number of cases in the second trimester with CNS and face and neck anomalies was statistically significantly higher than that in the first trimester (p=0.002, p=0.037, respectively). In all, 28.3% of terminations were performed in the first trimester and 71.7% in the second trimester.

Conclusion: When the distribution of TOP indications over the years was examined, it was observed that the number of cases related to chromosomal anomalies, cardiovascular system anomalies, and genetic diseases had increased gradually.

Keywords: Aneuploidy, congenital anomalies, karyotype, prenatal diagnosis, termination of pregnancy

ÖZ

Amaç: Kliniğimizde Ocak 2015-Ekim 2020 yılları arasında yapılan fetal anomalilere bağlı gebelik terminasyonlarının endikasyonlarını incelemek ve yıllar arasındaki farklılıkları belirlemektir.

Yöntemler: Çalışmamız, Karadeniz Teknik Üniversitesi, Farabi Hastanesi, Perinatoloji Kliniği'nde, fetal anomaliler sebebiyle 24. gebelik haftasından önce terminasyon uygulanan 385 olguyu içeren retrospektif bir çalışmadır. Terminasyon verileri, 11-14 hafta (1. trimester) arası olgular ve 15-24 hafta (2. trimester) arası olgular olarak iki gruba ayrılarak analiz edilmiştir.

Bulgular: Terminasyon olgularının %81,3'ünü yapısal malformasyonlar, %14,5'ini kromozom anomalileri ve %4,2'sini genetik hastalıklar oluşturmaktaydı. %43,4 ile santral sinir sistemi (SSS) anomalileri, terminasyonların en sık nedeniydi. Karyotip analizi yapılan 161 olgunun 56'sında (%34,8) anöploidi mevcuttu. Hem 1. trimesterde hem de 2. trimesterde gerçekleşen terminasyon sayıları, 2019 yılında en yüksekti. Değerlendirilen yıllar içerisinde terminasyon sayılarında devamlı bir artış olduğu görüldü. Sistemler ayrı ayrı değerlendirildiğinde, SSS ve yüz ve boyun anomalileri açısından 2. trimesterdeki olguların 1. trimesterdeki olgulara göre istatistiksel olarak anlamlı derecede yüksek olduğu görüldü (sırasıyla; p=0,002, p=0,037). Olguların %28,3'ü 1. trimesterde, %71,7'si 2. trimesterde termine edilmişti.

Sonuç: Terminasyon olgularının yıllar içindeki dağılımı incelendiğinde; kromozom anomalileri, kardiyovasküler sistem anomalileri ve genetik hastalıklara bağlı olguların sayısının giderek arttığı görülmektedir.

Anahtar Kelimeler: Anöploidi, gebelik terminasyonu, karyotip, konjenital anomaliler, prenatal tanı

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Introduction

In Turkey, termination of pregnancy (TOP) is permitted under three conditions. The first of these are unintended pregnancies, and these pregnancies can be terminated according to the couple's decision until the 10th pregnancy week, which is the legal limit (1). Maternal medical conditions, in which pregnancy threatens maternal life, are another reason, and there is no gestational week time limit for termination. Fetal anomalies that cause severe morbidity or mortality are another condition that permit termination (1,2).

The development of both advanced technology ultrasound devices and prenatal screening tests has now enabled clinicians to detect many structural malformations and chromosomal anomalies in the intrauterine period (3). The changing world and technological developments over the years have also affected people's view of medical practices. A pregnant woman bearing a fetus with an anomaly and her partner face a difficult decision: Will they continue with the pregnancy, or will they decide to terminate?

This article aims to examine the indications for termination due to fetal anomalies performed in our clinic between 2015 and 2020 and to determine the differences between years.

Methods

The study was conducted per the principles of the Declaration of Helsinki. This study approval was obtained from Karadeniz Technical University Local Ethics Board (approval number: 2019/29, date: 15.02.2019).

This study is a retrospective, observational study involving 385 cases who underwent TOP before the 24th week due to fetal anomalies between January 2015 and October 2020. Unintended pregnancies, multiple pregnancies, TOP cases due to maternal indications, and cases without a fetal heartbeat at the time of hospital admission were excluded. If an anomaly incompatible with life was detected after 24 weeks, the parents were given the necessary consultancy, and if these patients requested termination, they were transferred to centers where the termination process could be performed. Maternal age, gravida, parity, TOP gestational week, fetal weight, fetal gender, length of hospital stay, karyotype analysis (if present), and fetal diagnosis information of TOP cases were recorded from our hospital's data processing database. Termination data were analyzed by dividing the sample into two groups consisting of cases between 11 and 14 weeks (first trimester) and those between 15 and 24 weeks (second trimester) of gestation. Perinatology specialists performed fetal ultrasonographic examination via Voluson 730 (GE Medical Systems, Zipf, Austria) and Voluson E10 (General Electrics Healthcare, Zipf, Austria). Genetic counseling was given to each family who underwent karyotyping for prenatal diagnosis. Chorionic villus sampling, amniocentesis, or cordocentesis was applied to the cases per the weeks of gestation for genetic diagnosis. Cases in which the patient did not agree to karyotyping or karyotyping did not yield a clear result were not included in the chromosomal anomalies group. The decision to terminate the pregnancy was made by a multidisciplinary committee composed of experts in perinatology, medical genetics, pediatric surgery, pediatric cardiology, and pediatric neurology. Couples were informed about the termination methods and their possible risks, and informed consent was obtained from all patients who agreed to undergo the procedure. A fetal autopsy was recommended to all patients who underwent termination.

The preferred method of medical termination in our hospital is misoprostol (Cytotec, Ali Raif, İstanbul, Turkey). The route of administration of misoprostol (vaginal or oral), dosage, and intervals were determined according to the gestational week, personal obstetric history, and clinical features of the patient (4,5). If necessary, oxytocin induction or intracervical Foley catheter application was used to contribute to cervical dilation in addition to misoprostol. After the fetus and placenta were discarded, the remaining products of conception were removed by manual vacuum aspiration or dilatation and curettage. A hysterotomy was performed in patients with unsuccessful induction despite medical treatment and the use of an intracervical Foley catheter and also in patients with a history of three or more cesarean surgeries. Indications for termination were classified according to the International Classification of Diseases, Version-10.

Statistical Analysis

SPSS Statistics, Version 20 (IBM Corp. Armonk, NY) was used for statistical analysis. All continuous variables were defined as mean and standard deviation. Categorical variables were expressed as a percentage of the total. The Pearson's chi-square independence test and Fisher's exact test were used to examine the interdependence between categorical variables.

Results

Within the scope of the study, a total of 385 TOP cases related to fetal anomalies were evaluated. The mean maternal age was 29 (range: 18-43), and the mean gestational age at termination was 19 (range: 12-24) weeks. The number of cases who underwent karyotyping was 161 (41.8%). The demographic data on the cases are shown in Table 1.

Considering all causes of TOP due to fetal anomalies, central nervous system (CNS) anomalies (43.4%), chromosomal anomalies (14.5%), and cardiovascular system (CVS) anomalies (13.5%) were the most common causes. When the distribution of all TOP cases was analyzed by year, an increase was observed in the number of cases in recent years: The lowest proportion (12.2%) was seen in 2015 and the highest (22.3%) in 2019. Also, the number of terminations in both the first and the second trimesters was the highest in 2019 (Figure 1).

Table 1. Demographic characteristics of TOP cases

	Median
Age, year	29 (18-43)
Gravida	2 (1-5)
Parity	1 (0-4)
Gestational week at TOP* (week)	18 (12-24)
Fetal weight, grams	251 (70-682)
Length of hospital stay (days)	2 (1-8)
Prenatal karyotype, n (%)	161 (41.8%)
Fetal sex, F/M/I*, n (%)	134/139/112 (34.8%, 36.1%, 29.1%)

F: Female, M: male, I: indefinite, TOP: termination of pregnancy

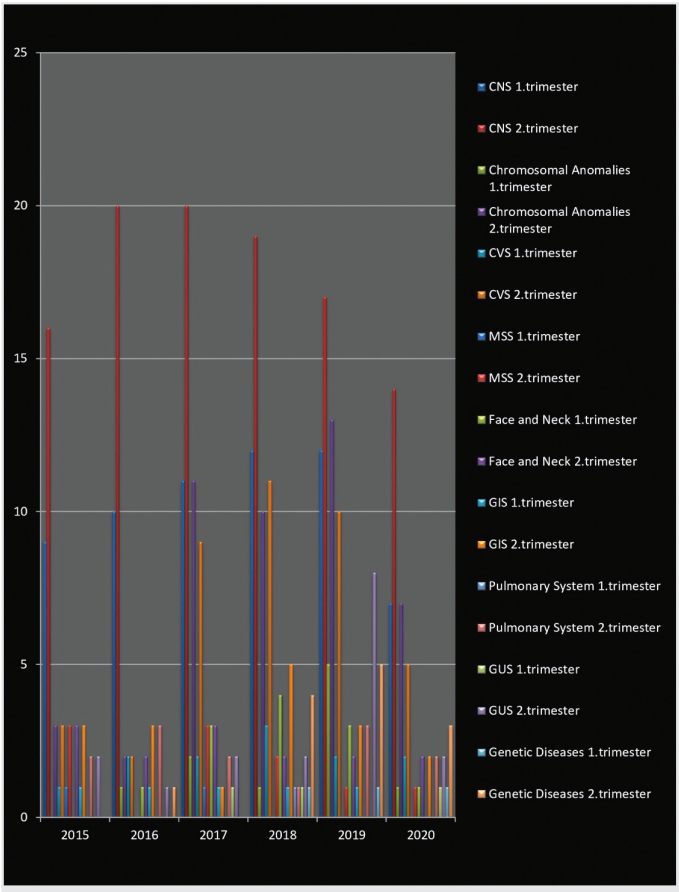

Figure 1. Distribution of TOP cases by years

TOP: Termination of pregnancy, CNS: central nervous system, MSS: musculoskeletal system, GIS: gastrointestinal system, GUS: genitourinary system

The cases were divided into two groups according to gestational age at termination. The first group consisted of cases terminated between 11 and 14 weeks, and the second consisted of cases terminated between 15 and 24 weeks. The mean gestational age at termination time of the patients in the first group was 13 weeks (range: 12-14), and the mean gestational age at termination of the patients in the second group was 21 weeks (range: 15-24). When the systems were evaluated individually, it was observed that the number of CNS and face and neck anomalies was statistically significantly higher among cases terminated in the second trimester than among those terminated in the first trimester (p=0.002, p=0.037, respectively). CNS anomalies are the most common TOP indication in both the first (56%) and second (38.4%) trimesters. When all 385 TOP cases were evaluated, the second group constituted 71.7% (276/385) of cases, and the first group constituted 28.3% (109/385) (Table 2).

Table 3 shows the distribution of termination indications by system. Structural malformations constituted 81.3% of TOP cases, chromosomal anomalies constituted 14.5%, and genetic diseases constituted 4.2%. CNS anomalies, especially the anencephaly-acrania-exencephaly sequence and spina bifida, were the most common reasons for termination in both the first trimester and the second trimester in the 6-year study period. Chromosomal anomalies were second with 14.5%, and trisomy 21 was the most common chromosomal anomaly (9.1%). Aneuploidy

Table 2. Comparison of groups by termination week

	Frequency (%)		
Groups	**11-14 w**	**15-24 w**	**p**
CNS	61 (56%)	106 (38.4%)	**0.002**[a]
Chromosomal anomalies	10 (9.2%)	46 (16.7%)	0.060[a]
CVS	12 (11%)	40 (14.4%)	0.368[a]
MSS	2 (1.8%)	10 (3.6%)	0.522[b]
Face and neck	12 (11%)	14 (5.1%)	**0.037**[a]
GIS	5 (4.5%)	17 (6.2%)	0.549[a]
Pulmonary system	1 (0.9%)	13 (4.7%)	0.126[b]
GUS	3 (2.8%)	17 (6.2%)	0.175[a]
Genetic diseases	3 (2.8%)	13 (4.7%)	0.572[b]
Total	**109 (100%)**	**276 (100%)**	**-**

CNS: Central nervous system, CVS: cardiovascular system, MSS: musculoskeletal system, GIS: gastrointestinal system, GUS: genitourinary system, [a]: chi-square independent test, [b]: Fisher's exact test

was present in 56 (34.8%) of 161 cases for which karyotype analysis was available. Head and neck anomalies and CVS anomalies in cases terminated in the first trimester were in second place together (11%), and CVS anomalies in the cases terminated in the second trimester were in third place (14.5%). Omphalocele in gastrointestinal system anomalies, congenital diaphragmatic hernia in pulmonary system anomalies, and bilateral renal agenesis in genitourinary system anomalies were the most common termination indications of the mentioned systems. The most common termination cause due to genetic diseases was spinal muscular atrophy (1.3%).

In this study, pregnancies were terminated vaginally in 98.7% (98.7) of cases. In 26 cases (6.8%) with insufficient cervical dilatation with misoprostol, cervical dilation was achieved with an intracervical Foley catheter, and termination was performed. In 1.3% (1.3) of cases, hysterotomy was applied. Previous uterine surgery was the most important risk factor in choosing hysterotomy for gestational termination.

Discussion

Both medico-legal attitudes and cultural and ethical values and perceptions in the countries in question make termination practices a critical medical procedure (6,7). According to the Population Planning Law in Turkey, termination of unintended pregnancies is legal until the 10th gestational week upon the couple's request (or with the permission of the unmarried woman). Termination application after the 10th gestational week is only possible in life-threatening maternal situations or situations that may cause severe fetal disability, with the reasoned report of an obstetrician and a specialist from a related branch (1,2). While in some countries there is no upper limit on gestational age at termination, in others, this upper limit may change even among institutions. The upper limits of the termination week vary among health institutions in our country. Pregnancy terminations due to fetal anomalies are not accepted for ethical reasons after the 24th week of pregnancy, according to the Maternal-Fetal and Perinatology Society of Turkey Ankara Declaration (8-10). The decision made by our university's

Table 3. Detailed examination of termination indications

	n	%
Central nervous system	**167**	**43.4**
Anencephaly-acrania-exencephaly sequence	56	14.5
Spina bifida	38	9.9
Dandy-walker malformation	24	6.2
Hydrocephaly	23	6
Encephalocele	7	1.8
Holoprosencephaly	7	1.8
Agenesis of corpus callosum	6	1.6
Other	6	1.6
Chromosomal anomalies	**56**	**14.5**
Trisomy 21	35	9.1
Trisomy 18	9	2.3
Trisomy 13	3	0.8
Trisomy 16	1	0.3
Triploidy	1	0.3
Other	7	1.8
Cardiovascular anomalies	**52**	**13.5**
HLHS	20	5.2
VSD/AVSD	11	2.9
TOF	6	1.6
DORV	5	1.3
Ebstein anomaly	4	1
Other	6	1.6
Face and neck	**26**	**6.8**
Cystic hygroma	22	5.7
Cleft palate-cleft lip	2	0.5
Epignathus	2	0.5
Gastrointestinal system	**22**	**5.7**
Omphalocele	12	3.1
Gastroschisis	3	0.8
Esophageal atresia	3	0.8
Other	4	1
Genitourinary system	**20**	**5.2**
Bilateral renal agenesia	7	1.8
MCDK	5	1.3
PCKD	3	0.8
PUV	3	0.8
Other	2	0.5
Genetic diseases	**16**	**4.2**
Spinal muscular atrophy	5	1.3
Thalassemia major	4	1
DiGeorge syndrome	3	0.8
Other	4	1
Pulmonary system	**14**	**3.6**
CDH	9	2.3
CPAM	2	0.5
Lymphangioma	2	0.5
Laringeal atresia	1	0.3
Musculoskeletal system	**12**	**3.1**
Lethal skeletal dysplasia	8	2.1
Kyphoscoliosis	2	0.5
Other	2	0.5
Total	**385**	**100**

TOF: Tetralogy of fallot, AVSD: atrioventricular septal defect, VSD: ventricular septal defect, HLHS: hypoplastic left heart syndrome, DORV: double outlet right ventricle, CDH: congenital diaphragmatic hernia, CPAM: congenital pulmonary airway malformation, PCKD: polycystic kidney disease, PUV: posterior urethral valve, MCDK: multicystic dysplastic kidney

ethics committee complies with this statement and has determined the 24th week of pregnancy to be the upper limit for pregnancy termination due to fetal anomalies.

Between 3% and 5% of pregnancies are complicated due to structural anomalies or genetic disorders (11). Congenital structural anomalies are the most common causes of pregnancy termination, and among these anomalies, those originating from the CNS have been reported as the most frequently observed group (12). When we examine the literature, the most common causes of pregnancy termination in the study of Corbacıoğlu et al. (13) are CNS anomalies (51.8%), multiple anomalies (10.2%), and chromosomal anomalies (9.4%). In a study by Hern (14) published in 2014, the main causes of termination were structural and chromosomal anomalies. The development of ultrasound technology and increase in the experience of clinicians showed that almost all CNS anomalies, such as acrania, alobar holoprosencephaly, and encephalocele, could be recognized as early as the first trimester (15). This condition allowed pregnancies with these anomalies to be terminated early. According to our study results, structural malformations were evaluated as the main cause of TOP, and CNS anomalies were found to be the most common causes of structural malformation. The results we found in our study are compatible with the literature. The striking point is that, while the number of terminations in our clinic has been increasing gradually over the years, the distribution of CNS anomalies in first trimester TOP cases between 2017 and 2020 did not increase at the same rate year over year. This situation is thought to be the result widespread use of folic acid in the pregestational and early gestational period.

Screening for congenital defects began with the use of ultrasound for obstetric care in the 1950s. Real-time gray-scale imaging became available in the 1970s and provided prenatal diagnostic opportunities in the early stages (16). Prenatal screening concepts, which started by screening for neural tube defects with a single maternal serum marker, made more than one serum marker and ultrasound marker available for Down syndrome screening over time. Today, a completely new approach is available for aneuploidy screening with maternal plasma cell-free DNA (17). In the face of this development, countries have developed various national policies and recommendations regarding prenatal screening and diagnostic tests. When we evaluated the last 6-year period, the rate of chromosomal anomalies increased from 6.4% to 20.9% among all termination cases, and the general rate was 14.5%. This finding may be a result of the widespread use of chromosomal screening tests in Turkey. Moreover, the results show that more couples prefer termination for chromosomal anomalies. Despite this, our termination cases due to aneuploidies are at a low level compared with those in other studies (25%-39%) (18,19). The reason for this is that from the point of view of couples in our country, regarding prenatal diagnosis tests and termination, especially compared with those of couples in Western countries, religious and cultural differences still seem to be an essential factor. Prenatal screening strategies aim to identify fetal karyotype anomalies as early as possible. In this regard, scans are carried out in the early stages of the first and second trimesters. This finding is due to the changing attitude and awareness of couples and the improvement in prenatal screening programs. In our study, when the systems are evaluated separately, the group with the earliest termination is the

group with cases with chromosomal anomalies. In studies involving TOP cases that occurred after the 24th week of pregnancy, it was reported that terminations were performed mostly for isolated major structural anomalies, and the frequency of cases with chromosomal anomalies decreased with increasing gestational age (14,20). These results seem to be compatible with the objectives of screening strategies.

Due to clinicians' increasing experience in fetal echocardiographic evaluation, the frequency of termination due to CVS anomalies has increased. Moreover, the assessment of tricuspid regurgitation and abnormal ductus venous Doppler flow in addition to nuchal translucency in the first trimester has contributed to the early recognition of these diseases (21). In the study of Corbacıoğlu et al. (13), in TOP cases below the 24th week, the termination rate due to cardiac anomalies is 1.7%, while this rate is 13.5% in our study. The development in terms of early recognition of fetal cardiovascular diseases in the 8 years between the two studies is promising.

The fact that most of the genetic diseases cannot be cured has led to the development of genetic tests in the prenatal period. The introduction of new technologies used for the prenatal diagnosis of chromosomal anomalies into medical genetic practice has enabled the recognition of single-gene diseases. In our study, 4.2% of termination cases were performed due to genetic diseases. This rate is 1.4% in the study of Ozyuncu et al. (22). The main feature of our TOP cases with regard to genetic diseases is the fact that most of them were referred to our clinic by a primary or secondary healthcare center, and a detailed family history was available for them, which helped us with early diagnosis. Moreover, it is extremely important that these diseases are followed up by a multidisciplinary team in our clinic.

Terminations of pregnancy were mostly realized through the vaginal route in our study. All patients who underwent hysterotomy were second trimester TOP cases and had a history of uterine surgery. In the study by Garofalo et al. (23), while uterine surgery history was considered as a critical risk factor for maternal complications in second trimester TOP cases, it did not increase maternal complications in first trimester TOP cases. This condition shows that performing terminations due to fetal anomaly in the early weeks of gestation reduces maternal complications as well as facilitating couples' acceptance of the situation ethically and psychologically.

Study Limitation

The study's main limitations are that it was performed in a single-center, did not include cases of late termination (>24 weeks), and its design was retrospective.

Since our clinic is the largest perinatology center in the region, it accepts patients from many cities, and a study such as this one is therefore essential to provide detailed information about TOP cases.

Conclusion

When the distribution of TOP indications over the years is examined, it is observed that the number of cases related to chromosomal anomalies, CVS anomalies, and genetic diseases is increasing gradually. Thus, we believe that clinicians should conduct pregnancy follow-ups much more carefully and know all the medico-legal regulations in detail.

Ethics Committee Approval: The study was conducted per the principles of the Declaration of Helsinki. This study approval was obtained from Karadeniz Technical University Local Ethics Board (approval number: 2019/29, date: 15.02.2019).

Informed Consent: Informed consent was obtained from all patients who agreed to undergo the procedure.

Peer-review: Externally and internally peer-reviewed.

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

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Could Lycopene Protect Against Ischemia/Reperfusion Injury in the Uterus?

Likopen Uterustaki İskemi/Reperfüzyon Hasarına Karşı Koruyabilir mi?

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ABSTRACT

Introduction: Ischemia/reperfusion damage (IRD) is one of the most important factors in the success of organ transplantation. IRD plays a role in both acute and chronic rejection. This study aims to evaluate the effects of lycopene, which is known to be a powerful antioxidant, on experimental uterine IRD.

Methods: Twenty-four albino Wistar rats were included in the study and divided into three groups. No substances were administered the sham and ischemia/reperfusion groups. The ischemia/reperfusion and ischemia/reperfusion + lycopene groups were administered ischemia for 1 h and reperfusion for 2 h. The ischemia/reperfusion + lycopene group was administered 2.5 mg/kg lycopene reperfusion intraperitoneally half an hour before ischemia/reperfusion. Both uterine horns were extracted at the end of the procedure. Oxidative stress, inflammation, and apoptosis in the tissues were assessed.

Results: The malondialdehyde level, nuclear factor kappa-B immunoreactivity, and apoptotic cell number in the lycopene-administered group (ischemia/reperfusion + lycopene) were significantly decreased compared with those in the ischemia/reperfusion group ($p<0.05$).

Conclusion: The study found that lycopene reduced the effects of IRD on uterine tissue. Lycopene may positively affect the short- and long-term success of organ transplantation.

Keywords: Ischemia/reperfusion damage, oxidative stress, organ transplantation, lycopene

ÖZ

Amaç: İskemi/reperfüzyon hasarı (İRH) organ transplantasyonunun başarısının önündeki en önemli etkenlerden biridir. İRH hem akut hem de kronik rejeksiyonda rol oynamaktadır. Bu çalışmanın amacı güçlü bir antioksidan olduğu bilinen likopenin deneysel uterus İRH'de etkilerini değerlendirmektir.

Yöntemler: Çalışmaya alınan 24 Wistar albino rat 3 gruba ayrılmıştır. Sham ve iskemi/reperfüzyon grubuna hiçbir madde verilmemiştir. İskemi/reperfüzyon ve iskemi/reperfüzyon + likopen grubuna 1 saat iskemi ve 2 saat reperfüzyon uygulanmıştır. İskemi/reperfüzyon + likopen grubuna 2,5 mg/kg dozda likopen reperfüzyon yarım saat önce intraperitoneal olarak verilmiştir. İşlemin sonunda her iki uterin horn çıkarılmıştır. Dokularda oksidatif stres, enflamasyon ve apoptozis değerlendirilmiştir.

Bulgular: Likopen uygulanan grupta (iskemi/reperfüzyon + likopen) malondialdehit seviyesi, nükleer faktör kappa-B immünoreaktivitesi ve apoptotik hücre sayısı iskemi/reperfüzyon grubuna göre önemli ölçüde azalmıştır ($p<0,05$).

Sonuç: Likopenin İRH'nin uterin doku üzerindeki etkilerini azalttığı saptanmıştır. Likopen, organ naklinin kısa ve uzun vadeli başarısını olumlu yönde etkileyebilir.

Anahtar Kelimeler: İskemi/reperfüzyon hasarı, oksidatif stress, organ transplantasyonu, likopen

Introduction

Ischemia/reperfusion damage (IRD) is a process that starts with the reduction of perfusion in the tissue due to organ transplantation and acute myocardial infarction and then enters the main damaging period by ensuring reperfusion in the tissue. Although ensuring the perfusion in the hypoperfused tissue is the first step of treatment, preventing reperfusion damage that emerges due to reperfusion and affects organ function still poses a challenge for clinicians. One example of this situation is myocardial infarction. Interventions undertaken to ensure reperfusion in the early period decrease morbidity and mortality. Additionally,

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myocardial reperfusion affects infarction size through inflammation (1). These results lead scientists to examine pharmaceutical agents and methods that can reduce damage during the reperfusion process as much as possible.

Uterus transplantation is gaining increasing attention in the presence of unrecoverable uterine factor-induced infertility. After the first uterus transplantation was performed, the first live birth from a transplanted uterus was also achieved (2). One of the important obstacles to the success of the transplantation procedure is IRD. That IRD plays a role in both acute and chronic rejection is an accepted hypothesis. It has been shown during surgery that the treatment administered in the post-ischemia period may decrease acute rejection and increase the long-term success of transplantation (3). Various agents have been used to prevent IRD in numerous studies (4).

Nuclear factor kappa-B (NF-κB) is a family of pleiotropic transcription factors that was defined in 1986 and has various functions, such as embryonic development of tissues and the immune response (5). Regulation of NF-κB signaling is a complex process involving numerous genes and extracellular mediators, including free radicals. The effects of NF-κB on transplantation have been shown in experimental transplantation models (6,7).

Carotenoids are known to prevent oxidative damage in the cell (8). Lycopene (LYC) is one of the 600 carotenoids commonly found in nature (especially in tomato). LYC, which has anticancer, anti-proliferative, and neuroprotective properties, is also one of the most powerful antioxidants in the carotenoid family (9,10). It is used to prevent the negative effects of chemotherapeutic drugs on ovarian function (8). To our knowledge, there have been no studies examining the effect of LYC on uterine IRD. This study aimed to assess the effect of LYC on uterine IRD biochemically, immunohistochemically, and histologically.

Methods

Animals

Experimental animals were obtained from Saki Yenilli Experimental Animals Production and Research Laboratory. The number of subjects to be included in the study was determined with a 95% confidence interval and 0.9243 test power (PASS-11). In a One-Way analysis of variance study, eight samples were obtained from each of three groups whose means were to be compared. A total sample of 24 subjects using an F-test with a significance level of 0.05 was obtained 0.9243 power to detect differences between the means versus the alternative of equal means. The study used 24 Wistar albino female rats weighing 200-220 g. The rats were housed at 20 °C-22 °C, in 55%-65% humidity, and on a 12:12 h light/dark cycle until the day of the experiment. The study was conducted in compliance with the international guidelines (ARRIVE guidelines) and ethical rules after the approval of the Saki Yenilli Experimental Animals Production and Research Laboratory Local Ethics Committee was obtained (approval number: 04, date: 24.02.2020). Patient approval has not been obtained as it is performed on animals.

Experimental Groups

Rats were dove into three groups: Ischemia/reperfusion (IR, n=8), ischemia/reperfusion + 2.5 mm/kg bw lycopene (LIR, n=8), and sham (n=8). All rats were synchronized at the diestrus phase of the estrous cycle in compliance with the definition provided by Marcondes et al. (11).

Experimental Procedure

Rats were anesthetized by intraperitoneal injection of a xylazine hydrochloride 7 mg/kg (Bayer, Turkey) and ketamine hydrochloride 50 mg/kg (Eczacıbaşı, Turkey) combination. The rats were held in a supine position, and the abdominal region was wiped with antiseptic solution after shaving. The abdomen was entered through a 2-3 cm vertical incision made in this area. The abdomen was opened and closed without performing uterine ischemia in the sham group. Uterine ischemia was formed using the microvascular bulldog clamps according to Sahin et al. (4). The duration of ischemia was set as 1 hour, and the LIR group was administered LYC intraperitoneally 0.5 h before reperfusion. Following completion of the planned reperfusion duration (2 h), the rats were sacrificed under anesthesia by the decapitation method, and both uterine horns were extracted. The left uterine horn was removed for histology and immunohistochemical evaluation. The right uterine horn was maintained at -80 °C for biochemical evaluation.

Histological Analysis

The extracted uterine tissues at the end of the experiment were fixed in 10% formaldehyde solution. After the fixation process, the tissues were dehydrated by passage through a graded alcohol series (50%, 70%, 80%, 96%, and 100%). The tissues were cleared with xylene and embedded in paraffin. Five-micron-thick sections taken from paraffin blocks were stained with hematoxylin-eosin (H&E) and fixed to slides with mounting medium (Entellan®, Merck). The prepared slides were examined under an Olympus BX53 light microscope.

Immunohistochemical Analysis

The immunoreactivity of the NF-κB protein in uterine tissues in the rat models on which IR performed was determined by the Avidin-Biotin peroxidase method. In brief, citrate buffer was used to open the epitopes after deparaffinization of the sections (5 µm) (pH 6.0). Then, the slides were immersed in 3% hydrogen peroxide solution in methanol to prevent endogenous peroxidase activity. Ultra V block solution was used to prevent non-specific staining. Then, the sections were incubated with primary antibodies at 4 °C overnight. Biotinylated secondary streptavidin-horseradish peroxidase and 3,3′-Diaminobenzidine chromogens were applied, respectively, and then the sections were reverse stained with Gill Hematoxylin. The sections were dehydrated in a graded alcohol series and fixed to slides with Entellan mounting medium. The sections were examined under an Olympus BX53 light microscope. The immunoreactivity levels were quantified using the Image J program. Ten different areas were evaluated for every slide.

Biochemical Analysis

Tissue samples obtained from rats were used for biochemical analysis. Rat malondialdehyde (MDA) was quantified in uterine tissue using a commercial kit (cat. no: 201-11-0157, Sunred Bio) according to the manufacturer's protocol, and the concentration was measured at 450 nm with an ELISA plate reader. The results are presented as nmol/mL of MDA.

Terminal Deoxynucleotidyl Transferase-mediated dUTP Nick-end Labeling

Apoptotic cells in the sections obtained from the subjects were detected using the In Situ Cell Detection Apoptosis Fluorescein Kit (Roche). Staining was performed according to the manufacturer's instructions. Five-micron-thick uterus sections were deparaffinized and rehydrated then washed with PBS twice for 5 min each time. Afterwards, they were kept in a microwave oven in 0.01 M 5% sodium citrate buffer for 5 min at 350 W for antigen recovery then left to cool at room temperature for 10 min. Tissues were washed twice for 5 min each time with PBS then placed in a humidity chamber at 37 °C with the terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling (TUNEL) reaction mixture included in the kit and incubated in the incubator for 60 min. Opposite staining was performed on the tissues that were washed two times for five min each time with PBS using 4',6-diamidino-2-phenylindole. The tissues were covered with glycerol sealing solution and scanned at wavelength of 450-500 nm in an Olympus BX53 model florescent microscope. Apoptotic cells in 50 different areas under 200x objective magnification were counted for calculation of the apoptotic index by using the Image J program.

Statistical Analysis

The SPSS 22 statistical software program was used for the statistical analyses (SPSS Inc., Chicago, IL). The results are presented as median (IQR). The normality of the data distribution was evaluated by visual (histogram) and analytical (Kolmogorov-Smirnov test) methods. Intergroup comparisons were carried out with the One-Way Kruskal-Wallis test. The post-hoc Tamhane test was used for binary comparisons. Results were considered significant at $p<0.05$.

Results

Histochemical Results

Figure 1 shows the histopathological evaluation results. Accordingly, normal histological structures were observed in uterine tissues of the sham (Figure 1A) groups. The study observed that the lumen epithelium and glandular epithelium cells were vacuolized in the uterus section of the ischemia/perfusion (Figure 1B) group. The study also detected intensive neutrophil infiltration in endometrial areas. Vacuolization in the lumen epithelium and glandular epithelium in the IR + LYC group increased, and neutrophil infiltration decreased (Figure 1C).

Immunohistochemical Results

Figure 2A shows the NF-κB immunoreactivity in the uterine tissue. Accordingly, NF-κB expression increased significantly in the uterine tissue, which was only administered ischemia perfusion (IR) (Figure 2B), compared with all other experimental groups ($p<0.05$). NF-κB expression decreased significantly in uterine tissues that were administered 2.5 mg/kg LYC (Figure 2C), compared with the IR group ($p<0.05$).

Biochemical Results

The evaluation of the MDA results showed that there was a significant increase in the IR group compared with the control group. There was a significant decrease in the LYC group compared with the IR group (Table 1).

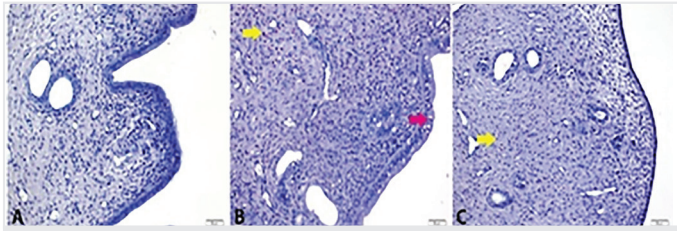

Figure 1. Hematoxylin-eosin staining images of uterine tissues of Sham A), ischemia/reperfusion B), and 2.5 mg/kg lycopene C) experimental groups. The pink arrow shows the vacuolization in lumen epithelium and glandular epithelium cells, and the yellow arrow shows a neutrophil cell

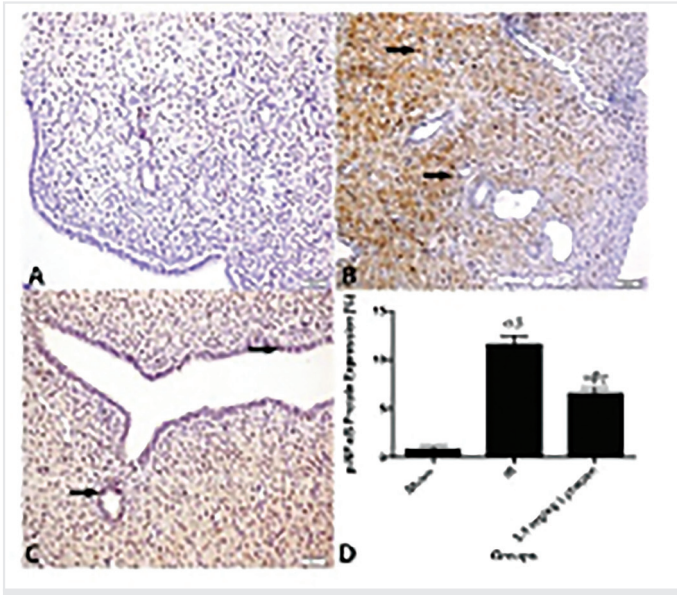

Figure 2. Nuclear factor kappa-B (NF-κB) immune staining in the uteruses of Sham A), ischemia/reperfusion (IR) B), and 2.5 mg/kg lycopene C) experimental groups. The black arrow shows the immunoreactive areas. NF-κB immunoreactivity data showed in the histogram graphic were expressed as mean ± standard deviation (a $p<0.05$ sham group; b $p<0.05$ IR group; g $p<0.05$ 2.5 mg/kg lycopene group)

Table 1. MDA and TUNEL results in the uterine tissue

Groups	Sham	IR	LIR	p
MDA (nmol/mL)	0.74 (0.11)[a]	2.42 (0.45)[b]	0.86 (0.11)[a]	<0.001
TUNEL (+) cell	1 (1)[a]	7 (3.5)[b]	1 (2)[a]	<0.001

The data were presented as median (IQR). The significance level was $p<0.05$. No significant differences were found between the groups with the same letters (a, b).
MDA: Malondialdehyde, TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling, IR: ischemia/reperfusion, LIR: lycopene

TUNEL Results

Table 1 and Figure 3 show the evaluation results of the apoptotic cells in the uterine tissue. Accordingly, the number of apoptotic cells significantly increased in the sham group compared with the IR group while 2.5 mg/kg LYC administration significantly decreased the increased number of apoptotic cells after IR.

Discussion

Oxidative stress-induced reperfusion damage increases acute and chronic rejection. Reducing IRD may increase the success of organ transplantation (3). This study examined the corrective effect of LYC on uterine IRD. MDA levels, NF-κB immunoreactivity, and the apoptotic index in the LIR group were significantly lower than those in the IR group. This experimental study revealed that LYC had positive effects on uterine IRD.

Oxidative stress, which causes the formation of reactive oxygen radicals (ROS), is the main outcome of IRD. Along with tissue hypoxia, dysfunction emerges in the electron transport chain in mitochondria. Decreased adenosine triphosphate (ATP) production in mitochondria increases anaerobic metabolism and impairment in the sodium-potassium pump. A vicious cycle starts during this period. Anaerobic metabolism causes decreased ATP and antioxidant agent production (12). Intracellular osmolarity increases, and pH decreases with the deterioration in the ion channels. The generation of ROS, which causes oxidative stress, increases due to low antioxidant defense in ischemic cells with reperfusion. Inflammatory processes and oxidative stress may cause cell damage with the cytokine production they induce (13). IRD is one of the factors that affect the short- and long-term success of organ transplantation (3). The severity of organ damage varies with the warm ischemia time, which is defined as the amount of time spent between extracting the organ from the body and washing it with hypothermic preservatives (14). A uterine transplantation study conducted on rats showed that a warm ischemia time longer than 5 h decreases the success of transplantation (14). Kisu et al. (15) revealed that the uterus might be more resistant to ischemia than other organs.

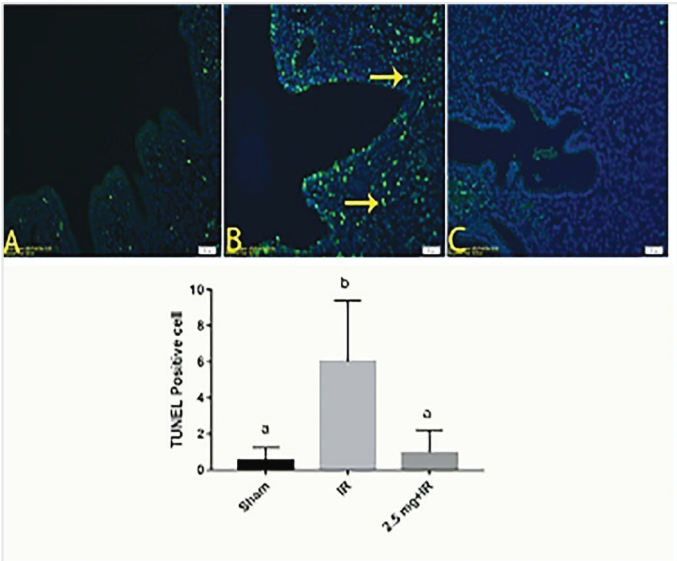

Figure 3. A) Sham group, B) IR group, C) 2.5 mg + IR group. The yellow arrow shows the apoptotic cells, x200

Previous studies used various substances such as pharmacologic agents in uterine IRD (4). LYC antioxidant, a natural carotenoid, is often used in experimental studies due to its antiapoptotic and anti-inflammatory prosperities (16). Another reason for using LYC frequently is that it is not toxic (17). Bayramoglu et al. (16) reported that LYC had a protective effect on liver IRD. Lei et al. (18) found that LYC had a neuroprotective and antiapoptotic effect on brain ischemia by increasing nuclear factor erythroid 2-related factor and heme oxygenase-1 expression levels. Premature ovarian failure may emerge as an undesirable effect of cancer treatment at the reproductive age. A study examining the effects of chemotherapeutics on the ovary determined that LYC positively affected fertility by reducing ovarian failure (19). However, there are no studies that examine the effect of LYC on uterine IRD.

Xanthine oxidoreductases consisting of xanthine dehydrogenase and xanthine oxidase are active in the process that breaks purine up to uric acid. Although various enzymes play a role in purine metabolism, xanthine oxidase has an important role in the formation of ROS. Toxic substances such as MDA form with lipid peroxidation due to increased ROS (20). The MDA level is one of the best indicators of oxidative stress. Ischemia-reperfusion studies showed that the MDA levels were high (4). The present study found that the MDA was significantly different between the IRG and LIRG groups, in line with the literature. The study showed that LYC had a positive effect on oxidative stress in the uterus.

ROS leads to activation of the cytokine cascade and increased expression of adhesion proteins (21). NF-κB is one of the redox-sensitive proinflammatory transcription factors. The effects of oxidative stress on the NF-κB pathway were assessed in different studies. Tumor necrosis factor alpha, lipopolysaccharide, and interleukin-1 were found to be NF-κB pathway activators (22). A subsequent study in human T cells showed that very low levels of hydrogen peroxide can activate the NF-κB pathway (23). However, the latest studies have indicated that hydrogen peroxide may be a modulator rather than an activator (24). This turns NF-κB into the target molecule in oxidative stress studies. It was found that NF-κB inhibition with JSH-23 increased oxidative stress in the hearts of rats with hereditary hypertriglyceridemia (25). On the other hand, cannabinoid-2 receptor activation with JWH-133 was found to significantly reduce the number of NF-κB-positive cells in kidney tissue and thus reduced kidney damage (26). The present study showed that LYC significantly decreased NF-κB immunoreactivity. This decrease in immunoreactivity may be due to the decreasing effect of LYC on IR.

IRD-induced ROS plays a role in various processes, such as cell proliferation and apoptosis. Apoptosis, autophagy, necrosis, and necroptosis may occur in the cell with prolonged IRD (12). Numerous studies showed that apoptosis has an important role in IRD (27). The majority of cell deaths after ischemia are due to apoptosis (28). Therefore, the opinion that "prevention of apoptosis reduces IRD" is coherent. A study examining the effect of procyanidin on myocardial IRD revealed that procyanidin reduced myocardial IRD by inhibiting the apoptotic pathways (29). Apoptosis is assessed using techniques based

on morphologic changes, cytoplasmic changes, DNA fragmentation, and membrane changes in the cell. The TUNEL technique assesses apoptosis through DNA fragmentation. There was a significant difference between the groups in terms of the number of TUNEL-positive cells in this study. This result shows the antiapoptotic propensity of LYC in uterine IRD.

Conclusion

LYC, a natural carotenoid, can be an alternative for reducing organ rejection, which is an important problem in organ transplantation. LYC reduced oxidative stress, inflammation and apoptosis in uterine IRD, even in low dosages, such as 2.5 mg/kg. Due to the wide availability of LYC in nature, the required amount can be provided with a simple diet change. Moreover, its non-toxicity is an important advantage.

Ethics Committee Approval: The study was conducted in compliance with the international guidelines (ARRIVE guidelines) and ethical rules after the approval of the Saki Yenilli Experimental Animals Production and Research Laboratory Local Ethics Committee was obtained (approval number: 04, date: 24.02.2020).

Informed Consent: Patient approval has not been obtained as it is performed on animals.

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The Platelet/Lymphocyte Ratio in Patients with Ischemic Stroke Treated with Intravenous Thrombolysis and Its Relationship with Mortality, Disability, and Prognosis

İntravenöz Tromboliz ile Tedavi Edilen İskemik İnme Hastalarında Platelet/Lenfosit Oranının Mortalite, Disabilite ve Prognoz ile İlişkisi

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ABSTRACT

Introduction: The platelet/lymphocyte ratio (PLR) has been studied frequently to determine the prognosis of cardiovascular diseases, chronic inflammatory diseases, and malignancies. Particularly, the PLR is an indicator of systemic inflammation and atherosclerosis. In this study, we aimed to evaluate the value of the PLR and its relationship with mortality, cerebral hemorrhagic transformation, and short-term prognosis in patients with stroke treated with intravenous thrombolysis.

Methods: Two hundred fifty stroke patients treated with intravenous thrombolysis were included in the study. Initial symptoms, comorbidities, and localization of cerebral ischemia were recorded. Disability was scored on the National Institutes of Health (NIH) stroke scale. At the 24th and 72nd hours after treatment, hemorrhagic transformation was evaluated by brain computed tomography. The in-hospital mortality rate was calculated. Patients were divided into groups according to the difference in the NIH stroke scale (between admission and discharge). Serum platelet and lymphocyte levels and PLR values were determined.

Results: There were 128 (51.2%) female and 122 (48.8%) male patients included in the study. Their mean age was 71.88±12.36 years. The lymphocyte count was low and the PLR was high in patients with a high level of initial disability ($p<0.01$). The lymphocyte count was higher in patients with clinical improvement ($p=0.023$). The lymphocyte count was lower and the PLR was higher in patients who died ($p<0.01$). The platelet level was lower in patients with hemorrhagic transformation ($p=0.024$). The lymphocyte level and PLR were similar in the hemorrhagic transformation groups ($p=0.156$, $p=0.675$).

Conclusion: In this study, it was determined that mortality is related to the PLR, and hemorrhagic transformation is related to platelet levels in patients with ischemic stroke treated with intravenous thrombolysis.

Keywords: Ischemic stroke, intravenous thrombolysis, platelet/lymphocyte ratio

ÖZ

Amaç: Platelet/lenfosit oranı (PLO) kardiyovasküler hastalıkların, kronik enflamatuvar hastalıkların ve malignitelerin prognozunu belirlemek için sıklıkla çalışılmıştır. PLO özellikle sistemik enflamasyonun ve aterosklerozun bir göstergesidir. Bu çalışmada, intravenöz tromboliz uygulanan inme hastalarında PLO değerinin mortalite, serebral hemorajik transformasyon ve kısa dönem prognoz ile ilişkisini değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya intravenöz tromboliz ile tedavi edilmiş 250 inme hastası alındı. Başvuru semptomu, ek hastalıkları ve serebral iskemi lokalizasyonu kaydedildi. Disabilite Ulusal Sağlık Enstitüleri (NIH) inme skalası ile hesaplandı. Tedavi sonrası 24. ve 72. saatlerde beyin bilgisayarlı tomografi ile hemorajik transformasyon değerlendirildi. Hastane içi mortalite oranı hesaplandı. Hastalar başvuru ve taburculuk arası NIH inme skalası sonucu farkına göre gruplara ayrıldı. Serum trombosit, lenfosit seviyesi ve PLO değerleri belirlendi.

Bulgular: Çalışmada 128 (%51,2) kadın ve 122 (%48,8) erkek hasta vardı. Yaş ortalamaları 71,88±12,36 idi. Başvuru disabilitesi yüksek hastalarda lenfosit sayısı düşük, PLO yüksekti ($p<0,01$). Klinik düzelme görülen hastalarda lenfosit sayısı yüksekti ($p=0,023$). Mortal seyredenlerde lenfosit sayısı düşük, PLO yüksekti ($p<0,01$). Hemorajik transformasyon olan hastalarda platelet seviyesi düşüktü ($p=0,024$). Lenfosit seviyesi ve PLO hemorajik transformasyon gruplarında benzerdi ($p=0,156$, $p=0,675$).

Sonuç: Bu çalışmada intravenöz tromboliz ile tedavi edilen iskemik inme hastalarında mortalitenin PLO değeri ile hemorajik transformasyonun trombosit düzeyi ile ilişkili olduğu saptanmıştır.

Anahtar Kelimeler: İskemik inme, intravenöz tromboliz, trombosit/lenfosit oranı

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Introduction

Acute ischemic stroke (AIS) is one of the most prevalent causes of mortality and disability; moreover, it imposes a considerable economic and social burden (1). The most common subtype of stroke is ischemic stroke (2). Endovascular treatment (intraarterial thrombolysis, mechanical thrombectomy, etc) and intravenous thrombolytic treatment (IVT) are the most frequently employed treatments for AIS (3). However, some complications occur with recanalization (cerebral hemorrhagic transformations, brain edema and reoclusion, etc). These complications affect mortality and functional status (4).

Platelet activation and aggregation is important in the pathogenesis of AIS. Platelet aggregation induces thrombosis and vascular occlusion. Thus, clinical conditions (such as ischemic stroke and myocardial infarction) occur (5). The immune response is critically important and starts after stroke. Serum leukocytes pass into the cerebral anoxic tissue following disruption of the blood-brain barrier. Neutrophils and lymphocytes are recruited to this area, and the immune response begins with cytokines. Thus, platelets and coagulation factors increase, and the ischemic area expands (6,7).

Blood tests are performed routinely before IVT in patients with AIS (especially hemogram and coagulation tests). The platelet/lymphocyte ratio (PLR) is a more stable test than individual tests for platelets and lymphocytes. It is an easily accessible, inexpensive, and routine test (8). Recent studies have confirmed that the PLR can be used for myocardial infarction, ischemic stroke, pulmonary embolism, and peripheral ischemia (9-11).

In this study, we aimed to determine serum platelet and lymphocyte levels, calculate the PLR value, and evaluate its relationship with in-hospital mortality, cerebral hemorrhagic transformation, and short-term prognosis in patients with stroke treated with intravenous thrombolysis.

Methods

Ethics and Patient Population

The study was approved by University of Health Sciences Turkey, Konya Training and Research Hospital Ethic Committee (approval number: 38-16, date: 08/05/2020). The principles of the Declaration of Helsinki and Guidelines for Good Clinical Practice were adhered to during the study.

The data were collected retrospectively. The study population included AIS patients who were hospitalized and treated with IVT. The purpose and probable complications of IVT were described. Patients or their relatives signed an informed consent form prior to inclusion in the study. Informed consent was obtained from all patients and/or their relatives routinely before IVT. Some diseases (that could affect the study data) were excluded (Table 1). Patients were questioned about their age, gender, and any chronic diseases they might have (hyperlipidemia, hypertension, diabetes mellitus, etc). Initial symptoms were grouped as consciousness, sensory, hemi/mono-paresis, cerebellar, and others (cranial neuropathy, dysarthria/aphasia, dysphagia, convulsion, cortical blindness, delirium).

The data were collected from patients hospitalized in the neurology clinic between January 2013 and March 2020. Three hundred twenty AIS patients treated with IVT were included in the study. However, 70 patients were excluded from the study due to comorbid diseases and missing data. The data on 250 AIS patients were included.

Definition of the Treatment Period

The treatment was administered according to AIS early treatment management recommendations of the American Heart Association/American Stroke Association (3). Before treatment, diagnosis of ischemic stroke and affected vascular areas were confirmed by brain computed tomography (CT) and cerebral CT angiography. Vascular occlusions were divided into two groups, anterior and posterior. If treatment was not contraindicated, alteplase (0.9 mg/kg, maximum 90 mg) was started (10% in 1 minute, the remaining dose in 1 hour, intravenously). If the neurological examination was disrupted after treatment, brain CT was immediately performed. Otherwise, brain CT was routinely performed at the 24th and 72nd hours after treatment. As a result of these neuroimaging studies, intracerebral hemorrhage was evaluated. Patients were divided into two groups (cerebral hemorrhagic transformation positive or negative).

Disability was scored before treatment using the National Institutes of Health (NIH) stroke scale (12). A decrease (between discharge and baseline) of five points or more of the NIH stroke scale score was accepted as clinical improvement. All other patients were scored as "no clinical improvement". Mortality was calculated.

Blood Tests

Blood samples were obtained before IVT from the antebrachial vein. Hemogram was tested with an Automated Blood Cell Analyzer (Pentra 120 Retic Hematology Analysis Device, ABX, Montpellier, France). Platelet and lymphocyte results were obtained from the hemogram test. After the test, PLR was calculated using the formula "PLR=platelet count/lymphocyte count".

Statistical Analysis

Data were analyzed with SPSS® version 17.0 statistical package software (SPSS Inc., Chicago, IL, United States). Mean ± standard deviation and median (minimum-maximum) values were used to summarize numerical data. Categorical data were summarized as number (n) and percentage (%). Categorical data were compared with a chi-square test or Fisher's exact test. The distribution of the data was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Comparisons of numerical

Table 1. Inclusion and exclusion criteria for the study

Inclusion criteria
- Patients with acute ischemic stroke treated with intravenous thrombolysis
- Over the age of 18
Exclusion criteria
- Chronic liver diseases, rheumatologic, hematological diseases
- Malignancies
- Presence of active infection
- History of chronic disease requiring transfusion
- Current therapy with steroids or nonsteroidal anti-inflammatory drugs

data between two groups were performed with a Student's t-test or a Mann-Whitney U test (according to the data distribution). The cut-off point for the PLR was calculated according to receiver operating characteristic (ROC) curve analysis. The cut-off point was determined according to the sensitivity and specificity values. The area under the curve (AUC) was calculated. The 95% confidence interval (95% CI) was determined. The relationship between numerical data was evaluated with the Spearman correlation test. Correlation coefficients were defined as follows: 0-0.25 weak, 0.25-0.50 weak-medium, 0.50-0.75 strong, and 0.75-1.00 very strong correlation. Results were considered statistically significant at $p<0.05$.

Results

General Results

Two hundred fifty patients [128 (51.2%) female and 122 (48.8%) male] treated with IVT were included in the study. The mean age was 72.88±12.39. The most common initial symptom was hemi/mono-paresis (n=211, 84.4%). Ischemia was detected especially in the anterior vascular areas (n=205, 82.0%). Hypertension was the most common chronic disease (n=167, 66.8%). Patients demographic characteristics and blood values are summarized in Table 2.

Clinical improvement was higher in patients with a high NIH stroke scale score ($p<0.001$). Also, mortality and hemorrhagic transformation were higher in these patients ($p<0.001$, $p=0.009$). Patients treated with IVT in less than 3 hours had better clinical improvement ($p=0.042$). There was no difference in hemorrhagic transformation or mortality between treatment time groups ($p>0.05$). The mean age of patients with clinical improvement was lower [74.17±11.35 (43-95) and 69.95±12.87 (35-95)]. Blood values of all patients were serum platelet ($10^3/mm^3$) level 245.49±80.83 (107-559), lymphocyte ($10^3/mm^3$) level 2.10±0.89 (0.56-6.87), and PLR value 136.59±78.38 (24.16-622.35).

Table 2. Gender and disease characteristics of all patients

		Number (n)	Percentage (%)
Gender	Female	128	51.2
	Male	122	48.8
Symptom-treatment time	0-1 hour	2	0.8
	1-2 hours	44	17.6
	2-3 hours	92	36.8
	3-4.5 hours	112	44.8
Initial symptom	Consciousness	104	41.6
	Hemi/mono-paresis	211	84.4
	Sensory symptoms	118	47.2
	Cerebellar disorder	16	6.4
	Others	139	55.5
Ischemia localization	Anterior	205	82.0
	Posterior	70	28.0
Chronic diseases	Diabetes mellitus	73	29.2
	Hypertension	167	66.8
	Hyperlipidemia	34	13.6
	Others	68	27.2

The Association of PLR Levels with Initial Disability

Patients were compared in two groups according to disability score before IVT (mild disability = NIH stroke score <15, severe disability = NIH stroke score ≥15). There was mild disability in 162 (64.8%) patients and severe disability in 88 (35.2%) patients. The PLR was higher in patients with severe disability ($p<0.001$) (Figure 1). The serum lymphocyte level was lower in the group with severe disability ($p<0.001$). There was no difference in the platelet level between the two groups ($p=0.236$). The platelet, lymphocyte, and PLR values of the groups are summarized in Table 3A. A negative correlation was detected between the NIH stroke score and the lymphocyte level ($p=0.026$, $r=-0.48$). There was a positive correlation with the PLR level ($p=0.001$, $r=0.59$).

In ROC analysis, the PLR cut-off value was calculated as 121.72 with 62.5% sensitivity and 61.0% specificity ($p=0.000$, AUC: 0.651, 95% CI: 0.58-0.72) (Figure 2). The lymphocyte cutoff value was calculated as 1.86 with 66% sensitivity and 65% specificity ($p=0.000$, AUC: 0.694, 95% CI: 0.62-0.76).

The Association of PLR Levels with Clinical Improvement

Patients were divided into two groups according to the difference in the NIH stroke scale, and the groups were compared. There was clinical improvement in 136 (54.4%) patients and not in 114 (45.6%). There was no statistically significant difference between the degree of clinical improvement and the PLR ($p=0.072$). The serum lymphocyte level was higher in patients in the group with clinical improvement ($p=0.023$). There was no difference between groups in the serum platelet levels ($p=0.390$). The platelet, lymphocyte, and PLR values of the groups are summarized in Table 3B.

In ROC analysis, the lymphocyte cut-off value was calculated as 1.95 with 56.6% sensitivity and 54.4% specificity ($p=0.023$, AUC: 0.584, CI: 0.51-0.65).

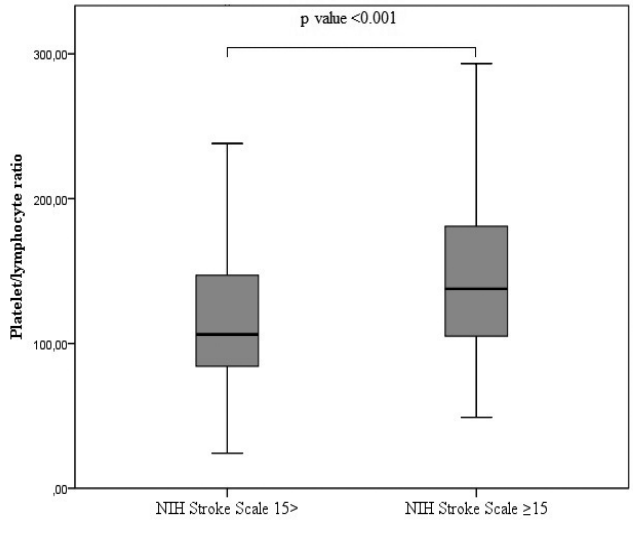

Figure 1. Box plot graph: platelet/lymphocyte ratio according to initial disability in patients treated with intravenous thrombolysis

NIH: National Institutes of Health

Table 3. Blood parameters according to disability, clinical improvement, mortality, and hemorrhagic transformation. Data are shown as mean ± standard deviation and min-max

A	NIH stroke scale <15 (n=162)		NIH stroke scale ≥15 (n=88)		p
Platelet (10^3/mm^3)	249.50±79.84	108-559	238.11±82.58	107-529	0.236
Lymphocytes (10^3/mm^3)	2.30±0.90	0.56-6.87	1.74±0.77	0.64-3.86	<0.001
Platelet/lymphocyte ratio	123.7±67.3	24.1-579.5	160.3±91.1	48.9-622.3	<0.001
B	**Clinical improvement (-) (n=114)**		**Clinical improvement (+) (n=136)**		
Platelet (10^3/mm^3)	241.53±77.95	107-529	248.80±83.32	108-559	0.390
Lymphocytes (10^3/mm^3)	2.00±0.97	0.64-6.87	2.09±0.82	0.56-4.70	0.053
Platelet/lymphocyte ratio	145.61±86.23	24.1-622.3	129.03±70.58	40.5-579.5	0.072
C	**Mortality (-) (n=219)**		**Mortality (+) (n=31)**		
Platelet (10^3/mm^3)	246.21±77.82	108-559	240.41±99.96	107-529	0.292
Lymphocytes (10^3/mm^3)	2.18±0.88	0.56-6.87	1.55±0.83	0.64-3.86	<0.001
Platelet/lymphocyte ratio	129.25±67.70	24.1-579.5	188.4±120.5	48.9-622.3	0.001
D	**Hemorrhagic transformation (-) (n=223)**		**Hemorrhagic transformation (+) (n=27)**		
Platelet (10^3/mm^3)	249.07±80.81	107-559	215.92±76.19	108-418	0.024
Lymphocytes (10^3/mm^3)	2.13±0.90	0.56-6.87	3.86±1.90	0.66-3.86	0.156
Platelet/lymphocyte ratio	137.45±80.20	24.1-622.3	129.60±61.98	48.9-305.8	0.675

NIH: National Institutes of Health

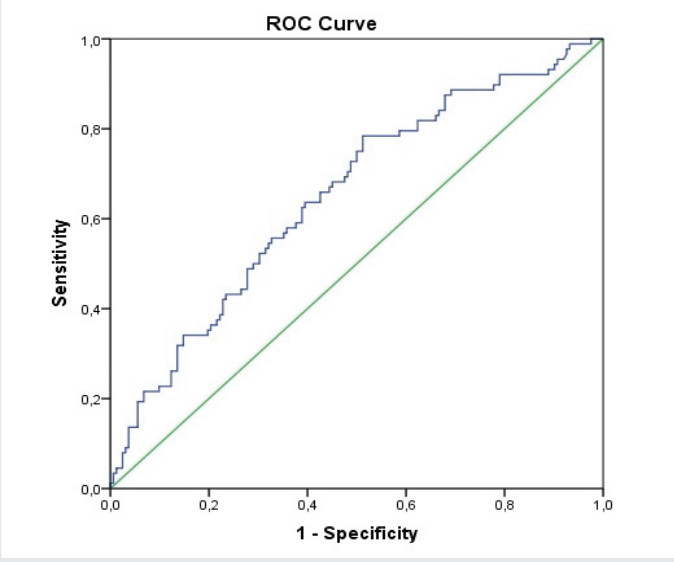

Figure 2. Receiver operating characteristic curve analysis: platelet/lymphocyte ratio according to initial disability in patients treated with intravenous thrombolysis

ROC: Receiver operating characteristic

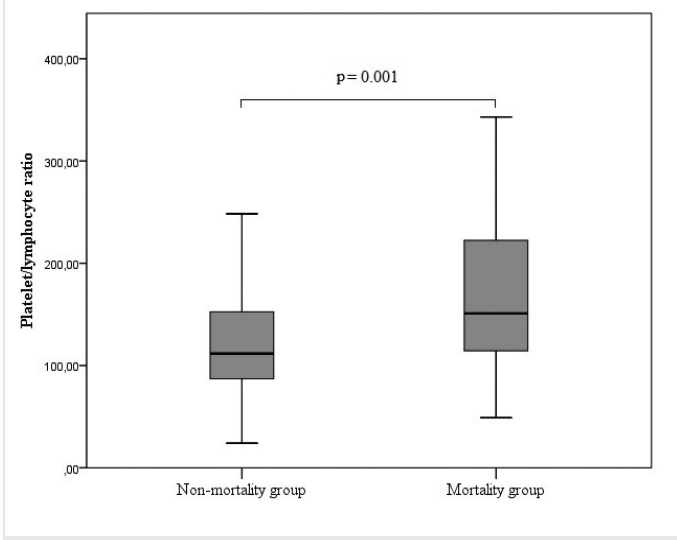

Figure 3. Box plot graph: platelet/lymphocyte ratio according to in-hospital mortality in patients treated with intravenous thrombolysis

The Association of PLR Levels with In-hospital Mortality

The in-hospital mortality rate was 12.4% (n=31). The PLR was higher in patients with mortality (p<0.001) (Figure 3). Serum lymphocyte levels were lower in these patients (p=0.001). There was no between-group difference in platelet levels (p=0.236).

In ROC analysis, PLR cutoff value was calculated as 131.43 with 61.3% sensitivity and 63.0% specificity (p=0.001, AUC: 0.668, CI: 0.58-0.79) (Figure 4). The lymphocyte cut-off value was calculated as 1.66 with 68.8% sensitivity and 67.7% specificity (p=0.000, AUC: 0.735, CI: 0.63-0.83).

The Association of PLR Levels with Hemorrhagic Transformation

The hemorrhagic transformation rate was 10.8% (n=27). The serum platelet level was lower in patients with hemorrhagic transformation (p=0.024) (Figure 5). There was no difference between the lymphocyte level and PLR in these patients (p=0.156, p=0.675). The platelet, lymphocyte, and PLR values of the groups were summarized in Table 3D.

In ROC analysis, the platelet cut-off value was calculated as 211.0 with 67.7% sensitivity and 63.0% specificity (p=0.024, AUC: 0.633, CI: 0.51-0.75) (Figure 6).

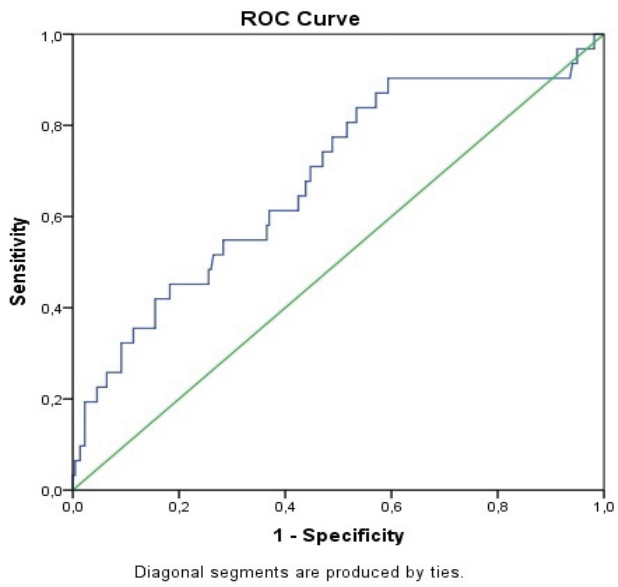

Figure 4. Receiver operating characteristic curve analysis: platelet/lymphocyte ratio according to in-hospital mortality in patients treated with intravenous thrombolysis

ROC: Receiver operating characteristic

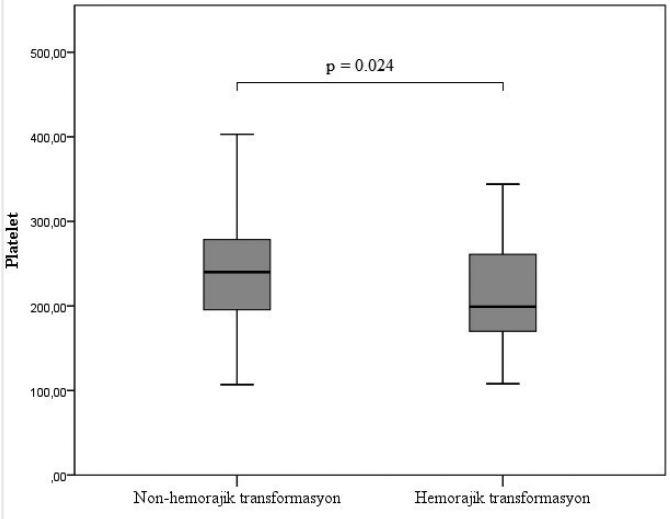

Figure 5. Box plot graph: platelet/lymphocyte ratio according to hemorrhagic transformation in patients treated with intravenous thrombolysis

Discussion

This is the second study in the literature to evaluate the relationship between mortality, disability, and the PLR in AIS patients treated with IVT (13). In our study, the cut-off point was hospital discharge time. In another study, the 90 day prognosis and mortality were evaluated.

Lymphocyte and platelet levels are important in the pathogenesis and prognosis of ischemic vascular diseases (especially ischemic stroke and myocardial infarction). Increased platelet levels and decreased lymphocyte levels are associated with severe disability and poor

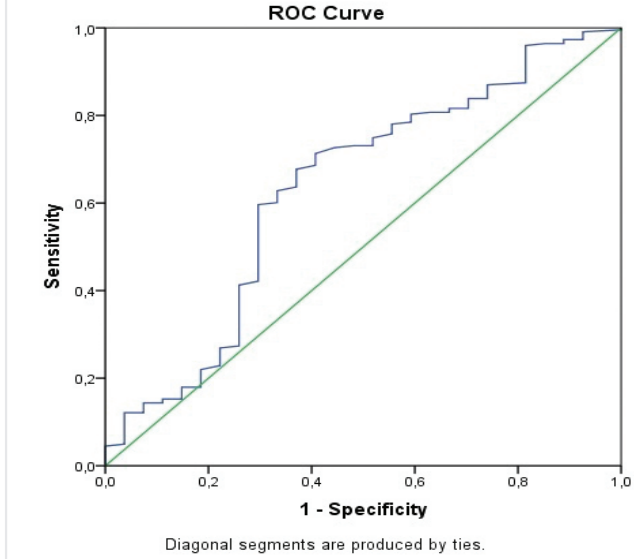

Figure 6. Receiver operating characteristic curve analysis: platelet/lymphocyte ratio according to hemorrhagic transformation in patients treated with intravenous thrombolysis

ROC: Receiver operating characteristic

prognosis in ischemia (14-17). Overactivation of platelets during ischemic stroke causes thrombosis and vascular occlusion (18). In this process, increased stress activates the hypothalamus-pituitary-adrenal glands. As a result of increased cortisol, the lymphocyte concentration is partially reduced (19). In our study, the lymphocyte level was lower in groups with high initial disability and mortality. This result suggested that the lymphocyte level may be related to prognosis and disability in stroke patients treated with IVT.

The relationship of the PLR with ischemic vascular diseases has been reviewed in the literature. As the PLR increases, the risk of peripheral vascular occlusion increases. In addition, PLR is associated with occurrence of vascular events (11,20). The PLR has been shown to be an independent predictor of cardiovascular disease recurrence and in-hospital mortality in patients with acute myocardial infarction (21,22). In stable angina pectoris, the PLR is higher in patients with decreased coronary collateral flow (23). Regarding the ischemic stroke-PLR relationship, an increased PLR is an independent predictor of stroke (24). A higher PLR is associated with increased cerebral ischemia volume and poor recanalization in patients with ischemic stroke treated with endovascular mechanical thrombectomy. In addition, an increased PLR is associated with postoperative stroke risk and depression after carotid endarterectomy (25,26).

In an earlier study, investigating the PLR in AIS patients treated with IVT, blood samples were drawn within the first 24 hours after symptom onset, and patients were evaluated after 3 months. The PLR was higher in patients with unfavorable outcomes. After 3 months, 38 (13.3%) of these patients died. The PLR was higher in these patients. In conclusion, a high PLR in this study was associated with unfavorable outcomes and death in patients with ischemic stroke treated with IVT (13). Platelet and lymphocyte values can be affected by IVT. Therefore, we obtained blood

samples before treatment. In our study, a high PLR was associated with increased in-hospital mortality and a high initial disability scale score. There was no relationship between short-term clinical improvement and the PLR. In our study, clinical improvement was evaluated between the pre-discharge and hospitalization period. The relationship with long-term clinical improvement could not be evaluated.

The immune response begins rapidly after ischemic stroke. This is especially associated with disruption of the blood-brain barrier structure. Lymphocytes and platelets are blood cells that actively participate in this process, and they are associated with the severity of stroke (5-7). The lymphocyte value is a predictive marker for microvascular occlusion (27,28). A low platelet level is associated with increased symptomatic intracerebral hemorrhage in patients with ischemic stroke treated with IVT. The risk of hemorrhagic transformation is higher in thrombocytopenic patients. However, no relationship has been detected between poor outcome risk, mortality, and PLR (29). In our study, the lymphocyte value was lower in patients who died. A low lymphocyte level was associated with increased in-hospital mortality. The lymphocyte cut-off value was calculated as 1.66 with 68.8% sensitivity and 67.7% specificity for mortality. A low platelet level was associated with hemorrhagic transformation. The platelet cut-off value was calculated as 211.0 with 67.7% sensitivity and 63.0% specificity for hemorrhagic transformation. There was no relationship between the PLR and hemorrhagic transformation.

Study Limitation

This study had several limitations. First, it was a retrospective study conducted in only one center. Second, the number of patients included in the study was limited. Third, the difference in PLR (before and after treatment) could not be calculated, and its relationship with prognosis could not be determined. Fourth, the relationship of chronic diseases with the PLR and prognosis could not be evaluated.

Conclusion

In blood tests before IVT treatment in AIS patients, a low lymphocyte level is associated with the initial severity of stroke disability. Also, a low platelet level is associated with hemorrhagic transformation. A higher PLR is associated with high initial disability and in-hospital mortality. The PLR may be an inexpensive, easily accessible, and effective marker for evaluating stroke severity and predicting mortality.

Ethics Committee Approval: The study was approved by University of Health Sciences Turkey, Konya Training and Research Hospital Ethic Committee (approval number: 38-16, date: 08/05/2020).

Informed Consent: Informed consent was obtained from all patients and/or their relatives routinely before IVT.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - F.E., A.D.; Concept - F.E., A.D., G.E.; Design - F.E., A.D., G.E.; Data Collection or Processing - F.E., A.D.; Analysis or Interpretation - F.E., G.E.; Literature Search - F.E., G.E.; Writing - F.E., A.D., G.E.

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

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