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A Strong Clue on Chest Radiography for Metabolic Syndrome in Patients with Obstructive Sleep Apnea: Aortic Arch Calcification

Obstrüktif Uyku Apneli Hastalarda Metabolik Sendrom İçin Göğüs Radyografisi Üzerinde Güçlü Bir İpucu: Aortik Ark Kalsifikasyonu

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ABSTRACT

Aim: Obstructive sleep apnea (OSA) is associated with increased atherosclerosis and metabolic syndrome (MetS). Vascular calcification plays a pivotal role in the development of atherosclerosis. However, data regarding vascular calcification and MetS is insufficient. The aim of the present study was to investigate the association between MetS and aortic arch calcification in patients with OSA.
Material and Methods: Patients who underwent an overnight polysomnography and diagnosed with OSA were enrolled into the study. Patients were classified into two groups based on the presence of MetS. Two examiners who were unaware of the results of polysomnographic assessment reviewed the chest radiograms.
Results: A total of 314 patients with OSA were included in the study. 33.1% of the patients were female and mean age was 51.2±10.9. Of these, 43.6% had mild OSA, 30.9% had moderate OSA, and 25.5% had severe OSA. Aortic arch calcification was detected in 56.4% (n=177) and MetS was detected in 58.6% (n=184) of the patients. Prevalence of aortic arch calcification was higher in patients with MetS than in those without MetS (p<0.001). By multiple logistic regression analysis found that body mass index (1.148, 95% CI, 1.089-1.210), apnea hypnea index (1.039, 95% CI, 1.016-1.062), and aortic arch calcification (4.986, 95% CI, 2.887-8.610) were found to be predictors of MetS.
Conclusion: Aortic arch calcification seen in chest radiography is strongly associated with MetS in patients with OSA. Aortic arch calcification may be an alerting finding for clinicians regarding the development of MetS in patients with OSA.
Keywords: Obstructive sleep apnea; aortic arch calcification; metabolic syndrome.

ÖZ

Amaç: Obstrüktif uyku apnesi (OSA), ateroskleroz ve metabolik sendrom (MetS) gelişimi için önemli bir risk faktörüdür. Vasküler kalsifikasyon ateroskleroz gelişiminde önemli bir rol oynamaktadır. Buna rağmen, literatürde MetS ile vasküler kalsifikasyon arasındaki ilişkiyi gösteren veriler yetersizdir. Bu çalışmanın amacı, OSA'lı hastalarda MetS ile aortik ark kalsifikasyonu arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntemler: Bir gece polisomnografi laboratuvarında yatan ve OSA tanısı koyulan hastalar çalışmaya dahil edildi. Hastalar MetS varlığına göre iki gruba ayrıldı. Polisomnografik değerlendirme sonuçlarından habersiz olan iki araştırmacı akciğer grafilerini inceledi.
Bulgular: Çalışmaya OSA tanısı alan toplam 314 hasta dahil edildi. Hastaların %33,1 kadın ve ortalama yaş 51,2±10,9 idi. Çalışmaya alınan hastaların %43,6'sında hafif OSA, %30,9'unda orta derecede OSA ve %25,5'inde ağır OSA varlığı saptandı. Hastaların %56,4'ünde (n=177) aortik ark kalsifikasyonu, %58,6'sında (n=184) ise MetS saptandı. Aortik ark kalsifikasyonu prevalansının MetS saptanan hastalarda MetS saptanamayan hastalara göre daha yüksek olduğu bulundu (p<0,001). Çoklu lojistik regresyon analizinde, vücut kitle indeksinin (1,148; %95 GA 1,089-1,210), apne hipopne indeksinin (1,039; %95 GA, 1,016-1,062) ve aortik ark kalsifikasyonunun (4,986; 95% GA 2,887-8,610) MetS varlığı için bağımsız prediktörler olduğu bulundu.
Sonuç: OSA'lı hastalarda akciğer grafisinde görülebilen aortik ark kalsifikasyonu ile MetS arasında güçlü bir ilişki olduğu bulundu. Aortik ark kalsifikasyonu, OSA'lı hastalarda MetS gelişimi ile ilgili klinisyenler için uyarıcı bir bulgu olabilir.
Anahtar kelimeler: Obstruktif uyku apne; aort ark kalsifikasyonu; metabolik sendrom.

Presented as a poster at 34th Turkish Cardiology Congress (October 20-23, 2018, Antalya).

INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by intermittent partial or total obstruction of the upper airway during sleep (1). OSA is a systemic illness with debilitating effects on the cardiovascular system. Obesity is the most significant risk factor for the development of OSA, as is metabolic syndrome (MetS) which is usually accompanied by OSA (2). The increased prevalence of MetS causes a further increase in cardiovascular morbidity and mortality (3). MetS refers to the co-existence of metabolic disorders such as abdominal obesity, glucose intolerance or diabetes mellitus with insulin resistance, dyslipidemia, and hypertension. Each component of MetS is an independent risk factor for cardiovascular diseases (CVD). Moreover, the combination of these risk factors further increases the prevalence and severity of CVD (4). MetS starts with an increase in insulin resistance (5), which accelerates atherosclerosis and the development of type 2 diabetes. Inflammation, endothelial damage, reactive oxygen species, as well as vascular calcification play important roles in the pathogenesis of atherosclerosis (6).

Vascular calcification occurs due to calcium accumulation in the intima or the media layer of the vascular bed. Calcification of the vascular bed is an important predictor of subclinical atherosclerosis and cardiovascular events (7), and is associated with increased atherosclerotic plaques in the same vascular segment. Both OSA and MetS are risk factors for atherosclerosis, and synergistically accelerate its development (8). Therefore, we hypothesized that vascular calcification is increased in patients diagnosed with OSA and presenting symptoms of MetS. Aortic arch calcification (AAC) refers to the presence of calcified deposits in the aortic arch and a part of the descending aorta in standard chest x-rays (9). AAC is the easiest tool to assess vascular calcification and can be detected easily with a routine chest x-ray, a simple and cost-effective test. However, no data are available regarding the use of AAC in predicting MetS in patients with OSA. The aim of the present study, therefore, was to determine the association between AAC and Mets in patients with OSA.

MATERIAL AND METHODS

Clinical Characteristics of the Patients

Patients hospitalized at the sleep laboratory of Karabuk University between January 2015 and January 2017 were consecutively assessed. Inclusion criteria were as follows: a) age over 18 years, b) apnea/hypopnea index (AHI) ≥5, and c) willingness to participate in the study. Exclusion criteria were a) AHI <5, b) previous history of cardiac surgery, c) pregnancy, d) presence of active infection or malignancy, e) improper chest x-ray examination, or f) inconclusive sleep test. The patients were stratified into a non-MetS, or a MetS group based on the presence/absence of metabolic syndrome. A detailed medical history, including cardiovascular diseases/risk factors and current medications were obtained from all study participants. Hypertension was defined as blood pressure of ≥140/90 mm Hg and/or current use of antihypertensive medications. Patients who were on oral anti-diabetic agents and/or insulin treatment, or who had a fasting blood glucose level of ≥126 mg/dL, at least two times, were considered to have diabetes mellitus. Current smokers or patients who had quit smoking within the last month were regarded as smokers. Patients with total cholesterol level >200 mg/dL, low-density lipoprotein cholesterol (LDL-C) >100 mg/dL or receiving lipid-lowering medications were considered hyperlipidemic (10). The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (11). BMI was calculated by dividing the weight (kg) by the square of the height (m) (12), and BSA was calculated by dividing the square root of the weight (kg) and height (cm) by 3600 (13). Standard chest x-rays and echocardiograms were obtained from all patients. Abant Izzet Baysal University Clinical Researches Ethics Committee approved the study protocol (23.02.2017, 2015/19), and each subject gave written informed consent.

Definition of MetS

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) defines MetS as follows; (i) waist circumference of >102 cm in males and >88 cm in females, (ii) fasting serum triglycerides ≥150 mg/dL or use of medical therapy for elevated triglycerides, (iii) HDL cholesterol <40 mg/dL in males and <50 mg/dL in females or use of medical therapy to reduce HDL cholesterol, (iv) high blood pressure, i.e., diastolic blood pressure ≥85 mmHg and systolic blood pressure ≥130 mmHg, or use of medical therapy for hypertension, or (v) high glucose levels (fasting serum glucose ≥100 mg/dL) or use of medical therapy for elevated glucose levels (4).

Evaluation of AAC

The standard chest x-ray (40 cm × 40 cm; Curix HT 1.000G Plus, Agfa, Mortsel, Belgium) was taken with the patient in standing position (Thoramat, Siemens, Erlangen, Germany), with a focus-patient distance of 150 cm. An automated exposure control with a fixed tube voltage of 117 kV was used. AAC was graded as follows: Grade 0 with no visible calcification, Grade I with small spots of calcification or thin calcification on the aortic knob, Grade II with one or more areas of thickened calcification, and Grade III with circular calcification on the aortic knob (9) (Figure 1). Two examiner who were blinded to the sleep laboratory findings reviewed AAC on the chest x-ray. One hundred chest x-rays randomly selected for AAC evaluation were independently evaluated by two cardiologists to assess the reliability of the AAC diagnosis, and the Kappa value was found to be 0.812 and $p<0.001$.

Polysomnography

The diagnosis of OSA was based on polysomnographic study (Alice Sleepware; Philips Respironics, Inc., Murrysville, Pa., USA). All variables were recorded on a commercially available computerized system, which included electroencephalography (F3M2, F4M1, C3M2, C4M1, O1M2 and O2M1), bilateral electrooculography, submental electromyography, uncalibrated inductive plethysmography which measured thoracic and abdominal movements, finger oximeter for measuring oxyhemoglobin saturation (SaO_2), thermistors to record airflow through the nose and mouth, two contiguous ECG leads, a snoring microphone and video monitoring with an infrared video camera. The entire recording was observed by an experienced sleep technician. Apnea was defined as the cessation of airflow for >10 sec, and hypopnea was defined as a reduction in airflow of ≥30% lasting for ≥10 sec accompanied by a decrease in oxygen saturation (SpO_2)

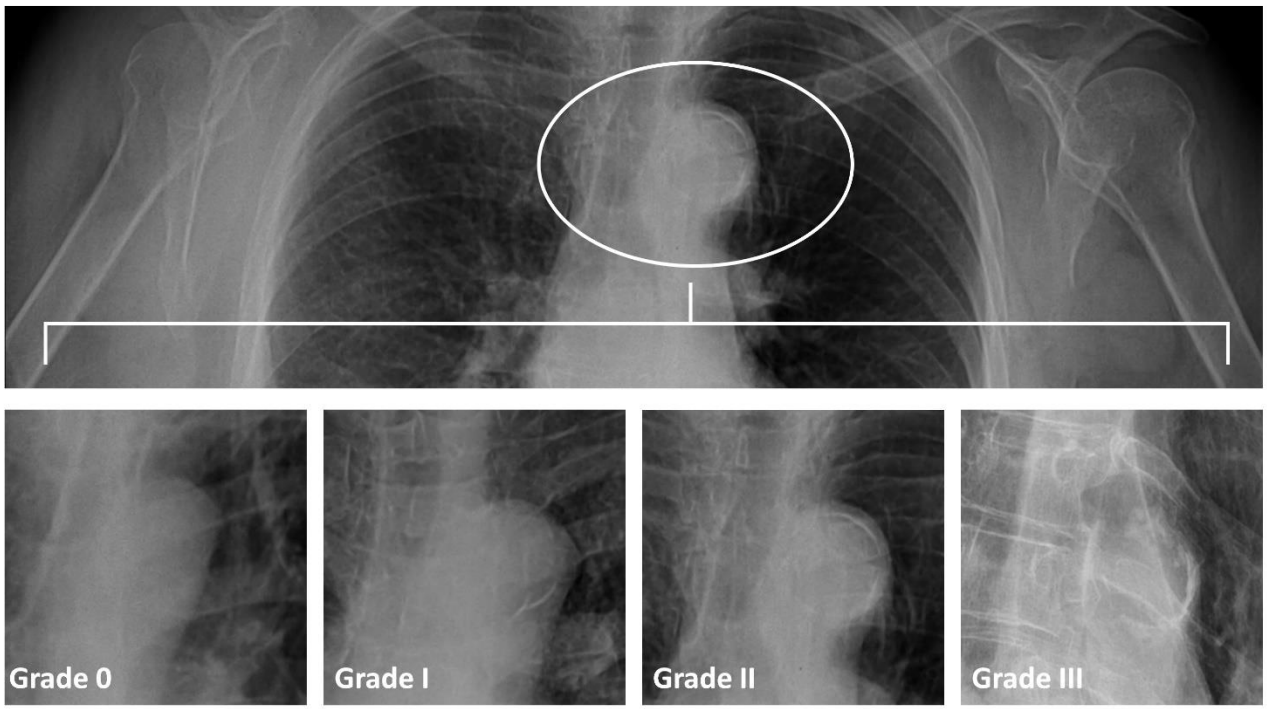


Figure 1. Grading of aortic arch calcification

by at least 3% (14). The duration for which SpO_2 was <90% during sleep and the minimum SaO_2 was calculated for each patient. Apnea-hypopnea index values were calculated as the number of episodes of apnea and hypopnea per hour over the total duration of sleep. Patients with an AHI ≥5 were considered to have OSA and enrolled in the study. The severity of OSA was classified according to the AHI (mild: ≥5 and <15, moderate: ≥15 and <30 and severe: ≥30) (15).

Echocardiographic Examination

All patients were examined using a commercially available system (Vivid 4; GE Medical Systems, Horten, Norway) with a phased-array 3.5-MHz transducer. The conventional M-mode, B-mode, and Doppler parameters were measured according to the American Society of Echocardiography guidelines. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters and posterior (PWT) and interventricular septal (IVST) wall thicknesses were measured. Left ventricular mass (LVM) was calculated using the Devereux equation: $LVM = 0.8 \times 1.04 \times [(LVEDD + IVST + PWT)^3 - (LVEDD)^3] + 0.6$; LVM index (LVMI) was calculated by dividing the LVM by the body surface area. Left ventricular hypertrophy was defined as LVMI >115 g/m^2 for men and >95 g/m^2 for women (16).

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analyses. All data were summarized using appropriate descriptive statistics (Mean, Standard Deviation, Median, Minimum, Maximum, Frequency and Percentage). Student's t test was used for comparison of variables with normal distribution while Mann-Whitney U test was used for comparison of variables with non-normal distribution. Backward multiple logistic regression analysis was used for the assessment of risk factors affecting MetS. Pearson's Chi-Square test was used for comparison of the qualitative data. The cutoff points based on MetS for statistically significant parameters were calculated by using Receiver operator characteristics (ROC) curve analysis. A p value of <0.05 were considered to be statistically significant.

RESULTS

Comparison of Clinico-Demographical Parameters

The study included 314 OSA patients, of which 105 (33.4%) were female, and the mean age of the cohort was 51.2±10.9 years. The mean BMI was 32.7±6.1 kg/m^2, mean waist circumference was 111.4±15.1 cm, and mean neck circumference was 40.4±4.1 cm. Eighty-three (26.4%) patients were smokers, 47.8% (n=150) had hypertension, 24.8% (n=78) had diabetes, and 7% (n=22) had hyperlipidemia (Table 1). AAC was detected in 56.4% (n=177) of the patients and 58.6% (n=184) had MetS (Table 2). In terms of sleep diagnosis, 43.6% (n=137) of the patients had mild OSA, 30.9% (n=97) had moderate OSA, and 25.5% (n=80) had severe OSA.

The MetS and non-MetS patient groups did not significantly differ in terms of age (p=0.193) or gender (p=0.909). In contrast, the BMI (p=0.001), waist circumference (p=0.001), and neck circumference (p=0.001) were significantly higher in the MetS group compared to the non-MetS group. The prevalence of hypertension (p=0.001), diabetes (p=0.014) and hyperlipidemia (p=0.022) were also significantly higher in the MetS group than in the non-MetS group. In addition, the systolic arterial (p=0.001) and diastolic arterial pressure (p=0.001) were significantly higher in the MetS group, as was left ventricular hypertrophy prevalence (p=0.015), LVESD (p=0.002), LA (p=0.002), IVST (p=0.003), PWT (p=0.001), and AHI (p=0.001) compared to the non-MetS group. In terms of biochemical indices, serum glucose (p=0.001), urea (p=0.048), triglycerides

(p=0.001), uric acid (p=0.004), CRP (p=0.046), and BSA (p=0.001) levels were significantly higher, while HDL (p=0.001), LVEF (p=0.001) and GFR (p=0.005) were significantly lower in the MetS patients compared to the non-MetS patients (Table 3). ROC curve analysis yielded a strong predictive ability of AAC for the presence of MetS (AUC=0.721, 95%CI 0.663 to 0.779, p<0.001). Presence of AAC on chest radiography had a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 76.8%, 64.9%, 73.9%, 68.4% and 71.6%, respectively, for the presence of MetS (Figure 2).

Logistic Regression Analysis

The effects of different risk factors including BMI, neck circumference, AAC, LVH, LVEDD, LVESD, LA, AHI, SO_2 duration, CRP, BSA, LVEF, and GFR on MetS were assessed using backward logistic regression analysis. The model describing the risk factors is shown in Table 4. At the end of step 11, BMI, AAC, and AHI were the significant risk factors (p<0.001) affecting MetS. The explanatoriness coefficient of the model was 74.8%. The odds ratios were as follows; for BMI, 1.148 (95% CI, 1.089-1.210); for AAC, 4.986 (95% CI, 2.887-8.610); and for AHI, 1.039 (95% CI, 1.016-1.062).

DISCUSSION

The prevalence of MetS is higher in patients with OSA (17), and is also the reason for the higher cardiovascular risk seen in these patients. Consistent with previous studies (17), the prevalence of MetS in patients with OSA was 58.6% in the present study. In addition, we found an independent and strong association between MetS and AAC in patients with OSA. Vascular calcification increases with age and has debilitating effects on the cardiovascular system. It results in increased arterial stiffness and myocardial workload, and impaired diastolic coronary perfusion, resulting in a higher risk of stroke, hypertension, myocardial infarction, diabetes mellitus, renal failure, hyperlipidemia, and left ventricle hypertrophy (18-21). Consistent with previous studies, we found that AAC increased with age and was significantly associated with hypertension, diabetes, hyperlipidemia and left ventricular hypertrophy, in addition to being negatively correlated with GFR.

The important factors affecting vascular calcification in patients with OSA and MetS include intermittent hypoxia, inflammation, oxidative stress, and the renin-angiotensin system (22-24). Several studies have shown an association between OSA and vascular calcification (25,26) and consistent with these studies, we also found an association between AHI and AAC, a prototype for vascular calcification, suggesting that the latter could also be the cause of increased arterial stiffness in patients with OSA. In fact, vascular calcification has been shown to play the main role in increased arterial stiffness (27). Arterial stiffness increases due to the presence and severity of OSA irrespective of hypertension and obesity (1). We demonstrated a strong association between OSA and AAC, which suggests that increased arterial stiffness in OSA patients may be due to increased vascular calcification. In addition, we found an independent and strong association between MetS and AAC, suggesting that the increased prevalence of vascular calcification in OSA patients may be due to increased prevalence of MetS.

Table 1. Baseline characteristics of groups

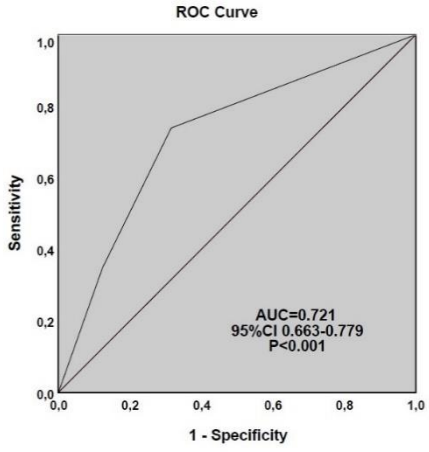
	Non-MetS (n=130)	MetS (n=184)	p
Age (year)	50.2±10.9	51.9±10.9	0.193
Female gender, n (%)	43 (33.1)	62 (33.7)	0.909
Body mass index (kg/m2)	30.2±5.8	34.6±5.6	**0.001**
Waist circumference (cm)	104.7±14.9	116.1±13.3	**0.001**
Neck circumference (cm)	39.2±4.2	41.2±3.8	**0.001**
Smoking, n (%)	35 (26.9)	48 (26.1)	0.869
Hypertension, n (%)	47 (36.2)	103 (56.0)	**0.001**
Diabetes mellitus, n (%)	23 (17.7)	55 (29.9)	**0.014**
Hyperlipidemia, n (%)	4 (3.1)	18 (9.8)	**0.022**
Systolic blood pressure (mm Hg)	119.7±13.9	127.6±15.7	**0.001**
Diastolic blood pressure (mm Hg)	72.6±10.0	76.9±10.4	**0.001**
Apnea Hypopnea Index (events/h)	11 (5-50)	20 (5-88)	**0.001**
Lowest SO_2 (%)	80 (0-97)	78 (0-93)	0.318
Time SO_2 <90 (min)	15 (0-96)	21 (0-96)	0.078
Total sleep time (min)	376.0±53.2	376.8±55.7	0.894
Obstructive sleep apnea, n (%)			
Mild	77 (59.2)	60 (32.6)	
Moderate	36 (27.7)	61 (33.2)	**0.001**
Severe	17 (13.1)	63 (34.2)	

MetS: metabolic syndrome, continuous variables distributed normally summarized with mean±standard deviation while median (minimum-maximum) were used for variables distributed not normally

Table 2. Aortic arch calcification grades in groups, n (%)

	Non-MetS (n=130)	MetS (n=184)	p
Aortic arch calcification			
Grade 0	89 (68.5)	48 (26.1)	
Grade 1	25 (19.2)	72 (39.1)	**<0.001**
Grade 2	12 (9.2)	48 (26.1)	
Grade 3	4 (3.1)	16 (8.7)	
Grade ≥1	41 (31.5)	136 (73.9)	**<0.001**
Grade ≥2	16 (12.3)	64 (34.8)	**<0.001**
Grade ≥3	4 (3.1)	16 (8.7)	**0.045**

MetS: metabolic syndrome



AUC: Area under the curve, AAC: Aortic arch calcification, CI: Confidence interval

Figure 2. ROC curve analysis for AAC

Table 3. Laboratory and echocardiographic findings

	Non-MetS (n=130)	MetS (n=184)	p
Left ventricular end-diastolic diameter (mm)	47.3±4.1	48.3±4.5	0.059
Left ventricular end-systolic diameter (mm)	29.1±4.6	30.8±4.8	**0.002**
Left atrial diameter (mm)	35.8±3.1	36.9±2.9	**0.002**
Interventricular septal thickness (mm)	11.2±1.3	11.6±1.4	**0.003**
Posterior wall thickness (mm)	10.4±0.9	10.8±1.0	**0.001**
E (cm/sec)	40-127 (70)	43-135 (70)	0.808
A (cm/sec)	32-115 (75)	38-136 (76)	0.619
E/A	0.6-1.9 (0.9)	0.5-2.2 (0.9)	0.693
Glucose (mg/dL)	65-283 (95.5)	58-422 (104)	**0.001**
Urea (mg/dl)	12.7-96 (29.2)	13-80 (32)	**0.048**
Creatinine (mg/dL)	0.8±0.2	0.9±0.2	0.054
Total cholesterol (mg/dL)	193.5±38.7	199.8±40.2	0.169
Triglyceride (mg/dL)	40-447 (129.5)	63-511 (188)	**0.001**
High-density lipoprotein (mg/dL)	42.9±7.7	38.6±7.7	**0.001**
Low-density lipoprotein (mg/dL)	120.1±33.5	117.7±34.2	0.528
Gama-glutamyl transferase, (U/L)	7-160 (25)	7-395 (25)	0.831
Uric acid, (mg/dL)	5.6±1.6	6.1±1.6	**0.004**
C-reactive protein, (mg/L)	0-22.7 (2.7)	0-21 (3.5)	**0.046**
Body surface area (m^2)	2.0±0.2	2.1±0.2	**0.001**
Left ventricular mass index (gr/m^2)	92.7±20.2	95.2±20.1	0.289
Left ventricular ejection fraction (%)	63.2±7.2	60.2±8.0	**0.001**
Glomerular filtration rate ($mL/min/1.73m^2$)	99.0±11.4	95.5±10.9	**0.005**

MetS: metabolic syndrome, continuous variables distributed normally summarized with mean±standard deviation while median (minimum-maximum) were used for variables distributed not normally

Table 4. Logistic regression analysis for metabolic syndrome

	OR	95% CI	p
Body mass index	1.148	1.089 - 1.210	**0.001**
Aortic arch calcification ≥1	4.986	2.887 - 8.610	**0.001**
Apnea Hypopnea Index	1.039	1.016 - 1.062	**0.001**

OR: Odds ratio, CI: Confidence Interval

MetS is frequently seen in patients with OSA. Parish et al. (17) reported a 60% prevalence of MetS in patients with OSA; in accordance with this, we found it to be 58.6% in the present study. Insulin resistance forms the basis of MetS and is known to accelerate vascular calcification (5). In addition, the individual components of MetS including hypertension, diabetes, hyperlipidemia, and obesity have also been associated with vascular calcification (28,29). Therefore, it is highly likely that the deleterious effect of vascular calcification on the cardiovascular system is a result of the synergistic action of the illnesses constituting MetS. An association has been demonstrated between MetS and calcification in the mammary gland (30), coronary arteries (31), and thoracic arteries (32). In addition to further strengthening the known association between vascular calcification and MetS, the results of the present study are also the first to show an association between MetS and vascular calcification in patients with OSA.

Another important finding of the present study is that BMI and apnea/hypopnea index were found to be other independent predictors of MetS. Based on these results, we hypothesize that in addition to obesity, OSA is an important risk factor for MetS. Consistent with our results, Alam et al. have reported obesity as one of the most important risk factors for both OSA and MetS, acting via induction of inflammatory pathways (33). Further, the close link between MetS and apnea/hypopnea index shows that the prevalence of MetS increases with the severity of OSA. Consistent with our results, Parish et al. (17) have shown a close relationship between MetS and AHI.

CONCLUSION

Obstructive sleep apnea is frequently accompanied by metabolic syndrome. Detection of MetS is an essential part of treatment. AAC seen in chest radiography is strongly associated with MetS in patients with OSA. AAC may be an alerting finding for clinicians regarding the development of MetS in patients with OSA.

Limitations

This study has several limitations. First, it was a single-center study and had a relatively low number of patients. Second, only OSA patients were included. Thus, our results cannot be generalized for all cases. Third, we did not study possible mechanistic link between MetS and AAC. Fourth, AAC grading was performed with visual observation of chest x-ray which may reduce its

reproducibility. Finally, we did not study prognostic significance of the AAC for MetS in patients with OSA.

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Disclosure of Interest
The authors report no conflicts of interest exist.

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Alteration of Inspiratory Muscle Strength is Related to Change in Deep Breathing Heart Rate Variability in Patients Submitted to Open-Heart Surgery

Açık Kalp Ameliyatı Geçiren Hastalarda İnspiratuar Kas Gücündeki Değişimin Derin Solunum Kalp Hızı Değişkenliğindeki Değişim ile İlişkisi

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ABSTRACT

Aim: Despite the reduction of respiratory muscle strength and cardiac autonomic modulation after open-heart surgery has been demonstrated, the association between changes in both variables has not been investigated. This study aimed to determine the correlation between change in inspiratory muscle strength and change in deep breathing heart rate variability in patients submitted to open-heart surgery.
Material and Methods: An observational cross-sectional study was conducted among 32 participants aged between 35 and 60 years who were undergoing coronary artery bypass graft and cardiac valve surgery. Inspiratory muscle strength was assessed by measuring maximal inspiratory pressure using a respiratory pressure meter (RPM 01, Micro Medical Ltd., United Kingdom). Deep breathing heart rate variability was collected using a Polar heart rate monitor (Polar Electro Ltd., Finland) during a slow and deep breathing control. Evaluations were performed on the day of admission and discharge.
Results: There was statistically significant reduction in maximal inspiratory pressure and deep breathing heart rate variability indices in discharge period ($p<0.05$). The difference of expiratory/inspiratory ratio and inspiratory-expiratory differences was significantly correlated with the change in maximal inspiratory pressure in both absolute ($r=-0.864$, $p=0.003$ and $r=-0.841$, $p=0.004$, respectively) and percentages of predicted values ($r=-0.868$, $p=0.003$ and $r=-0.834$, $p=0.005$, respectively).
Conclusion: Inspiratory muscle weakness was related to impair cardiac vagal modulation in patients who had undergone open-heart surgery. The present study could provide rehabilitation targets to improve inspiratory muscle strength and cardiac vagal tone.
Keywords: Inspiratory muscle strength; heart rate variability; open-heart surgery.

ÖZ

Amaç: Açık kalp ameliyatı sonrası solunum kas kuvvetinde ve kardiyak otonomik modülasyonda azalma olmasına rağmen, her iki değişkendeki değişimler arasındaki ilişki araştırılmamıştır. Bu çalışmada açık kalp ameliyatı geçirmiş olan hastalarda inspiratuar kas gücündeki değişim ile derin solunum kalp hızı değişkenliğindeki değişim arasındaki korelasyonun belirlenmesi amaçlandı.
Gereç ve Yöntemler: Koroner arter bypass ameliyatı ve kalp kapak ameliyatı geçiren yaşları 35 ile 60 yıl arasında olan 32 katılımcı ile gözlemsel kesitsel bir çalışma yapıldı. İnspiratuar kas gücü, solunum basıncı ölçer (RPM 01, Micro Medical Ltd., Birleşik Krallık) kullanılarak maksimum inspiratuar basıncın ölçülmesiyle değerlendirildi. Derin solunum kalp hızı değişkenliği, yavaş ve derin solunum kontrolü sırasında Polar kalp atım hızı monitörü (Polar Electro Ltd., Finlandiya) kullanılarak ölçüldü. Değerlendirmeler kabul ve taburcu günü yapıldı.
Bulgular: Taburculuk döneminde maksimum inspiratuar basınç ve derin solunum kalp hızı değişkenliği endekslerinde istatistiksel olarak anlamlı şekilde bir azalma vardı ($p<0,05$). Ekspirasyon/inspirasyon oranı farkı ve inspiratuar-ekspiratuar farkları ile maksimum inspiratuar basınçtaki hem mutlak (sırasıyla $r=-0,864$; $p=0,003$ ve $r=-0,841$; $p=0,004$) hem de öngörülen değerlerin yüzdelerinin (sırasıyla $r=-0,868$; $p=0,003$ ve $r=-0,834$; $p=0,005$) değişimi arasında istatistiksel olarak anlamlı bir korelasyon vardı.
Sonuç: İnspiratuar kas güçsüzlüğü, açık kalp ameliyatı geçiren hastalarda kardiyak vagal modülasyonun bozulmasına neden oldu. Bu çalışma inspiratuar kas gücünü ve kardiyak vagal tonusunu iyileştirmek için rehabilitasyon hedefleri sağlayabilir.
Anahtar kelimeler: İnspiratuar kas gücü; kalp hızı değişkenliği; açık kalp cerrahisi.

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INTRODUCTION

Postoperative pulmonary changes after open-heart surgery are caused by numerous factors involved in surgical manipulation, anesthetic agents, cardiopulmonary bypass, chest drain, thoracotomy pain, and immobilization (1,2). These changes are associated with the restrictive pulmonary pattern and impaired inspiratory muscle strength (IMS) that was presented by a decrease in maximal static inspiratory pressure (MIP) postoperatively (3-5).

Heart rate variability (HRV) is a non-invasive indicator used to investigate cardiac autonomic functions. Alteration of HRV reflects the imbalance of sympathovagal tone that modulates cardiac rhythm (6). Moreover, HRV measurement with deep breathing maneuver (HRVdb) was highly accepted in clinical laboratories to measure cardiovagal modulation in a wide range of disorders (7). According to previous studies, it was shown that HRV indices were reduced in patients who had undergone coronary artery bypass graft (8) and cardiac valve surgery (9).

The respiratory cycle has synchronism with cardiac rhythm, which is known as respiratory sinus arrhythmia (RSA). The heart rate was increased during inspiration due to parasympathetic withdrawal to the sinus node and reversed it during expiration (10,11). Hence, the attenuation of IMS can affect the fluctuation of cardiac vagal tone. The previous study revealed that the patients with chronic heart failure, who had inspiratory muscles weakness showed a positive correlation with the reduction of HRVdb (12).

Although the reduction of MIP and HRV after open-heart surgery have been demonstrated, the alteration of HRVdb and its association with the IMS has not been elucidated. Thus, this study aimed to investigate whether inspiratory muscle weakness would relate to the changes in cardiac autonomic functions in patients submitted to open-heart surgery.

MATERIALS AND METHODS

Study Design and Subjects

This study was designed as an observational, cross-sectional study. Thirty-two patients, including males and females who have age within 35-60 years and were undergoing open-heart surgery that was recruited from Thammasat University Hospital, Thailand. The participants who presented chronic lung diseases, chronic heart failure, sinus rhythm disorders, myocardial infarction, unstable angina, experienced previous cardiac surgery, implanted a cardiac pacemaker, uncontrolled diabetes mellitus, uncontrolled blood pressure, neurological disorders, and used mechanical ventilator more than 24 hours after surgery were excluded.

The minimum required sample size was calculated, based on the correlation coefficient between MIP and high frequency power of HRV from the previous report by Reis et al. (12). The statistical power, level of significance, and effect size were set at 90%, 5%, and 0.84, respectively. This study was approved by The Human Research Ethics Committee of Thammasat University No.3 (Feb 2, 2018; 152/2560), and all participants have signed a written informed consent.

Inspiratory Muscle Strength Assessment

IMS was obtained by measuring MIP during a maximum inspiratory effort from the residual volume using respiratory pressure meter (RPM 01, Micro Medical Ltd., United Kingdom). Participants were instructed to breathe as much effort and maintained for at least one second. Three satisfactory attempts with an acceptable by no leakage of air and met the reproducible with the variation of less than 20% were used for analysis (13). The MIP values were expressed as a percentage of predicted values according to sex and age following the equations of Neder et al. (14).

Deep Breathing Heart Rate Variability Assessment

RR intervals were recorded using a V800 Polar heart rate monitor (Polar Electro Ltd., Finland) at a sampling rate of 1000 Hz. HRVdb was recorded during deep breathing maneuver for 4 minutes in a supine position. Participants were instructed to do a deep and slow inhalation and exhalation to provide a maximal lung volume that varied from the total lung capacity to the residual volume. Each breathing cycle was performed for 10 seconds, divided into 5 seconds for inspiration and 5 seconds for expiration, which provides a maximal RSA response according to a previous report (15,16). Participants controlled their respiratory cycles via a pointer clock on the computer screen and received verbal feedback from the researcher.

HRVdb was analyzed in a linear method (time and frequency domains) by Kubios HRV software version 3.0.2 (Biosignal Analysis and Medical Imaging Group, University of Eastern Finland, Finland) following to the Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology (6).

Time domain analysis was computed from the mean of the longest RR intervals obtained during the expiratory phase divided by the mean of the shortest RR intervals obtained during the inspiratory phase (expiratory/inspiratory ratio; E/I), the difference between the mean of the highest heart rate obtained during the inspiratory phase and the mean of the lowest heart rate obtained during the expiratory phase (inspiratory-expiratory difference; ΔIE), the mean of RR intervals (MeanRR), the standard deviation of all normal RR intervals (SDNN), and the root mean square of the successive difference (RMSSD). E/I ratio and ΔIE have been indicated cardiac sympathovagal balance, MeanRR and SDNN have been indicated cardiac autonomic modulation, and RMSSD has been indicated cardiac vagal modulation, subsequently. The Fast Fourier Transform (FFT) on the time series was utilized as a frequency domain. This FFT algorithm was applied to determine power spectrum density which consisted of low frequency power (LF: 0.04-0.15 Hz) and high frequency power (HF: 0.15-0.4 Hz). Spectral components were obtained in normalized units (nu). LF power has been predominantly indicated sympathetic tone, HF power has been indicated parasympathetic tone, while LF/HF ratio has been indicated cardiac sympathovagal balance, respectively.

The MIP and HRVdb indices were always evaluated in the afternoon and controlled room temperature at 25° centigrade. Testing was conducted on the day of admission and discharge. In the post-operative period, all participants were received conventional physiotherapy intervention, which is followed the standard cardiac rehabilitation protocol of the hospital including breathing exercises, airway clearance techniques, early mobilization, exercise training, and ambulation training (17).

Statistical Analysis

Shapiro-Wilk test was used to determine data distribution. Paired t-test and Pearson's correlation were used for data fitting normal distribution, while Wilcoxon sign rank test and Spearman's rank correlation were used for data not consistent with a normal distribution. Using SPSS version 23 for carrying out all of analyses and level of statistical significance was defined as $p<0.05$.

RESULTS

A total of 39 participants were recruited, but seven participants were excluded because they had cardiac arrhythmias (n=2), unstable angina (n=3), and withdraw from the study (n=2). Characteristics of the participants are shown in Table 1. Comparison of IMS and HRVdb indices between admission and discharge periods are summarized in Table 2. Post-operative absolute and percentage values of MIP (p=0.013 and p=0.005, sequentially) and HRVdb indices including MeanRR (p=0.009), SDNN (p=0.016), RMSSD (p=0.025), Total power (p=0.012), and HFnu (p=0.016) were significantly lower, while LFnu (p=0.016) was significantly higher than those evaluated preoperatively. There were no significant difference between operation periods in terms of the E/I ratio (p=0.865), ΔIE (p=0.575), and LF/HF (p=0.111). Correlation between the changes (discharge-admission) of MIP and HRVdb indices are given in Table 3. The difference of E/I ratio and ΔIE was significantly correlated with the change in MIP in both absolute (r=-0.864, p=0.003 and r=-0.841, p=0.004, respectively) and % predicted values (r=-0.868, p=0.003 and r=-0.834, p=0.005, respectively). No significant correlation was found between the change of MIP and frequency domain of HRVdb.

DISCUSSION

The attenuation of MIP has indicated to inspiratory muscle weakness, which is shown as aforementioned that consistency of MIP was decreased after coronary artery bypass graft (3-5). The causes of these reductions may be

Table 1. Characteristics of the participants

Variables	Value
Age (years)	52.3±5.3
Male, n (%)	20 (62.5)
Body mass index (kg/m^2)	24.8±4.5
Left ventricular ejection fraction (%)	65.3±7.5
Diagnosis, n (%)	
Valvular heart disease	16 (50.0)
Coronary heart disease	22 (68.8)
Underlying disease, n (%)	
Hypertension	24 (75.0)
Diabetes mellitus	8 (25.0)
Dyslipidemia	18 (56.3)
Spirometrics	
Forced expiratory volume in 1 second (FEV1) (%)	88.1±10.3
Forced vital capacity (FVC) (%)	90.0±9.5
FEV1/FVC (%)	96.5±9.9
Length of hospital stay (days)	8 (7-9)

Values are presented as mean±standard deviation, median (interquartile range), or number of participants (%)

Table 2. Comparison of IMS and HRVdb indices between admission and discharge periods

	Admission	Discharge	p
Inspiratory muscle strength			
MIP (cm H_2O)	82.0±24.6	55.9±20.6	**0.013**
MIP (% predicted)	82.7±30.0	63.5±19.8	**0.005**
Time domain			
E/I ratio#	1.1 (1.0-1.3)	1.1 (1.0-1.6)	0.865
ΔIE (bpm)#	8.0 (1.6-20.6)	7.0 (2.8-34.3)	0.575
MeanRR (ms)	776.2±105.8	640.6±34.3	**0.009**
SDNN (ms)	18.9±10.7	10.7±7.1	**0.016**
RMSSD (ms)#	16.3 (2.7-27.7)	5.7 (2.5-21.4)	**0.025**
Frequency domain			
Total power (ms^2)#	584.7 (121.2-1143.2)	179.5 (104.2-864.7)	**0.012**
LFnu	26.1±13.3	53.6±23.1	**0.016**
HFnu	73.9±13.3	46.4±23.1	**0.016**
LF/HF	0.4±0.1	1.7±0.7	0.111

Data analyzed by Paired t-test or #Wilcoxon signed rank test, Values are presented as mean±standard deviation or median (interquartile range), IMS: inspiratory muscle strength, HRVdb: heart rate variability measurement with deep breathing maneuver, MIP: maximal inspiratory pressure, E/I ratio: expiratory/inspiratory ratio, ΔIE: inspiratory-expiratory differences, MeanRR: mean of R to R intervals for normal beats, SDNN: standard deviation of all R to R intervals, RMSSD: square root of the mean of the sum of the squares of differences between adjacent R to R intervals, LFnu: low frequency power in normalized units, HFnu: high frequency power in normalized units, LF/HF: the ratio between low and high frequency power.

Table 3. Correlation between change in MIP and change in HRVdb indices

	ΔMIP		ΔMIP (% predicted)	
	r	p	r	p
Time domain				
ΔE/I ratio	-0.864	**0.003**	-0.868	**0.003**
ΔIE difference (bpm)	-0.841	**0.004**	-0.834	**0.005**
ΔMeanRR (ms)	0.034	0.468	0.061	0.443
ΔSDNN (ms)	-0.255	0.271	-0.355	0.194
ΔRMSSD (ms)	-0.169	0.345	-0.146	0.356
Frequency domain				
ΔTotal power (ms^2)	-0.466	0.122	-0.429	0.145
ΔLFnu	-0.294	0.240	-0.263	0.264
ΔHFnu	0.294	0.240	0.263	0.264
ΔLF/HF#	0.190	0.326	0.262	0.265

Data analyzed by Pearson's correlation or #Spearman's rank correlation, MIP: maximal inspiratory pressure, HRVdb: heart rate variability measurement with deep breathing maneuver, ΔMIP: delta change of maximal inspiratory pressure, ΔE/I ratio: delta change of expiratory/inspiratory ratio, ΔIE differences: delta change of inspiratory-expiratory differences, ΔmeanRR: delta change of mean of R to R intervals for normal beats, ΔSDNN: delta change of standard deviation of all R to R intervals, ΔRMSSD: delta change of square root of the mean of the sum of the squares of differences between adjacent R to R intervals, ΔLFnu: delta change of low frequency power in normalized units, ΔHFnu: delta change of high frequency power in normalized units, ΔLF/HF: delta change of the ratio between low and high frequency power.

related to surgical manipulation, degree of sedation, cardioplegic agents, thermal damage, and cardiopulmonary bypass used that lead to change in pulmonary mechanics and respiratory compliance (3,18-21). Also, post-operative pain may cause of immobilizing and restrictive pulmonary pattern (22). However, the pain scales in this study showed no difference between admission and discharge periods. Thus, postoperative pain may not effect on the efficacy of MIP assessments.

The alteration of cardiac autonomic function that was obtained during deep breathing maneuver was provided with the abnormal activity of cardiac vagal tone (7). In this study, the participants who had undergone open-heart surgery were showed a reduction in parasympathetic regulation, cooperating with more increased sympathetic activity on the day of discharge. Therefore, the results of this study demonstrated the resemblance to the previous research that has substantiated in coronary artery bypass graft (8) and cardiac valve surgery patients (9), even if they used the different methods of HRV measurement.

The RSA is modulated by the interaction between the respiratory and cardiovascular functions (10,11). Hence, the alterations of breathing frequency and tidal volume can effect on this relation. In this study, as the respiratory rate was controlled during deep breathing manoeuver, therefore, the decrease of HRVdb values may be reflected from the reduction of tidal volume, which was possibly resulted from the decrease in inspiratory muscle strength and pulmonary compliance after surgery that was described above.

This study demonstrated the correlation between the reduction of MIP and HRVdb indices that are consistent with the previous report (12). This relation is probably occurred due to the post-operative pulmonary dysfunction that was represented by a restrictive pulmonary pattern. Assuming that inspiratory muscle weakness leads to rapid and shallow breathing with can be limited to the normal incursion of the inspiratory muscles. Thus, the firing rate of the sinus node was more inhibited in cardiac vagal tone, caused by early and extensive provoked of a pulmonary stretch receptor at peak inflation of each respiratory cycle (23,24).

Although the present study had limitation slightly that is the tidal volume, as well as the end tidal of carbon dioxide, were not measured and controlled during the deep breathing protocol, we instructed the participants to breathe as deep and slow as they can also with monitored pulse oxygen saturation. Furthermore, the participants also received beta-blockers, which could generate an impact on HRV data; however, this study intended to investigate real-life situations.

CONCLUSION

This study revealed that inspiratory muscle weakness was related to impair cardiac vagal modulation in patients who had undergone open-heart surgery. This finding could provide rehabilitation targets to improve inspiratory muscle strength and restore heart rate variability.

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The Effects of Pyridoxine on Retinal Nerve Fiber Layer in Tuberculous Treatment

Piridoksinin Tüberküloz Tedavisinde Retina Sinir Lifi Tabakası Üzerindeki Etkileri

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ABSTRACT

Aim: Ethambutol and isoniazid, two of the main drugs used in the treatment of tuberculosis, can lead to optic neuropathy. Optical coherence tomography (OCT) is a non-invasive, repeatable, high resolution imaging technique used in the diagnosis and follow-up of optic nerve diseases. The purpose of this study was to investigate the effect of pyridoxine added to antituberculous therapy on retinal nerve fiber layer (RNFL) thickness and the effectiveness of OCT in the early diagnosis and monitoring of optic neuropathy.
Material and Methods: Twenty four patients diagnosed with pulmonary or non-pulmonary tuberculosis were included in the study. Patients divided into two groups. One group received antituberculous therapy alone, and the other group received 50 mg pyridoxine in addition to antituberculous therapy. RNFL thickness in both eyes was measured using OCT before treatment and 2-month after treatment.
Results: The change in the second month of treatment according to baseline in terms of average RNFL thicknesses in the right eyes, showed a statistically significant difference between the groups using and not using pyridoxine (p=0,038). However, there was no significant difference in the left eyes in terms of RNFL thickness in any of the quadrants between the groups.
Conclusion: Despite a decrease in RNFL thickness in patients receiving antituberculous therapy alone, no change in RNFL thickness occurred in patients receiving pyridoxine in addition to antituberculous therapy. We think that early ototoxicity can be detected with RNFL thickness measurement using OCT in asymptomatic patients and that the addition of pyridoxine to antituberculous therapy prevents ototoxicity.
Keywords: Isoniazid; optical coherence tomography; retinal nerve fiber layer thickness.

ÖZ

Amaç: Tüberküloz tedavisinde kullanılan başlıca ilaçlardan ikisi olan etambutol ve izoniazid, optik nöropatiye yol açabilir. Optikal kohorens tomografi (OCT), optik sinir hastalıklarının tanı ve takibinde kullanılan noninvaziv, tekrarlanabilir, yüksek çözünürlüklü bir görüntüleme yöntemidir. Bu çalışmanın amacı, antitüberküloz tedavi ile birlikte verilen piridoksinin, retinal sinir lifi tabakası (RNFL) kalınlığı üzerindeki etkisini ve OCT'nin, optik nöropatinin erken tanı ve takibindeki etkinliğini araştırmaktır.
Gereç ve Yöntemler: Çalışmaya pulmoner veya pulmoner olmayan tüberküloz tanısı alan yirmi dört hasta dahil edildi. Hastalar iki gruba ayrıldı. Bir gruba sadece antitüberküloz tedavi uygulandı, diğer gruba ise antitüberküloz tedaviye ek olarak 50 mg piridoksin verildi. Her iki gözde de RNFL kalınlığı tedaviye başlamadan önce ve tedaviye başladıktan 2 ay sonra OCT cihazı kullanılarak ölçüldü.
Bulgular: Sağ gözlerde ortalama RNFL kalınlıkları bakımından başlangıca göre tedavinin 2. ayındaki değişim, piridoksin kullanan ve kullanmayan gruplar arasında istatistiksel olarak anlamlı bir farklılık göstermekteydi (p=0.038). Bununla birlikte, olguların sol gözlerinde ise gruplar arasında hiçbir kadranda RNFL kalınlıkları açısından anlamlı bir farklılık bulunmadı.
Sonuç: Sadece antitüberküloz tedavi alan hastalarda RNFL kalınlığında bir azalma olmasına rağmen, antitüberküloz tedaviye ek olarak piridoksin de alan hastalarda RNFL kalınlığında herhangi bir değişiklik olmadı. Asemptomatik hastalarda OCT cihazı kullanılarak yapılan RNFL kalınlık ölçümü ile erken ototoksisitenin saptanabileceğini ve antitüberküloz tedaviye piridoksin eklenmesinin ototoksisiteyi önlediğini düşünüyoruz.
Anahtar kelimeler: İzoniazid; optikal koherens tomografi; retina sinir lifi tabakası kalınlığı.

INTRODUCTION

Although the cause of tuberculosis is known, and despite the fact it is possible to treat and protect against the condition, it remains one of the most fatal diseases worldwide (1). It progresses with multisystemic involvement, and most commonly affects the lungs. It is mainly seen in developing countries. The most important feature distinguishing the treatment of tuberculosis from other infections is long-term multidrug use. Drug side-effects are therefore an important problem. The antituberculous drug isoniazid causes several neuropsychiatric side-effects, such as hallucination, convulsion, transient diplopia, peripheral neuropathy, aggression, memory loss, anxiety and depression (2). Although isoniazid-induced optic neuritis is not common, it can lead to optic neuropathy in adults (3,4). It is difficult to exactly determine the optic nerve toxicity that can emerge during antituberculous therapy including isoniazid, and the incidence thereof, due to the variation in symptoms and the different approaches adopted by clinicians. In addition, malnutrition, alcohol use and existing brain diseases all increase the neurotoxic effect (5). Although the physiopathological basis of isoniazid is still not completely certain, the probable mechanism involves accumulation of isonicotonic acid hydrazide preventing metabolism of active pyridoxine through inhibition of pyridoxine-dependent enzyme systems (6-8). Optic coherence tomography (OCT) is a non-invasive, repeatable, high resolution imaging technique used in the diagnosis and monitoring of glaucoma and various retinal diseases (9). Retinal nerve fibers (RNF) in the internal part of the retina consist of ganglion cell axons. These fibers transmit impulses from photoreceptors to the central visual cortex through the optic nerve. Axonal injury is characterized by thinning of the retinal nerve fiber layer (RNFL). Decreased visual acuity may result from RNFL thinning. Several neurodegenerative (10,11) and some metabolic diseases (12,13) affect RNFL thickness.

Very few studies have used RNFL thickness measurement with OCT in the diagnosis and monitoring of optic neuropathy and the preventive effect of pyridoxine against optic neuropathy in patients receiving antituberculous therapy. The purpose of this study was to investigate the effect of pyridoxine administered together with antituberculous treatment on RNFL thickness and the effectiveness of OCT in the early diagnosis and monitoring of optic neuropathy.

MATERIAL AND METHODS

This study was performed at Recep Tayyip Erdoğan University Medical Faculty Chest Diseases and Eye Diseases clinics, Turkey. The study protocol followed the guidelines of the Declaration of Helsinki. Recep Tayyip Erdoğan University Clinical Researches Ethics Committee approval (07.10.2016 and 2016-65) and signed informed consent forms from patients were obtained before the study began. Thirty patients diagnosed with pulmonary or non-pulmonary tuberculosis between January 2014 and December 2016 were included. Before starting on antituberculous therapy, patients received corrected visual acuity examination, standard ophthalmological examination, fundoscopy and visual field examination at the Eye Diseases Clinic. Two patients meeting exclusion criteria were excluded. Fifty milligrams pyridoxine was administered to half of the remaining 28 patients, but not the other half. Four patients receiving pyridoxine were excluded due to not using the drug regularly over a 2-month period. The study was completed with 24 patients, 10 subjects receiving pyridoxine and 14 not receiving it. RNFL thickness of 48 eyes of these 24 patients was measured using an OCT device before treatment. Patients were started on antituberculous therapy consisting of isoniazid 5 mg/kg, rifampicin 10 mg/kg, ethambutol 15 mg/kg and pyrazinamide 25 mg/kg. When treatment was completed after 2 months, RNFL thickness measurements were repeated. Ethambutol and pyrazinamide were discontinued after 2 months' treatment. Isoniazid and rifampicin therapy was completed in 6 months.

Exclusion Criteria

Patients with diseases affecting RNFL thickness, such as diabetes mellitus, obstructive sleep apnea syndrome, multiple sclerosis and Parkinson's, with high myopia (<-6 diopters) or hypermetropia (>6 diopters), with a history of intraocular surgery, glaucoma, uveitis or ocular trauma or with intraocular pressure exceeding 21 mmHg in both eyes were excluded from the study.

RNFL Thickness Measurement

RNFL thickness was measured using a Cirrus HD spectral domain OCT (Carl Zeiss Meditec, Dublin, CA) device. Measurement was performed in the superior, inferior, nasal and temporal quadrants in the peripapillary region. Mean RNFL thickness was also determined.

Statistical Analysis

Statistical analyses were performed with IBM-SPSS (SPSS version 22; SPSS Inc., Chicago, IL, USA) software. Normality assumption of variables were determined using the Shapiro-Wilk test. Continuous variables were expressed as mean±standard deviation and categorical variables as frequency and percentage. The analysis of variance with repeated measures was used to compare pre and post-treatment RNFL thicknesses in patients receiving treatment with and without pyridoxine. A p value of <0.05 was regarded as statistically significant.

RESULTS

Twenty-four patients with tuberculosis, 6 (25.0%) female and 18 (75.0%) male, were included in the study. Patients' mean age was 37.8±14.2 years. Mean age was 34.4±12.2 and 40.3±15.4 in groups using and not using pyridoxine, respectively. There was no statistically significant difference between the two groups in terms of age ($p=0.327$). Ten (41.7%) of the 24 patients were using pyridoxine together with antituberculous therapy. The remaining 14 (58.3%) patients received antituberculous therapy only. In terms of smoking status, 13 (54.2%) patients were still smoking, 3 (12.5%) had quit and 8 (33.3%) had never smoked. Six (25.0%) patients used alcohol regularly. All these were male, and all consisted of patients who were still smoking. Additional diseases were present in three patients. Four patients were receiving treatment for psychiatric disorders, while hypertension was present in two. Based on the site of involvement, pulmonary tuberculosis was present in 19 patients, pleural tuberculosis in three and tuberculous lymphadenitis in two. Patients' demographic characteristics are shown in Table 1.

RNFL thickness was measured using OCT, before and at the end of the second month of treatment, in 48 eyes of the 24 patients enrolled, 10 using pyridoxine and 14 not using pyridoxine. The change at the second month of treatment according to baseline in terms of average RNFL thicknesses in the right eyes, showed a statistically significant difference between the groups using and not using pyridoxine (p=0.038). The change amount at the second month of treatment according to baseline in terms of average RNFL thicknesses in the group not using pyridoxine was higher than the pyridoxine group (Figure 1). No significant change in other quadrant RNFL thickness in the right eye was determined between the groups with and without receiving pyridoxine, at the second month of treatment according to baseline (Table 2). However, no statistical significance occurred in the second month of treatment according to baseline in left eyes in terms of average or superior, nasal, inferior or temporal quadrant RNFL thickness between the groups using pyridoxine and not using pyridoxine (Table 3).

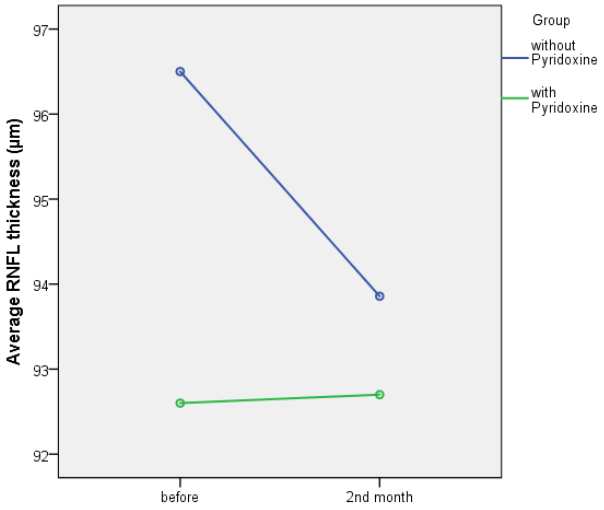
DISCUSSION

Various researchers have long emphasized that induced polyneuropathy and optic neuropathy occur immediately following the use of isoniazid in the treatment of tuberculosis. The incidence of this induced polyneuropathy has been shown to be closely associated with isoniazid dosage. Biehl et al. (6,14) reported that neuropathy developed in 44.0% of patients receiving high-dose isoniazid and in 2.0% of those receiving low doses. In addition to the dose of isoniazid, factors such as patients' nutritional status and the rate of acetylation also increase the risk of neuropathy (15-18). With the effect of all these factors, an increased blood concentration of isoniazid raises the drug's side-effect potential (7,19-21).

Optic neuropathy occurs as RNFL thickness decreases as a result of several neurodegenerative and metabolic-toxic diseases. Although isoniazid-induced optic neuritis is generally seen in adults, it may very rarely also be seen in childhood (3,4,22-29). Optic neuropathy developing in tuberculous patients receiving isoniazid therapy is reported to take place together with a decrease in pyridoxal phosphate synthesis which depletes neurotransmitter flow (3). There are studies showing that the need for pyridoxine supplementation in tuberculous patients receiving isoniazid therapy, as in the present study, in order to prevent this (22).

Table 1. Patient characteristics

Age (years), mean±standard deviation	37.8±14.2
Sex, n (%)	
Female	6 (25.0%)
Male	18 (75.0%)
Smoking status, n (%)	
Still smoking	13 (54.2%)
Quit	3 (12.5%)
Never smoked	8 (33.3%)
Alcohol use, n (%)	6 (25.0%)
Site of involvement	
Lungs	19 (79.1%)
Pleura	3 (12.5%)
Lymphadenitis	2 (8.3%)
Comorbidities, n (%)	
Hypertension	2 (8.3%)
Psychiatric disease	4 (16.6%)



RNFL: Retinal Nerve Fiber Layer

Figure 1. Average RNFL thickness in the right eye before and 2nd month of the treatment

Table 2. Comparison of RNFL thicknesses (µm) in the right eye before and 2nd month of the treatment

		Without Pyridoxine (n=14)	With Pyridoxine (n=10)	p
Superior	Before	123.07±14.05	111.70±17.24	0.059
	After	115.71±12.14	110.20±15.10	
Inferior	Before	120.71±15.68	119.80±11.39	0.247
	After	116.71±15.07	119.30±11.06	
Nazal	Before	75.21±10.23	75.10±12.06	0.588
	After	76.64±11.42	78.00±13.71	
Temporal	Before	66.93±6.87	63.60±5.54	0.353
	After	63.64±8.98	62.80±5.01	
Average	Before	96.50±7.59	92.60±9.06	**0.038**
	After	93.86±7.30	92.70±8.43	

RNFL: Retinal Nerve Fiber Layer

Table 3. Comparison of RNFL thicknesses (µm) in the left eye before and 2nd month of the treatment

		Without Pyridoxine (n=14)	With Pyridoxine (n=10)	p
Superior	Before	122.86±11.30	121.80±17.81	0.407
	After	118.93±11.77	112.50±30.37	
Inferior	Before	118.64±9.95	120.50±10.22	0.082
	After	111.21±15.23	121.00±11.41	
Nazal	Before	74.21±10.75	72.80±9.45	0.614
	After	70.71±11.09	71.00±15.28	
Temporal	Before	63.50±8.23	61.20±8.11	0.527
	After	63.29±7.98	62.70±6.91	
Average	Before	95.50±6.95	93.60±7.89	0.671
	After	92.00±7.50	91.00±12.27	

RNFL: Retinal Nerve Fiber Layer

However, many physicians do not give patients a pyridoxine combination, due to the idea that neuropathy is rare at standard isoniazid doses, cost and effect analysis and that there may be a decrease in the antibacterial effect of isoniazid.

Carlson et al. (30) and Ross RR. (31) showed that the administration of pyridoxine together with isoniazid can prevent this neuropathy. Low-dose pyridoxine has been shown to prevent neuropathy complications without obstructing antibacterial activity (32).

Kulkarni et al. (33) reported that following the development of bilateral optic neuritis during antituberculous therapy including isoniazid due to tuberculous meningitis, the symptoms and findings of optic neuritis resolved entirely when isoniazid was discontinued and pyridoxine support given. Those authors also suggested that pyridoxine combination therapy in patients with tuberculosis receiving isoniazid should be reviewed in favor of such administration and that it is vitally important for such cases to be reported through active pharmacovigilance programs and medical journals.

No reliable data are available that can fully determine the effect of individual metabolic enzyme levels and pyridoxine requirement for the evaluation of early diagnosis and monitoring and response to treatment of optic neuropathy that may develop in patients receiving isoniazid therapy. Visual symptoms during optic neuropathy may develop after the 10th day of tuberculous therapy or after 3 months (3,4,34). Vision loss, impaired color vision and scotomas at perimetric examination may occur (3,4). Normal findings are generally present in the early period in addition to pathological changes at fundoscopic and perimetric examination (3). It is difficult to detect these symptoms and findings in the early period, and assessment is more subjective. It is not possible to predict toxicity, and toxicity may also be overlooked since a significant proportion of patients are not symptomatic. RNFL thinning may be detected as an indication of early toxicity more fundus changes become pronounced.

Isoniazid used in tuberculous therapy is known to cause optic neuropathy, but the number of studies objectively revealing its effect on RNFL thickness is limited. RNFL measurement, an objective and quantitative method, can identify optic nerve toxicity in the early period in patients receiving tuberculous therapy, and potential permanent complications can thus be prevented. Kim et al. (35) assessed RNFL thickness using OCT in five patients developing visual impairment in association with tuberculous therapy. Although that research involved a low number of patients, it is one of the rare studies to show the effect on RNFL thickness of drugs used in tuberculous therapy. Chai et al. (36) reported a decrease in RNFL thickness in eight patients with ETB-related optic neuropathy. In our study, we observed thinning in the RNFL in the superior and inferior quadrants of the 14 patients not given pyridoxine. Some previous studies have measured RNFL have shown that optic nerve damage commences in the superior and inferior quadrants, particularly in glaucomatous optic neuropathy. However, there are no fully agreed studies concerning which quadrants are most affected by toxicity. Although some studies have reported that the temporal quadrant is affected, we think that this finding may be a late-stage symptom of papillomacular bundle fiber involvement. The common features of the two studies cited above are that RNFL thickness was evaluated after development of toxicity and their low patient numbers. Apart from these two studies, we encountered no other publications in the literature monitoring RNFL thickness using OCT in optic neuropathy developing in association with antituberculous drugs.

Our measurement of RNFL thickness using OCT before and 2 months after treatment in tuberculous patients receiving isoniazid therapy between with and without receiving pyridoxine groups showed a significant difference in average RNFL thickness in the right eye. We evaluated RNFL decreases in the group not receiving pyridoxine as a finding of early toxic optic neuropathy (Figure 1). We interpreted this as a potential effect of isoniazid on the optic nerve in association with pyridoxine metabolism. Consequently, we considered this difference between groups as a reflection of the positive effect of pyridoxine on RNFL thickness.

Genotypic screening is not routinely used because screening of Nat-2 levels before isoniazid therapy does not always show toxicity, and due to the restricted availability of genetic analysis in developing countries and high costs (37). However, we think that monitoring RNFL using OCT will be very advantageous in clinical practice, both because of its easy and rapid application at all levels and to its low cost, in the early diagnosis of optic neuropathy associated with toxicity that may develop in tuberculous patients receiving isoniazid and in follow-up after treatment with pyridoxine. For that purpose isoniazid combined with pyridoxine support must be provided in tuberculous patients with regular toxicity monitoring with RNFL measurements, and that isoniazid must be stopped in patients in whom thinning in the RNFL is observed despite this.

We recommend frequent and close follow-up with OCT of patients with decreased RNFL thickness. OCT is a good, non-invasive imaging technique capable of assessing retinal microstructure with high sensitivity. It must be used in the early diagnosis and monitoring of potential optic neuropathy associated with tuberculous therapy.

CONCLUSION

In conclusion, although isoniazid-related optic neuritis exhibits severe progression accompanied by pronounced symptoms and findings, we recommend RNFL measurement with OCT for the detection of optic neuropathy that may develop at the subclinical level. While isoniazid should be stopped in the event of a marked optic neuritis attack, we think that optic neuropathy involving latent symptoms and findings at the subclinical level, RNFL monitoring with pyridoxine support is important in the effective administration of antituberculous therapy and in the prevention of optic nerve function disorders such as impaired contrast sensitivity and color vision that may occur in the late period in patients developing subclinical optic neuropathy.

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Conflict of Interest

The authors report no conflicts of interest exist.

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Our Results of Endovenous N-Butyl Cyanoacrylate Treatment in Varicose Veins

Variköz Venlerde Endovenöz N-Bütil Siyanoakrilat Tedavisi Sonuçlarımız

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ABSTRACT

Aim: In this study, we aimed to evaluate the results of endovenous N-Butyl Cyanoacrylate (NBCA) technique which is a non-tumescence endovenous ablation technique in patients with varicose veins.

Material and Methods: A total of symptomatic 542 patients with single or bilateral saphenofemoral failure who presented to our center between April 2014 and August 2016 were included in the study. NBCA was applied to 657 lower extremities of 542 patients, 115 of whom were bilateral. The patients had C2, C3, C4, C5, C6 venous insufficiency according to CEAP classification. Vena saphena magna (VSM) diameter was at least 5.5 mm at the knee level, at least 6 mm at the saphenofemoral junction (SFJ) level, and reflux time was 2 seconds or longer.

Results: The mean CEAP classification of 657 lower extremities was 3.1±0.6, the VSM diameter was 6.7±1.1 mm at the knee level, 8.3±2.1 mm at the SFJ, the procedure time was 15.2±2.9 minutes, and the hospital stay was 1.7±0.6 hours. At 6 months follow-up, only 7 (1.1%) partial recanalization of VSM, 1 (0.2%) deep vein thrombosis in the popliteal vein in the lower limb, and 9 (1.4%) thrombophlebitis in the distal 1/3 segment at over the knee of VSM healing with medical treatment. All of the procedures were completed without any complications.

Conclusion: Newly developing techniques rapidly replace traditional methods and increase patient comfort. NBCA; It has become an effective method among endovenous ablation therapies with its technical advantages, high success rates in early and midterm.

Keywords: Cyanoacrylates; endovenous ablation therapy; venous insufficiency; laser therapy.

ÖZ

Amaç: Bu çalışmada kliniğimizde variköz venli hastalarda non-tümesan endovenöz ablasyon tekniği olan endovenöz N-Bütil Siyanoakrilat (NBSA) tekniğinin sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Nisan 2014 ve Ağustos 2016 tarihleri arasında merkezimize başvuran tek ya da iki taraflı safenofemoral venöz yetmezliği olan, semptomatik 542 hasta çalışmaya dahil edildi. Yüz on beşi bilateral olmak üzere 542 hastanın toplam 657 alt ekstremitesine NBSA uygulandı. Hastaların CEAP sınıflamasına göre C2, C3, C4, C5, C6 venöz yetmezliği mevcuttu. Vena safena magna (VSM) çapı diz seviyesinde en az 5,5 mm, safenofemoral bileşke (SFB) düzeyinde ise en az 6 mm ve reflü süresi 2 saniye veya daha uzundu.

Bulgular: Altı yüz elli yedi alt ektremitenin ortalama CEAP sınıflandırması 3,1±0,6, VSM çapı diz seviyesinde 6,7±1,1 mm, SFB'de 8,3±2,1 mm, işlem süresi 15,2±2,9 dakika ve hastanede kalış süresi 1,7±0,6 saat idi. Altı aylık takipte sadece 7 (%1.1) VSM'de parsiyel rekanalizasyon, 1 (%0.2) alt ekstremitede popliteal vende derin ven trombozu ve 9 (%1.4) VSM'de dizüstü 1/3 distal kesiminde medikal tedavi ile düzelen tromboflebit gözlendi. Yapılan işlemlerin tamamı herhangi bir komplikasyon oluşmadan tamamlandı.

Sonuç: Yeni gelişen teknikler hızla geleneksel yöntemlerin yerini alarak hasta konforunu arttırmaktadır. NBSA; tekniğe has avantajları, erken ve orta dönemdeki yüksek başarı oranları ile endovenöz ablasyon tedavileri arasında etkin bir yöntem olarak yerini almıştır.

Anahtar kelimeler: Siyanoakrilat; endovenöz ablasyon tedavi; venöz yetmezlik; lazer terapi.

INTRODUCTION

Lower extremity chronic venous insufficiency (CVI) and varicose veins are an important disease that is very common in the society and causes serious losses in quality of life and labor force. In many studies, it has been reported that CVI is seen in 25-50% of the adult individual population (1-3). The most common symptoms of CVI are pain in the leg, fatigue, burning sensation, swelling, itching and tingling and these symptoms significantly impair the quality of life of patients. CVI may occur only as a cosmetic problem in the clinic or may cause serious complications such as venous ulcers. The rate of serious complications varies between 20-40% (3,4). The CVI is classified worldwide by the Clinical Etiologic Anatomic Pathophysiologic (CEAP) classification (Table 1). Surgical techniques have been the preferred method for the treatment of CVI over a hundred years. However, complications due to surgical treatment and anesthesia, and frequent recurrence after treatment have necessitated alternative treatment methods for surgical treatment. In a recent meta-analysis, it has been shown that endovenous treatments are effective methods with acceptable success rates in symptomatic saphenous vein insufficiency (5). In the last 20 years, there have been very serious developments in the diagnosis and treatment of CVI. The most important of these is the use of color Doppler ultrasonography (CDUS) in the diagnosis and treatment of venous insufficiency. With these advances, endovenous laser ablation (EVLA), radiofrequency ablation (RFA), foam sclerotherapy and recently endovenous treatment methods with N-butyl cyanoacrylate (NBCA) have been developed under CDUS. These methods, which are applied by CDUS with local anesthesia, have become widespread all over the world and have largely replaced surgical treatment. Because of its ease of application and pleasant results, NBCA has been popular day by day and it is a liquid embolizer that has been known for a long time, it reacts very quickly when it comes into contact with blood and it quickly causes inflammation (6,7). This effect has been frequently used in the embolic treatment of vascular malformations and intracerebral aneurysms, as well as in the treatment of gastrointestinal bleedings, mesenteric aneurysms, arteriovenous fistulas, bone cysts, and has been frequently used in the treatment of saphenous vein deficiency in recent years (8-10). In this study, we aimed to evaluate the results of endovenous NBCA technique which is a non-tumescence endovenous ablation technique in varicose vein patients in our clinic.

MATERIAL AND METHODS

A total of 542 patients with single or bilateral saphenofemoral insufficiency who presented to Karabük Medikar Hospital Cardiovascular Surgery Clinic between April 2014 and August 2016 were included in the study. The study was approved by the local Ethics Committee of Düzce University Medical Faculty (01.04.2019 - 2019/70). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients were evaluated according to the CEAP classification and the patients were examined for the presence of reflux with venous lower extremity CDUS and vena saphena magna (VSM) diameters before the operation. Patients with chronic or acute thrombophlebitis, deep venous insufficiency, severe peripheral arterial disease, history of deep venous thrombosis (DVT), immobility, systemic infection, focal venous aneurysm enlargement were excluded.

Patients with VSM diameter greater than 5.5 mm and reflux current 2 sec or longer were included in the study. VSM diameter is at least 5.5 mm at knee level, 6 mm at saphenofemoral junction (SFJ) level and 2 sec or longer reflux time; VSM isn't severely tortiose; according to the CEAP classification are in the stages C2, C3, C4, C5, C6; NBCA was applied to 657 lower extremities of 542 patients with 115 bilateral. Demographic data of the patients are given in Table 2. NBCA isn't applied to the patients who had chronic or acute thrombophlebitis, deep venous insufficiency, severe peripheral arterial disease, DVT history, immobility, systemic infection, focal venous aneurysm enlargement, and other endovenous ablation techniques were used. All patients were evaluated according to CEAP classification. Before the procedure; seven symptoms including pain, cramps, swelling, itching, feeling of fatigue, burning sensation, tingling, numbness were investigated in the patients. Elastic bandage was applied to all patients after the procedure. During the first 24 hours, the bandage was not opened and it was recommended to use mid-pressure varicose stockings for two months. The patients were discharged on the same day and the patients were offered frequent mobilization on the same day. The patients were called for polyclinic control at the first postoperative week and CDUS control at the first and sixth months. In the sixth month after the procedure, a questionnaire was applied to the patients in order to evaluate the above seven symptoms as full recovery, mild improvement, no change and increase.

Technic

The lower extremities of the patients were sterilized and covered. Because the procedure was performed under CDUS guidance, the probe was placed in a sterile camera case. Patients were hydrated by intravenous 1000 cc of 0.9% saline due to the difficulty of puncturing non-dilatable VSMs. VSM was punctured under local anesthesia under US guidance from just below the knee joint and from 1/3 proximal of cruris. A 7F vascular sheath

Table 1. Clinical Etiologic Anatomic Pathophysiologic (CEAP) Classification

C (Clinic)	E (Etiology)	A (Anatomy)	P (Pathophysiology)
C0 = Normal	Ec = Congenital	As = Superficial veins	Pr = Reflux
C1 = Spider / reticular veins	Ep = Primer	Ad = Deep veins	Po = Obstruction
C2 = Varicose veins	Es = Seconder	Ap = Perforane veins	
C3 = Edema			
C4 = Skin changes			
C5 = Healing ulcer			
C6 = Active ulcer			

was inserted into the VSM over the guidewire. The J guide wire was inserted to the SFJ through the 7F vascular sheath with CDUS guidance. After the microdelivery catheter was located 3 cm distal to the SFJ, a total of 2 cc NBCA injector was applied to each 10 cm VSM segment with 0.3 cc NBCA at 5 sec intervals. After the procedure, saphenous venous occlusion was checked with CDUS and the procedure was completed.

Statistical Analysis

The statistical evaluation of this study was performed using the statistical program SPSS v.11.5 (SPSS Inc, Chicago, IL). Descriptive statistics were given as mean±standard deviation for continuous variables and, as frequency and percentage for categorical variables.

RESULTS

In our clinic, the gender distribution of the patients who underwent endovenous NBCA treatment due to VSM deficiency were 341 female (62.9%), 201 male (37.1%) and the mean age of patients was 46.0±9.6 (Table 2). The mean CEAP classification of the 657 lower extremities was 3.1±0.6 (range, 2 to 5), the mean VSM diameter was 6.7±1.1 mm at the knee level, 8.3±2.1 mm at the SFJ, and the total procedural duration was 15.2±2.9 min (range, 7 to 34 min). The mean duration of hospital stay was 1.7±0.6 h (range, 40 min to 4h). At 6 months of follow-up of 657 lower extremities, no recanalization was observed in any VSM but only 7 (1.1%) partial recanalization was observed in the lower extremity VSM. DVT developed in 1 (0.2%) lower extremity popliteal vein. Thrombophlebitis was observed in 9 (1.4%) lower extremity, which was treated by medical treatment in the 1/3 distal part of the VSM. No allergic reaction, infection, ecchymosis and hematoma were observed in any patient. Table 3 shows the symptoms (pain, cramps, swelling, itching, feeling of fatigue, tingling, burning sensation, numbness) according to the questionnaire forms of the patients in the postoperative sixth month.

DISCUSSION

If CVI is not treated, it causes venous hypertension by progressing, resulting in complications that may cause loss of extremities with venous ulcers. Among the symptoms of CVI; Cosmetic problems, pain, itching, fatigue sensation, superficial thrombophlebitis, dermatitis and skin ulcers can be found. Endovenous ablation therapy in VSM deficiency is rapidly becoming an alternative to surgical treatment. In the treatment of endovenous ablation, there is a significant decrease in the morbidity related to surgery, complications related to anesthesia, loss of labor and hospital cost rates (11,12). When deciding on the method of treatment, cosmetic results are important for patients as well as for the treatment of symptoms. In the treatment of VSM deficiency, less invasive sclerotherapy, RFA and EVLA treatment methods are used. Endovenous ablation treatments are easier to apply and have been used more frequently than surgery because of better cosmetic results (13). Endovenous ablation therapies have been shown to be a reliable and effective method with high success rate in symptomatic VSM deficiency in many studies. No significant difference was found between EVLA and RFA technical and clinical results. It is reported that occlusion success in the saphenous vein ablated in both techniques is over 90% in the first year and 90% in the third and fifth years (14,15). Rasmussen et al. (16) performed a randomized controlled trial comparing EVLA, RFA, surgical stripping and foam sclerotherapy in 580 lower extremities in the treatment of symptomatic VSM reflux. As a result of the study, the rate of recanalization was found to be 16.3% in the first year after foam sclerotherapy, 4.8% after EVLA and surgical stripping, and 5.8% after RFA. Due to high recurrence, foam sclerotherapy is not preferred by many centers for the purpose of closing VSM. Previous studies have shown that

Table 2. Demographic data of patients undergoing NBCA

Age	46.0±9.6
Gender, n (%)	
Female	341 (62.9%)
Male	201 (37.1%)
Preoperative mean VSM diameter (mm)	
Knee level	6.7±1.1 mm
At the SFJ	8.3±2.1 mm
CEAP	3.1±0.6 (range, 2 to 5)
Total procedural duration	15.2±2.9 min (range, 7 to 34 min)
Hospitalization time	1.7±0.6 h (range, 40 min to 4 h)

Descriptive statistics were shown as number of patients and (percent) or mean±standart deviation, VSM: Vena saphena magna; CEAP: Clinical etiologic anatomic pathophysiologic, NBCA: N-Butil Ciyanoacrilat

Table 3. Evaluation of the symptoms of lower extremities after NBCA treatment sixth month

Symptoms	Before the Procedure	After the Procedure			
		Full healing	Partial healing	No change	Deterioration
Pain	657 (100)	479 (72.9)	171 (26.0)	7 (1.1)	-
Cramp	583 (88.7)	460 (78.9)	113 (19.4)	10 (1.7)	-
Swelling	614 (93.4)	492 (80.1)	121 (19.7)	1 (0.2)	-
Itching	308 (46.9)	146 (47.4)	138 (44.8)	24 (7.8)	-
Fatigue feeling	632 (96.2)	335 (53.0)	291 (46.0)	6 (0.9)	-
Numbness	571 (86.9)	253 (44.3)	318 (55.7)	-	-
Tingling	476 (72.5)	257 (54.0)	219 (46.0)	-	-
Burning sensation	438 (66.7)	225 (51.4)	212 (48.4)	1 (0.2)	-

Descriptive statistics were shown as number of patients and (percent), NBCA: N-Butil Ciyanoacrilat

RFA and EVLA may cause complications such as burns on the skin, hematoma, superficial nerve damage, as well as ecchymosis, hematoma, pain and sensory nerve damage due to tumescence anesthesia (5,17-19). In this study, we found that none of these complications seen in RFA and EVLA were seen in patients who underwent NBCA. Another important result we found is that NBCA is an effective method for the elimination of symptoms of patients. Again in a recent study comparing EVLA and NBCA, the rates of occlusion in the 12th month were 92.2% in EVLA and 95.8% in NBCA (20). In the same study, early postoperative pain, ecchymosis, thrombophlebitis, skin pigmentation and paresthesia were less common in NBCA (20). Gürkan et al. (21) reported that EVLA of great saphenous vein with a radial laser fiber by using a 1470 nm diode laser and automated pull back system is a safe and efficient treatment option. In our study, the 6-month occlusion rate was 98.9% and was consistent with the literature. As in most randomized clinical trials, endovenous treatments are as effective as surgery. In addition, cosmetically, endovenous treatments are easier to apply, hospital costs are lower than surgery because of the advantages such as lower labor force loss and less complications due to surgery and anesthesia, because they are less invasive methods than surgery. We believe that there is an advantage for patients. As a result, we think that NBCA has advantages such as lack of risk of thermal damage, no need for anesthesia and ease of application, and it will have an important place among endovenous methods in the treatment of venous insufficiency with early results.

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The Use of Tissue-Selective Ultrasonic Aspirators in the Surgical Treatment of Brain and Spinal Cord Tumors

Beyin ve Omurilik Tümörlerinin Cerrahi Tedavisinde Doku Seçici Ultrasonik Aspiratörlerin Kullanılması

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ABSTRACT

Aim: Ultrasonic surgical aspirators are surgical instruments operated with high frequency sound waves. The brain and/or spinal cord tumors can be removed safely with minimal damaging to neurovascular structures by using tissue-selective ultrasonic aspirators. Besides its benefits to the patient, by shortening the duration of operation, it may also provide cost savings in terms of hospital management. The aim of this study is to evaluate the utility and feasibility of ultrasonic aspirator in central nervous system tumors.
Material and Methods: Forty patients who apply to the Department of Neurosurgery at Duzce University Medical Faculty between March 2013 and September 2017 due to brain or spinal cord tumor and operated for a brain or spinal cord tumor were included. Ultrasonic aspirator was used during the operations, and duration of operations were recorded.
Results: The total operation time was compared between the groups that their operations performed by using ultrasonic aspirator and by not using it. The mean operation time was significantly higher in the group performed operations by using ultrasonic aspirator (253.8±87.5, 195.4±48.7, p=0.014). Whereas ultrasonic aspirator usage did not change the duration of operation in patients with glioblastoma (237.8±56.3, 235.5±31.9, p=0.689).
Conclusion: Technological instruments, that become a part of surgical treatment, are devices that ensure maximum efficiency with minimum damage. However, these devices require prior training on how to use them. Training of healthcare staff in the use of ultrasonic aspirator is very important. Further studies are needed following the training of the assistant healthcare staff in this subject.
Keywords: Brain tumor; spinal cord tumor; ultrasonic aspirator.

ÖZ

Amaç: Ultrasonik cerrahi aspiratörler yüksek frekanslı ses dalgaları ile çalışan cerrahi aletlerdir. Tümör cerrahisinde dokuya seçici ultrasonik aspiratörlerin kullanılması ile normal nöral dokuya en az zarar verecek şekilde beyin ve/veya omurilik tümörlerinin güvenle çıkartılması mümkündür. Ameliyat süresinin kısalması ve hastaya sağladığı yararların dışında hastane işletmesi açısından da maddi tasarruf sağlanmasını mümkün kılabilir. Bu çalışmanın amacı santral sinir sistemi tümörlerinde ultrasonik aspiratörün yarar ve uygulanabilirliğini değerlendirmektir.
Gereç ve Yöntemler: Mart 2013 ve Eylül 2017 tarihleri arasında beyin veya omurilik tümörü nedeniyle Düzce Üniversitesi Tıp Fakültesi, Beyin ve Sinir Cerrahisi Anabilim Dalına başvuran, beyin veya omurilik tümörü nedeniyle ameliyatı yapılan 40 hasta çalışmaya alınmıştır. Ameliyat sırasında ultrasonik aspiratör kullanılmış ve ameliyat süreleri kaydedilmiştir.
Bulgular: Ameliyatları ultrasonik aspiratör kullanılarak yapılan grup ile ultrasonik aspiratör kullanmadan yapılan gruplar arasında toplam operasyon süresi karşılaştırılmıştır. Ultrasonik aspiratör kullanılan grupta ortalama ameliyat süresinin anlamlı düzeyde yüksek olduğu tespit edilmiştir (253,8±87,5; 195,4±48,7; p=0,014). Oysa ultrasonik aspiratör kullanımının glioblastoma tanılı hastalarda ameliyat süresini değiştirmediği tespit edilmiştir (237,8±56,3; 235,5±31,9; p=0,689).
Sonuç: Cerrahi tedavinin bir parçası haline gelen teknolojik aletler, en az hasar ile maksimum verim alınmasını sağlayan cihazlardır. Ancak bu cihazlar nasıl kullanılacakları konusunda önceden eğitim gerektirirler. Ultrasonik aspiratör kullanımında yardımcı sağlık personelinin eğitimi çok önemlidir. Bu konuda yardımcı sağlık personelinin eğitiminin ardından yapılacak daha fazla çalışmalara ihtiyaç vardır.
Anahtar kelimeler: Beyin tümörü; omurilik tümörü; ultrasonik aspiratör.

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INTRODUCTION

Ultrasonic surgical aspirators are surgical instruments operated with high frequency sound waves, with the use of sound waves which are effective on the surface they contact during the brain surgery, they can only prevent the destruction of tumor tissue, normal brain tissue and vascular structures. The vibrations created by the device divide the tumor tissues into small pieces and then absorb the pieces and completely eliminate the tumor tissue (1-4). In the surgical technique, tumoral tissue should be removed during tissue excision without damaging the surrounding normal tissues and with minimal bleeding. With the ultrasonic aspirator tissue technology, increasing the selectivity during the removal of tissues enables the maximum extraction of tumor tissue from the surgical field (1,2). The device, which provides more control to the surgeon during the dissection of sensitive tissues, provides the opportunity to choose according to tissue with its high amplitude adjustment. With this technology, which is widely used in surgery, the operation time gets shorter, blood loss during surgery and complications may decrease (5). Therefore, it allows to minimize the possible problems during and after the surgery.

In the neurosurgery practice, Cavitron Ultrasonic Surgical Aspirator (CUSA) Excel + ultrasonic aspirator device is used to protect high-strength tissues such as vein and neural tissue during the resection of low-strength tissues such as tumors (6-8).

The aim of this study is to evaluate the usefulness, usability of ultrasonic aspirator in central nervous system tumors and to evaluate whether it has made a difference in terms of patient's operation time.

MATERIAL AND METHODS

In this study, 40 patients who apply to the Department of Brain and Nerve Surgery at Duzce University Medical Faculty between March 2013 and September 2017 due to brain or spinal cord tumor and operated for a brain or spinal cord tumor were evaluated. This study was prospectively conducted and was approved by the Abant Izzet Baysal University Ethics Committee (2013/02). Patients with brain or spinal cord tumor whose consent had been taken were included in the study. Patients with advanced cardio-pulmonary insufficiency who cannot get anesthesia, inoperable brain or spinal cord tumors were excluded from the study. During the operation, care was taken not to differentiate in terms of age and sex when selecting patients with and without CUSA.

The duration of operation of the patients included in the study, whether there is a vascular pathology in and around the operation region after the operation, whether ultrasonic aspirator is used during tumor resection, whether there is a change in the duration of operation and damage to the surrounding tissue between the patients with which ultrasonic aspiration has been used and with which it has not, both being histopathologically same, are investigated. CUSA Excel + Integra tips containing Tissue Select feature and enabling to use three different types of hand applicators have been used in different diameters, lengths and geometries, depending on the type of operation.

Statistical Analysis

Normality assumption for continuous data were examined by Shapiro-Wilk test, and Independent samples t test was used to compare two study groups with and without ultrasonic aspirator for data with normal distribution, while Mann-Whitney U test was used to compare these two groups for data with non-normal distribution. Descriptive statistics were expressed as mean±standard deviation and median (minimum-maximum), where appropriate. Categorical data such as gender and Glioblastoma diagnosis were analyzed with Chi-square test and summarized as frequency and percentages. Statistical significance level was accepted as $p<0.05$, and statistical analyses were done using SPSS v.20.0 statistical package.

RESULTS

A total of 40 patients were included in the study; 23 (57.5%) were males and 17 (42.5%) were females, aging between 18 and 82 (mean 56.9±17.4). Ultrasonic aspirator was used in 20 patients and in 20 of them it was not used. The age of the patients with ultrasonic aspirator was between 18 and 57 years and the mean age was 51.7±19.6 years. The age of the patients without ultrasonic aspirator was between 33 and 82 years and the mean age was 61.1±13.4 years. There were 11 (55.0%) males and 9 (45.0%) females in the ultrasonic aspirator group; while 12 (60.0%) male and 8 (40.0%) female patients were in the ultrasonic aspirator group (Table 1). No statistically significant difference was found between the two groups in terms of age and sex (p=0.091, p=0.749 respectively). When total operation time between 20 patients with ultrasonic aspirator group and 20 patients without ultrasonic aspirator was compared, in the ultrasonic aspirator group, median operation time was 233 minutes (minimum 120, maximum 475 minutes) and the mean duration was 253.8±87.5 minutes. In the group that did not use ultrasonic aspirator, median operation time was calculated as 199 minutes (minimum 85, maximum 275 minutes) and the mean time was 195.4±48.7 minutes (Table 2). The mean operation time was significantly higher in the ultrasonic aspirator group (p=0.014).

Table 1. Age and sex in groups with and without CUSA

	CUSA (+) (n=20)	CUSA (-) (n=20)	p
Age (year)	51.7±19.6	61.1±13.4	0.091
Sex			
Male	11 (55.0%)	12 (60.0%)	0.749
Female	9 (45.0%)	8 (40.0%)	

CUSA: Cavitron Ultrasonic Surgical Aspirator

Table 2. Comparison of operation times (minutes) in groups with and without CUSA

Operation time	CUSA (+) (n=20)	CUSA (-) (n=20)	p
Mean±SD	253.8±87.5	195.4±48.7	
Median	233	199	**0.014**
(Min-Max)	(120-475)	(85-275)	

CUSA: Cavitron Ultrasonic Surgical Aspirator, SD: Standard Deviation, Min: minimum, Max: maximum

When glioblastoma was compared, 9 (%45.0) patients' pathology were glioblastoma in the ultrasonic aspirator group and 6 (%30.0) patients' pathology were glioblastoma in the group without ultrasonic aspirator. There was no statistically significant difference between two groups in terms of glioblastoma case (p=0.327). When the operation time of glioblastoma cases in ultrasonic aspirator used and unused groups was compared (Table 3), the duration of operation in the ultrasonic aspirator group was minimum 185 minutes, maximum 360 minutes, median time was 220 minutes and mean time was 237.8±56.3 minutes; in the group that did not use ultrasonic aspirator, the operation time was minimum 190 minutes, maximum 275 minutes, median time was 234 minutes and mean time was 235.5±31.9 minutes and it was found to be not statistically significant (p=0.689).

Table 3. Comparison of operation times (minutes) for glioblastoma cases in groups with and without CUSA

Operation time	CUSA (+) (n=9)	CUSA (-) (n=6)	p
Mean±SD	237.8±56.3	235.5±31.9	
Median (Min-Max)	220 (185-360)	234 (190-275)	0.689

CUSA: Cavitron Ultrasonic Surgical Aspirator, SD: Standard Deviation, Min: minimum, Max: maximum

DISCUSSION

CUSA is a device that was started to use in the 1970s. Malhotra et al. (9), one of the first research groups, investigated whether ultrasonic aspirated tissue can be used for histopathological studies and obtained accurate results in all resected tumors. Similar findings were made by Blackie and Gordon (10) who investigated tumor tissue fragments from 17 resections and were able to give the correct diagnosis for all aspirated specimens. Nowadays, it is used safely in brain tumor resection (6-8,11).

In the surgical technique, tumoral tissue should be removed during tissue excision without damaging the surrounding normal tissues and with minimal bleeding. With the ultrasonic aspirator tissue technology, increasing the selectivity during the removal of tissues enables the maximum extraction of tumor tissue from the surgical field and with this technology, the operation time gets shorter, blood loss during surgery and complications may decrease (1,2,5) Thus, it will be possible to minimize the possible problems during and after the surgery.

With the vibrations which ultrasonic aspirator created, it divides the tumor tissues into small particles, then absorb the pieces and completely eliminate the tumor tissue. In our study, it was seen that CUSA Excel + ultrasonic aspirator device can provide protection of highly resistant tissues such as vein and neural tissue during resection of low resistant tissues such as tumor.

In cases with selective ultrasonic aspirator, it was observed that tumor tissue could be removed at maximum level without damaging normal tissue and vascular tissue. However, it is fixed by surgical experiences where the tumor tissue is removed by dissection, normal brain tissue can be damaged. Some authors have reported that they provide important information about the vessels that feed the tumor especially in intracranial meningiomas and accordingly, the resection of the tumor may be better, thus it can reduce postoperative morbidity (1-5,12,13).We experienced the benefit of the ultrasonic aspirator for the protection of normal vascular structure in meningioma cases and the intraoperative monitoring of the structure of the nutrient vessels.

Technological tools that become a part of surgical treatment are the devices that provide maximum efficiency with minimum damage. However, the practical use of these devices requires a learning curve, which enables the instrument to use in what type of surgeries, how often the instrument will be used, how the instrument operates, and the correct assessment of the data provided by this technology. In our study, the duration of operation in cases with ultrasonic aspiration was found to be significantly higher than those were not used. One of the reasons for this, and perhaps the most important one, was the fact that the auxiliary health personnel did not know exactly how to install the device. The installation sequence is required before the operation of the device, and even if the staff are trained to do so, there is a need for repeated training when new assistive personnel are involved in the operation of each new case, which creates difficulties in practice. As surgeons should give full attention to surgery during surgery, during the installation, the auxiliary health personnel should be able to perform the set up and operation control sequence and in the event of any disruption they should be able to correct the problem. We believe that this period may be shortened if the continuity of the trained assistant personnel is ensured.

In conclusion, the aim of tumor surgery is to remove all of the tumoral tissue with minimal damage to the surrounding tissue, and the removal of the tumoral tissue with the use of ultrasonic aspirator, thus less bleeding, shortening the duration of anesthesia and shortening the length of hospitalization in the postoperative period reduces the total cost. Training of assisted health personnel is very important for the use of ultrasonic aspirators.

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Investigation of Tetanus Antibody Levels in Adults

Erişkinlerde Tetanoz Antikor Düzeylerinin Araştırılması

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ABSTRACT

Aim: Tetanus is an acute and lethal disease caused by exotoxins named tetanospasmin produced by *Clostridium tetani*. Despite being vaccine-preventable, tetanus is still a toxic-infectious disease with high mortality. In this cross-sectional study, it is aimed to determine levels of tetanus anti-toxin IgG and factors affecting it in adults in the region.
Material and Methods: This cross-sectional study was conducted with patients applied to the blood sampling laboratory unit of Düzce University Hospital. Tetanus anti-toxin IgG Enzyme-Linked Immuno Sorbent Assay kits (Catalog number: EI 2060-9601 G, Euroimmun, Germany) were used for detection of tetanus antibodies. Those with tetanus anti-toxin IgG >0.1 IU/ml were considered immunized. Socio-demographic information of participants were collected using a questionnaire during blood collection.
Results: Sufficient tetanus antibody was detected in 140 (39.3%) of 356 patients. Protective antibody ratios were found as 49 (70.0%) in 30-40 age group, 39 (54.9%) in 41-50 age group, 22 (31.0%) in 51-60 age group, 16 (22.2%) in 61-70 age group and 14 (19.4%) in >71 age group. Tetanus immunity ratios were significantly reduced with aging ($p<0.001$). Protective antibodies were found to be higher in the groups who had more education and who were vaccinated in adult ages for any reason than in the other groups (both $p<0.001$).
Conclusion: It was thought that the childhood immunity should be reinforced with the booster doses during adulthood by routine tetanus immunization program. In addition, the high level of tetanus immunity in those with high educational level has shown the importance of education.
Keywords: Adult vaccination; tetanus; tetanus anti-toxin IgG; tetanus vaccine.

ÖZ

Amaç: Tetanoz, *Clostridium tetani* tarafından oluşturulan tetanospazmin isimli ekzotoksinlerin neden olduğu, akut ve ölümcül bir hastalıktır. Aşılama ile önlenebilir olmasına rağmen tetanoz halen mortalitesi yüksek olan toksi-infeksiyoz bir hastalıktır. Bu kesitsel çalışmada, bölgemizdeki erişkinlerde tetanoz anti-toksin IgG seviyelerinin ve tetanoz anti-toksin IgG seviyelerini etkileyen faktörlerin saptanması amaçlanmıştır.
Gereç ve Yöntemler: Bu kesitsel çalışma, Düzce Üniversitesi Sağlık Uygulama ve Araştırma Merkezi Laboratuvarı kan alma ünitesine başvuran hastalar ile yapılmıştır. Tetanoz antikorlarının saptanmasında Tetanus anti-toksin IgG Enzyme-Linked Immuno Sorbent Assay kitleri (Katalog no: EI 2060-9601 G, Euroimmun, Almanya) kullanılmıştır. Tetanoz anti-toksin IgG ≥0,1 IU/ml olanlar bağışık kabul edilmiştir. Çalışmaya katılan kişilere ait sosyodemografik bilgiler kan alma esnasında anket yapılarak toplanmıştır.
Bulgular: Toplam 356 hastanın 140 (%39,3)'ında yeterli tetanoz antikoru saptanmıştır. Koruyucu düzeyde antikor, 30-40 yaş grubunda 49 (%70,0), 41-50 yaş grubunda 39 (%54,9), 51-60 yaş grubunda 22 (%31,0), 61-70 yaş grubunda 16 (%22,2), >71 yaş grubunda 14 (%19,4) oranlarında saptanmıştır. Tetanoza bağışıklık oranlarının yaşlanma ile birlikte belirgin biçimde azaldığı görülmüştür ($p<0,001$). Eğitim süresi fazla olanlar ve herhangi bir nedenle erişkin yaşlarında aşı yapılan gruplarda koruyucu düzeydeki antikorlar diğer gruplara göre daha yüksek oranda bulunmuştur (her iki $p<0.001$).
Sonuç: Çocukluk çağındaki bağışıklığın, yetişkinlik döneminde rutin tetanoz bağışıklık programı ile rapel dozlarla güçlendirilmesi gerektiği düşünülmüştür. Ayrıca eğitim seviyesi yüksek olanlarda tetanoz bağışıklık oranının da yüksek bulunması eğitimin önemini göstermiştir.
Anahtar kelimeler: Erişkin aşılaması; tetanoz; tetanoz anti-toksin IgG; tetanoz aşısı.

Presented as a poster at 4th National Clinical Microbiology Congress (November 8-12, 2017, Antalya).

INTRODUCTION

Despite being vaccine-preventable, tetanus is a toxic-infectious disease with high mortality, affecting neonates and young adults in developing countries and elderly in developed countries. Tetanus is an acute disease caused by tetanospasmin named exotoxins produced by *Clostridium tetani*, an anaerobic bacillus; often lethal and characterized by generalized rigidity and spasms in the musculoskeletal (1). It is estimated that the worldwide incidence of tetanus is 18 out of 100000 people, or about a million cases per year in the world (2). In developed countries, the incidence of disease has fallen to less than 2 per million thanks to the implementation of regular vaccination programs. In developing countries, tetanus is an important cause of mortality, especially in newborns, whereas in developed countries it is more common in unvaccinated or under-vaccinated adults (3). Although the incidence of both neonatal and non-neonatal tetanus in Turkey has declined over the years, it remains as an important health problem. The incidence of non-neonatal tetanus was reported to be 0.02 per a hundred thousand in 2006, while it was 0.21 per a hundred thousand in 1990. Of the 923 non-neonatal tetanus cases reported to the Ministry of Health in 1990-2006, 161 died and the ratio of fatality was 17.4%; of the 658 cases of neonatal tetanus, 305 died and the ratio of fatality was 46.4%. Between 2007 and 2015, 119 cases of adult tetanus and 19 cases of neonatal tetanus were observed (4). After tetanus vaccination in childhood, booster doses of tetanus vaccine could not usually be done, and the level of antitoxin could be lost in people over time. Since there is no current adult immunization program in Turkey, only women get vaccinated during pregnancy and men get vaccinated during military service, also, after an accident or injury people get vaccinated. This situation suggests that people, especially those with primer vaccination problems due to reasons such as incomplete vaccination, become susceptible to tetanus in older ages due to decreased levels of antibodies over time (5).

In this study, it is aimed to determine the levels of tetanus antitoxin IgG and the factors of affecting tetanus anti-toxin IgG levels in adult patients in the region.

MATERIAL AND METHODS

This study was supported by Duzce University Scientific Research Projects Department with project number 2015.04.01.301. It was done with approval of the Duzce University Ethics Committee, dated 23.12.2014 and numbered 2014/100.

Approximately 120000 patients visit the outpatient clinics of Duzce University Hospital annually. In this study, 356 people with 95% confidence level were included in the study according to the CDC epi info Stat Calc program when it was accepted that 45% of the patients who had come to the hospital for any reason and had had blood test were over 30 years of age. Patients participating in the study were classified as a total of five age groups, 30-40, 41-50, 51-60, 61-70 and >70 years old, with male and female ratios being equal in each age group. In order to obtain sociodemographic information about people who were involved in the study, a questionnaire was conducted during blood drawing. Age, sex, educational status, occupation, involvement in agriculture and livestock breeding, injury history and vaccination against tetanus were questioned. 7-8 ml of venous blood was collected to tubes without anticoagulant from the subjects who were surveyed. The serum samples obtained from these blood samples after centrifugation for 10 min at 3000 rpm were stored at -20°C until serological analysis. Tetanus anti-toxin IG ELISA (Catalog number: EI 2060-9601 G, Euroimmun, Lübeck, Germany) kits were used for detection of tetanus antibodies. Tetanus anti-toxin IgG antibody was accepted as an antibody at a protective level of ≥0.1 IU/ml (4).

Statistical Analysis

Descriptive values of categorical variables were given numbers and percentage. Categorical data were analyzed by Pearson Chi-square test and post hoc Bonferroni method. Statistical analyses were done using SPSS for Windows v.16.0 statistical package program and $p<0.05$ considered as statistical significance level.

RESULTS

A total of 356 patients aged 30 years and over, 178 women and 178 men, who came to the Duzce University Hospital laboratory between November 2014 and December 2015 were included in the study. Sixty two (34.8%) of the women and 78 (43.8%) of the men had protective level of antibodies, while 216 (60.7%) of total 356 patients were found to be susceptible to tetanus. There was no significant difference in terms of protective tetanus antibody proportions according to gender ($p=0.083$). When the protective tetanus antibody proportions were compared according to the age groups immunity decreased as the age increased ($p<0.001$). According to the post hoc test results, statistically significant decrease started from 51-60 age group continued in advancing age groups. Protective tetanus anti-toxin IgG level according to age groups was shown in Figure 1. In addition, proportions of protective tetanus anti-toxin IgG in each age groups was shown in Table 1.

When tetanus antibody levels were compared according to the patients' education time, tetanus immunity proportions were increased as the education year increased ($p<0.001$). Both 6-11 years and ≥12 years groups had higher protective proportions than ≤5 years group according to the post hoc test results. Protective tetanus anti-toxin IgG level according to education time groups was shown in Figure 2. In addition, proportions of protective tetanus anti-toxin IgG according to the education time groups was shown in Table 2.

When the occupations of patients are categorized as occupations at risk and others in terms of tetanus, 29 (33.0%) of those 88 patients with professions at risk and 111 (41.4%) of those 268 patients with other professions had antibodies at the protective level. There was no relationship between occupational groups and protective tetanus antibody proportions ($p=0.158$). When the tetanus antibody levels were examined, 31 (36.0%) of 86 farmers had protective level of antibodies, and 22 (44.0%) the 50 patients who were engaged in livestock breeding had protective level of antibodies. Fifty five (64.0%) of the people engaged in farming and 28 (56.0%) of the people engaged in livestock breeding were found to be susceptible to tetanus disease. There was no difference between farming and livestock breeding in terms of protective tetanus antibody proportions ($p=0.359$).

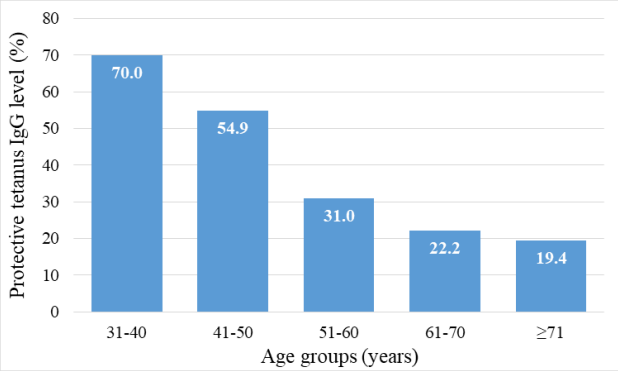

Figure 1. Protective tetanus IgG level according to age groups

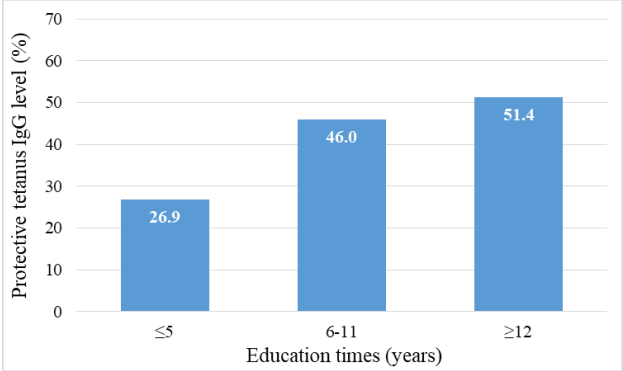

Figure 2. Protective tetanus IgG level according to education

Table 1. Protective tetanus anti-toxin IgG level according to age groups, n (%)

	31-40 (n=70)	41-50 (n=71)	51-60 (n=71)	61-70 (n=72)	≥71 (n=72)	p
<0.1 IU/ml	21 (30.0)	32 (45.1)	49 (69.0)	56 (77.8)	58 (80.6)	**<0.001**
≥0.1 IU/ml	49[a] (70.0)	39[a] (54.9)	22[b] (31.0)	16[b] (22.2)	14[b] (19.4)	

Table 2. Protective tetanus anti-toxin IgG level according to education time, n (%)

	≤5 years (n=145)	6-11 years (n=137)	≥12 years (n=74)	p
<0.1 IU/ml	106 (73.1)	74 (54.0)	36 (48.6)	**<0.001**
≥0.1 IU/ml	39[a] (26.9)	63[b] (46.0)	38[b] (51.4)	

When the history of injury of the patients was questioned, only 45 (48.9%) of the 92 patients with serious injury story had tetanus antibody at the protective level and it is remarkable that half of them still does not have tetanus immunity. In 264 patients with no history of injury, the immunity rate was 95 (36.0%), and it was found that the immunity rate was lower than the patients with history of injury (p=0.029). Proportions of protective tetanus antibody levels with tetanus vaccination status in adulthood were shown a statistically significant difference (p<0.001). Protective tetanus anti-toxin IgG level according to vaccination status was shown in Figure 3. Significantly more antibodies were detected at protective level in vaccinated people during adulthood. In addition, proportions of protective tetanus anti-toxin IgG according to vaccination status is shown in Table 3.

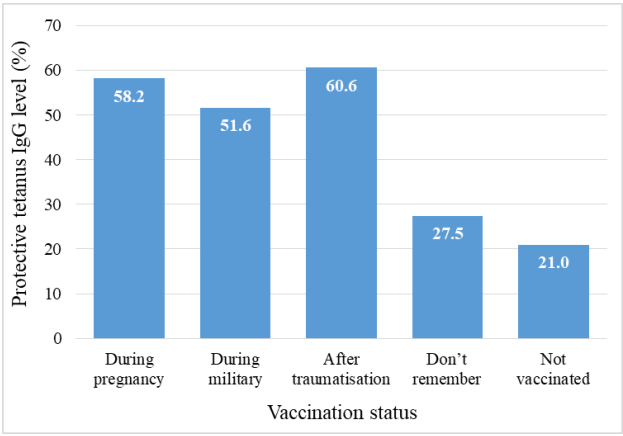

Figure 3. Protective tetanus anti-toxin IgG level according to vaccination status

Table 3. Protective tetanus anti-toxin IgG level according to vaccination status, n (%)

	During pregnancy (n=55)	During military (n=31)	After traumatisation (n=66)	Don't remember (n=142)	Not vaccinated (n=62)	p
<0.1 IU/ml	23 (41.8)	15 (48.4)	26 (39.4)	103 (72.5)	49 (79.0)	**<0.001**
≥0.1 IU/ml	32[a] (58.2)	16[ab] (51.6)	40[a] (60.6)	39[bc] (27.5)	13[c] (21.0)	

DISCUSSION

Most cases of tetanus are not immunized or insufficiently immunized people. The incidence of the disease increases with age (4). According to the current vaccination program in Turkey, primary vaccination is started as diphtheria, acellular pertussis, tetanus, inactive polio and *Haemophilus influenzae* type b vaccine in the second month of life and they administered in three doses with eight week intervals. Booster dose is administered at 18-24 months. Single dose adult tetanus and diphtheria vaccine intensification doses are given in the first and eighth grade of primary school. It is recommended to re-vaccinate every ten years for the immunity to continue (6). In Turkey, tetanus vaccination is given after injury, during pregnancy and during military service. However, this is not as regular as primer vaccination.

Tetanus is one of the vaccine-preventable diseases and vaccinations have been continuing in Turkey since 1968. Three doses are given from birth to one-year-old and booster doses are given at 18 months and 1st grade of primary school. In this way, children in the primary school age are immune to tetanus. However, adult vaccination is not a regular practice in Turkey. In this case, tetanus immunity is gradually decreasing from the age of thirty.

When evaluated in terms of age groups; in this study, when the age groups of patients and tetanus antibody levels were compared, it was observed that the immunity decreased rapidly with age. The protective antibody level was accepted as ≥0.1 IU/ml. Protective antibody levels according to age groups were found as follows: 49 (70.0%) in the 31-40 age group, 39 (54.9%) in the 41-50 age group, 22 (31.0%) in the 51-60 age group; 16 (22.2%) in the 61-70 age group and 14 (19.4%) in the ≥71 age group. Seroepidemiological field surveys were conducted in Antalya, Diyarbakır and Samsun between February 2000 and October 2001 within the scope of the "Infection Disease Control Project" in Turkey. In this study involving 2094 people over 6 months, the percentage of those in the 40-49 age group who were below the protective level were found as 26.8% in Antalya, 30.8% in Diyarbakır and 20.3% in Samsun. Susceptibility to tetanus in over 50 years of age was found to be 40.6% in Antalya, 51.4% in Diyarbakır and 67.4% in Samsun (7). When other studies in Turkey were reviewed, it was found in a study conducted by Dündar et al. (8) in Kocaeli that the tetanus susceptibility increased in the subjects at the age of 40 and over and that 5% of those under 40 years of age, 23.7% of the 40-60 age group and 34.5% of people over 60 years of age were below the protective value of tetanus antibody levels. Looking at the examples around the world, in a study conducted in Denmark with 30-70 years of age in 1984, 51% of patients were found to have antibody levels below the protective value. Looking at age groups, 20% of the 30-39 age group and 68% of the 50-69 age group were found not to be immune to tetanus (9). In a study conducted in Australia, 2884 individuals of various age groups were investigated for tetanus antibody levels, and the protection levels were reported as 91-97% in 30-39 age group, 67-76% in 50-59 age group and 42-52% over 70 age group (10). Rapisarda et al. (11) reported tetanus seropositivity in Italy as 97% in 18-27 age group, 86% in 28-37 age group, 76% in 38-47 age group, 62% in 48-57 age group, and 49% over 57 age group. Ang et al. (12) reported that the tetanus antibody levels decline with age in the seroprevalence study in Singapore.

When evaluated in terms of sex, women and men were taken on equal numbers in this study. 43.8% of males and 34.8% of females were found to have protective antibodies. Although there was no statistically significant difference for tetanus antibody levels in terms of sex, it was thought that the higher ratio of protective antibodies in men might be due to routine tetanus vaccination in military service. Similar comments were made in some studies where protection was found to be higher. Looking at the studies in Turkey, it was reported in a study conducted with people age range 3-104 years in Ankara that protective tetanus antibody levels were found in 45.2% of females and in 54.8% of males (13). There were no significant differences between males and females in terms of protectiveness in other studies conducted in Turkey (8,13-15). Looking at the examples from the world, it was found that 37% of men and 64% of women were below the protective level of antibody titers in a study conducted in a 30-70 age group in Denmark (9). In the study conducted on individuals over 20 years old in Greece's Northern Halkidiki region, it was found that 82.1% of males and 52.7% of females were immune to tetanus and this difference was not only in the 21-30 age group but antibody titers were found to be higher in males in all age group over 30 (16).

In this study, when tetanus immunity ratios were examined according to the education time, protective antibody levels were found in 39 (26.9%) of those with less than 5 years of education, in 63 (46.0%) of those with 6-11 years of education and in 38 (51.4%) of those with more than 12 years of education. It was observed that tetanus immunity increased as the years of education increases. Looking at the examples from the world, in studies conducted in the USA by Gergen et al. (17) and McQuillan et al. (18), it was found that as the level of education increased, the ratio of protective antibodies against tetanus also increased. This is thought to be due to the fact that people with higher education levels have more knowledge about the subject and are more sensitive about vaccination. When immunity is evaluated according to occupational status, despite the fact that all individuals in the community are at risk of tetanus, the risk for farmers, construction workers and industrial workers is higher. There was no statistically significant relationship between occupational groups and tetanus antibody levels in this study. In another study conducted in Turkey, protective antibody levels were found 68.0% in soldiers, 53.0% in students, 35.0% in mothers and infants and 35.0% in farmers (19). In a study by Hayney et al. (20), it was found that the percentage of having tetanus antibody titers at the protective level is higher for farmers than non-farmers. In this study, there was no significant relationship between tetanus antibody levels and farmers and livestock breeding. In a study carried out by Papilla et al. (21) in Elazığ, Turkey with 100 construction workers, 100 industrial workers, 100 farmers and 100 control donors, the protectiveness level of the control group was found 49%, 44% in construction workers, 74% in industrial workers and 31% in farmers. They were researched the levels of tetanus antitoxin in construction workers, industry workers and farmers considered as risk groups and 68% of those vaccinated in the last five years, 70% of those who passed 6-10 years after the last vaccination, and 31% of those who passed more than 10 years were detected protective antibody presence. Protectiveness ratios were detected as follows 77% at 10-19 years, 68% at 20-29 years and 29% at 30 years in the same study. Tetanus vaccination and protective level of tetanus antibodies during pregnancy, post-injury and military vaccination were found as follows respectively 32 (58.1%), 32 (48.4%) and 16 (51.6%). The ratio of detection of protective antibodies in those who did not remember about their vaccination and who said that they were not vaccinated are 29 (14.1%) and 13 (20.9%) respectively. It was observed that vaccinated people were significantly more immune. There was a statistically significant correlation between tetanus vaccination status and tetanus antibody levels. It was found that the ones with vaccine history had antibody titers at a 2-fold higher protective level than non-vaccine history. As a result, it is observed that the vaccine has a protective immunity in the 10 years period, whereas it has decreased after 10 years' time. This result shows that vaccination at least every 10 years is necessary. When examples from Turkey reviewed, Ozturk et al. (15) found the percentages of protectiveness against tetanus were 29.2% in those who were vaccinated

once, 47.6% in those who had two or more vaccines, and 16.1% in those without vaccination stories in their study in Kayseri. In Turkey, protectiveness in 100 people aged 1-78 was found as 71.1% in those vaccinated in the last five years and 2.8% of those vaccinated 10 years ago (22). Dundar et al. (8) reported in their studies conducted in adults over 20 years of age that 97.7% of women with a history of vaccination in their pregnancies and 68.5% of those without vaccination stories have protective antibody levels. Aydın et al. (23) studied 21 cases of tetanus who were followed up and treated between 1991-1995 in Karadeniz Technical University, Faculty of Medicine, Department of Infectious Diseases. In the study, when consultation to the doctor was evaluated, it was found that eight cases never consulted to a doctor and the ones who consulted to a doctor were not given immunoglobulin even though they were not immunized and only 4 cases were vaccinated. Looking at the examples around the world, it was found in a study conducted in Germany with people aged 19-90 that the protective effect is especially high in vaccinated young people but it declines rapidly with aging without booster doses (24). Hosseini Shokouh et al. (25) investigated to immunity to diphtheria and tetanus in army personnel and adult civilians in Mashhad, Iran. For both diseases, geometric mean antitoxin titers and the proportion of participants with at least basic protection were higher in subjects with a history of vaccination in the last 10 years, higher in men than women, and in army personnel than civilians in each age group. In this study, 45 (48.9%) of the 92 patients with serious injury history were found to have tetanus antibody at the protective level when the injury history of the patients was questioned. Since there are high levels of antibodies in the post-injury vaccination, it is important to use the opportunities of any injuries for vaccination for tetanus immunity as there is no routine adult immunization program.

In conclusion, completion of primary vaccinations during childhood, vaccination of women during pregnancy, post-injury vaccination protects adults against tetanus until a certain term, but this protection diminishes with age. With the prolongation of the life span, the elderly immune status will become more important, so that routine tetanus immunization program for adults will be a necessity.

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Efficacy of Intramedullar Locking Plate in Mild to Moderate Hallux Valgus Deformity: Early Outcomes

Hafif Orta Evre Halluks Valgus Tedavisinde Intramedullar Plak Uygulamasının Etkinliği: Erken Dönem Sonuçlar

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ABSTRACT

Aim: Hallux valgus is a complex deformity of the first metatarsophalangeal joint characterized by varus deformity of the first metatarsal bone, valgus deformity of the big toe, and lateral deviation of the extensor tendons and sesamoid bones. Several surgical methods have been described for correction of the deformity. Distal metatarsal osteotomy is a commonly used procedure in mild-to moderate hallux valgus. Different materials have been used for the fixation of osteotomy. The aim of this study was to evaluate radiological and clinical efficacy of intramedullar locking plate in hallux valgus surgery.
Material and Methods: Postoperative 6th month data of patients with mild-to moderate hallux valgus deformity who underwent distal metatarsal osteotomy using an intramedullary locking plate between 2012 and 2014 were evaluated retrospectively. The surgical procedure was applied by Mitchell technique. Clinical and radiological features of the patients were analyzed.
Results: Thirty-six (29 female, 7 male) patients whit a mean age of 51.00±12.96 years were enrolled the study. Eight patients underwent bilateral surgery. There were statistically significant improvement in hallux valgus angle, distal metatarsal articular angles, and American Orthopaedic Foot and Ankle Society hallux valgus scores in the postoperative 6th month (all p values <0.001). No statistically significant difference were found between the preoperative and postoperative 6th month inter-metatarsal angle values (p=0.058).
Conclusion: The intramedullar locking plate usage in surgery of mild-to moderate hallux valgus deformity is an effective method providing strong fixation and quick recovery that led patients to gain an early improvement in the daily life activities.
Keywords: Hallux valgus; intramedullar locking plate; distal metatarsal osteotomy.

ÖZ

Amaç: Halluks valgus, birinci metetarsal kemiğin varus deformitesi, başparmağın valgus deformitesi, sesamoid kemikler ve ekstensör tendonların laterale yer değiştirmesi ile karakterize, birinci metatarso-falangial eklemin kompleks deformitesidir. Bu deformitenin düzetilmesi için çeşitli cerrahi yöntemler tarif edilmiştir. Distal metatarsal osteotomi hafif orta evre halluks valgus cerrahisinde en sık kullanılan yöntemlerden biridir. Metatars osteotomi hattının fiksasyon materyali olarak çeşitli implantlar kullanılmaktadır. Bu çalışmanın amacı halluks valgus cerrahisinde intrameduller plak uygulamasının kısa dönem klinik ve radyolojik sonuçlarını ortaya koymaktır.
Gereç ve Yöntemler: 2012-2014 yılları arasında distal metatarsal osteotomi sonrası osteotomi hattı intramedüller kilitli plak kullanılarak tespit edilen halluks valgus hastalarının operasyon sonrası 6. ay verileri retrospektif olarak değerlendirildi. Cerrahi yaklaşım olarak Mitchell distal metatarsal osteotomi tekniği uygulandı. Hastaların klinik ve radyolojik özellikleri incelendi.
Bulgular: Çalışmaya yaş ortalaması 51,00±12,96 yıl olan toplam 36 (29 kadın, 7 erkek) hasta dahil edildi. Sekiz hastaya her iki ayağından cerrahi uygulandı. Ameliyat sonrası 6. ayda yapılan değerlendirmelerde halluks valgus açısı, distal metatarsal eklem açıları ve Amerikan Ortopedik Ayak ve Ayak Bileği Birliği halluks valgus skorlarında istatistiksel olarak anlamlı düzelme izlendi (her üç p değeri <0,001). İntermetetatarsal açı değerlendirildiğinde preoperatif ve ameliyat sonrası 6. ay arasında anlamlı bir değişiklik saptanmadı (p=0,058).
Sonuç: Hafif orta evre halluks valgus cerrahisinde ostetomi hattının tespitinde intramedüller kilitli plak uygulaması, güçlü bir tespit sağlaması, hızlı iyileşme ve hastaların günlük yaşam aktivitelerine hızlı dönüş imkanı sağlaması açısından efektif bir metottur.
Anahtar kelimeler: Halluks valgus; intramedullar kilitli plak; distal metatarsal osteotomi.

INTRODUCTION

Hallux valgus (HV) is a complex deformity of the first metatarsophalangeal (MTP) joint, characterized by varus deformity of the first metatarsal bone, valgus deformity of the big toe, and lateral deviation of the extensor tendons and sesamoid bones (1). Several surgical methods have been described for the correction of HV deformity (2). The location, characteristics, and the severity of the pathology play an important role in choosing the surgical method. However, there is no universal method. Nevertheless, distal metatarsal osteotomy (DMO) is a commonly used procedure in mild-to moderate HV deformity (3,4).

Intramedullar locking plate (ILP) is one of the new generation implants with titanium which is used in the surgical treatment of HV. It has two types in clinical use with mono and multi locking distal holes. The ILP type with multi locking holes is widely used for more lateralization and stable fixation of big metatarsal head (Figure 1). Additionally, different materials such as screw, kirshner-wire, staple and plates have been used for the fixation of osteotomy (5). Despite the successful results reported about these implants, some complications such as implant loosening, recurrence, rotation, malunion, soft tissue irritation or foreign body reaction were mentioned in literature (6-8).

Based on these aspects, the aim of this study was to evaluate the early outcomes of ILP in patients with HV deformity in terms of radiological and clinical efficacy. According to our literature knowledge and review, our study is the first to assess the early outcomes of the ILP system in HV surgery.

MATERIAL AND METHODS

This retrospective study includes the patients with mild-to moderate HV who were above 18 years old, and underwent DMO with the Mitchell technique using ILP between the years 2012 and 2014. Study was approved by the Ethics Committee of Duzce University (Date: 13.07.2018 and Number: 2018/112).

Surgical Procedure

All the patients underwent surgery with the Mitchell technique using an ILP (V-TEK titanium) for fixation. The surgical procedures were performed in the supine position under spinal anesthesia and with a pneumatic tourniquet by the same surgical team. An approximately 3-cm dorsal medial incision over the first MTP joint, and a linear capsular incision were made. Release of articular space and of soft tissues was made from same incision. The bunion was then shaved (exostectomy). A transverse osteotomy was performed using a 10×35×0.4 mm oscillating saw blade from the level of the metatarsal neck. The osteotomy was translocated and an appropriate-size plate was inserted intramedullary to the proximal part of first metatarsal under fluoroscopic imaging. It was fixed with 2 screws to the proximal cortex with the help of a guide. The lateralized metatarsal head was fixed with distal lag screws to the plate. The MTP joint capsule was closed by placing it in the joint reduction position. The tourniquet was opened after skin closure and bandage application and bleeding control was provided by compression. On the first postoperative day, a partial weight-bearing was allowed with modified HV shoe.

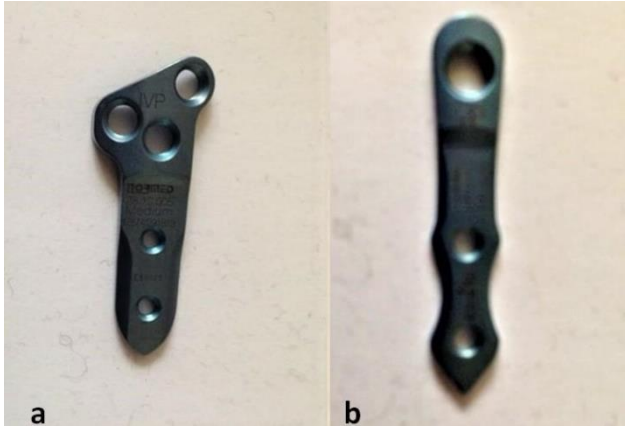

Figure 1. Two kinds of intramedullar locking plate (v-tek titanium)

Clinical Evaluation

Clinical evaluation comprised extensive ligamentous laxity, ankle deformity, the presence of bursitis, deformities in other toes, and skin thickening of the foot. American Orthopaedic Foot and Ankle Society (AOFAS) HV scores were used in assessments (9). Patients were evaluated with monthly follow-up visits within six months period, postoperatively. During these follow-up visits, all patients were interviewed face-to-face to evaluate the sensitivity of the operation site and mobilization.

Full weight-bearing was permitted by modified HV shoes after the removal of the skin sutures in the 15th day, postoperatively. In the 1st month following surgery, all patients were allowed to turn their normal daily activities.

Radiological Assessment

HV angle (HVA) was measured by plain radiogram, in which the angle between the longitudinal axis of the first metatarsal and proximal phalanx was calculated (10,11). The distal metatarsal articular angle (DMAA) was evaluated as the angle between the long axis of the first metatarsal and the perpendicular line passing through the distal articular surface and the most distal line connecting the medial and lateral margins (12).

When the lateral side of the proximal phalanx passes the lateral joint boundary of the first metatarsal bone, the first MTP joint was considered as the subluxation (10). The tibial sesamoid position was graded according to the standard recommendations (13). The severity of the disease was based on the HVA value as follows: <15° normal, 16-20° mild, 21-39° moderate and >39° severe (14).

The improvement in the HVA was considered to be the most important indicator of the success of the surgical procedure (10). Bone bridging was evaluated in 4 cortices on the radiographs (15). A postoperative HVA above 20° was accepted as recurrence (16,17). On lateral views, the metatarsal osteotomy line was considered as malunion if it was welded to the long axis of the sagittal plane bone (18).

Statistical Analysis

The data were analyzed using the SPSS v.22 statistical package. Shapiro-Wilk test was used to analyze normality assumption and paired sample t-test was used to compare preoperative and follow-up inter-metatarsal angle (IMA), HVA, DMAA and AOFAS scores, a value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 36 patients (29 females, 7 males) with a mean age of 51.00±12.96 years (range 19-75 years) were included in this study. Bilateral surgery was applied to 8 patients.

The mean HV, DMAA, and AOFAS scores were determined to have significantly improved at the postoperative 6-month follow-up visit compared to the preoperative values (all p values <0.001). There was no statistically significant difference between the preoperative and postoperative 6 month IMA values of the patients (p=0.058) (Table 1).

In the evaluation of complications, the cortical fissure was seen in 2 patients and a drill was broken intra-medullary in one patient. Fixation with cerclage wires was applied to 2 patients and broken or of drill was left in place. Union problem was not observed in these patients. (Figure 2). Superficial wound infection was seen in 5 patients. None of the complications such as avascular necrosis, malunion, non-union, recurrence or nerve insult were observed.

Table 1. Comparison of preoperative and postoperative 6th month HVA, IMA, DMAA and AOFAS scores

	Baseline	Postoperative 6th month	p
HVA	25.65±6.67	12.91±3.60	**<0.001**
IMA	12.98±5.14	12.09±5.03	0.058
DMAA	20.95±6.88	8.40±2.98	**<0.001**
AOFAS	48.14±8.70	86.30±5.20	**<0.001**

The data are given as mean±standard deviation, HVA: Halluks Valgus Angle, IMA: Inter-Metatarsal Angle, DMAA: Distal Metatarsal Articular Angles, AOFAS: American Orthopaedic Foot and Ankle Society

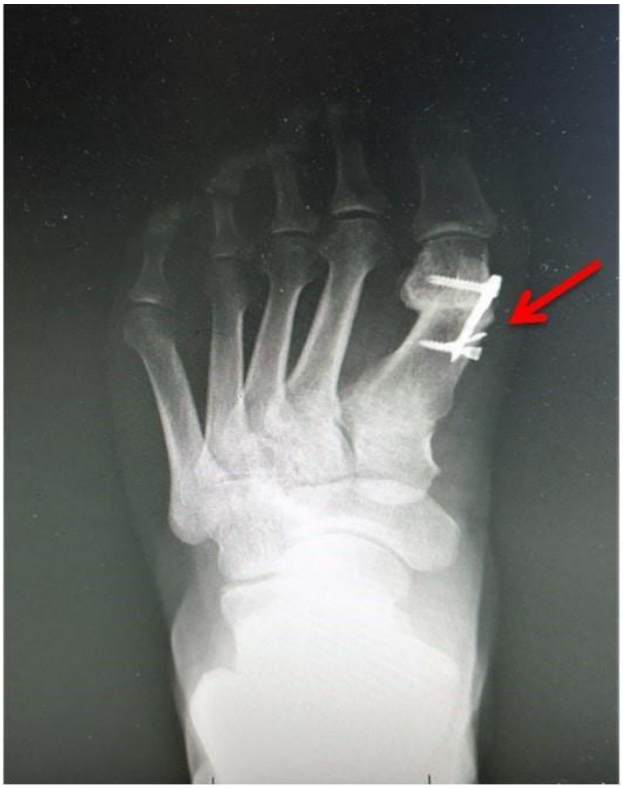

Figure 2. Broken drill did not cause any nonunion or poor outcome

DISCUSSION

This study aimed to evaluate the clinical and radiological outcomes of the ILP used by Mitchell technique for the treatment of mild-to moderate HV deformity and to discuss the results on healing time and return to daily life in the light of the pertinent literature.

Surgical treatment should be performed in patients who do not respond to conservative methods. The selected surgical technique should correct all components of the deformity: the medial bulge, increased valgus angulation of the proximal phalanx, increased first-second IMA, compliance of the MTP joint, sesamoid subluxation, pronation of the big toe, normal biomechanics of the first MTP joint and pain relief (10). At the same time, the chosen surgical method should not impair the function/biomechanics of the forefoot. When surgical treatment for HV deformity is planned, it is helpful for the physician to determine the radiographic examination findings together with the underlying complaint to which the surgical procedure is to be applied (19).

Surgical treatment options in HV include MTP soft tissue reconstruction, distal or proximal osteotomy of the first metatarsal, proximal phalangeal osteotomy, medial cuneiform osteotomy, MTP joint arthrodesis, and resection arthroplasty (19). In this context, different surgical methods such as proximal metatarsal osteotomy or DMO have been previously described (2). Mitchell technique has been accepted as an effective surgical method for mild to moderate HV surgery for many years (20). DMO has a limited efficacy in patients with severe HV that is more likely to develop postoperative complications (6,21).

The fixation materials are vital because of their primarily effect on the outcomes. Reduction problems or recurrence can also be seen due to fixation complications (6,16,22). The application of an ILP has some advantages over other methods, in terms of union, stability, and recovery time, as well as the complication rates, which are more likely to be reduced (23). In our study this fixation method showed not only radiological, but also clinical improvement. Furthermore, no recurrence, malunion, removal of the plate, or wound complications developed during the follow-up period.

The ILP system allows correction at the metatarsal head in a prone, supine or neutral position after transverse DMO. ILP provides strong fixation on osteotomy site, early bone bridging and weight-bearing. Compared to other endolog implants, the main disadvantage is that the locking screws, which are inserted into the metatarsal cottage in osteoporotic patients, can create fissures in the cortex, but this can be prevented with cerclage wires (23). This complication developed in 2 patients of the current study but they had no complaints of discomfort or unstable fixation. At all the stages of surgery, procedure is short and the method is easy to apply. Major advantages of the ILP system that we have demonstrated in our study were strong fixation, avoidance of metatarsal head migration, and rotation.

Supporting the literature knowledge revealing that early mobilization and full weight-bearing leading to an early maintenance of daily living activities after ILP usage in HV (24), our results were found to be consistent in which the patients were able to maintain full and early weight bearing one month after HV surgery with ILP (Figure 3).

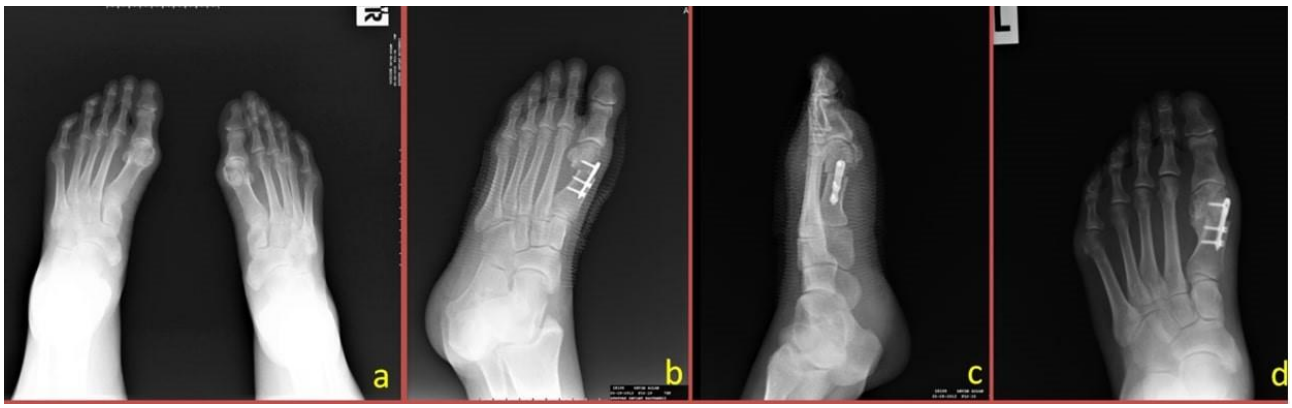

Figure 3. (a) Preoperative A-P x-ray, (b-c) Postoperative 2th day x-ray, (d) Postoperative 6th month x-ray

Limitations of our study were the lack of control group to make a comparison, and the short postoperative duration to observe the outcomes of HV surgery with ILP. Further prospective, and larger scale studies with comparison groups are needed to evaluate and demonstrate the efficacy of ILP in HV surgery in details.

CONCLUSION

According to our literature knowledge and review, our study is the first to assess the early outcomes of the ILP system in HV surgery, in which strong fixation and an early return to daily living activities were gained. ILP system in HV can be considered as a safer, easier, and effective surgical option in HV surgery.

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Is there a Risk of Hearing Loss in Dental Technicians? A Case Control Study

Diş Teknisyenlerinde İşitme Kaybı Riski Var mıdır? Bir Vaka Kontrol Çalışması

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ABSTRACT

Aim: Dental technicians are exposed to noise and chemical hazards that may lead to hearing loss in workplace. The aim of this study is to investigate the hearing loss risk of dental technicians working in dental laboratories.
Material and Methods: A hundred and five dental laboratory technicians who applied to Ankara Occupational Diseases Hospital for periodic check and 120 control subjects were included in the study. All of the subjects in both the dental technician and control groups were male. Audiograms of dental laboratory technicians was compared with audiograms of control subjects. Mann Whitney-U test and Spearman correlation analysis were used for statistical analysis of data.
Results: The hearing threshold values of the dental technicians at all frequency in both ears were found to be significantly higher than the control group. There were statistically significant correlation between age and hearing thresholds at all frequencies (except at 250 Hz and 1000 Hz) in dental technician group. There were statistically significant correlation between age and hearing thresholds at only 4000 Hz and 8000 Hz in control group. It was found that there were statistically significant correlations between exposure time and hearing thresholds at 2, 4 and 8 kHz frequencies in dental technician group.
Conclusion: Results of this study indicate that hearing loss is a serious occupational health problem in dental technicians. Dental technicians are exposed to noise and chemical hazards that may constitute a risk for hearing loss. Dental technicians must take preventive measures for hearing loss during working.
Keywords: Hearing loss; noise; dental technician; audiometry.

ÖZ

Amaç: Diş teknisyenleri iş yerlerinde işitme kaybına neden olabilecek gürültü ve kimyasal tehlikelere maruz kalmaktadırlar. Bu çalışmanın amacı dental laboratuvarlarda çalışan diş teknisyenlerinin mesleki işitme kaybı gelişme riskini araştırmaktır.
Gereç ve Yöntemler: Çalışmaya periyodik kontrol için Ankara Meslek Hastalıkları Hastanesi'ne başvuran 105 diş teknisyeni ve 120 kontrol birey dahil edildi. Hem diş teknisyenleri grubunda hem de kontrol grubundaki deneklerin tümü erkekti. Diş teknisyenlerinin odyogramları kontrol grubu bireylerinin odyogramları ile karşılaştırıldı. Verilerin istatistiksel analizi için Mann Whitney U testi ve Spearman korelasyon analizi kullanıldı.
Bulgular: Diş teknisyenlerinin her iki kulakta tüm frekanslarda işitme eşik ortalamaları kontrol grubundan istatistiksel olarak anlamlı şekilde yüksek bulundu. Diş teknisyenleri grubunda tüm frekanslarda (250 Hz ve 1000 Hz hariç) işitme eşikleri ve yaş arasında istatistiksel olarak anlamlı bir korelasyon vardı. Kontrol grubunda yalnızca 4000 Hz ve 8000 Hz frekanslarda işitme eşikleri ve yaş arasında istatistiksel olarak anlamlı korelasyon vardı. Diş teknisyenleri grubunda 2, 4 ve 8 kHz frekanslarında maruz kalma süresi ile işitme eşikleri arasında istatistiksel olarak anlamlı korelasyon olduğu saptandı.
Sonuç: Bu çalışmanın bulguları işitme kaybının diş teknisyenleri için ciddi bir sağlık sorunu olduğunu göstermektedir. Diş teknisyenleri iş yerlerinde işitme kaybı için risk oluşturabilecek gürültü ve kimyasal tehlikelere maruz kalmaktadırlar. Diş teknisyenleri işitme kaybı açısından çalışma sırasında mutlaka koruyucu önlemler almalıdırlar.
Anahtar kelimeler: İşitme kaybı; gürültü; diş teknisyeni; odyometri.

INTRODUCTION

Dental technicians are exposed to many chemical and biological hazards and risks in dental laboratories. These hazards include solvents, mineral acids, gases, vapors, dust coming from plaster, metal alloys, ceramics and acrylic resins. Many chemicals have been found in laboratories such as silica, butylene glycol, hexane, ethyl acetate, nitrocellulose, glutaraldehyde, benzoyl peroxide, hydroquinone, corundum, bisphenol-A, kaolin, oxides of titanium, iron, boron, methyl methacrylate (MMA), triethyleneglycol di-methacrylate (TEGDMA), ethyleneglycol di-methacrylate (EGDMA), 2-hydroxy-ethyl-methacrylate (HEMA), vitallium, wisil, duralium, and vironite (1). There is a risk of developing pneumoconiosis because of exposure to dust with high silica concentrations and cobalt, chromium and molybdenum (2). Also there is noise hazard in dental laboratories. The noise in the dental laboratories is mostly caused by grinding, cutting, polishing operations. The literature data about the issue whether the noise in dental laboratories is exceeding the critical harmful level or not is insufficient and inconsistent (3-5). It is known that the risk of hearing loss is increased with vibrations (6). Dental technicians are exposed to hand/arm vibrations while working with various hand pieces. Usual suspects that causing hearing loss in dental technicians are the noise, vibration, and chemical hazards.

In this article, we aimed to determine the risk of hearing loss in dental technicians.

MATERIAL AND METHODS

This research is a retrospective case control study and was approved by ethics review board of Keçiören Education and Research Hospital (date: 22.02.2012 and number: 20). The study was carried out in accordance in the Declaration of Helsinki. The study was conducted in Ankara Occupational Diseases Hospital. In this hospital different occupational groups are routinely examined at certain times. A hundred and five dental technicians and 120 workers as control group were included in this study. The workers in control group were selected from 4 different occupations (office workers, secretaries, cook and meal servers) that were exposed to neither noise nor chemicals. Medical records of subjects including physical examinations, otorhinolaryngological examinations, personal data, such as smoking habits, detailed history of current and previous occupational jobs, history of chronic drug intake, and any previous ear operations, pus discharge or hearing problems were obtained from periodic examination files. Subjects with a history of chronic illness, such as diabetes mellitus or hypertension, were excluded from study. The age and number of working years of the participants were recorded. All of the subjects in both the study and control groups were male. All of the subjects were examined by two otolaryngologists and had normal tympanic membrane examinations. Two subjects with tympanic membrane perforation and one subject with otosclerosis were excluded from this study.

Audiometric test was done using a pure tone manual diagnostic audiometer (Model GSI 61, Grason-Stadler, Inc) by a single audiologist at the Audiology Laboratory, Ankara Occupational Disease Hospital. The subjects were tested in a sound-isolated chamber. Pure tone audiometry was conducted with the subjects at frequencies of 0.5, 1, 2, 3, 4, 6, and 8 kHz using both air and bone conduction. Subjects should try to discriminate low sound levels of different frequency pure tones and respond by pressing a button. The lowest tone heard at each frequency was considered as the hearing threshold level. The thresholds in the frequency range of 0.5-2 kHz were averaged, and average hearing threshold was determined.

Statistical Analysis

Data were analyzed using the SPSS version 21.0 software program (Statistical Package for Social Sciences v.21, IBM, Chicago, IL). As descriptive statistics, the mean, standard deviation, median, minimum and maximum values for hearing levels and ages were given. The data were checked by the Kolmogorow-Smirnow test for normal distributions. Mann Whitney-U test was used to compare hearing levels and ages between two groups because values were not normally distributed. Spearman correlation analysis was applied to investigate correlation between hearing levels and age, and noise exposure time. A p value <0.05 was considered statistically significant.

RESULTS

Total 225 subjects, 105 subjects in dental technician group and 120 subjects in the control group were included in the study. Dental technicians have been working an average of 8 hours a day for 5-28 years in dental laboratory. The mean age of dental technician group was 37.00±8.22 years. The mean age of control group was 35.88±7.79 years. There was no difference in terms of age between groups ($p=0.281$). The hearing threshold values of the dental technicians at all frequency in both ears were found to be significantly higher than the control group (Table 1).

For determining effect of age on hearing, Spearman correlation analysis was applied between hearing levels and age in both groups (Table 2). In dental technician group there were statistically significant correlation between age and hearing thresholds at all frequencies (except at 250 Hz and 1000 Hz). In control group there were statistically significant correlation between age and hearing thresholds at only 4000 and 8000 Hz.

For determining effect of noise exposure time on hearing in dental technician group, Spearman correlation analysis was applied between hearing levels and exposure time. It was found that there were statistically significant correlations between exposure time and hearing thresholds at 2, 4 and 8 kHz frequencies (Table 3).

DISCUSSION

Hearing loss is one of the common occupational health disorders. Beside noise exposure, daily life noise exposure, ototoxic chemical exposure, use of tool with vibration, aging, smoking, hyperlipidemia, hypertension, diabetes mellitus and ototoxic medication also contribute to occupational hearing loss (6-9). Noise-induced hearing loss is one of the most important causes of hearing loss in the adult population worldwide (10). After noise damage, reactive oxygen levels in the cochlea increase, and cochlear blood flow is disturbed (11). Noise induced hearing loss starts when the level of noise is significantly high enough. The Occupational Safety and Health Administration accepted noise level of 90 dB (A) for 8 hours in a day as safe in terms of hearing loss (12). Dental

Table 1. Comparison of audiogram findings (dB) of dental technician group and control group

		Dental Technician (n=105)	Control (n=120)	p
PTA	R	10.44±7.81 8 (5-65)	6.47±2.15 5 (5-18)	**<0.001**
	L	11.41±9.67 8 (5-68)	6.89±2.60 5 (5-17)	**<0.001**
250 Hz	R	10.72±6.58 10 (5-45)	8.23±4.14 5 (5-20)	**<0.001**
	L	12.59±8.97 10 (5-60)	8.69±4.34 10 (5-20)	**<0.001**
500 Hz	R	8.65±6.58 5 (5-55)	5.96±2.28 5 (5-15)	**<0.001**
	L	9.66±8.25 5 (5-60)	6.38±3.04 5 (5-20)	**<0.001**
1000 Hz	R	10.24±8.79 5 (5-70)	5.96±1.98 5 (5-10)	**<0.001**
	L	9.81±8.24 5 (5-65)	6.21±2.83 5 (5-25)	**<0.001**
2000 Hz	R	11.53±11.32 5 (5-70)	6.34±3.36 5 (5-20)	**<0.001**
	L	12.88±13.12 10 (5-90)	6.68±3.92 5 (5-25)	**<0.001**
4000 Hz	R	33.60±19.63 30 (5-110)	10.08±8.15 5 (5-50)	**<0.001**
	L	36.97±20.24 33 (5-90)	9.85±6.09 10 (5-30)	**<0.001**
8000 Hz	R	35.04±20.93 30 (5-105)	11.51±6.99 10 (5-40)	**<0.001**
	L	38.79±23.48 35 (5-110)	11.72±6.52 10 (5-30)	**<0.001**

PTA: Pure Tone Average, Hz: Hertz, R: Right ear, L: Left ear, values are presented as mean±standard deviation and median (minimum-maximum)

Table 2. Correlation analysis between hearing levels and age in both groups

		Dental Technician (n=105)		Control (n=120)	
		r	p	r	p
PTA	R	0.271	**0.005**	0.043	0.644
	L	0.254	**0.009**	0.055	0.556
250 Hz	R	0.570	0.568	0.072	0.436
	L	0.163	0.098	0.096	0.298
500 Hz	R	0.226	**0.021**	-0.042	0.646
	L	0.215	**0.029**	-0.038	0.685
1000 Hz	R	0.250	**0.011**	0.033	0.723
	L	0.144	0.145	0.020	0.833
2000 Hz	R	0.225	**0.021**	0.076	0.412
	L	0.248	**0.011**	0.118	0.203
4000 Hz	R	0.278	**0.004**	0.176	0.055
	L	0.291	**0.003**	0.242	**0.008**
8000 Hz	R	0.237	**0.015**	0.172	0.061
	L	0.313	**0.001**	0.223	**0.015**

PTA: Pure Tone Average, Hz: Hertz, R: Right ear, L: Left ear

Table 3. Correlation analysis between hearing levels and exposure time in dental technician group

		Dental Technician (n=105)	
		r	p
PTA	R	0.181	0.067
	L	0.186	0.059
250 Hz	R	0.111	0.262
	L	0.159	0.108
500 Hz	R	0.154	0.119
	L	0.160	0.105
1000 Hz	R	0.173	0.080
	L	0.085	0.391
2000 Hz	R	0.162	0.100
	L	0.218	**0.026**
4000 Hz	R	0.226	**0.021**
	L	0.206	**0.036**
8000 Hz	R	0.167	0.089
	L	0.215	**0.029**

PTA: Pure Tone Average, Hz: Hertz, R: Right ear, L: Left ear

technicians are at risk population in terms of hearing loss because of commonly use of high speed drill and dental instruments, presence of chemical and biological hazards in their clinic. There are very few studies related to occupational noise exposure and existing studies related to dental technicians are contradictory (13-16). Also these studies were including all dental professionals especially dentist not only dental technicians whereas dental technicians are most risky group among dental professionals. The purpose of this study is to investigate the presence of hearing loss in dental technicians.

The results of the current study suggest that there was a statistically significant difference in hearing sensitivity between dental technicians and the control group. Brusis et al. (5) found that noise exposure of dental technicians is below the inner ear damaging limit of 85 dB (A). Also they indicated in their study that there is no risk of permanent hearing loss among dental health care workers. In other study, it was determined that noise levels were not exceeded allowable limits in a pediatric dentistry residency clinic (17). Conversely study conducted by Choosong et al. (3) measured that the highest impulsive noise levels of the dental technicians are exposed is 137.1 dB C in the personal hearing zone. They explained these findings that the noise level of a micro-motor hand piece at the dental clinic was lower than at dental laboratory. Dentists rarely use the maximum speed of the air turbine micromotor hand piece during dental treatment while in the dental laboratory air turbine tools are always used at the higher speeds. In addition, dental technicians generally work in the same room, in this room there are multiple instruments and the other noise sources (aspirator, music, etc).

Dental technicians are exposed to many chemical and biological hazards as well as noise. These hazards may also contribute to hearing loss. Also there is a risk of developing pneumoconiosis in dental technicians and chronic pulmonary diseases may pose a potential risk in terms of hearing loss (18).

There were significant correlations between age and hearing thresholds at all frequencies (except at 250 Hz and 1000 Hz) in dental technician group, while significant correlation was found only at 4000 and 8000 Hz frequencies in the control group. In control group there were correlations at 4000 and 8000 Hz frequencies due to presbycusis. But there were correlations at almost all frequencies in dental technician group due to noise exposure. In the light of this result it can be said that noise exposure in dental technicians is affecting all along the cochlea. Significant correlations were determined between exposure time and hearing levels at 2, 4, 8 kHz frequencies. This reflects that noise exposure affects rather high frequencies (7).

In the current study, it was found that dental technicians have significantly increased risk of hearing loss. The protection of dental technicians in terms of occupational hearing loss is only possible by taking adequate protective measures, using modern equipment and raising awareness. Prevention programs as legal requirements should base on medical check-ups. Also educations, engineering controls, administrative controls should be made. Toxic materials should be replaced by less harmful alternatives, where possible. Local ventilation systems must be properly constructed in dental laboratories to prevent respiratory and skin exposure to airborne contaminants. Adequate general ventilation and enclosure systems are also important. Hearing protection devices must be worn and special anti-vibration gloves could be of some help for hearing protection.

The limitations of the study are that hearing assessment is performed only by audiometry test. Further analysis of the hearing system can be done by adding otoacoustic emission test and evoked response audiometry test.

In conclusion, our results indicate that hearing loss is a serious occupational health concern for dental technicians. Dental technicians are exposed to noise and chemical hazards that may constitute a risk factor for hearing loss. Protective measures should be taken.

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Comparison of Surgical Results of Patients Undergoing On-pump and Off-pump Coronary Artery Bypass Grafting

On-pump ve Off-pump Koroner Arter Bypass Greft Ameliyatı Yapılan Hastaların Cerrahi Sonuçlarının Karşılaştırılması

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ABSTRACT

Aim: The aim of this study is to evaluate the clinical results of the patients undergoing off-pump and on-pump coronary artery bypass grafting (CABG) retrospectively in consideration of current literature.
Material and Methods: A total of 1672 patients undergoing CABG between October 2014 and August 2016 and having a postoperative sinus rhythm were enrolled in the study. Patients who underwent an additional procedure in addition to CABG and underwent open heart surgery except CABG were excluded from the study. Off-pump CABG was applied to 783 and on-pump CABG to 889 of 1672 patients.
Results: In comparison of operative data, duration of operation ($p<0.001$), number of bypasses to the coronary arteries ($p<0.001$), number of bypasses of the right coronary artery to the posterior descending artery ($p<0.001$), and diffuse coronary artery disease ($p<0.001$) were less in the off-pump CABG group and there was a statistically significant difference. In comparison of postoperative data, postoperative atrial fibrillation development ($p<0.001$), intubation time ($p<0.001$), intensive care unit stay ($p<0.001$), length of hospital stay ($p<0.001$), reexploration ($p=0.006$), vasopressor drug usage ($p<0.001$), positive inotropic drug usage ($p<0.001$), total drainage ($p<0.001$), blood and blood product used ($p<0.001$), and mortality rate ($p=0.001$) were less in the off-pump CABG group and statistically significant difference was found between groups.
Conclusion: In this study, we found that off-pump CABG has many advantages. In a selected group of patients having a coronary artery disease performing CABG in beating heart would avoid the patient from morbid and mortal negative effects of cardiopulmonary bypass.
Keywords: Off-pump; on-pump; coronary artery bypass; cardiopulmonary bypass.

ÖZ

Amaç: Bu çalışmanın amacı on-pump ve off-pump koroner arter baypass greftleme (KABG) yapılan hastaların klinik sonuçlarını retrospektif olarak güncel literatür ışığında değerlendirmektir.
Gereç ve Yöntemler: Çalışmaya Ekim 2014 ile Ağustos 2016 tarihleri arasında KABG uygulanan ve postoperatif sinüs ritmi olan toplam 1672 hasta dahil edildi. KABG yanında ek bir işlem uygulanmış ve KABG dışında açık kalp ameliyatı geçiren hastalar çalışma dışı bırakıldı. Toplam 1672 hastadan 783'üne off-pump KABG ve 889'una on-pump KABG uygulandı.
Bulgular: Operasyonel verilerin karşılaştırılmasında, operasyon süresi ($p<0.001$), koroner arter baypass sayısı ($p<0.001$), posterior desenden artere yapılan sağ koroner arter baypasslarının sayısı ($p<0.001$) ve yaygın koroner arter hastalığı ($p<0.001$), off-pump KABG grubunda daha azdı ve istatistiksel olarak anlamlı bir farklılık vardı. Ameliyat sonrası verilerin karşılaştırılmasında, ameliyat sonrası atriyal fibrilasyon gelişimi ($p<0.001$), entübasyon süresi ($p<0.001$), yoğun bakımda kalma süresi ($p<0.001$), hastanede kalma süresi uzunluğu ($p<0.001$), reeksplorasyon ($p=0.006$), vazopressör ilaç kullanımı ($p<0.001$), pozitif inotropik ilaç kullanımı ($p<0.001$), toplam drenaj ($p<0.001$), kullanılan kan ve kan ürünü ($p<0.001$) ve mortalite oranı ($p=0.001$) off-pump KABG grubunda daha azdı ve gruplar arasında istatistiksel olarak anlamlı bir farklılık olduğu bulundu.
Sonuç: Bu çalışmada off-pump KABG'nin birçok avantajı olduğu saptanmıştır. Koroner arter hastalığı olan seçilmiş bir hasta grubunda çalışan kalpte KABG uygulanması hastaları kardiyopulmoner baypassın morbidite ve mortaliteye neden olan negatif etkilerinden korur.
Anahtar kelimeler: Off-pump; on-pump; koroner arter baypass; kardiyopulmoner baypass.

INTRODUCTION

Performing coronary artery bypass grafting (CABG) surgery with cardiopulmonary bypass (CPB) had been the gold standard technique from the beginning of coronary artery surgery. However, due to the negative effects of CPB and the increasing age of patient population undergoing CABG leading to the increasing numbers of accompanying systemic diseases off-pump coronary artery bypass grafting (OPCAB) have been popular for the last two decades.

In the studies, hemostasis, neurological, renal and gastrointestinal functions deteriorated as a result of systemic inflammatory reaction initiated by the extracorporeal circuit, mechanical blood trauma, activation of various immunological cascades (complement, cytokines) as negative effects of CPB (1,2). In addition, it has been shown that aortic cannulation and cross clamp application in the on-pump coronary artery bypass grafting (ONCAB) technique may cause negative effects such as neurological and end organ damage as a result of microembolics (3).

In recent studies, it has been shown that CPB increases morbidity and mortality. These negative effects of CPB led surgeons to techniques that allow coronary bypass without CPB. As a result of different techniques, OPCAB recently gained popularity among surgeons. Devices developed for such surgeries and new anesthesia techniques have become applicable to the majority of patients undergoing CABG surgery. In this study, we aimed to compare the results of 1672 patients who were operated with OPCAB and ONCAB technique with the diagnosis of coronary artery disease retrospectively and to compare them with the literature review.

MATERIAL AND METHODS

A total of 1672 patients who underwent CABG operation and had preoperative sinus rhythm, were included in the study between January 2014 and August 2016. Patients with mechanical complications of myocardial infarction, such as a ventricular septum defect, papillary muscle rupture, and mitral valve regurgitation, and patients with cardiogenic shock persisting for a length of 24 hours were excluded from this study. Besides, combined procedures, impaired left ventricular function as assessed by angiography (ejection fraction <30%), patients requiring chronic dialysis, oliguria and anuria, a high-serum creatinine level (≥2.5 mg/dL), emergency surgery or reoperation, respiratory impairment, and coagulopathy not included in the study. Patients who underwent additional procedures with CABG operations and underwent open heart surgery other than CABG, were excluded from the study. Of these patients, 783 patients had OPCAB and 889 patients had ONCAB.

The study was approved by the local Ethics Committee of Düzce University Medical Faculty (date: 01.04.2019 and number: 2019/69).

In addition to the routine preoperative laboratory and radiological examination, each patient was applied respiratory function test. Bilateral carotid colored Doppler ultrasonography was applied to the patients older than 55 years old and having a unilateral or bilateral carotid sufl or a history of cerebrovascular accident. In case of determining a carotid artery disease, a selective carotid artery angiography was applied. With preoperative transthoracic echocardiography each patient was examined in terms of left ventricular ejection fraction, valvular anatomy, and cardiac spaces. OPCAB technique was preferred in the patients who had severe atheromatous plaques and severe calcification in the ascending aorta, who have high risk or contraindication of the use of CPB and aortic cross-clamp, have impaired renal function or chronic renal failure with a risk of embolization, rupture or dissection, who had cerebrovascular event, elderly, respiratory problems, systemic disease which increased the surgical risk or other comorbidities (4). ONCAB technique was preferred in the patients who had a poor vascular quality, had an intramyocardial target vessel, a target vessel disease was diffuse, and the target vessels were calcified and planned to undergo endarterectomy in the target vessels, hemodynamic instability, severely impaired left ventricular functions and previous myocardial infarction. Median sternotomy was performed for all CABG operations. The technique we use in OPCAB operations is described in detail by Yanagawa and Puskas (5). Two patients who underwent OPCAB surgery but were switched to emergency CPB due to intraoperative hemodynamic impairment were included in the CABG group under CPB. After cardiac arrest with antegrade and retrograde cold crystalloid cardioplegia and topical hypothermia, cardiac arrest was achieved with intermittent retrograde cold blood cardioplegia. Operations were completed under moderate (28 °C) hypothermia. In 1662 of 1672 patients undergoing CABG, left internal mammarian artery (LIMA) was used in left anterior descending artery position. In 10 patients, saphenous vein grafts were used because LIMA flow was not good. Saphenous vein grafts were used in the bypasses of the other coronary arteries. Hot blood cardioplegia was given before the cross clamp was removed. Preoperative and operative age, gender, body mass index, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, echocardiography findings, coronary angiography findings, coronary artery bypass count, coronary artery grafts used in bypass, duration of operation, aortic cross clamp and total CPB duration of ONCAB operations, total amount of cardioplegia used, postoperative vasopressor therapy, positive inotropic treatment, intra-aortic balloon pump need, intubation time, intensive care unit and hospital stay, total amount of red blood product, total amount of drainage, reexploration, development of postoperative atrial fibrillation (POAF) and hospital mortality were evaluated retrospectively.

Statistical Analysis

Statistical analyses were performed using the statistical program SPSS v.11.5 (SPSS Inc, Chicago, IL). Normality assumption of variables were determined using the Kolmogorov-Simirnov test. Student's t test was used for comparison of variables with normal distribution while Mann-Whitney U test was used for comparison of variables with non-normal distribution. Descriptive statistics for continuous variables were expressed as mean±standard deviation and median (minimum-maximum). Categorical data were presented in frequency and percentage, and compared using Pearson Chi-square or Fisher's Exact test, and p values of 0.05 or fewer were considered significant.

RESULTS

The mean age of cases was 58.3±8.7 years in the off-pump group and 59.5±9.7 in the on-pump group. Body mass index was 28.4±3.9 in the off-pump group and 28.5±4.3 in the on-pump group. While 53.8% of patients in the off-pump group had hypertension, this rate was 58.3% in the on-pump group. The standard EuroSCORE calculation was 3.6±2.7 in the off-pump group and 3.2±2.5 in the on-pump group. There was no significant difference in terms of preoperative features except age, left ventricular ejection fraction and EuroSCORE (Table 1).

In comparison of operative data, duration of operation (p<0.001), number of bypasses to the coronary arteries (p<0.001), number of bypasses of the right coronary artery to the posterior descending artery (p<0.001), and diffuse coronary artery disease (p<0.001) were less in the OPCAB group and there was a statistically significant difference between groups (Table 2).

In comparison of postoperative data, total drainage amount was 486.4±56.3 mL in the off-pump group while it was 696.4±34.7 mL in the on-pump group. Intra-aortic balloon pump usage rate was 1.1% in the off-pump group and 3.6% in the on-pump group. Reexploration rates were 1.1% in the off-pump group and 3.1% in the on-pump group. Mortality rates were 0.1% in the off-pump group and 1.7% in the on-pump group. In the comparison of postoperative data, POAF development (p<0.001), intubation time (p<0.001), intensive care unit stay (p<0.001), length of hospital stay (p<0.001), re-exploration (p=0.006), vasopressor drug usage (p<0.001), positive inotropic drug usage (p<0.001), intra-aortic balloon pump need (p=0.001), total drainage (p<0.001), blood and blood product used (p<0.001), and mortality rate (p=0.001) were less in OPCAB group, and statistically significant difference was found between groups (Table 3).

Table 1. Comparison of preoperative characteristics of patients in OPCAB and ONCAB groups

	OPCAB (n=783)	ONCAB (n=889)	p
Age (years)	58.3±8.7	59.5±9.7	0.008
Gender			
Male	345 (44.1%)	391 (44.0%)	0.974
Female	438 (55.9%)	498 (56.0%)	
Body mass index (kg/m^2)	28.4±3.9	28.5±4.3	0.620
Diabetes mellitus	381 (48.7%)	451 (50.7%)	0.398
Hypertension	421 (53.8%)	518 (58.3%)	0.064
Chronic obstructive pulmonary disease	193 (24.6%)	205 (23.1%)	0.446
Previous myocardial infarction	410 (52.4%)	473 (53.2%)	0.730
Left ventricular ejection fraction (%)	47.5±8.3	49.1±9.4	<0.001
Standart EuroSCORE	3.6±2.7 3 (0-7)	3.2±2.5 3 (0-8)	<0.001

OPCAB: Off-pump Coronary Artery Bypass Grafting, ONCAB: On-pump Coronary Artery Bypass Grafting, EuroSCORE: European System for Cardiac Operative Risk Evaluation, values were expressed as mean±standard deviation and median (minimum-maximum) for continuous variables, and n (%) used for categorical data.

Table 2. Comparison of operative properties of patients undergoing OPCAB and ONCAB

	OPCAB (n=783)	ONCAB (n=889)	p
Cross-clamp time (min)	NA	65.2±21.4 62 (31-82)	
Cardiopulmonary bypass time (min)	NA	97.1±26.9 86 (75-128)	
Operation duration (min)	137±35 132 (110-161)	231±49 226 (180-320)	<0.001
Total amount of cardioplegia used (ml)	NA	1518±437 1400 (1000-1600)	
Number of anastomoses performed			
2 and less	574 (73.3%)	346 (38.9%)	<0.001
3 and more	209 (26.7%)	543 (61.1%)	
Diffuse coronary artery disease	205 (26.2%)	498 (56.0%)	<0.001
Left internal mammary artery usage	782 (99.9%)	880 (99.0%)	0.024
Right coronary artery or right coronary posterior descending artery grafts	97 (12.4%)	786 (88.4%)	<0.001

OPCAB: Off-pump Coronary Artery Bypass Grafting, ONCAB: On-pump Coronary Artery Bypass Grafting, NA: not applicable, values were expressed as mean±standard deviation and median (minimum-maximum) for continuous variables, and n (%) used for categorical data.

Table 3. Comparison of postoperative characteristics of patients with OPCAB and ONCAB

	OPCAB (n=783)	ONCAB (n=889)	p
Vasopressor therapy (adrenalin, noradrenalin)	32 (4.1%)	147 (16.5%)	<0.001
Positive inotropic therapy (dopamine)	97 (12.4%)	246 (27.7%)	<0.001
Intra-aortic balloon pump	9 (1.1%)	32 (3.6%)	0.001
Total drainage (mL)	486.4±56.3 465 (150-850)	696.4±34.7 682 (175-925)	<0.001
Total amount of red blood product used (mL)	463.5±78.4 442 (225-625)	743.5±35.6 734 (250-850)	<0.001
Intubation time (hours)	6.1±1.6 4 (2-18)	11.7±3.4 9 (4-26)	<0.001
Intensive care unit stay (days)	2.2±1.3 1 (1-8)	3.5±1.5 2 (1-14)	<0.001
Hospital stay time (days)	5.1±2.6 4 (3-8)	7.4±3.8 5 (4-14)	<0.001
POAF development	79 (10.1%)	251 (28.2%)	<0.001
POAF development times (hours)	42.4±12.1 36 (24-46)	47.1±13.2 38 (22-42)	<0.001
Re-exploration	9 (1.1%)	28 (3.1%)	0.006
Mortality	1 (0.1%)	15 (1.7%)	0.001

OPCAB: Off-pump Coronary Artery Bypass Grafting, ONCAB: On-pump Coronary Artery Bypass Grafting, POAF: Postoperative atrial fibrillation, values were expressed as mean±standard deviation and median (minimum-maximum) for continuous variables, and n (%) used for categorical data.

DISCUSSION

In previous studies, OPCAB technique has many advantages over ONCAB technique. OPCAB technique reduces systemic inflammatory response caused by CPB, operative trauma, postoperative complication rate, length of rehabilitation, duration of intensive care unit stay, hospital stay, morbidity and hospital cost, but also decreases stroke, neurocognitive dysfunction, organ dysfunction and atrial fibrillation (AF), these benefits confirmed by clinical trials (6,7). In addition, OPCAB technique has shown advantages such as less blood loss, less blood transfusion requirement, need for less inotropic support, less morbidity, less mortality and less cost (8-12). The OPCAB technique will continue to be beneficial for the patient with the concomitant pathology of atherosclerotic plaques or the situation of a porcelain aorta. Other patient cohorts are those with further contraindications for the use of extracorporeal circulation as those with liver cirrhosis or evolving failure. There is no doubt, that the OPCAB technique will play its special role in the future. Long- term results by those groups who are using the latter in the majority of their patients, should clarify the current question, whether the OPCAB technology is detrimental to our patients or an enrichment of the surgical armamentarium.

The authors concluded that off-pump techniques may reduce early mortality in selected patients undergoing re-operative CABG; however, this does not persist into mid-term follow-up. OPCAB may also lead to intraoperative conversion and, although this did not affect outcomes in this study, these results are constrained by the limited data available. Furthermore, OPCAB may increase target vessel revascularization and, consequently, incomplete revascularization which, whilst not reflected in the short-term outcomes, requires longer-term follow-up in order to be fully assessed (13).

Patients with higher eGFR stages had statistically more reduced long-term survival, and this pattern was similar in the three treatment groups, also including the OPCAB group, who had the lowest survival in patients with eGFR stage 4. The authors concluded that patients with low GFR (Stages 3-4) undergoing ONCAB were at increased risk of early mortality. In contrast, there were no significant differences in operative mortality among eGFR groups in OPCAB patients. This 'off-pump advantage' on early outcomes was not observed at the long-term follow-up (14).

In addition to these two major trials several detailed questions in this matter were answered by various authors. Keeling and co-workers (15) analyzed the effect of off-pump versus on-pump coronary revascularization in patients with low ejection fraction. Between January 1, 2008 and June 30, 2011 data of 25667 patients with an EF of less than 0.3 according to the Society of Thoracic Surgeons National Data Base, who underwent primary non-emergent CABG were analyzed. 20509 had an ONCAB procedure and 5158 an OPCAB procedure. Propensity scores were estimated using 32 covariates and multivariate logistic regression was used to compare risk-adjusted outcomes between groups. The results showed that patients undergoing planned OPCAB were older, more frequently female and had a lower body mass index than those who underwent ONCAB. Unplanned conversion to CPB occurred in 270 (5.2% of the 5158 patients). OPCAB was associated with a significant lower adjusted risk of death (Odds Ratio (OR)=0.82, stroke (OR=0.67) and major adverse cardiac events (OR=0.75) and prolonged intubation (OR=0.78), postoperative transfusion rates were significantly lower in the OPCAB group (54.8% vs 51.6%). There were no adverse outcomes that occurred more commonly in OPCAB patients. The advantages associated with OPCAB were found in the

entire Society of Thoracic Surgeons National Database and among high-volume and low-volume OPCAB centres (15).

In recent studies, it has been shown that the complications related to CPB are higher in high-risk patients and consequently, mortality, morbidity and cost rates increase in these patient groups (16-19).

The CORONARY trial (20) is a large trial (n=4502 patients) designed to compare the two strategies. The final 5-year results showed similar outcomes with OPCAB and ONCAB. The difference between OPCAB and ONCAB in terms of number of grafts (3.0 vs. 3.2) and incidence of incomplete revascularization (11.8% vs. 10.0%) was only marginal. In the CORONARY, each procedure was performed by a surgeon who had expertise in the specific type of surgery (completion of more than 100 cases of the specific technique either off-pump or on-pump). A limitation of the CORONARY is that only patients at higher risk were enrolled and this aspect might limit the generalizability of the study findings.

In contrast, in the ROOBY trial (21), which enrolled 2203 patients, OPCAB has been recently reported to be associated with increased 5-year mortality (15.2% in the OPCAB group versus 11.9% in the ONCAB group, Relative Risk (RR)=1.28; 95.0% CI=1.03 to 1.58), and MACCE rates (31.0% in the OPCAB group versus 27.1% in the ONCAB group (RR=1.14; 95.0% CI=1.00 to 1.30). This trial has also demonstrated that the patency rate of the off-pump arm was lower than that of the on-pump arm on 12-month angiography. Such findings can be partially explained on the basis that the 53 participating surgeons enrolled on average only eight patients per year during the study period and had unacceptably high conversion rates to on-pump surgery (12.0%) and incomplete revascularization (18.0%). Moreover, in 60.0% of the cases, a resident was the primary surgeon again raising concerns about the relative inexperience translating into poor graft patency.

The survival advantage consistently associated with ONCAB over OPCAB has been attributed to the higher rates of incomplete revascularization, and worse graft patency with OPCAB compared with ONCAB observed in randomized trials and retrospective studies. Patients undergoing OPCAB have repeatedly been shown to receive fewer bypass grafts either than planned or than the number of diseased territories, in comparison with patients undergoing ONCAB. In a meta-analysis of 76 randomized trials reporting the number of grafts performed, OPCAB was associated with fewer grafts compared with ONCAB. The incidence of graft occlusion within 30 days was also higher in patients who underwent OPCAB compared with ONCAB in this meta-analysis (7.3% vs. 4.4%), and the rate of repeat revascularization within 1 year was higher after OPCAB (2.2% vs. 1.5%) (21). Our data confirm the higher rates of incomplete revascularization with OPCAB. These differences have been attributed to differential expertise bias in randomized and observational studies, due to the greater technical challenges of anastomosing a coronary artery on a beating heart, compared with the arrested heart in ONCAB. To address this, our study inclusion criteria specified surgical proficiency (experience of at least 100 on-pump or off-pump cases) for inclusion in each treatment arm. In this pool of relatively expert surgeons, OPCAB was still associated with fewer anastomoses and greater likelihood of incomplete revascularization, which we found to be an independent risk factor for late mortality in all patients.

In our study with literature compatible, better postoperative results were obtained in the OPCAB group. However, in this study, in the patients group with ONCAB; when the operative data were analyzed, the number of the bypassed veins, the number of bypasses to the right coronary posterior descending artery and the high number of patients with diffuse coronary artery disease suggest that it may be effective in the postoperative results. Ascione et al. (22) have shown that; AF, which is the most common arrhythmia type after CABG operations, develops significantly less in OPCAB patients. In our study, AF was less observed in OPCAB patients (10.1% vs 28.2%). In this study, the need for vasopressor therapy, the need for positive inotropic therapy, the need for intra-aortic balloon pump, the amount of chest tube drainage, the total amount of red blood product used, the duration of intubation, the duration of intensive care unit stay, hospital stay, reexploration, mortality and POAF development in patients with OPCAB was found statistically significantly lower than the patients who underwent ONCAB (23).

Finally, it has been argued that advances in technology and clinical practice, including optimal medical therapy, intraoperative epiaortic assessment, and CPB, have addressed more limitations of ONCAB surgery than OPCAB. We believe that these findings have clear implications for the optimal choice of procedure in the majority of patients undergoing surgical revascularization who do not have contraindications to CPB.

CONCLUSION

As a result, we think that OPCAB patient group has better postoperative results in terms of morbidity, mortality and cost, so it is safer to choose OPCAB technique for selected appropriate patient groups planned for CABG surgery as much as possible.

To conclude we could say that short term morbidity and mortality is less in very high-risk patients with off-pump, possibly because the procedure is shorter. It would be right to say that shorter the procedure, the better, especially for older, sicker patients. The length of the procedure is significantly shorter with off-pump than on-pump. However we suggest that the technique used should depend on the ease of the surgeon doing the operation as both the methods seem almost equally efficient according to the review otherwise. Certainly more data over large randomized trials is required before off-pump superiority over on-pump can be firmly established.

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Comparison of Three Different Treatment Modalities in the Treatment of Chronic Plantar Fasciitis: Corticosteroid Injection, Extracorporeal Shock Wave Therapy and Radiofrequency Nerve Ablation

Kronik Plantar Fasiit Tedavisinde Üç Farklı Tedavi Yönteminin Kıyaslanması: Kortikosteroid Enjeksiyonu, Ekstrakorporeal Şok Dalga Tedavisi ve Radyofrekans Sinir Ablasyonu

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ABSTRACT

Aim: In this study, it was aimed to compare the clinical and functional outcomes of three popular conservative treatment options in the treatment of chronic plantar fasciitis (PF): corticosteroid injection (CSI), extracorporeal shock wave therapy (ESWT) and radiofrequency nerve ablation (RFNA).

Material and Methods: Patients with chronic PF refractory to other conservative treatment methods were included in this retrospective study. From January 2017 to February 2019, all the patients with the diagnosis of chronic PF who were treated with conservative treatment modalities were evaluated. Forty eight patients who met our eligibility criteria and treated either with CSI, ESWT or RFNA methods were included in the study. Clinical and functional assessments of the patients were done by American Orthopaedic Foot and Ankle Society (AOFAS) scoring system and Visual Analogue Scale (VAS) just before the treatment, at 6^{th} and at 12^{th} weeks of the last session.

Results: There was a statistically significant difference in terms of VAS scores between the groups both for before treatment and for 6^{th} week (both $p<0.001$), but there was not a statistically significant difference between the groups in terms of VAS scores at 12^{th} week ($p=0.436$). Also, there was not a statistically significant difference between the three groups in terms of AOFAS scores before treatment, 6^{th} and 12^{th} week assessments ($p=0.076$, $p=0.081$, $p=0.478$ respectively).

Conclusion: Although the three treatment modalities showed significant improvements in the chronic PF treatment, no differences were found among effectiveness of them at the final follow-up period.

Keywords: Corticosteroids; extracorporeal shockwave therapy; plantar fasciitis; ablation techniques.

ÖZ

Amaç: Bu çalışmada kronik plantar fasiit (PF) tedavisinde kullanılan üç farklı popüler konservatif tedavi yöntemi olan kortikosteroid enjeksiyonu (KSE), ekstrakorporeal şok dalga tedavisi (ESWT) ve radyofrekans sinir ablasyonu (RFSA) tedavi yöntemlerinin klinik ve fonksiyonel sonuçlarının karşılaştırması amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya diğer konservatif tedavi yöntemlerine dirençli olan kronik PF'li hastalar dahil edildi. Ocak 2017 ile Şubat 2019 arasında konservatif tedavi yöntemleriyle tedavi edilmiş olan kronik PF tanılı tüm hastalar incelendi. Uygunluk kriterleri ile uyumlu olan ve KSE, ESWT veya RFSA yöntemlerinden biri ile tedavi edilen kırk sekiz hasta çalışmaya dahil edildi. Hastaların klinik ve fonksiyonel değerlendirmeleri tedaviden hemen önce ve son seansın 6. ve 12. haftalarında, Amerikan Ortopedik Ayak ve Ayak Bileği Birliği (AOFAS) skorlama sistemi ve görsel analog skala (VAS) ile yapıldı.

Bulgular: Gruplar arasında hem tedavi öncesi hem de 6. Hafta için VAS skorları bakımından istatistiksel olarak anlamlı düzeyde bir farklılık vardı (her iki $p<0,001$), ancak 12. hafta VAS skorları bakımından gruplar arasında istatistiksel olarak anlamlı bir farklılık yoktu ($p=0,436$). Ayrıca üç grup arasında, tedavi öncesi, 6. ve 12. hafta değerlendirmelerindeki AOFAS skorları açısından da istatistiksel olarak anlamlı bir fark yoktu (sırasıyla $p=0,076$, $p=0,081$, $p=0,478$).

Sonuç: Üç tedavi yöntemi de kronik PF tedavisinde önemli iyileşmeler göstermesine rağmen, son takip döneminde bu tedavilerin etkinlikleri açısından aralarında anlamlı bir fark bulunamamıştır.

Anahtar kelimeler: Kortikosteroidler; ekstrakorporeal şok dalga tedavisi; plantar fasiit; ablasyon teknikleri.

INTRODUCTION

Plantar fasciitis (PF) is one of the most frequent causes of heel pain occurring commonly in the middle aged to elderly patients and related to reduction in quality of life of the patients (1). The exact cause is unknown in most of the cases but some intrinsic and extrinsic risk factors have been well defined. The intrinsic factors include age (middle age), obesity, tightness in the Achilles tendon, pes planus and pes cavus and also the extrinsic factors include prolonged weight bearing, running, walking on hard surfaces and poor footwear (2).

The pathology of the PF usually results from collagen damage to the plantar fascia due to repetitive microtrauma. The normal fascia is replaced by a fibroblastic tissue that became spread to the surrounding tissue. A soft tissue ossification can also be seen at the origin of the plantar fascia named as heel spur (3). The patients usually feel pain near the medial side of the calcaneal tuberosity. This heel pain generally occurs in the morning with first steps or after a prolonged sitting. The diagnosis of plantar fasciitis usually based on a detailed medical history and physical examination (4).

There are many treatment modalities for PF without any consensus on clinical approach. The literature is lacking for a single treatment option supported by a highest level of evidence (5). The reason for this can be due to the fact that most of the treatment options are used in combination (6). Stretching exercises, orthoses, night splints, physical therapy, corticosteroid (CS), platelet-rich plasma (PRP) and botilunum toxin A injections, extracorporeal shock-wave therapy (ESWT) and radiofrequency nerve ablation (RFNA) have been employed in the treatment of PF (7-12). CS injection (CSI) acts as reducing the soft tissue inflammation and the swelling around the plantar fascia (13). The mechanism of action of ESWT is not understood completely but neovascularization, suppressive effects on nociceptors and hyperstimulation mechanism blocking the gate-control system have been described to explain its effects (14). An alternative conservative treatment option in PF is RFNA; an electrode is placed on the sensitive region of the heel and electromagnetic energy is transmitted to the tissues through this electrode leading to protein denaturation and ablation of the injured nerve endings (12). It has been using since 1990's with a success rate of more than 90%.

The purpose of this current study was to compare the clinical and functional outcomes of three popular conservative treatment options; CSI, ESWT and RFNA in the treatment of chronic PF.

MATERIAL AND METHODS

Patients with chronic PF refractory to other conservative methods were included in this study. From January 2017 to February 2019, all the patients with the diagnosis of chronic PF who were treated with conservative treatment modalities were followed up. The ethics committee of Düzce University approved the study with a number of 2019/124, and all the patients were provided informed consent about the study prior to treatment. The data of all the patients were analyzed and finally 48 patients who met our eligibility criteria and treated either with CSI, ESWT or RFNA were included in the study. The inclusion and exclusion criteria of the patients are listed in Table 1.

Table 1. Inclusion and exclusion criteria of the patients

Inclusion Criteria
- Patients who accept to participate in the study
- Patients with unilateral PF
- Between the ages of 18-55
- Heel spur on lateral radiograph of the foot
- Pain on palpation of medial calcaneal tubercle for >6 months
- Failure to respond to conservative treatment modalities other than CSI, ESWT and RFNA
- Patients treated with
- One CSI
- Three sessions of ESWT weekly
- One session of RFNA
Exclusion Criteria
- Patients who withdrawn from the study
- Patients with bilateral PF
- Age <18 and >55
- Pregnancy or lactation
- Neurological foot problem, clubfoot, pes cavus or pesplanovalgus
- Coagulopathy and any previous injection (PRP, prolotherapy, etc.)
- Previous foot trauma or any infection of the affected limb

PF: Plantar Fasciitis, CSI: Corticosteroid Injection, ESWT: Extracorporeal Shock Wave Therapy, RFNA: Radiofrequency Nerve Ablation, PRP: Platelet Rich Plasma

Diagnoses of the patients were confirmed with a detailed physical examination and radiographic evaluations (lateral X-Rays of the feet and ankles). All the patients were refractory to a minimum of 6 months of standardized traditional non-operative treatment modalities like muscle stretching exercises, nonsteroidal anti-inflammatory drugs (NSAIDs), heel cups, arch supports, night splints and PRP injection.

Treatment Protocol

The patients have been treated with either single dose CSI, three sessions of ESWT or single session of RFNA.

Corticosteroid Injection (CSI) Group: 1 mL of betamethasone (40 mg/mL) and 2 mL of bupivacaine (5 mg/ml) were injected into the site of the maximal tenderness.

Extracorporeal Shock Wave Therapy (ESWT) Group: Three sessions of radial ESWT (2000 pulses per a session in a dose of 10 Hz and 3 bar) were administered weekly for three weeks in every patient with a Swiss Dolorclast Master® ESWT machine (EMS SA, CH-1260, Nyon, Switzerland).

Radiofrequency Nerve Ablation (RFNA) Group: The most sensitive points and the possible traces of the tibial, medial calcaneal (MCN), lateral plantar (LPN) and medial plantar (MPN) nerves were marked on the heel with marker pen. Under sterile conditions the skin of the medial border of the heel was anesthetized with 0.5 mL of lidocaine HCl (20 mg/ml). The radiofrequency probe was advanced to the medial border of calcaneal tuberosity under fluoroscopy. Low-energy impulses were applied at 2 Hz and the occurrence of fasciculation or toe movements was checked to exclude the presence of the probe near a motor nerve. After making sure we're not near the motor nerve, to find the appropriate position we started at 50 Hz from 0 V and gradually increased the voltage until the patient experienced a tingling sensation. Then, the voltage was reduced and the probe was considered to be close to the

sensory nerve where the tingling sensation continued at levels <0.5V. At this point the sensory nerve was ablated at a temperature of 90 °C for 90 seconds. The CoATherm AK-A304 (Gyeonggi-do, South Korea) multi-channel pain control system was used in this procedure.

Clinical Assessment

Functional scores and pain were measured by American Orthopaedic Foot and Ankle Society (AOFAS) and Visual Analogue Scale (VAS) scoring systems respectively. The scoring records were subsequently obtained before the treatment, at 6th and at 12th weeks of the last session. AOFAS measures function (50 points), pain (40 points) and alignment (10 points) with the 100 points representing the best result. VAS is a scale and is useful for measuring pain that is believed to range across a continuum of values and cannot easily be directly measured.

Statistical Analysis

In this study, statistical analysis was done by NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. Distribution of continuous variables were analyzed by Shapiro-Wilk test. One-way analysis of variance was used for inter-group comparisons of variables with normal distribution, while Kruskal Wallis test followed by Dunn's multiple comparison test was used for comparison of groups in terms of variables that did not show normal distribution. Friedman Test was used for comparison of variables not show normal distribution measured in different times. Pearson Chi-square and Fisher-Freeman-Halton tests were used for comparison of qualitative data. A p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 48 patients with unilateral chronic PF were randomly assigned to the CSI, ESWT or RFNA groups. No patients were withdrawn from the study. The baseline demographic data of the groups were similar and there were no statistically significant differences in terms of age, gender, body mass index (BMI), side and dominant extremity distributions (Table 2).

There was a statistically significant difference in terms of VAS scores between the groups both for before treatment and for 6th week (both p<0.001). According to post hoc test results, there were statistically significant differences between CSI and RFNA groups (p<0.001), and ESWT and RFNA groups (p=0.006) while there was no difference between CSI and ESWT groups (p=0.293) for before treatment comparisons. Similarly, at the 6th week assessment, there were statistically significant differences between CSI and RFNA groups (p<0.001), and ESWT and RFNA groups (p=0.002) while there was no difference between CSI and ESWT groups (p=0.518). However, at 12th week there was not a statistically significant difference between three groups in terms of VAS scores (p=0.436). The change of VAS scores for before treatment, 6th and 12th week assessments in each group (all p<0.001) were also statistically significant (Table 3).

Although there was no statistically significant difference in the before treatment, 6th and 12th week AOFAS scores of the groups (p=0.076, p=0.081, p=0.478 respectively), the before treatment, 6th and 12th week AOFAS score differences in each group (all p<0.001) were statistically significant (Table 4).

Table 2. Subject characteristics in groups

	CSI (n=16)	ESWT (n=16)	RFNA (n=16)	p
Age	41.38±9.32	40.25±11.06	45.00±8.48	0.358
BMI	27.93±4.59	28.87±4.81	26.31±3.48	0.252
Gender				
Male	5 (31.25)	6 (37.50)	3 (18.75)	0.619
Female	11 (68.75)	10 (62.50)	13 (81.25)	
Side				
Right	8 (50.00)	9 (56.25)	8 (50.00)	0.920
Left	8 (50.00)	7 (43.75)	8 (50.00)	
Dominant Extremity				0.999
Right	15 (93.75)	15 (93.75)	16 (100.0)	
Left	1 (6.25)	1 (6.25)	0 (0.00)	

CSI: Corticosteroid Injection, ESWT: Extracorporeal Shockwave Therapy, RFNA: Radiofrequency Nerve Ablation, BMI: Body Mass Index, values presented as mean±standard deviation and frequency (percentage)

Table 3. Comparison of VAS scores

VAS	CSI (n=16)	ESWT (n=16)	RFNA (n=16)	p
Before treatment	9.31±0.48 9 (9-10)	8.75±0.86 9 (8-9)	7.44±0.96 7 (7-8)	**<0.001**
6th week	8.50±1.26 9 (8-9)	7.56±1.59 8 (6-9)	5.13±1.36 5 (4-6)	**<0.001**
12th week	3.63±2.19 4 (2-6)	3.88±2.92 4 (1-7)	2.69±1.49 3 (2-3)	0.436
p	**<0.001**	**<0.001**	**<0.001**	

CSI: Corticosteroid Injection, ESWT: Extracorporeal Shockwave Therapy, RFNA: Radiofrequency Nerve Ablation, VAS: Visual Analogue Scale, values presented as mean±standard deviation and median (interquartile range)

Table 4. Comparison of AOFAS scores

VAS	CSI (n=16)	ESWT (n=16)	RFNA (n=16)	p
Before treatment	55.13±9.92 58 (55-61)	58.75±4.91 59 (55-61)	61.5±4.82 62 (58-64)	0.076
6th week	75.31±7.96 72 (70-83)	72.19±6.41 73 (68-77)	77.19±5.27 78 (75-81)	0.081
12th week	85.25±7.27 85 (79-90)	87.19±9.36 89 (79-95)	88.19±8.48 88 (83-95)	0.478
p	**<0.001**	**<0.001**	**<0.001**	

CSI: Corticosteroid Injection, ESWT: Extracorporeal Shockwave Therapy, RFNA: Radiofrequency Nerve Ablation, AOFAS; American Orthopaedic Foot and Ankle Society, values presented as mean±standard deviation and median (interquartile range)

Percentage changes of VAS and AOFAS scores between the groups were also analyzed. There was a statistically significant difference in the before treatment/6th week change of VAS scores between the groups (p<0.001), but the before treatment/12th week and 6th week/12th week changes of VAS scores between the groups showed no statistically significant difference (p=0.773, p=0.656 respectively). Although there was not a statistically significant difference between the groups in terms of before treatment/6th week and before treatment/12th week changes of AOFAS scores (p=0.323 and p=0.761, respectively), the difference between 6th/12th week change of AOFAS scores showed statistically significant differences (p=0.036).

DISCUSSION

In this retrospective study we compared the effectiveness of the three treatment modalities which have been using widely for the treatment of chronic PF; local CSI, ESWT and RFNA. We have encountered significant improvements both in VAS and AOFAS scores in each group. Although the RFNA showed better VAS scores at 6th week, the VAS at the 12th week and AOFAS scores at the 6th and 12th weeks did not show any statistically significant difference. These findings indicate that these common treatment methods have a potential to improve the symptoms of chronic PF that is irresponsive to other conservative treatment modalities without superiority to each other.

Local CSI have been using as a popular method to treat the PF since 1950s (15). CSI has some advantages like low cost, low complexity and rapid pain relief but it is not without complications like tendon rupture, local skin atrophy and hypersensitivity reactions (16). The therapeutic benefit of CSI was shown to be nearly 90% and its effectiveness could last for about 1 year (17). But according to a systematic review by Crawford et al. (18) CSI can be useful only in short term. In a recent meta-analysis evaluating the randomized controlled trials; it is proposed that the CSI are effective in reducing heel pain in PF patients and their effects are usually short term lasting about 4-12 weeks (5). In our study CSI were found to be effective at the 6th and 12th week follow-ups.

ESWT has success rates changing from 48% to 88% and a potential to improve the VAS and activity scores in patients with chronic PF (19). Therapeutic benefits of ESWT usually starts about 2 weeks after the application and according to Kudo et al. (20), ESWT offers benefits on pain and activity levels for more than 3 months after treatment. Buch et al. (21) and Rompe et al. (22) reported significant improvements in the ESWT group compared with the placebo. But in some other studies the effectiveness of ESWT over placebo could not be shown (23,24).

Because the pain in any part of the body is transmitted by a nerve, RFNA can be used in various types of heel pain like nerve entrapments, classic plantar fasciitis or calcaneal bursitis (25). Whereas, RFNA is not recommended for some conditions like diabetic neuropathy, regional pain syndrome and pain including large areas (26). In this present study, we report the results of patients with chronic heel pain associated with only plantar fasciitis. The success rates with RFNA treatment have been reported as much as 90% in some studies and no difference between the plantar or medial calcaneal approaches was observed (26-28). We applied RFNA through medial calcaneal approach in this study.

There are some studies in the literature comparing the effectiveness of various conservative treatment modalities for chronic PF. In a study by Xiong et al. (29), ESWT was found to be a better alternative than CSI for the management of chronic PF at the 12 week post treatment evaluations. In a recent randomized controlled trial, Uğurlar et.al. (30) evaluated the CSI, ESWT, PRP and prolotherapy effectiveness in the management of chronic PF. They reported that the CSI was found to be more effective at the 3 months of follow-up, the effects of prolotherapy and PRP were seen within 3-12 months. But at the 36 month follow-up; they did not found any differences among 4 treatments. In another prospective study by Ozan et.al. (31), the ESWT and RFNA were compared for the management of chronic PF and both of the treatment modalities were found to be safe and effective without superiority to each other.

The present study is not without some limitations. First, we had a small number of patients which resulted from eligibility criteria of the study. The follow-up time could have been longer. The study could also include a placebo control group. Aside, the aim of this study was not to show the individual effects of the treatment modalities, but to compare their effectiveness.

CONCLUSION

Although the three treatment modalities showed significant improvements in the chronic PF treatment, we found no differences among them at the final follow-up period. The results of this study need replication in the future prospective, randomized, placebo-controlled and double-blinded researches that would focus on the long-term effectiveness.

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Opinions on Using Operating Room Effectively in Chronic Subdural Hematoma Surgery

Kronik Subdural Hematom Cerrahisinde Ameliyathanenin Etkin Kullanımı Hakkındaki Görüşler

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ABSTRACT

Aim: Chronic subdural hematoma is one of the most common extracerebral hemorrhages that causes significant morbidity with increasing human life. Associations with mild head trauma are reported in 60-80% of the literature. The aim of this study is to investigate whether local and general anesthesia performed in the operation of chronic subdural hematoma patients make a difference in terms of operative time, operation cost and total times for using the operating room.

Material and Methods: The records of 27 patients who were operated with diagnosis of unilateral chronic subdural hematoma between the years 2016 and 2018 in Duzce University Medical Faculty Training and Research Hospital, Neurosurgery Department were reviewed retrospectively. Age, gender, ASA score, operative time, time between entry and exit to the operating room, length of hospital stay and operating costs were recorded.

Results: It was found that the operating cost and total time between entry and exit to the operating room were shorter in patients undergoing local anesthesia, and the difference between patients undergoing general anesthesia was found statistically significant (both p values are <0.001).

Conclusion: In our study, a significant difference was found between the time of entrance and exit of patients who underwent local and general anesthesia. In the general anesthesia group, the costs were significantly higher. In patients with chronic subdural hematoma, local anesthesia is a more useful method in terms of efficient use of hospital operating room and reduction of operating costs. We believe that this practice will also contribute to the national economy.

Keywords: Chronic subdural hematoma; local anesthesia; general anesthesia; cost analysis.

ÖZ

Amaç: Kronik subdural hematom insan ömrünün artmasıyla birlikte sıklığı daha da artan önemli morbiditelere neden olan ve oldukça sık görülen ekstraserebral kanamalardandır. Literatürde hafif kafa travmaları ile birlikteliğinin %60-80 oranında olduğu bildirilmektedir. Bu çalışmanın amacı kronik subdural hematom hastalarının ameliyatında uygulanan lokal ve genel anestezinin ameliyat süresi, ameliyat maliyeti ve toplam ameliyathane odasını kullanım süreleri açısından bir farklılığa sebep olup olmadığını araştırmaktır.

Gereç ve Yöntemler: Düzce Üniversitesi Tıp Fakültesi Sağlık Araştırma ve Uygulama Hastanesi Nöroşirürji Anabilim Dalında 2016 ve 2018 yılları arasında tek taraflı kronik subdural hematom tanısı ile opere edilmiş olan toplam 27 hastanın kayıtları geriye dönük olarak incelenmiştir. Yaş, cinsiyet, ASA skoru, ameliyat süresi, ameliyat odasına giriş ve çıkış zamanları arasındaki süre, hastanede kalış süresinin uzunluğu ve ameliyat maliyetleri kaydedildi.

Bulgular: Lokal anestezi uygulanan hastalarda ameliyat maliyetinin ve ameliyathane odasına giriş ve çıkış arasındaki toplam sürelerinin daha kısa olduğu ve genel anestezi uygulanan hastalar ile arasındaki farklılığın istatistiksel olarak anlamlı olduğu saptanmıştır (her iki p değeri de <0,001).

Sonuç: Çalışmamızda lokal ve genel anestezi uygulanan hastaların giriş ve çıkış zamanları arasında anlamlı bir fark bulundu. Genel anestezi grubunda, maliyetler anlamlı derecede yüksekti. Kronik subdural hematomlu hastalarda lokal anestezi, hastane ameliyathanesinin etkin kullanımı ve işletme maliyetlerinin azaltılması açısından daha faydalı bir yöntemdir. Bu uygulamanın ülke ekonomisine de katkı sağlayacağına inanıyoruz.

Anahtar kelimeler: Kronik subdural hematom; lokal anestezi; genel anestezi; maliyet analizi.

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INTRODUCTION

Chronic subdural hematoma (CSDH) is one of the most common extracerebral hemorrhages that causes significant morbidity and its frequency increases with increasing human life (1-3). The association with mild head trauma is reported to be 60-80% in the literature (4,5). CSDH may be asymptomatic or may show up with many clinical findings such as headache, fatigue, memory impairment, focal neurological deficit and seizure (1). The definitive treatment is the surgical drainage of the hematoma. Twist-drill craniostomy, craniotomy and craniostomy with single or two burr-holes are the most commonly used surgical techniques (6). Today, the most preferred technique is Burr-Hole drainage because it is less invasive, it can be done with local anesthesia and its success rate is high in elderly patients with high risk.

In this study, it was aimed to investigate whether local anesthesia and general anesthesia in the treatment of CSDH did make a difference in terms of operative time, operation cost and total entrance and exit times to the operating room.

MATERIALS AND METHODS

The records of 27 patients who were operated with the diagnosis of unilateral CSDH between the years of 2016-2018 in Duzce University Medical Faculty Training and Research Hospital, Department of Neurosurgery were retrospectively reviewed after obtaining the local ethics committee approval. This study was approved by local ethics committee of Duzce University (dated 18.02.2019 and numbered 2019/17).

Patients included in the study were divided into two groups according to the anesthesia method. Eleven patients with unilateral CSDH who were operated with general anesthesia were included in the first group and 16 patients with unilateral CSDH who were operated with local anesthesia were included in the second group.

Patients with Glasgow coma scores (GCS) more than 13 and Karnofsky performance index (Table 1) more than 70 was included in both groups.

Table 1. Karnofsky Performance Index

Karnofsky Index	Score
Normal, no complaints, no symptoms	100
Can perform normal activity, there may be a few symptoms or signs of the disease	90
It continues its normal activity with some difficulties, the disease has minor signs and symptoms	80
Can look after himself, cannot do normal activity and his job	70
Can meet the requirements, need rare help, needs some help	60
Frequent assistance and medical care required	50
Special care and assistance required	40
Disabled enough to require hospital care, but there is no risk of death	30
Very ill, need active support treatment in hospital	20
About to die	10
Death	0

In order to access the patient data, the hospital computer system, which is used to keep patient records and information and which is called MIA-MED information system, was used.

Age, gender, American Society of Anesthesiologists (ASA) score, GCS, Karnofsky performance index, operative time, time of entrance and exit times to the operating room, length of hospital stay and operating costs of patients divided into two groups were recorded.

Statistical Analysis

Statistical analysis of all obtained data was performed using SPSS v.16.0 software. Descriptive statistics were given as mean±standard deviation and median (minimum-maximum), as appropriate. Distribution of continuous data were examined by Shapiro-Wilk test, and Independent samples t test was used to compare groups for data with normal distribution, while Mann-Whitney U test was used for data with non-normal distribution. Chi-square test was used for evaluation of categorical data, and summarized as numbers and percentages. A p value of <0.05 was considered statistically significant.

RESULTS

Of the 27 patients included in the study, 12 (44.4%) were female and 15 (55.6%) were male. Their age ranged from 31 to 93 years and the mean age was 74.67±15.21 years. All patients included in the study underwent surgery for unilateral double burr-hole drainage with CSDH. Data were obtained from 11 patients who underwent hematoma with general anesthesia and 16 patients who underwent hematoma with local anesthesia. There were 10 (62.5%) males and 6 (37.5%) females in the local anesthesia group; while 5 (45.5%) male and 6 (54.5%) female patients were in the general anesthesia group. No statistically significant difference was found between the two groups in terms of age and sex (p=0.089, p=0.452 respectively).

When the patients compared according to ASA score, while median ASA of the patients who were operated with general anesthesia were found as 3 (2-3) with mean and standard deviation of 2.73±0.47, median ASA of those operated with local anesthesia was 3 (2-4) with mean and standard deviation of 3.12±0.62. It was determined that the difference between the groups in terms of ASA score was not statistically significant (p=0.162).

When the patients compared according to GCS, while median GCS of the patients who underwent surgery with general anesthesia were found as 13 (13-15) with mean and standard deviation of 13.64±0.81, median GCS of those operated with local anesthesia was 14 (13-15) with mean and standard deviation of 13.69±0.79. It was determined that the difference between the groups in terms of GCS was not statistically significant (p=0.865).

In terms of Karnofsky performance index, similarly there was no statistically significant difference between groups (p=0.451). Median Karnofsky score of the general anesthesia group was found as 80 (70-100) with mean and standard deviation of 80.91±9.44, while median Karnofsky score was found as 80 (70-100) with mean and standard deviation of 83.75±8.85 in the local anesthesia group.

ASA, GCS and Karnofsky performance index comparison between local anesthesia and general anesthesia groups were given in Table 2.

Table 2. Comparison of ASA, GCS and Karnofsky performance index in groups

	Local Anesthesia (n=16)	General Anesthesia (n=11)	p
ASA Score	3.13±0.62 3 (2-4)	2.73±0.47 3 (2-3)	0.162
GCS	13.69±0.79 14 (13-15)	13.64±0.81 13 (13-15)	0.865
Karnofsky	83.75±8.85 80 (70-100)	80.91±9.44 80 (70-100)	0.451

ASA: American Society of Anesthesiologists, GCS: Glasgow Coma Scale, values are presented as mean±standard deviation and median (minimum-maximum)

The median duration of hospitalization of 11 patients who received general anesthesia was 9 (5-16) days and the median hospitalization period of 16 patients who received local anesthesia was 8 (5-11) days. There was no statistically significant difference between the duration of hospitalization of the two groups (p=0.422).

When the operation time was compared, the mean operation time was 47.73±9.58 minutes in patients receiving general anesthesia and 44.69±11.32 minutes in patients receiving local anesthesia. When the two groups were compared, there was no statistically significant difference between the duration of operation of the patients operated with general and local anesthesia (p=0.473).

When compared to the total operating room entry-exit times, the mean time of entry-exit time of the patients who received general anesthesia was 93.64±14.33 minutes and the mean time of entry-exit time of the patients who received local anesthesia was 60.94±12.68 minutes. When the time of entry and exit of the two groups were compared, it was found that the duration of operation of the local anesthesia group was shorter in the operating room compared to the general anesthesia group and the difference between the groups was statistically significant (p<0.001).

When the cost of surgery was compared, the median operation cost of 11 patients who received general anesthesia was 139.39 (80.99-323.61) TL, and the median operation cost of 16 patients with local anesthesia was 9.07 (6.86-68.38) TL. Considering the difference between the groups in terms of cost of surgery; it was found that the operations performed with local anesthesia were less costly than those performed with general anesthesia and the difference between the groups was statistically significant (p<0.001).

Comparison of hospital stay, operation time, entrance and exit time to the operating room and cost in local and general anesthesia groups were given in Table 3.

DISCUSSION

CSDH was first reported by JJ Wepfer in 1656 (7). CSDH occurs frequently in elderly patients because of the decrease in brain weight due to aging and the increase in extracerebral volume (8). The increase in the elderly population with the prolongation of human life increases the frequency of CSDH. It is reported that the average age is 53-63 years and it is more common in men (9). The mean age of the patients in this study was 74.67±15.21 and the number of male patients was higher than that of female patients.

It is reported that anticoagulant use due to cardiovascular diseases that are common in this age group is also a reason to frequent occurrence in elderly patients.

There are many publications in the literature about the choice of surgical technique. Mc Kissock et al. (10) provided a significant reduction in mortality by Burr-Hole drainage in the surgical treatment of CSDH. Çelikoğlu et al. (9) reported that single or double Burr-Hole application was faster and less morbid.

In the treatment of CSDH, which occurs more frequently in elderly patients, the development of serious complications after surgical procedures under general anesthesia and the emergence of other comorbidities have led to the preference of the surgeries under local anesthesia. In recent studies, the minimization of the surgical field has been prominent as well as local anesthesia (11,12).

First of all, it is also necessary to take into account the conditions of the country in every medical procedure where patient benefit is considered. In recent years, a significant increase in the number of patients undergoing surgical treatment due to increased diagnosis and treatment methods due to the developments in technology is evident from the data of the Republic of Turkey Ministry of Health (13). Increasing the number of patients undergoing surgery, patients not waiting long surgery queues, efficient use of operating rooms to increase the income rates of hospitals has gained great importance. In order to avoid problems caused by the absence of empty operating room, which is one of the biggest problems of hospitals, operating rooms should be used as efficiently as possible in terms of time. The decrease in hospital expenses will increase the rate of hospitals' profits and will cause less damage to public institutions.

In this study, a significant difference was found between the time of entrance and exit to the operating room of the patients who underwent local and general anesthesia. The most important reason for this is the time spent in the intubation and extubation of the patient to be given general

Table 3. The effect of local and general anesthesia on hospital stay, duration of operation, and cost

	Local Anesthesia (n=16)	General Anesthesia (n=11)	p
Hospitalization period (days)	8.19±1.91 8 (5-11)	9.45±3.42 9 (5-16)	0.422
Duration of operation (minutes)	44.69±11.32 45 (25-65)	47.73±9.58 45 (35-65)	0.473
Entry-exit time to the operating room (minutes)	60.94±12.68 58 (40-80)	93.64±14.33 95 (70-115)	<**0.001**
Cost of surgery (Turkish lira)	17.81±19.47 9.07 (6.86-68.38)	166.17±84.52 139.39 (80.99-323.61)	<**0.001**

Descriptive statistics are presented as mean±standard deviation and median (minimum-maximum)

anesthesia. Making patients that have undergone general anesthesia wait until their vital signs are stabilized after the extubation also prolongs the period. Since these steps were not available in local anesthesia, the entrance and exit times to the operating room were shortened and the difference was found to be statistically significant. Türk et al. (14) reported that it did not change in patients with CSDH under local and general anesthesia similar to our study. However, a study which calculates the entrance and exit time to the operating room was not found. We believe that the operation methods that will shorten the entrance and exit times to the operating room will help operation rooms to be used more efficiently.

Another important issue for hospitals is the costs. In the study, the costs were significantly higher in the general anesthesia group. The reason for this is the intubation tube used for intubation and the medical drugs (rocuronium bromide, midazolam, fentanyl, propofol, bridion). On the other hand, in the local anesthesia group, medical drugs (fentanyl citrate, propofol, midazolam, dexmedetomidine) were used for mild sedation and prilocaine was used during the scalp incision.

When these conditions are considered, Burr-Hole craniostomy under local anesthesia in patients with chronic CSDH is the method that can be preferred because of the decrease in duration of patient stay in the operating room and reduction in hospital costs. In this way, more patients can be operated during the day and also the loss of public institutions can be prevented with lower cost rates.

In recent years, there has been a significant increase in the number of patients undergoing surgical treatment due to increased diagnosis and treatment methods due to technological developments (13). Increasing the number of patients undergoing surgery, patients not waiting for long periods of time, and increasing the rate of income of hospitals is essential for efficient use of operating rooms. In order to avoid problems caused by the absence of empty operating room, which is one of the biggest problems of hospitals, operating rooms should be used as efficiently as possible in terms of time. Once again, the decrease in hospital expenses will increase the rate of hospitals' profits and will cause less damage to public institutions.

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Prevalence of Obstructive Sleep Apnea Syndrome in Psoriasis Patients

Psoriazis Hastalarında Obstrüktif Uyku Apne Sendromu Semptom Sıklığı

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ABSTRACT

Aim: Psoriasis is a frequently seen chronic systemic inflammatory disease accompanied by several comorbid conditions that affects 2-3% of the general population. One of the comorbidities rarely accompanying psoriasis is obstructive sleep apnea syndrome (OSAS). OSAS is a disease characterized by recurrent complete (apnea) or partial (hypopnea) upper airway obstruction episodes and frequently by decreased blood oxygen saturation. The purpose of this study was to evaluate the risk factors for OSAS by investigating OSAS symptoms in psoriasis patients.

Material and Methods: Eighty-two patients aged over 16, diagnosed with psoriasis, and under follow-up by the Duzce University Medical of Faculty, Dermatology and Venereal Diseases Polyclinic, Turkey, were included in the study. Patients' OSAS symptoms were investigated. The Epworth Sleepiness Scale was used to assess excessive daytime somnolence.

Results: Of the patients 51.2% (n=42) were male and 48.8% (n=40) female. Patients' mean age was 47.09±14.10 years. Patients' mean time of psoriasis diagnosis was 16.97±10.55 years, and mean Psoriatic Area Severity Index (PASI) score was 11.25±6.32. Severe disease was present in 54.9% of patients (n=45) based on PASI classification. Prevalence of 56.1% for snoring, 25.6% for excessive daytime sleepiness, and 15.9% for witnessed apnea were determined in these patients. Forty-seven (57.3%) cases had at least one major symptom. The most common minor symptoms were inability to sleep with 25.6% (n=21) and insufficient disrupted sleep with 22.0% (n=18).

Conclusion: Prevalence of OSAS symptoms in psoriasis patients were found high. Psoriasis patients with OSAS symptoms must be referred to relevant specialists for polysomnographic evaluation.

Keywords: Psoriasis; obstructive sleep apnea syndrome; symptom.

ÖZ

Amaç: Psoriazis toplumda sık görülen, genel nüfusun %2-3'ünü etkileyen, birçok komorbiditenin eşlik ettiği kronik sistemik enflamatuvar bir hastalıktır. Psoriazis'e eşlik eden nadir görülen komorbiditeler arasında obstrüktif uyku apne sendromu (OUAS) yer almaktadır. OUAS uyku sırasında tekrarlayan tam (apne) veya parsiyel (hipopne) üst solunum yolu obstrüksiyonu epizodları ve sıklıkla kan oksijen satürasyonunda azalma ile karakterize bir hastalıktır. Bu çalışmanın amacı psoriazis hastalarında OUAS semptomları sorgulanarak, OUAS risk faktörlerini değerlendirmektir.

Gereç ve Yöntemler: Düzce Üniversitesi Tıp Fakültesi Deri ve Zührevi Hastalıkları polikliniğinden takipli ve Psoriazis tanılı 16 yaşından büyük 82 hasta çalışmaya alındı. Hastalar OUAS semptomları açısından sorgulandı. Aşırı gündüz uykululuğu değerlendirmek için ise Epworth uykululuk skalası kullanıldı.

Bulgular: Hastaların %51,2 (n=42)'sı erkek, %48,8 (n=40)'i kadındı. Hastaların yaş ortalaması 47,09±14,10 yıl idi. Hastaların ortalama psoriazis tanı süreleri 16,97±10,55 yıl, ortalama Psoriatik Alan Şiddet İndeksi (PAŞİ) 11,25±6,32 idi. PAŞİ sınıflamasına göre hastaların %54,9 (n=45)'ü şiddetliydi. Bu hastalarda horlama için %56,1, gündüz aşırı uyku hali için %25,6, tanıklı apne için %15,9'luk prevalans saptandı. En az bir semptomu olan olgu sayısı 47 (%57,3) idi. Minör semptomlar sorgulandığında en sık gözlenen %25,6 (n=21) ile uyuyamama ve %22,0 (n=18) ile yetersiz bölünmüş uyku şikayetiydi.

Sonuç: Psoriazis hastalarında OUAS semptom sıklığı yüksek olarak bulunmuştur. OUAS semptomları olan psoriazis hastaları muhakkak polisomnografik değerlendirme için ilgili uzmanlara yönlendirilmelidir.

Anahtar kelimeler: Psoriazis; obstruktif uyku apne sendromu; semptom.

INTRODUCTION

Psoriasis was previously thought to be limited to the skin, but is now regarded as a chronic systemic inflammatory disease accompanied by several comorbidities; it is frequently seen in the community and affects 2-3% of the general population (1). The most common comorbidity is psoriatic arthritis. Other comorbidities include metabolic syndrome, hypertension, dyslipidemia, atherosclerotic diseases, ocular findings (uveitis), inflammatory bowel diseases, and non-alcoholic fatty liver disease. Chronic obstructive pulmonary disease (COPD) and obstructive sleep apnea syndrome (OSAS) are rarer comorbidities (2). The number of studies investigating the prevalence of OSAS in psoriasis patients is limited. Prospective studies of the prevalence of OSAS in psoriasis may help reveal the causal relationship between the two diseases.

OSAS is a disease characterized by recurrent complete (apnea) or partial (hypopnea) upper airway obstruction episodes and frequently by decreased blood oxygen saturation (3). The major symptoms of OSAS, which affects approximately 5% of Western society, include snoring, witnessed apnea, and excessive daytime sleepiness. Minor symptoms may accompany major OSAS symptoms. These include a sensation of suffocation during sleep, atypical chest pain, disrupted sleep, insomnia, decision-making and concentration problems, palpitations, weight gain, personality changes, altered mental state, abnormal motor activity during sleep, dry mouth, morning headaches, nocturnal coughing, and enuresis (4).

The purpose of this study was to perform a preliminary scan of sleep disorders by investigating the prevalence of obstructive sleep apnea (OSA) symptoms in psoriasis patients, and at the same time to determine the prevalence of the rare comorbidity OSAS.

MATERIAL AND METHODS

Study Group

Eighty-two patients aged over 16, diagnosed with psoriasis, and being followed-up by the Düzce University Medical of Faculty, Dermatological and Venereal Diseases Polyclinic, Turkey, were included in the study. The study was performed between January and May, 2019. Approval for the study was granted by the Düzce University ethical committee (01.04.2019 and 2019-91).

Exclusion Criteria

Patients with chronic inflammatory diseases, malignancy, thyroid diseases, chronic kidney or liver diseases, or cerebrovascular diseases were excluded from the study.

Evaluation of Psoriasis Severity

Psoriasis severity was evaluated using the Psoriasis Area Severity Index (PASI).

Sleep Symptom Evaluation

General sleep disorder and excessive daytime sleepiness (EDS) were evaluated in all patients. At sleep disorder evaluation, major OSAS symptoms such as snoring (nocturnal snoring at least four times a week), witnessed apnea (defined as loud and irregular snoring witnessed by the spouses or relatives of OSAS patients and ceasing with respiration), and excessive daytime sleepiness (increased fatigue and a disposition to somnolence during the day following insufficient nocturnal sleep), and minor symptoms (a sensation of suffocation during sleep, atypical chest pain, interrupted sleep, insomnia, decision-making and concentration problems, palpitations, abnormal motor activity during sleep, dry mouth, morning headache, nocturnal coughing, and enuresis) were investigated using a questionnaire. The Epworth Sleepiness Scale (ESS) was used to assess excessive daytime sleepiness (Table 1). The questionnaire was scored from 0 to 3 based on the prevalence of eight different situations occurring in the majority of individuals' daily lives, although not necessarily every day. Scored between 0 and 24 in total. Higher values indicate greater daytime sleepiness. Total scores greater than 10 indicate excessive daytime sleepiness, regarded as a clinical characteristic of OSAS (5).

Statistical Analysis

Statistical analysis was performed on Statistical Package for the Social Sciences software (Windows 20.0; SPSS Inc., IL, USA). Descriptive statistics were calculated as mean±standard deviation (minimum, maximum) for continuous variables, and frequency and percentage for categorical variables.

Table 1. Epworth Sleepiness Scale (5)

QUESTION	Never	Rarely	Frequently	Always
Do you doze off when reading a newspaper or a book in a seated position?	0	1	2	3
Do you doze off when watching television?	0	1	2	3
Do you doze off when sitting inactive in a public place, such as the cinema or theater?	0	1	2	3
Do you doze uninterruptedly for at least 1 as a passenger in a car?	0	1	2	3
Do you doze when lying down to rest in the afternoon?	0	1	2	3
Do you doze off when sitting and talking to someone?	0	1	2	3
Do you doze when sitting quietly after lunch, without having consumed alcohol?	0	1	2	3
Do you doze off in a car while stopped for a few minutes at a red light?	0	1	2	3

RESULTS

Eighty-two patients diagnosed with psoriasis were enrolled in the study. Male constituted 51.2% (n=42) of the patient group and female 48.8% (n=40). Patients' mean age was 47.09±14.10 (minimum=19, maximum=73), and mean body mass index (BMI) was 18.82±5.01 (minimum=28.66, maximum=42.97). Mean time since diagnosis of psoriasis was 16.97±10.55 (minimum=2, maximum=57) years, and mean PASI score was 11.25±6.32 (minimum=0, maximum=34.20). Forty-five (54.9%) patients were classified as severe based on PASI. In terms of additional diseases, hypertension was determined in 19 (23.2%) patients, diabetes in nine (11.0%), heart disease in two (2.4%), and gastro-esophageal reflux in one (1.2%).

At least one major symptom was present in 47 (57.3%) cases, two symptoms in 20 (24.4%), and all three symptoms in three (3.7%). The most common minor symptoms in patients diagnosed with psoriasis were inability to sleep in 25.6% (n=21) and insufficient, interrupted sleep in 22.0% (n=18). The prevalence of major and minor symptoms are shown in Table 2.

The mean ESS value was 3.01±3.90, and 9.8% (n=8) of patients were ESS-positive (Table 1). Prevalence of 56.1% (n=46) for snoring, 25.6% (n=21) for excessive daytime sleepiness, and 15.9% (n=13) for witnessed apnea were determined in these patients (Figure 1).

DISCUSSION

Psoriasis is a common chronic inflammatory disease, with a general prevalence of 2-3%, affecting more than 7.5 million individuals in the USA and approximately 125 million worldwide, and progressing with attacks followed by periods of remission (6). Polygenetic and environmental factors have long been known to be involved in the pathogenesis of the disease. A complex immune reaction due to abnormal keratinocyte differentiation resulting in epidermal hyperproliferation occurs in psoriasis (7). Psoriasis was formerly regarded as being limited to the skin, but is now considered a chronic systemic inflammatory disease accompanied by various comorbidities. Seventy-three percent of patients are thought to have at least one comorbid condition (8). These include cardiovascular diseases, obesity, metabolic syndrome, hypertension, dyslipidemia, atherosclerotic diseases, diabetes, malignancy, non-alcoholic fatty liver disease, inflammatory bowel diseases, ocular findings (uveitis), mood alterations, erectile dysfunction, COPD, OSAS, and psoriatic arthritis. The most common comorbidity is psoriatic arthritis. Newly identified psoriatic comorbidities include COPD, peptic ulcer disease, sexual function disorder, and OSAS. Comorbid conditions are more prevalent in patients with existing moderate-severe psoriasis, due to the inflammatory effect and a common pathogenesis. The prevalence of all comorbid diseases, particularly cardiovascular diseases, increases with the duration and severity of psoriasis (6,9). Psoriasis patients must therefore be evaluated using a multidisciplinary and systemic approach. Examination must not be limited to cutaneous findings, but must also encompass potential comorbidities. This will permit the identification of accompanying diseases, and treatment can be regulated in the light of existing comorbid conditions.

Very few studies have investigated the association between psoriasis and OSAS. Studies have shown a relation between OSAS and metabolic syndrome, atherosclerotic diseases (10,11). The risk of metabolic syndrome and atherosclerotic diseases is also higher in psoriasis patients, and due to the close association between

Table 2. Prevalence of major and minor symptoms in patients diagnosed with psoriasis (n=82)

Major Symptom Comorbidity	n (%)
Major symptom-negative	35 (42.7)
1 major symptom	47 (57.3)
2 major symptoms	20 (24.4)
3 major symptoms	3 (3.7)
Minor Symptom	n (%)
Sensation of suffocation during sleep	10 (12.2)
Atypical chest pain	9 (11.0)
Insufficient, interrupted sleep	18 (22.0)
Insomnia	21 (25.6)
Decreased decision-making ability	10 (12.2)
Impaired memory, forgetfulness	16 (19.5)
Palpitations	6 (7.3)
Weight gain	10 (12.2)
Character and personality changes	7 (8.5)
Difficulty in adapting to one's environment	2 (2.4)
Anxiety, depression	8 (9.8)
Abnormal motor activity during sleep	4 (4.9)
Dry mouth	17 (20.7)
Nocturnal hyperhidrosis	4 (4.9)
Morning headache	8 (9.8)
Nocturnal coughing	6 (7.3)
Nocturia, enuresis	7 (8.5)
Decreased sexual desire	4 (4.9)
Loss of hearing	7 (8.5)

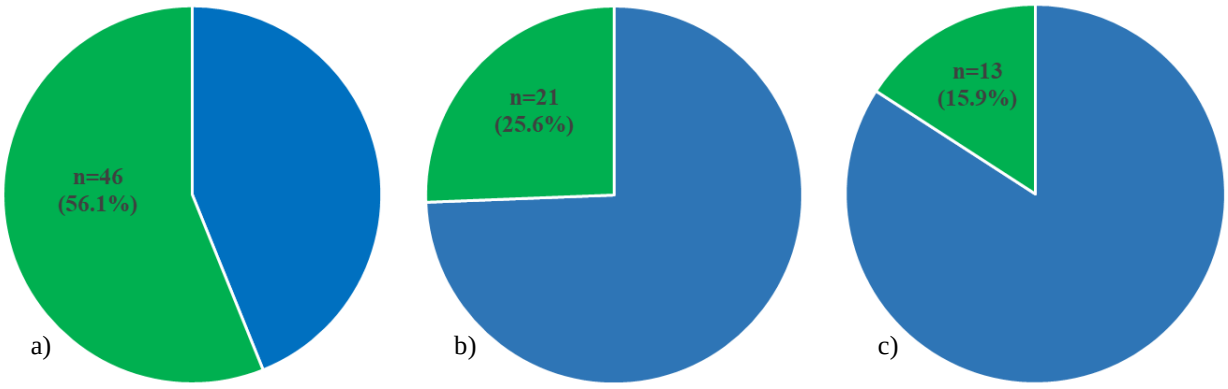

Figure 1. Prevalence of major symptoms in patients a) snoring, b) excessive daytime sleepiness, c) witnessed apnea

these conditions and OSAS. There is also a greater probability of a potential relation between OSAS and psoriasis.

The major symptoms of OSAS are snoring, witnessed apnea, and excessive daytime sleepiness. The most common symptom is snoring, and this is also the most frequent presentation symptom. Snoring for at least four nights a week is clinically significant. In the Wisconsin sleep cohort study, habitual snoring was present in 28% of women and 44% of men (12). Snoring was present in 56.1% of our psoriasis patients, much higher than in the normal population. The incidence of excessive daytime sleepiness is 8-30% in the normal population, but may be as high as 50% in patients diagnosed with OSAS (13). In their cohort study, Young et al. (12) determined excessive daytime sleepiness in 16% of male OSAS patients and 23% of female patients. Excessive daytime sleepiness was present in 25.6% of our patients. The reported prevalence of witnessed apnea in the community is 3.8-6% (14). The prevalence in our patients was quite high, at 15.9%. At least one major symptom was present in 47 (57.3%) of our cases, two symptoms were present in 20 (24.4%), and all three symptoms were present in three cases (3.7%). The most common minor symptoms in patients diagnosed with psoriasis were insomnia in 25.6% (n=21) and insufficient, interrupted sleep in 22.0% (n=18). OSAS may be the cause in patients presenting due to insomnia or interrupted sleep. Frequent waking may be seen in patients with apnea-related interrupted sleep. Due to excessive daytime sleepiness may also prolong time taken to fall asleep.

At the same time, hypoxia developing in patients with OSAS has also been implicated in vascular complications by leading to endothelial dysfunctions through an increase in sympathetic system activity. Endothelial dysfunction, increasing with severity of OSAS, has been observed in OSAS patients compared to healthy individuals (15). Recurrent apnea and hypoxia attacks increase oxidative stress as a result of increased release of free oxygen radicals in the vascular endothelium, leading to atherosclerotic diseases (16). Psoriasis is a risk factor for the development of atherosclerotic vascular disease including in which cardiovascular, cerebrovascular and peripheral vascular disease (17). Psoriasis has been identified as an independent risk factor for development of myocardial infarction (18). OSAS, one potential comorbid condition in psoriasis patients, can exacerbate the development of atherosclerotic diseases by causing hypoxia-ischemia. OSAS symptoms must therefore be investigated in patients with psoriasis. Patients with existing OSAS symptoms should be referred for polysomnographic examination.

Karaca et al. (19) determined OSAS in 18 (54.4%) out of 33 patients with psoriasis. OSAS was mild in 11 of these 18 patients, moderate in two, and severe in five. Şereflican et al. (20) investigated 405 OSAS patients, but psoriasis was present in only three. In a Danish cohort study simultaneously examining the potential two-way relations between psoriasis and OSAS, Egeberg et al. (21) reported an increased risk of sleep apnea in psoriasis patients. In a study from Taiwan, Yang et al. (22) compared 2258 psoriasis patients with a three-year follow-up period and 11255 healthy controls in terms of prevalence of sleep apnea, and reported that the incidence of sleep apnea was twice as high in the psoriasis patients. In our study, snoring was present in 56.1% of psoriasis patients, excessive daytime sleepiness in 25.6%, and witnessed apnea in 15.9%. These rates were significantly higher than in the general population.

In conclusion, we observed a high incidence of OSAS symptoms in our psoriasis patients. We think that psoriasis patients should also be examined in terms of OSAS symptoms at polyclinic check-ups. Patients with OSAS symptoms should be referred for polysomnographic examination by relevant specialists.

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Association of Pericentric Inv(12)(p11.2q14) with Infertility and Recurrent Miscarriages: Case Report and Literature Review

Perisentrik inv(12)(p11.2q14)'nin İnfertilite ve Tekrarlayan Düşüklerle İlişkisi: Vaka Örneği ve Literatür Taraması

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ABSTRACT

Infertility, reported in 15% of the couples who want to have children, is an important worldwide health problem. Recurrent miscarriage, observed in 15–25% of pregnancies, is another important health issue affecting millions of couples in the world. Despite many genetic factors have been associated with infertility or recurrent miscarriages especially in recent years, the genetic and epigenetic factors underlying these problems are mostly unknown. Most of the pericentric inversions do not affect phenotypes of the individuals carrying balanced rearrangements. However, the pericentric inversions may cause chromosomally unbalanced sperm/ovum during the meiotic crossover leading to infertility or recurrent miscarriages. In this case report, we report a familial pericentric inv(12)(p11.2q14) in eight individuals with infertility or recurrent miscarriages in three different families.
Keywords: Infertility; recurrent miscarriages; pericentric inversion; inv(12)(p11.2q14).

ÖZ

Çocuk sahibi olmak isteyen çiftlerin %15'inde görülen infertilite, tüm dünyada önemli bir sağlık sorunudur. Gebeliklerin %15-25'inde gözlenen tekrarlayan düşükler, dünya genelinde milyonlarca çifti etkileyen bir diğer önemli sorundur. Özellikle son yıllarda infertilite ya da tekrarlayan düşüklüklerle pek çok genetik faktör ilişkilendirilmiş olsa da, bu sorunların altında yatan genetik ve epigenetik faktörlerin çok büyük kısmı henüz bilinmemektedir. Perisentrik inversiyonların çoğu, taşıyıcı bireylerin fenotipini etkilemez. Bununla birlikte mayoz bölünmenin krosing over aşamasında hatalara neden olabilen perisentrik inversiyonlar infertiliteye veya tekrarlayan düşüklere yol açabilir. Bu olgu sunumu çalışmasında, üç farklı aileden sekiz bireyde tespit ettiğimiz pericentric inv(12)(p11.2q14)'ün infertilite ve tekrarlayan düşüklerle ilişkisi üzerinde durulmuştur.
Anahtar kelimeler: İnfertilite; tekrarlayan düşükler; perisentrik inversiyon; inv(12)(p11.2q14).

INTRODUCTION

Infertility is a disease defined by the failure of achieving a pregnancy after one year or more of regular unprotected sexual intercourse (1). Recurrent miscarriage is defined as 3 or more consecutive clinical pregnancy losses before 20 weeks of gestational age (2). Despite many genetic factors have been associated with infertility or recurrent miscarriages especially in recent years, the genetic and epigenetic factors underlying these problems are mostly unknown (3). When a chromosome breaks at two points, occasionally the region of chromosome among the breaks rotates 180° before reinserted to the same chromosome (1). This event is called as inversion, which is one of the mutations at the chromosomal level. First evidence of inversion was published by Alfred Sturtevant in 1921 (4). Most of the pericentric inversions do not affect phenotypes of the individuals carrying balanced rearrangements. However, the pericentric inversions may cause chromosomally unbalanced sperm/ovum during the meiotic crossover leading to infertility or recurrent miscarriages (5). Here, we report a familial pericentric inv(12)(p11.2q14) in eight individuals with infertility or recurrent miscarriages in three different families (Figure 1). Informed written consents for the publication of clinical details and images were obtained from the patients.

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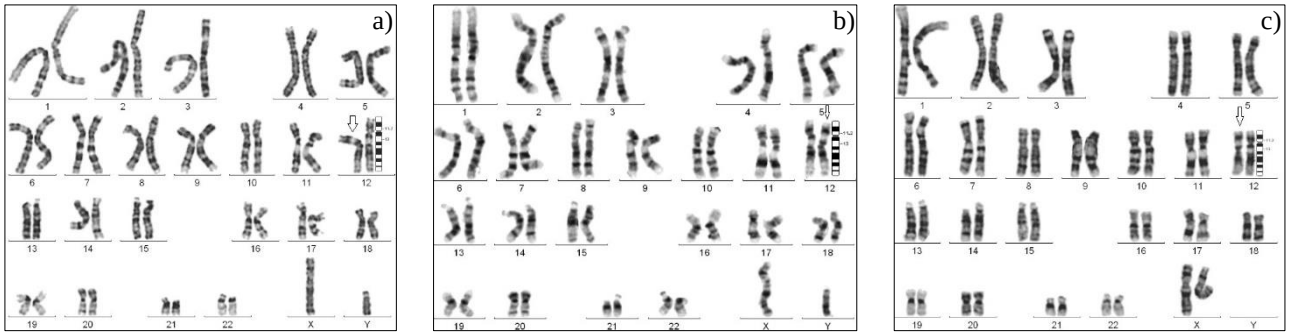

Figure 1. Karyotypes of the three patients included into the study. The Inv(12) chromosomes marked with arrow. a) The karyotype of the patient with recurrent miscarriages in family 1, b) The karyotype of the case with infertility in family 2, c) The karyotype of the patient with infertility in family 3

CASE REPORT

Family 1

A couple with a history of recurrent miscarriages was referred to the Medical Genetics Department of Istanbul Medical Faculty at Istanbul University for cytogenetic evaluation. The husband was a 35-year-old healthy male and the wife (proband) was a 32-year-old female. The couple experienced four intrauterine fetal deaths before the 18th week of pregnancy and had a healthy three years old girl. The wife had 8 phenotypically normal siblings. The husband had a normal karyotype (46, XY), although the wife's karyotype was 46, XX, inv(12)(p11.2q14). Further karyotype analysis for her parents and 4 siblings demonstrated that her mother and her three siblings had normal karyotypes, however, her father and her brother had the same balanced chromosomal inversion. Moreover, the brother carrying the same inversion had an extra Y chromosome (47, XYY, inv(12)(p11.2q14)) and he had two healthy girls. There was not any miscarriage or infertility history in proband's family.

Family 2

The second family had also infertility problem. The proband was a 33-year-old man with a history of four years of primary infertility. His wife was apparently healthy. The patient and his wife were not consanguineous. The proband had one unmarried sister and his parents had no history of miscarriage or infertility. Both testes of the case are located in the scrotum with a normal volume. Semen analysis of the proband revealed azoospermia. His endocrine hormone levels were within normal limits: Follicle-Stimulating Hormone (FSH) was 3.6 IU/L (normal range 1.2–12.4 IU/L); Luteinizing hormone (LH) was 5.12 IU/L (normal range 1.7-8.6 IU/L); testosterone was 2.5 ng/mL (normal range 2.3-8 ng/mL). Y microdeletion analysis of the proband demonstrated that there was no microdeletions on azoospermia factor regions (AZFa, AZFb and AZFc) of the Y chromosome. Karyotype analysis was carried out for the proband, his parents, and his sister. His karyotype was 46, XY, inv(12)(p11.2q14). The mother and the sister had a normal 46, XX karyotype, however, the proband's father had the same inversion with the proband; 46, XY, inv(12)(p11.2q14).

Family 3

The third family had infertility history. The proband was 36-year-old male with infertility. His wife was a healthy 33-years-old female. Proband's basal endocrine hormone levels were normal: FSH was 11.71 IU/L; LH was 8 IU/L; and testosterone was 3.5 ng/mL Semen analysis of the proband revealed azoospermia. Y microdeletion analysis showed that there was no microdeletions on Y chromosome. His mother was his father's cousin (consanguineous). He had a 30-years-old, unmarried brother. There wasn't any miscarriage history of his mother and there was no person with miscarriage or infertility history among his relatives. Karyotype of the proband was 46, XY, inv(12)(p11.2q14) and his brother had the same inversion. Chromosome analysis could not be carried out for proband's parents since they were dead.

DISCUSSION

There are two kinds of inversions: 1) Paracentric inversions that do not contain the centromere with the breakpoints present on the same arm of the chromosomes and 2) pericentric inversions, which include the centromere with the breakpoints found on distinct arms of the chromosomes (6). During the meiosis, loop formation occurs in order to the pairing of normal homologous chromosome and the inverted chromosome. This event may give rise to abnormal gametes with duplicated and deleted chromosome regions (7). In general, the patients with chromosomal inversions are phenotypically normal, however there is an increased risk (estimated 6.1% for de novo abnormalities) for neurodevelopmental disorders or developing congenital anomalies for these patients (8). Chromosomal inversions are usually associated with infertility, intellectual disability (ID) and ovarian failure (8). Sperm segregation studies demonstrated that the size of the inverted chromosomal segment is important for the occurrence of unbalanced gametes throughout the meiosis. The inverted segment being more than 100 Mbp may affect reproductive fitness of the carriers significantly (9). Balanced chromosomal rearrangements including inversions may only be detected by karyotype analysis, however small alterations on chromosomes may not be clarified by this valuable method due to its low resolution (nearly 5-10 Mb) (8). The breakpoints of the inversion can exist in a vital region of the DNA coding sequences and the inversion can directly disrupt or change gene expression of adjacent genes by dividing regulatory elements from the corresponding coding sequences. Furthermore, some inversions can lead to additional consequence of the predisposition to copy number alterations and chromosomal translocations (10).

Some of the apparently balanced chromosomal translocations or inversions can be familial, which may lead to discordant phenotypes in patients with the same chromosomal abnormality in the family. The interpretation and counseling of these chromosome abnormalities is extremely challenging due to the deficiency of routine techniques and the scarcity of publications (11). For instance, in the family 1, although the proband with familial inv(12) had four early pregnancy losses, there wasn't any miscarriage in her parents. Furthermore, the proband's parents had eight phenotypically normal children. In family 2 and family 3, although the probands' parents had not experienced any recurrent miscarriage or infertility problem, the probands were azoospermic men. A number of mechanisms have been proposed to explain how familial balanced chromosome abnormalities including inversions may lead to discordant phenotypes in carriers. One of them is the presence of complex chromosomal rearrangements or submicroscopic imbalances. The second one can be functional homozygosity because of the gene disruption by the rearrangement of one allele and unmasking of a recessive gene mutation on the allele inherited from the normal parent. The disruption of imprinted genes could be one of the other possible mechanisms. The position effect of the genes existing near the break points and reduced penetrance could be the other important mechanisms about discordancy (11). It has been suggested that if the patients have a neurodevelopmental disorder or congenital anomaly then especially the putative candidate genes in the break regions of the chromosome should be investigated with Next-Generation Sequencing (NGS) methods (8). The knowledge about possible functional effects of familial inversions on infertility or miscarriage is still limited. Unfortunately, until now, a few number of inversions have been studied in detail in humans. It should also be noted that the location of the inversion breakpoints within complex repeated chromosomal segments makes it difficult to analyze them. For this reason, the inversions have been overlooked for a long time (10).

The inversions have rarely been reported as an additional chromosomal abnormality. To our knowledge, inv(12) have previously been reported in five cases as an additional abnormality. It has been described in a patient with trisomy 21 and a familial pericentric inversion (12)(p13q13) (12). In a different study, a familial inv(12) has been found in a girl. Her karyotype was 46, XX, inv(12)(p13q22) / 47, XX, i(Xq),inv(12)(p13q22) (13). In another study, a familial inversion (12)(p13q13) was identified in a girl with Down Syndrome (14). A paracentric inversion inv(12)(q15q24) (15) and a centric inversion inv(12)(p10p13.3) have been described in two different patients with Klinefelter syndrome (16). In the family 1, proband's brother carrying inv(12) had an extra Y chromosome. To the best of our knowledge, coexistence of the inv(12) and extra Y chromosome was first shown in our report. Considering the previous and our cases, inv(12) seems to be associated with numerical chromosome abnormalities.

To date, pericentric inversion 12 have been reported in twelve families in seven studies (Table 1). In one study, it has not been reported whether the inv(12) is familial or de novo (22). In the current study, we report three familial pericentric inv(12). Literature findings and our study demonstrate that the pericentric inv(12) mostly occurred as familial chromosome abnormalities. No viable fetus or child was reported with unbalanced chromosome 12 derived from balanced pericentric inv(12) in parents. In none of the twelve families in those seven studies, the pericentric inv(12) has not been associated with infertility. However, we report two infertility patients with familial inv(12) in current study. The proband experienced recurrent miscarriage in family 1 and infertile probands having this abnormality in family 2 and family 3 might be evidences that the pericentric inv(12) may cause recurrent miscarriages and infertility.

Table 1. Previous studies reporting pericentric inv(12) as familial chromosome abnormality

	Break point	NF	Carriers	Family History	Rf
Previous Studies	inv(12)(p13q11)	1	Father and two children	Advanced maternal age	18
	inv(12)(p13;q11) inv(12)(p13;q13)	2	Two patients in different families	NA	12
	inv(12)(p11.2q13)	1	15 carriers out of 44 individuals in one 8 generation family	A previous stillborn child	19
	inv(12)(p11.2q13)	2	Two patients in two different families	Routine chromosome analysis	17
	inv(12)(p11q13)	2	Two different cases. One of them had paternal inversion and the other had maternal inversion	NA	20
	inv(12)(p13q13)	3	25 carriers out of a total number of 52 persons examined in three families	Family 1: a previous child with Down's syndrome Family 2: A preterm delivery and two late abortions Family 3: advanced paternal age	14
	inv(12)(p12.3q14)	1	A Child and her father	Advanced maternal age	21
	inv(12)(p12q12)	*	NA	Infertility	22
Current Study	inv(12)(p11.2q14)	1	A wife, her father and her brother had the same inversion	Recurrent Miscarriages The brother of the wife carrying the same inversion had an extra Y chromosome	F1
	inv(12)(p11.2q14)	1	A male patient and his father had the same inversion	Infertility	F2
	inv(12)(p11.2q14)	1	A male patient and his brother had the same inversion	Infertility	F3

*: It has not been mentioned whether this inversion is de novo or familial in this patient, NF: Number of the affected family in the studies, Rf: Reference, NA: Not available (This information was not found in the article), F1: Family 1, F2: Family 2, F3: Family 3

Consent: Informed written consents for the publication of clinical details and images were obtained from the patients.
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Paravertebral Abscess and Spondylodiscitis due to *Streptococcus agalactiae* after Transrectal Prostate Biopsy

Prostat Biyopsisi Sonrası *Streptococcus agalactiae*'ya Bağlı Gelişen Paravertebral Apse ve Spondilodiskit

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ABSTRACT

Streptococcus agalactiae, is the species designation for streptococci belonging to Lancefied group B and are facultative, gram-positive diplococci. In the previous years, it was known as urinary tract infection agent in pregnant women, it was rarely detected in other infections in adults. Nowadays, *S. agalactiae* is increasingly recognized as a cause of invasive infections such as bacteraemia without any focus, skin and soft tissue infections, upper respiratory tract infections, osteoarticular infections, peritonitis, cardiac infections, meningitis and other focal infections among non-pregnant adults, especially in the elderly and immunocompromised patients. Although rare in the literature, osteoarticular infections caused by *S. agalactiae* have been reported in adults. In this case report, we aimed to present a patient with iatrogenic spondylodiscitis due to *S. agalactiae* after ultrasound-guided transrectal prostate needle biopsy.
Keywords: Transrectal prostate biopsy; spondylodiscitis; *Streptococcus agalactiae*.

ÖZ

Streptococcus agalactiae, Lancefied sınıflamasına göre B grubuna ait, fakültatif, gram-pozitif koktur. Önceki yıllarda gebe kadınlarda idrar yolu enfeksiyonu etkeni olarak bilinirken, diğer erişkinlerde nadir görülen bir hastalık etkeni idi. Günümüzde ise *S. agalactiae*, gebe olmayan erişkinlerde özellikle immün sistemi baskılanmışlarda, kronik ve yaşlı hastalarda, kaynağı saptanamayan bakteriyemi, yumuşak doku enfeksiyonları, üst solunum yolu enfeksiyonları, osteoartikuler enfeksiyonlar, peritonit, kardiyak enfeksiyonlar, menenjit ve diğer odak enfeksiyonları gibi invaziv enfeksiyonların bir nedeni olarak giderek daha fazla saptanmaktadır. Literatürde nadir olmakla birlikte, erişkinlerde *S. agalactiae*'nin neden olduğu osteoartiküler enfeksiyonlar bildirilmiştir. Bu olgu sunumunda, ultrason eşliğinde transrektal prostat iğne biyopsisi sonrası *S. agalactiae*'ya bağlı iatrojenik spondilodiskit gelişen bir hastanın sunulması amaçlanmıştır.
Anahtar kelimeler: Transrektal prostat biyopsisi; spondilodiskit; *Streptococcus agalactiae*.

INTRODUCTION

Infection of the intervertebral disc, described as usually spondylodiscitis or vertebral osteomyelitis. In developed countries, the incidence of this disease varies between 1:100,000 and 1:250,000 and is more common in the elderly (1,2). Spondylodiscitis may develop spontaneously or iatrogenically. Although it is rare, spontaneous or iatrogenic spondylodiscitis may cause morbidity and long-term sequelae. Microorganisms can reach the intervertebral disc by hematogenous dissemination through arteries or veins or by directly inoculation (3). Some medical interventions like spinal surgery, intravenous catheter use, vascular or urogenital interventions may lead to iatrogenic spondylodiscitis.

Respiratory tract, skin, gastrointestinal tract, genitourinary tract, or the oral cavity infections are common primary sources for the haematogenous route of spine infection (3,4). In the etiology of pyogenic spondylodiscitis, *Staphylococcus aureus* is the most common pathogen (55.1%) isolated from cultures (2). The other common microorganisms frequently isolated in pyogenic spondylodiscitis are *Streptococcus* species and other Gram-negative bacilli (3).

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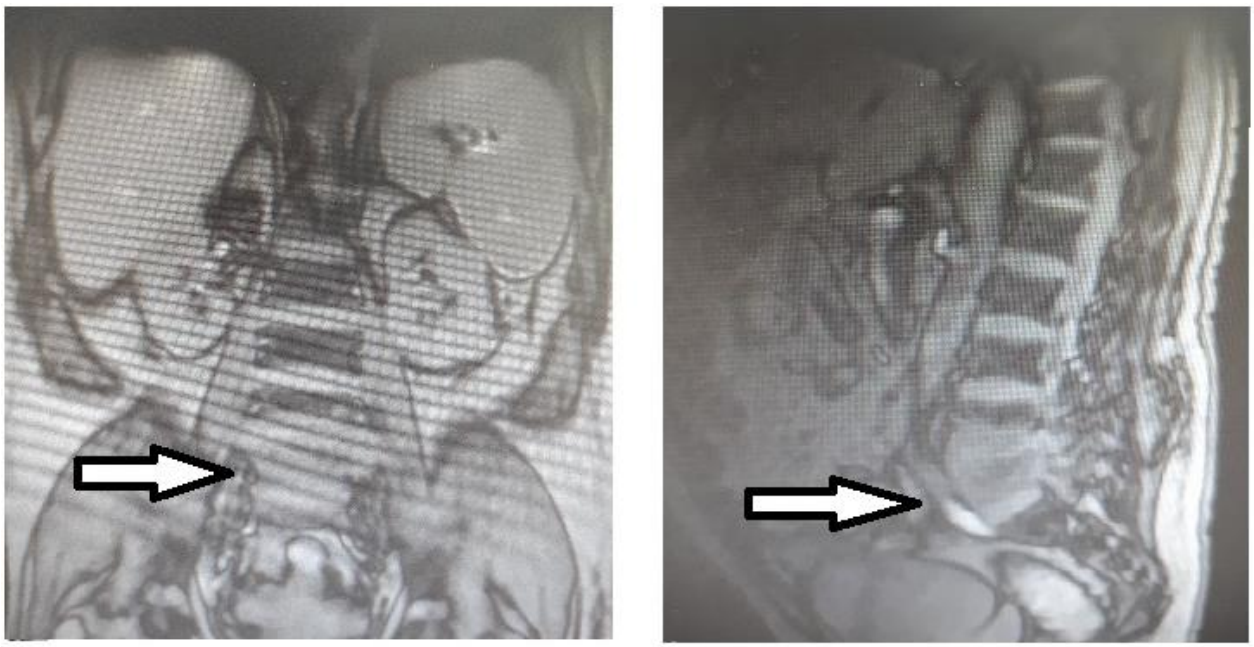
Streptococcus agalactiae is a member of the normal gastrointestinal flora in some humans and can spread to secondary sites. *Streptococcus agalactiae* may lead several invasive infections among non-pregnant adults who are usually elderly and have an underlying illness such as neurologic disease, cirrhosis, diabetes mellitus, renal failure, malignancies and immunosuppressive conditions such as acquired immunodeficiency syndrome and people those undergoing intravenous catheterization. They can rarely cause vertebral osteomyelitis and spondylodiscitis (5). In this case report, it was aimed to present a patient with iatrogenic spondylodiscitis due to *S. agalactiae* after ultrasound-guided transrectal prostate needle biopsy.

CASE REPORT

A 72-year-old male was admitted to the hospital with symptoms of fever, weakness, fatigue, anorexia and fever for two weeks. The patient did not have a history of trauma or known chronic illness (underlying chronic diseases including diabetes, cancer, renal/liver dysfunction and other any immunosuppressive conditions) except benign prostatic hypertrophy. In his medical history, he had a transrectal biopsy of the prostate performed one month ago. Before the transrectal biopsy of the prostate, he had used prophylactic oral ciprofloxacin (500 mg twice) treatment per day for three days. The two days after biopsy of the prostate, the patient experienced high fever, and two weeks after biopsy, he complained of pain localized to the lumbar spine. In physical examination, he was febrile (38,4ºC), heart rate was 90 beats/min, arterial blood pressure was 132/82 mmHg, respiratory rate was 18 beats/min and oxygen saturation was normal. Pulmonary and cardiac auscultation and his neurological examination, including sensory function and motor strength, were normal. There was a tenderness in the lumbar spine. He had no history for tuberculosis. There were no risk factors for brucellosis in his medical history and there was no consumption of fresh cheese and animal husbandry.

In his laboratory examinations: leukocyte count (WBC) was: 8970/mm^3 (neutrophil 80.5%), hemoglobin: 11.2 g/dL, erythrocyte sedimentation rate (ESR): 105 mm/h, C Reactive Protein: 86.3 mg/L (<5), RF: 10 IU/mL (<14). His serum creatinine, creatine kinase and liver enzymes were within normal values. Urine microscopy was normal. The Purified protein derivative (PPD) - tuberculin skin test was anergic. Rose Bengal test and Coombs anti-Brucella testes were negative. Serum result was negative for Human Immunodeficiency Virus (HIV).

Peripheral blood cultures and urine culture were performed on admission and treatment with sulbactam-ampicillin (1 g IV 4 times a day) were administered empirically. His blood and urine cultures were sterile. His chest radiograph, ultrasound imaging of the abdomen and transthoracic echocardiography were unremarkable. Vertebral Magnetic Resonance Imaging (MRI) was performed due to the patient's low back pain. The MRI revealed signs of spondylodiscitis and approximately 1x0.5 cm abscess was seen in the paravertebral area at the level of L2-L3 vertebra (Picture 1). An ultrasound-guided needle biopsy was performed to obtain a sample from the lesion described in MRI and tissue materials were cultured. The pathology of the biopsy material revealed spondylodiscitis. Gram-positive cocci were detected in gram staining of biopsy material and microbiological culture was positive for *S. agalactiae* by using API NH system (bioMerieux, NC, USA). The streptococcus strain was resistant to ciprofloxacin but susceptible to penicillin. Therefore the patient received intravenously penicillin (24 million of Units/day, divided in six doses) treatment for four weeks. After four weeks, his complaints decreased and he was discharged with sequential oral therapy and continued in ambulatory two weeks of therapy with amoxicillin plus clavulanic acid (2×1 g/day, po) as well as functional rehabilitation. In outcome and follow-up, the infection parameters declined in his laboratory examinations. There were no further episodes of fever, with significant reduction of the pain and there was no neurological deficit in physical examination.



Picture 1. Lomber vertebral MRI revealed signs of spondylodiscitis at the level of L2-L3 vertebra.

DISCUSSION

Transrectal ultrasound (TRUS)-guided prostate needle biopsy, under prophylactic antibiotics, is the method for diagnosing prostate diseases and is generally known to be a safe procedure. Infectious complications may occur after this procedure, such as symptomatic urinary tract infection, bacterial prostatitis, epididymitis, urethritis, prostatitis, fever, chills and sepsis (6). *Escherichia coli* is the most common bacteria isolated from cultures after TRUS-guided prostate needle biopsy, due to inoculation of bacteria during the TRUS-guided prostate needle biopsy as the needle passes through the contaminated rectum (7). Antibiotic prophylaxis for prostate biopsy reduces the incidence of infective complications after this procedure. Fluoroquinolones are the most commonly used antibiotics in prophylaxis. However, it has been reported in the literature that rectal flora elements are resistant to quinolones of 4% to 13% (8). The patient we presented had ciprofloxacin as prophylaxis too.

According to the source screening, in the literature six cases of spondylodiscitis following TRUBP have been reported previously (9). The incidence of iatrogenic spondylodiscitis is rising, possibly due to vascular devices or invasive procedures. This infection is more common in males than females and in fourth to fifth decades for unknown reasons. The most common location of spondylodiscitis is lumbar region (3). The case we present was 72 years old male; he had a recent history of prostate needle biopsy and had spondylodiscitis at the level of L2-L3 vertebra.

It is known that major symptoms associated with spondylodiscitis are pain (present in 90%) and fever (present in 52% of cases). However chills or fever spikes are rare (3). Our patient had fever and pain in the lumbar spine.

Elevated WBC scores rarely exceed in spondylodiscitis patients (present in 52% of cases). But ESR is usually above 40 mm/h and is seen in almost all cases of spondylodiscitis. Our case's ESR was elevated, too (2,3).

Blood, urine and bone cultures should be cultured before the antimicrobial therapy and this will help to guide the choice of antimicrobial therapy. Blood cultures may be positive in 50% of cases. We had taken the blood and urine cultures but there was no growth of the cultures. The patient's biopsy culture was positive for *S. agalactiae* and susceptible for penicillin.

MRI is a sensitive method for scanning spine and has become the gold standard in the evaluation of pyogenic spondylodiscitis. The findings on MRI can help early diagnosis. We had performed MRI, too.

The duration of intravenous treatment for susceptible microorganisms isolated in culture is recommended for six weeks or until ESR decreases significantly but there is no consensus on this issue (2,3,10). The coexistence of paravertebral abscess with spondylodiscitis greatly influences the duration and method of treatment (surgical or medical, IV / oral therapy). In most patients, treatment may need to be completed with parenteral therapy. But; if paravertebral abscess is not complicated, if there is no comorbidity, if there is oral susceptibility of the causative microorganism, if there is good response to the first parenteral treatment, bioavailability of the given oral treatment is good, the patient can continue with oral treatment after parenteral treatment (11). But there is no consensus on the minimum optimal duration of parenteral treatment in the treatment of spondylodiscitis (11,12). Our case had treatment for four weeks intravenously and continued in ambulatory two weeks of oral therapy.

CONCLUSION

In conclusion, pyogenic spondylodiscitis should be considered among the major complications of biopsy of the prostate and may occur despite prophylactic antibiotic use. There are no randomized or prospective studies concerning the optimal choice and duration of antibiotic treatment, as well as the role of surgery. The therapeutic approach is not standardized. As spondylodiscitis due to *S. agalactiae* is rare, large comparative prospective studies for the optimal length of the antibiotic treatment needed.

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Informed consent: Informed consent was obtained from the patient.

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Emergency Hybrid Treatment Strategy in Abdominal Aortic Injury during Microdiscectomy Operation: A Rare Case Report

Mikrodiskektomi Operasyonu Sırasında Abdominal Aort Yaralanmasında Acil Hibrit Tedavi Stratejimiz: Nadir Görülen Olgu

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ABSTRACT

Iatrogenic abdominal aortic injuries were previously reported during classical lumbar disc hernia repair. Microdiscectomy technique begun to used widely with time instead classical lumbar disc hernia due to its minimally invasive nature. Recently, microdiscectomy method is preferred more frequently among these methods. Small incisions, good exposures and low risk of bleeding are known advantages of the microdiscectomy method compared to the classical method. There was no iatrogenic abdominal aortic injury during microdiscectomy surgery reported in literature, as our knowledge. In this report, it is aimed to present a 62-year-old female patient who underwent an operation due to lumbar disc herniation and who had aortic injury during microdiscectomy in the neurosurgery clinic and emergently treated with endovascular aortic repair method.

Keywords: Emergency hybrid treatment; microdiscectomy; abdominal aortic injury.

ÖZ

Daha önceleri klasik lomber disk hernisi operasyonlarında, abdominal aort yaralanma olguları bildirilmiştir. Zamanla klasik disk hernisi operasyonu yerine, minimal invazif olması dolayısıyla mikrodiskektomi operasyonu yaygın olarak kullanılmaya başlandı. Son zamanlarda bu yöntemlerden mikrodiskektomi yöntemi daha sık tercih edilmektedir. Küçük cerrahi insiziyon, düşük kanama oranı ve iyi expojur sağlaması mikrodiskektomi yönteminin klasik yönteme göre bilinen avantajlarıdır. Literatürde, mikrodiskektomi operasyonuna bağlı olarak bildirilmiş abdominal aort yaralanması vakasına rastlayamadık. Bu olgu sunumunda, lomber disk hernisi nedeni ile operasyon planlanan, beyin cerrahisi kliniğinde mikrodiskektomi işlemi yapılırken aort yaralanması gelişen ve tedavide acil olarak endovasküler yöntem ile aort tamir uyguladığımız 62 yaşında kadın hastanın sunulması amaçlanmıştır.

Anahtar kelimeler: Acil hibrit tedavisi; mikrodiskektomi; abdominal aort yaralanması.

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INTRODUCTION

Lumbar disc herniation is a common disease nowadays. In recent years, minimally invasive methods have been used widely. Among these methods, microdiscectomy is the most effective method. Small incisions, good exposures and low risk of bleeding are known advantages of the microdiscectomy method (1). Abdominal aortic injuries are very rare to be occurred during the microdiscectomy.

In this case report, we aimed to present a 62-year-old female patient who underwent surgery due to lumbar disc herniation. She developed aortic injury while undergoing microdiscectomy in the neurosurgery clinic and was treated with endovascular method, emergently.

CASE REPORT

A 62-year-old female patient was diagnosed with disc herniation with complaint of low back pain. Microdiscectomy procedure was decided to be performed by the neurosurgery clinic. The patient underwent a microdiscectomy under spinal anesthesia and had massive bleeding from the abdominal aorta. The bleeding was immediately stopped via Floseal®. The patient was sent to a computerized tomography (CT) and the CT scan detected findings considered as extravasation-pseudoaneurysm, and emergent consultation to cardiovascular surgery clinic was requested (Figure 1).

The bleeding was stopped and hemodynamics was stable, it was decided to take the patient to a hybrid operating table for rapid treatment. As soon as the right femoral artery was explored, severe hypotension and abdominal distention developed. Upon this, we decided to perform open surgery immediately. Since the patient was in a hybrid operating room and the right femoral artery was exposed; we planned to introduce and inflate an occlusion balloon through femoral artery for temporary clamping until the abdomen was opened and aorta was clamped. Emergent angiograph was performed. For this purpose, angiography was performed immediately and it was seen that the infrarenal part of the abdominal aorta was long and the ruptured area was in the middle and posterior section (Video 1). It was thought that this rupture area could be closed with tubular graft. Measurements were made quickly. The injury in the abdominal aorta was repaired with endovascular method by Medtronic Endurant tubular aortic stent graft with dimensions of 25x25x49 mm. The graft was placed covering 20 mm below and 20 mm above the ruptured area on the intact aorta. Bleeding stopped after the procedure (Video 2). Following the operation, blood pressure values were brought to normal levels with appropriate fluid replacement and blood product transfusion.

General surgery consultation was requested in consequence of abdominal distention. As the pressure within the abdomen was too much, it was decided to open the abdomen and retroperitoneum for hematoma drainage to prevent abdominal compartment syndrome. The abdomen was opened; there was no free fluid and blood in the abdomen. When the retroperitoneum was opened, a large amount of hematoma and 2500 cc defibrinated blood were aspirated to cell saver. The aspirated blood was returned to the patient after washing. There was no bleeding from the aorta. The aorta was seen to be adherent to the paravertebral tissue. Retroperitoneum and abdomen were closed and the operation was terminated. There was no complication in the patient who was extubated on postoperative first day. The patient was transferred to the neurosurgery clinic.

On the 30th postoperative day, computed tomography showed no extravasation (Figure 2).

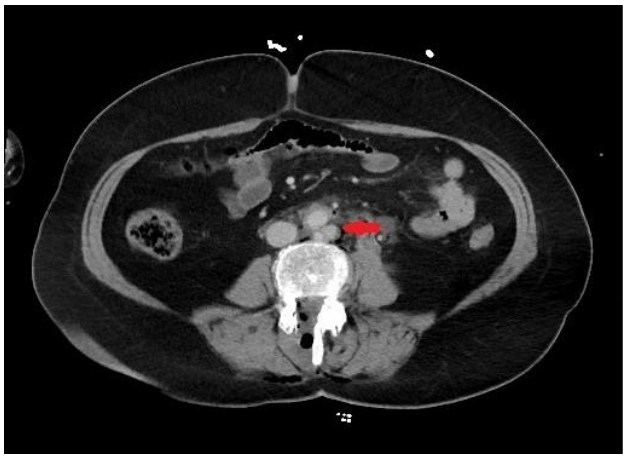
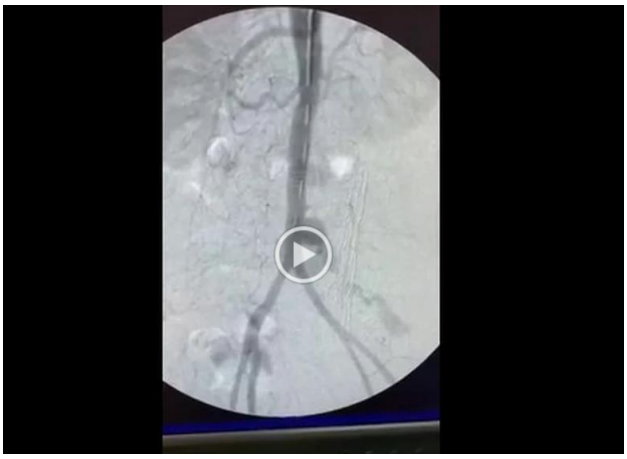


Figure 1. Preoperative CT image (arrow indicates the injured segment)



Video 1. Preprocedural angiographic view showing aortic injury

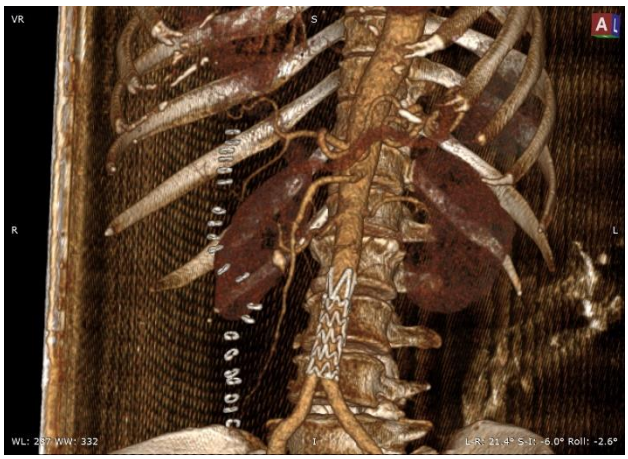
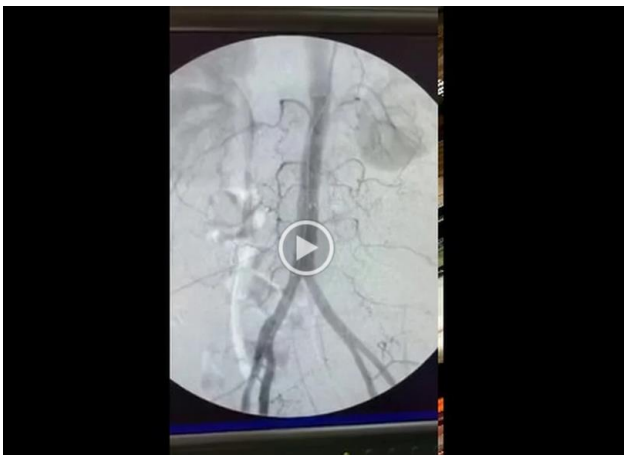


Figure 2. CT image on 30th postoperative day



Video 2. Postprocedural view

DISCUSSION

Endovascular treatment methods are performed by using catheters and radiological facilities. Hybrid procedures are performed in an operating room with C-arm scopy. Widespread use of hybrid operation rooms has led to a significant increase and progress in endovascular treatment of peripheral arterial diseases and aneurysms. As successful results were obtained, endovascular methods were used in the emergency treatment of ruptured aneurysms. Evidence of successful treatment of emergency procedures with endovascular methods has led to the idea that endovascular methods can be used in traumatic vascular injuries. Even complex vascular emergencies which can only be treated surgically in the past periods can be treated very quickly and successfully with hybrid procedures. There is no large series of studies using endovascular methods related to traumatic vascular injuries. Results are usually reported as case reports or case series. Sahin et al. (2), in a case series including 9 patients, showed that endovascular treatments can be applied in traumatic vascular injuries. These series of cases reported in the literature were usually pseudoaneurysm or arteriovenous fistulas and were relatively elective cases. In our case, it is unquestionable that when we consider rupture of abdominal aorta and bleeding even after hemostasis with Floseal, we are faced with a very emergent picture. In the literature, endovascular treatments have been reported for thoracic aorta injuries in such emergency situations but have not been reported for abdominal aorta. Today, endovascular treatment is successfully applied in traumatic injuries of the thoracic aorta (3). Abdominal aorta (due to its anatomical features, celiac trunk, renal artery side branches and bifurcation of aorta),is a disadvantageous region for placing tubular graft immediately in a traumatic injury. In our case, the injury was located in the middle and posterior of the infrarenal segment of the abdominal aorta (Video 1). In addition, the infrarenal segment of the abdominal aorta was long and the injury was in the middle section. These anatomical features and localization were some of the most important parameters that enabled the success and speed of the procedure. The guidelines of aortic surgery have been reported that an intact landing zones of minimum 20 mm in the proximal and distal region of the injury site should be covered with graft on the solid aorta. In our case, this distance was adjusted to be 22-23 mm from the proximal and distal. It would be time consuming to use bifurcated grafts or chimney technique in cases which iliac arteries or renal arteries were involved and it would be controversial for endovascular treatment to be the first choice. In addition, the absence of these materials in the hospital warehouse is a separate problem. The most important advantages of hybrid interventions compared to classical surgeries are being more minimally invasive, less mortality and morbidity. Mortality and morbidity were not observed in our case.

However, due to the serious retroperitoneal hematoma, the general surgery clinic decided to drain the hematoma and laparotomy was performed. For this reason, endovascular treatment was not minimally invasive for our case. On the other hand, when the retroperitoneum was opened, it was observed that the infrarenal abdominal aorta was highly adherent to the paravertebral tissue. If endovascular treatment would not be possible to perform for this case, it can be foreseen that open surgery will be technically challenging considering the adhesions in the aorta and the location of the ruptured part. Although laparotomy was performed for hematoma, we believe that it is possible to perform a faster operation with less mortality and morbidity by using the endovascular treatment method. On the other hand, it should not be overlooked that defibrinated blood aspirated with a cell saver during laparotomy was given back to the patient.

The most important drawback of endovascular treatment is the problems that may occur in the long term. The most common of these problems are endoleaks, which are commonly seen in stent grafts used in aneurysms (4). Although there are many reasons for this, the most common cause in the long term is aneurysmatic enlargement in the neck part of the stent graft due to the progressive nature of the aneurysm. In our case, there was no aneurysm in the etiology and there was no atherosclerotic pathology of the aorta.

In conclusion, if there is anatomic compliance and adequate equipment and an experienced team is available, endovascular treatment methods can be applied as the first choice for the traumatic injuries of the abdominal aorta.

Informed consent: Written informed consent was obtained from the patient.

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A Rare Cause of Breast Mass: Granular Cell Tumor

Memede Kitlenin Nadir Bir Nedeni: Granüler Hücreli Tümör

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ABSTRACT

Granular cell tumor is a rare type of soft tissue tumor originated from Schwann cells and often affecting head and neck region. Granular cell tumor, which may have many different organ involvements in the body, can rarely observed in breast tissue. A 57-year-old postmenopausal woman underwent excisional biopsy in another health facility due to a palpable rapidly growing painless mass on her left breast. Re-excision with wide surgical margins was performed to the patient whose biopsy was reported as granular cell tumor of breast with positive surgical margin. Postoperative follow-up was uneventful, and the patient was discharged without complication. Wide local excision should be performed to prevent local recurrence in the surgical treatment of granular cell breast tumor, which is similar to breast carcinoma in both radiological and clinic appearance. In this case report, we aimed to present diagnosis and treatment of granular cell tumor with current literature knowledge.

Keywords: Granular cell tumor; breast cancer; calretinin.

ÖZ

Granüler hücreli tümör sıklıkla baş ve boyun bölgesini etkileyen, Schwann hücrelerinden kaynaklanan, nadir bir yumuşak doku tümörü tipidir. Vücutta pek çok farklı organ tutulumu olabilen granüler hücreli tümör, nadir de olsa memede de gözlenebilmektedir. Elli yedi yaşında postmenopozal kadın hastaya sol memede hızlı büyüyen ele gelen ağrısız palpabl kitle nedeniyle dış merkezde eksizyonel biyopsi uygulanmıştı. Biyopsisi memenin granüler hücreli tümörü olarak raporlanan ve cerrahi sınır pozitifliği olan hastaya, geniş sağlam cerrahi sınırlarla reeksizyon yapıldı. Postoperatif takiplerinde bir problem yaşanmayan hasta sorunsuz bir şekilde taburcu edildi. Klinik ve radyolojik olarak meme karsinomuna benzerlik gösteren granüler hücreli meme tümörünün cerrahi tedavisinde lokal nüksü engellemek amacıyla geniş lokal eksizyon yapılmalıdır. Bu olgu sunumunda, granüler hücreli tümörün tanı ve tedavisini güncel literatür bilgisi eşliğinde sunmayı amaçladık.

Anahtar kelimeler: Granüler hücreli tümör; meme kanseri; calretinin.

INTRODUCTION

Granular cell tumor (GCT) is a type of soft tissue tumor which is originated from Schwann cells and was first described in the breast by Abrikossoff in 1931 (1). GCT can occur in any part of the body, and often affects the tongue, head, and neck region (1). The incidence of granular cell tumors of the breast is 6-8% (2). Although GCT usually has a benign character, 1% of all of the GCT cases can also reveal malign character (2). GCT of the breast is uncommon, and it is difficult to identify since granular cell breast tumor (GCBT) mimics breast carcinoma both clinically and radiologically. However, although they have similarities, it is vital to make a differentiation between them since the surgical and postoperative treatment approach and the prognosis are very different.

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CASE REPORT

A 57-year-old postmenopausal woman presented with a palpable rapid growing painless mass on the left breast, which caused a distorted skin. She had no family history of cancer and also had no history of chronic illness, drug use, operation, or smoking. Her breast ultrasonography (USG) revealed a non-selectable spicular contoured nodular opacity in the upper inner quadrant of the left breast. A tru-cut biopsy was performed with the suspicion of breast carcinoma. Since the tru-cut biopsy did not distinguish between benign and malignant, the patient underwent an excisional biopsy.

Histopathological results of the biopsy specimen macroscopically revealed a granular cell tumor which was 1.3x0.8x1 cm in size. Microscopically the tumor had low-grade mitotic activity without local invasion. Hormone receptors were negative, and surgical margin positivity was detected. Pathology preparates were consulted with the department of pathology, and the diagnosis of granular cell tumor was confirmed. Histopathological examination of the tumor consisted of cells with an oval-round nucleus and eosinophilic granular cytoplasm (Figure 1 and 2). Tumor cells were S100 positive (Figure 3) and CD68 negative immunohistochemically. It was also stained positively with PAS (Figure 4).

The patient was diagnosed with granular cell tumor, and re-excision was performed with clear surgical margins. Since the malignancy risk decrease in the cases of small-sized tumors without local invasion and low-grade mitotic activity, we did not perform sentinel lymph node biopsy. The patient was discharged on the postoperative second day without any complications. She was followed up for fourteen months without any local recurrence or distant metastasis.

DISCUSSION

GCTs of the breast is a rarely seen malignancy which originates from perineural Schwann cells between the lobular breast tissues (1,2). GCT mostly affects the head, and neck region, and soft tissue and generally has a benign character. Malignant features are present in 1% of the cases (1,2). The incidence of GCBT has increased in middle age, premenopausal, and black women (2,3).

Although GCT is mostly seen in the upper inner quadrant of the breast as in our case, breast carcinoma is usually located in the upper outer quadrant (3). GCBT often presents with a painless, mobile, mass (2,4). The mass can cause distorted skin. GCBT can be confused with breast carcinoma clinically because of distortion in breast skin and fibroadenoma with a mobile mass without pain (4,5).

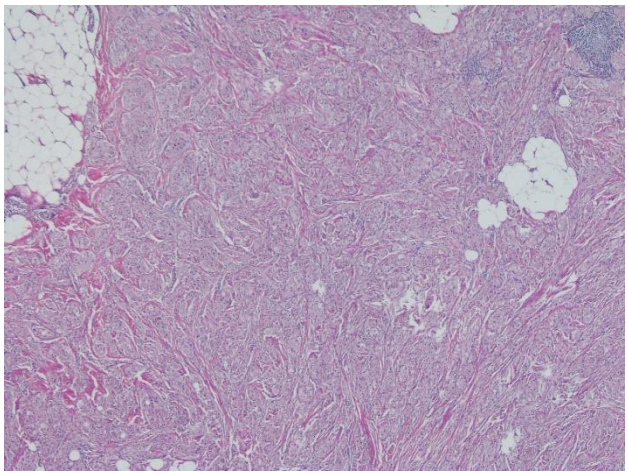

Figure 1. Tumor cells in adipose tissue (Hematoxylin & Eosin, 40x)

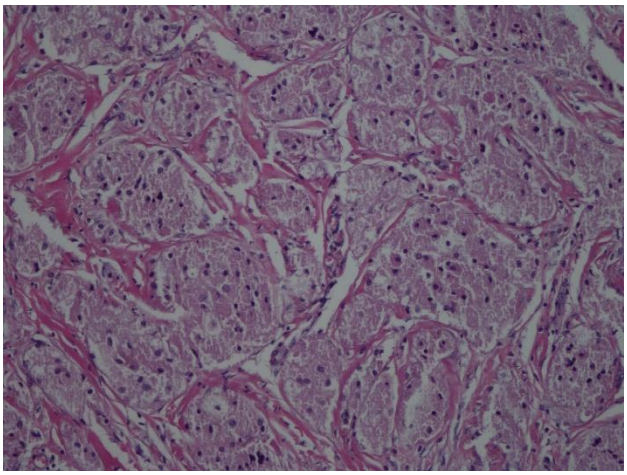

Figure 2. Oval-round nucleus, tumor cells with granular cytoplasm (Hematoxylin & Eosin, 40x)

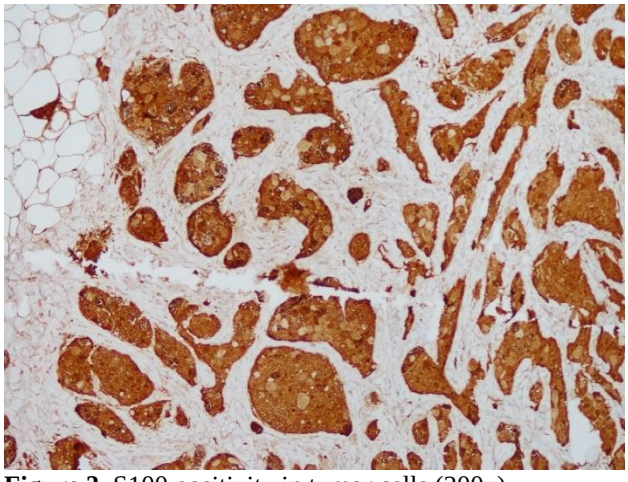

Figure 3. S100 positivity in tumor cells (200x)

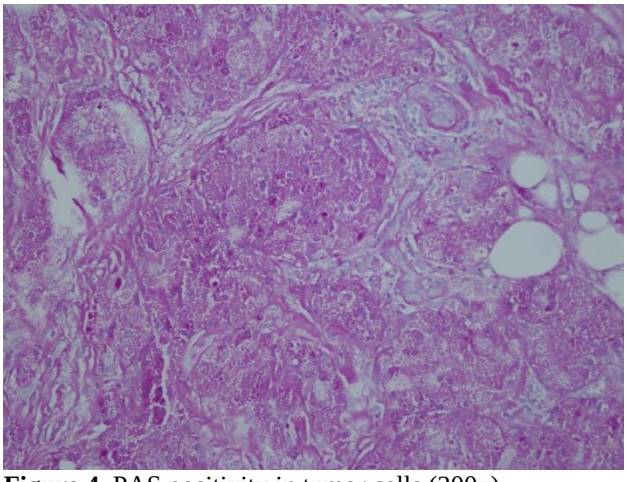

Figure 4. PAS positivity in tumor cells (200x)

USG and mammography can lead to a misdiagnose since carcinoma and GCBT have similar appearances such as irregularity, spiculation, stellation, and isodensity. Microcalcification in mammography is not an expected radiological finding for GCBT. GCBTs are more commonly described as spicular extensions or well-defined masses (2,4). PET-CT can accurately differentiate GCBT from a malignant tumor since it does not show increased glucose uptake (6).

The hormone receptor is negative, and neoplastic cells typically express S100 due to cytoplasmic lysosome content (4,5). S-100 protein, PAS-positive staining, and cytokeratin negativity differentiate GCBT from breast carcinoma immunohistochemically (4,5). Moreover, the study by Jiménez-Herrero et al. (7) showed that calretinin is an important marker in the differential diagnosis of GCBT and carcinoma.

Among the GCT, 1% of the cases have a malignant character with high rate metastasis and poor prognosis (8). Local invasion, increased mitotic rate, rapid growing, mass size (>4 cm), variation in cell size, and shape suggests the malignant variant of GCT (9). In our case, due to the small size and low mitotic activity of the tumor that indicated low malignancy risk, we did not prefer to perform sentinel lymph node biopsy as reported in the literature (4,5).

The primary treatment of GCBT is surgical resection. These tumors have a good prognosis and can be treated with wide surgical excision (4,5). Inadequate excision, or surgical margin positivity can cause local recurrences. However, Brown et al. (10) reported that after extensive excision, approximately 2-8% of recurrence rates could be observed. Except for the malignant cases, sentinel lymph node biopsy or axillary dissection is not routinely recommended (4,5,10). However, Brown et al. (10) reported that surgical excision is the only treatment for GCTs, adjuvant chemotherapy, or radiotherapy are not needed. The efficacy of postoperative radiotherapy and chemotherapy in the treatment of GCBT is not known due to the limited number of studies.

In conclusion, GCBT is a benign disease that can mimic breast cancer clinically and radiologically. GCBT diagnosis can be established with the immunohistochemical examination of S-100 and calretinin. Surgical removal of the mass with wide excision can prevent local recurrence.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Conflict of Interest: All the authors declared no conflict of interest.

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Air Embolism in Liver: A Rare Location

Karaciğerde Hava Embolisi: Nadir Bir Yerleşim Yeri

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ABSTRACT

Air embolism is a rare clinical entity that must be well recognized with high morbidity and mortality rates. Sensitive early diagnosis methods are available for air embolism, but these methods are not always easy to reach. With the detection of venous air embolism, mortality and morbidity can be reduced by rapid aspiration of air and concomitant treatment. It is important to recognize and prevent the problems that embolism may cause in the early period. In venous air embolism, the amount of aspirated air is directly proportional to mortality and morbidity. The most important approach here is to try to prevent the development of air embolism and to make an early diagnosis in possible cases, keeping in mind that it can always develop. In this case report, we present a 51-year-old female patient with the diagnosis of air embolism in the postoperative period and the treatments applied.

Keywords: Air embolism; laparoscopy; liver; intensive care unit.

ÖZ

Hava embolisi nadir görülen ancak yüksek morbidite ve mortalite oranları ile iyi tanınması gereken bir klinik durumdur. Hava embolisi için sensitif erken tanı yöntemleri bulunmaktadır, ancak her zaman bu yöntemlere ulaşmak kolay olmamaktadır. Venöz hava embolisinin saptanması ile birlikte, havanın hızla aspire edilmesi ve yandaş tedavilerin uygulanması ile mortalite ve morbiditede azalma sağlanabilmektedir. Önemli olan erken dönemde embolinin ortaya çıkarabileceği sorunların tanınması ve önlenmeye çalışılmasıdır. Venöz hava embolilerinde, aspire edilen hava miktarı ile mortalite ve morbidite doğru orantılıdır. Burada en önemli yaklaşım hava embolisi gelişimini engellemeye çalışmak ve her zaman gelişebileceğini akılda tutarak olası durumlarda erken tanı koymaktır. Bu olgu sunumunda 51 yaşında kadın hastada postoperatif dönemde hava embolisi tanısı konması ve uygulanan tedaviler sunulmuştur.

Anahtar kelimeler: Hava embolisi; laparoskopi; karaciğer; yoğun bakım ünitesi.

INTRODUCTION

Gas embolism is an iatrogenic clinical problem mainly caused by gas entering the vascular system. In the literature, the term air embolism is used because air is the most common culprit in most clinical situations. However, embolism may occur following the use of other gases such as carbon dioxide (used during laparoscopy) and nitrogen protoxide. In arterial air embolism (AAE), air passes from heart defects or transpulmonary shunts into the systemic circulation and is referred to as paradoxic air embolism (PAE). Venous and arterial embolism have different presentations and effects that can be fatal if not recognized or treated.

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The air entering the arterial system is well tolerated by most organs. However, organs with high oxygen consumption such as brain and heart are more prone to damage. Hypoperfusion and hypoxia develop as a result of end-arteriolar obstruction in these organs and cause cell damage. This further reduces oxygenation by causing edema in the tissue (1).

For the formulation of venous air embolism (VAE), there must be a connection between the gas and the vein and the pressure difference between them requires the gas to enter the venous system. The damage will depend on the amount of air entering, the speed of air entry and the position of the patient. Very high amounts of air such as 5 ml/kg are often required for major effects such as cardiovascular stability and cardiac arrest. However, clinical symptoms may occur even with small amounts such as 0.5 ml/kg/min (2).

With the detection of VAE, rapid aspiration of air can reduce mortality and morbidity. In sudden VAEs, the amount of aspirated air is directly proportional to mortality and morbidity (3). The frequency of VAE is reported in varying proportions depending on the monitoring methods used (4). Prudence and fast action are key to preventing morbidity and mortality in clinical situations at risk.

Air embolism is an uncommon complication in laparoscopic surgery, but can be fatal if encountered (5). After the pneumoperitoneum is formed, it may occur as a result of the progression of the operation and the transition of the gas into the opened venous system, or by accidentally introducing the gas into the vascular structure instead of the abdomen. In this case report, we aimed to present a case report of air embolism during laparoscopy and subsequent localization of the liver.

CASE REPORT

A 51-year-old female patient underwent surgery for elective laparoscopic nephrectomy (LN) because of the presence of a common source of infection. The patient had no additional problems other than known hypertension. The preoperative laboratory values of the patient were within normal limits. After routine non-invasive monitoring (ECG, noninvasive blood pressure, pulse oximeter), anesthesia was induced with propofol 2 mg/kg, rocuronium 0.6 mg/kg and fentanyl 1 µg/kg. Anesthesia was maintained with desflurane MAC 1 and 50% FiO_2 oxygen-nitrogen mixture. End-tidal carbon dioxide ($EtCO_2$) monitoring was performed.

After the left lateral decubitus position, a veress needle was placed and carbon dioxide gas was tried to be given. However, resistance was encountered. Insufflation ceased. The laparoscopy method was abandoned without the placement of the trocars and it was decided to perform nephrectomy with open access technique (Hasson technique). The patient's hemodynamic parameters were stable. After the peritoneum was opened, the patient's $EtCO_2$ level decreased to 18. Blood pressure was arterial (TA): 53/33, heart rate (HR): 40 and SpO_2: 83. ST elevation was observed on the ECG monitoring. Surgery was terminated and emergency closure was started. Nephrectomy could not be performed. The patient was ventilated with 100% O_2. Ephedrine 15 mg and atropine 1 mg were administered to the patient. The patient's TA and end-tidal levels recovered rapidly. 0.6 mg enoxaparin sodium was administered subcutaneously. The patient was started to awaken with suggamadex 200 mg when TA: 127/67, HR: 97, SpO_2: 99 and $EtCO_2$: 29. The patient was extubated without any problem. The patient's saturation after extubation was around 90 with mask oxygen. The patient was taken to intensive care unit with the preliminary diagnosis of myocardial infarction (MI) and pulmonary thromboembolism (PTE).

On admission to the intensive care unit, TA: 138/78, SPO_2: 93 (with oxygen), and KH: 88. The pH of the patient's blood gas was 7.35, PO_2: 59 and PCO_2: 34. Cardiac enzymes, D-Dimer, hemogram, biochemistry parameters, PT-INR were studied. A 12-lead ECG was obtained. T negativity was observed in V 4-5-6 on ECG. Biochemistry values were reported as troponin: 22 ng/L and CK-MB: 1.57 µg/L. The patient was consulted with cardiology clinic. Echocardiography showed no evidence of PTE. ECG changes were evaluated as nonspecific changes. D-Dimer was reported as 0 mg/L. The control troponin value was reported as 47 ng/L. MI diagnosis was ruled out. Intravenous contrast-enhanced thorax computed tomography (CT) was performed. Tomography was reported as 'PTE was not observed. There are air densities in the liver entering the gravitational area' (Figure 1). It was concluded that the patient developed air embolism. The patient had abdominal pain. She was consulted with general surgery clinic. Analgesic was not applied to the patient and a follow-up decision was made. Because of air embolism in the intestines, necrosis was thought to occur and lower-upper abdominal CT with intravenous contrast was performed. Abdominal CT showed disappearance of air densities observed in the liver (Figure 2). No pathology was observed in the bowel. Non-cardiogenic pulmonary edema was detected in the lungs. The patient's lung pathology improved and she was taken to the service for two days and discharged home without any problem.

DISCUSSION

With the development of laparoscopic devices and technology in recent years, laparoscopy has started to play an important role in the treatment of genitourinary problems. LN was described in 1991 by Clayman et al. (6). The reasons for LN being superior to open surgery can be listed as: lower mortality, less blood loss, shorter return to daily life and better cosmetic appearance (7).

In a multicenter study of laparoscopic complications in retroperitoneal and pelvic extraperitoneal cases, the most common type of complication was vascular injury (8). Veress needle was held responsible for 18% of input injuries (9). In fact, although this needle is thinner than the trocar, it causes a higher rate of injury than the trocar.

Complications due to carbon dioxide insufflation have been reported in 2-4% of cases. Common complications are cardiopulmonary system disorders, hypercarbia and pulmonary acidosis. Gas (air) embolism is the most feared but rare complication of carbon dioxide. In the treatment of gas embolism, it is necessary to stop the insufflation and evacuate pneumoperitoneum. Rapid treatment is the most important factor determining morbidity and mortality. The patient is moved to the trendelenburg and left lateral decubitis position, which helps to move the gas bubble from the pulmonary circulation to the right heart. The patient is hyperventilated with 100% oxygen.

Transesophageal ultrasound can be used to display the air and aspirate it by a central venous catheter. Hyperbaric oxygen therapy (HBOT) should be considered especially in hemodynamic disorders, cardiopulmonary insufficiency, neurological deficit and end-organ damage (10).

In our case, VAE was diagnosed with sudden decrease in $EtCO_2$ and hemodynamic disturbance as a result of ventilation perfusion incompatibility. First, PTE and MI were ruled out. In our case, it was observed that a small amount of air accidentally delivered to the systemic circulation went to the liver which is the top organ due to the patient's position. Since air embolism was not suspected initially in the patient, central catheter was not inserted and air was not aspirated. However, since there was no massive embolism, there was no life-threatening condition and the patient's hemodynamics recovered rapidly with supportive therapy.

The aim of this case report is to consider the suspicion of air embolism in case of resistance to CO_2 insufflation after the placement of veress needle in laparoscopic surgery as in our case. In such a case, CO_2 insufflation should be stopped first and the patient should be followed closely for hemodynamics, $EtCO_2$ and blood gases for at least 5-10 minutes in terms of air embolism. If necessary, postoperative intensive care therapy may be required.

Informed Consent: Informed Consent was obtained from patient about case presentation.

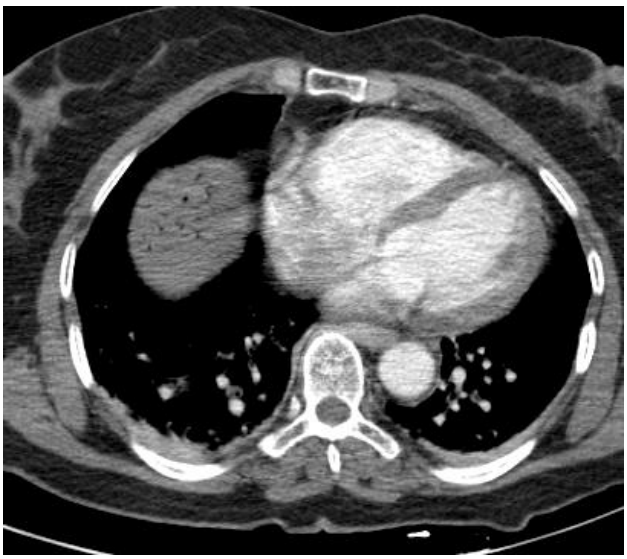

Figure 1. Air densities in liver

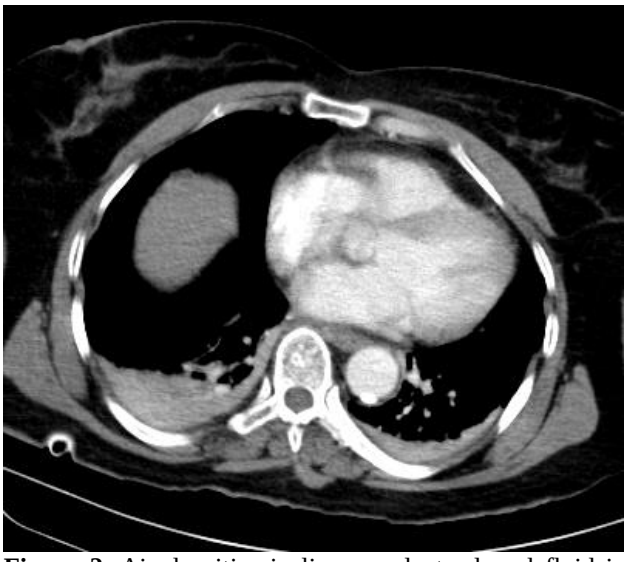

Figure 2. Air densities in liver are lost, pleural fluid is increased

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Revascularization in Erectile Dysfunction due to Pelvic Trauma

Pelvik Travma Sonrası Oluşan Erektil Disfoksiyonda Revaskülarizasyon

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ABSTRACT

Erectile dysfunction is defined as the inability to achieve penile erection necessary for sexual intercourse or to sustain erection sufficiently. Although the treatment options for erectile dysfunction are limited, the most common surgical treatment is penile prosthesis implantation. In addition, penile revascularization of the penis is very effective in the treatment of erectile dysfunction due to different vasculogenic reasons, especially pudendal artery occlusion, after perineal trauma. Modified Furlow Fisher technique including anastomosis of the inferior epigastric artery to the penile dorsal vein is a successful treatment option among the revascularization techniques. Despite invasive preliminary evaluations such as duplex Doppler ultrasound, dynamic cavernosometry, selective internal pudendal arteriography, and the long and difficult surgical procedure, it is highly effective in particularly selected young patients.

Keywords: Erectile dysfunction; revascularization; pelvic trauma.

ÖZ

Erektil disfonksiyon, cinsel ilişki için gerekli olan penil sertleşmeyi sağlayamamak veya ereksiyonu yeterince sürdürememek olarak tanımlanır. Erektil disfonksiyon ile ilgili tedavi seçenekleri sınırlı olmakla birlikte en sık başvurulan cerrahi tedavi yöntemi penil protez implantasyonudur. Bunun yanında vasküler hastalık olmaksızın perineal travma sonrası, başta pudental arter oklüzyonu olmak üzere farklı vaskulojenik sebeplerle gelişen erektil disfonksiyon tedavisinde, penisin yeniden kanlandırılması için yapılan penil revaskülarizasyon ameliyatı oldukça etkilidir. İnferior epigastrik arterin penil dorsal vene anastomozunu içeren Modifiye Furlow Fisher tekniği revaskularizasyon teknikleri içerisinde başarılı bir tedavi seçeneğidir. Revaskularizasyon cerrahisi, dubleks Doppler ultrason, dinamik kavernosometri ve selektif internal pudendal arteriyografi gibi ön değerlendirmelere, cerrahi işlemin uzun ve zorluğuna rağmen özellikle uygun seçilmiş genç hastalarda oldukça etkilidir.

Anahtar kelimeler: Erektil disfonksiyon; revaskülarizasyon; pelvik travma.

INTRODUCTION

Erectile dysfunction (ED) is defined as a permanent inability to maintain an adequate erection for satisfactory sexual performance in men (1). According to the possible etiology of ED, it may occur as physiological, neurogenic, endocrinological, vasculogenic, drug-induced or psychogenic (2). ED may also develop due to pudendal artery occlusion rarely occurring after pelvic trauma without atherosclerotic disease. Penile revascularization is an important and effective surgical option in the treatment of these patients. Penile revascularization surgery was developed by Vaclav Michal who aimed to treat arteriogenic ED due to decreased cavernosal artery perfusion pressure on the basis of increasing arterial blood flow and perfusion

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pressure for the first time (3). Virag et al. (4) reported improvement of erectile function in 69% of patients with arteriogenic ED by his technique based on anastomosis of the inferior epigastric artery and deep dorsal vein. Virag pioneered to development of different modifications of this technique such as Virag1-3, Furlow-Fisher, Lewis, and Carmignani. The basic principle of surgical technique is the microvascular anastomosis of the inferior epigastric artery to the dorsal vein, corpus cavernosum, or dorsal artery. In this article, we aimed to present the successful treatment of ED due to pudendal artery occlusion after trauma by anastomosis of the inferior epigastric artery to the penile dorsal vein (Modified Furlow Fisher Technique).

CASE REPORT

A 36-year-old man admitted to the clinic of urology with complaints of severe ED, occurred after a pelvic trauma due to vehicle accident two years ago. He had normal erections prior to his accident. The patient had no history of hypercholesterolemia, hypertension, diabetes and genitourinary surgery. He was a nonsmoker. The physical examination and basic laboratory tests were unremarkable. Patient's International Index of Erectile Function Score (IIEF-5) was 5 which means severe ED. He received tadalafil 20 mg on demand for two months but there was no improvement in his erection. Penile duplex Doppler ultrasonography (PDUS) revealed the peak systolic flow velocity was determined as 18 cm/sec at the 10th minute and penile angiography showed concentric stenosis in the middle part of the right pudendal artery (Figure 1). These findings were consistent with ED due to arterial insufficiency.

Because of his isolated right pudendal artery occlusion, the patient underwent microvascular arterial bypass surgery with modified Furlow-Fisher technique in which right inferior epigastric artery anastomosed to the penile dorsal vein. There were no significant complications in the postoperative period and the patient was externed on the third postoperative day. After one month, the patient experienced an immediate recovery of erectile function which allowed for sufficient erections during coitus up to 15 minutes. IIEF-5 score raised to 22. A follow-up PDUS showed the peak systolic flow velocity increased to 31 cm/sec at the 10th minute (Figure 2). Informed consent was obtained from the patient.

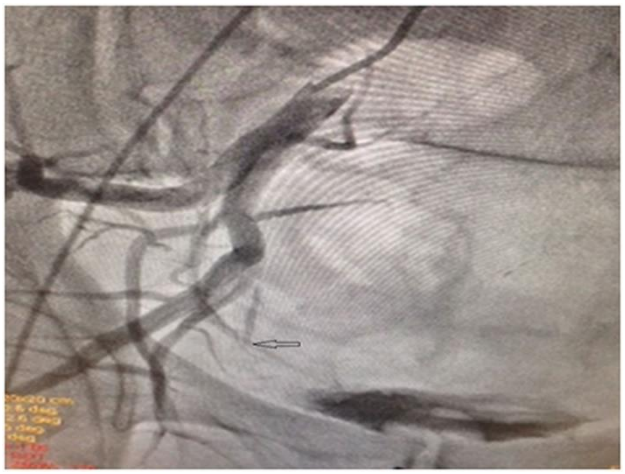

Figure 1. Angiogram shows concentric stenosis in the middle part of the right pudendal artery

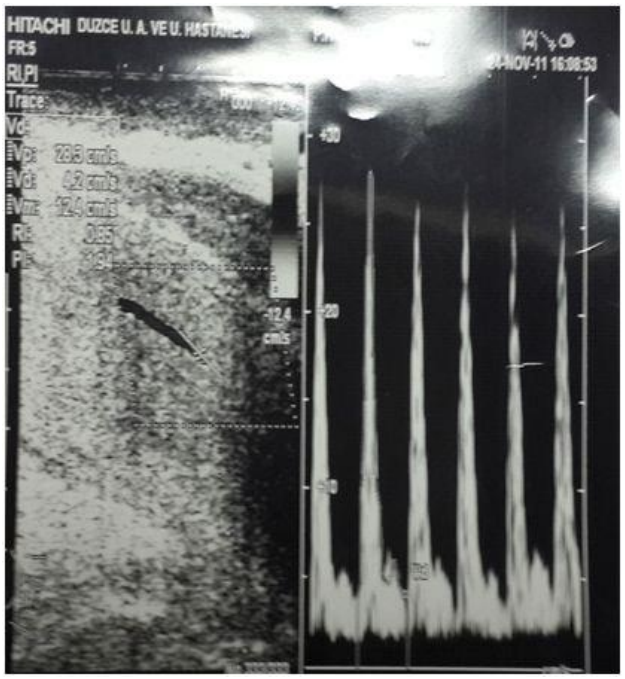

Figure 2. Postoperative penile Duplex Doppler ultrasonography

DISCUSSION

Erection has a complicated neurovascular mechanism. When evaluating the diagnosis of ED, it should be usually considered as multifactorial. The use of validated questionnaires such as the IIEF-5 should be taken account when evaluating the patient for ED (5). PDUS is a reliable and noninvasive diagnostic method for assessing ED for objective measurement of the blood flow of the penis. Maximum smooth muscle relaxation is achieved by pharmacological erection before Doppler ultrasound. It is accepted as arterial insufficiency if the right or left cavernosal artery peak systolic velocities are less than 30 cm/sec. End-diastolic velocity values greater than 5 cm/sec on ultrasound are defined as veno-occlusive dysfunction and exclude the patient from being a candidate for penile revascularization surgery (6).

Penile arteriography is the main component of diagnosis in patients undergoing penile revascularization surgery. Endothelial dysfunction causes focal atherosclerosis in young men with a history of blunt trauma. The plaque formation cascade event begins with the release of inflammatory cytokines, stimulation of smooth muscle proliferation, and infiltration of macrophages with endothelial damage. Endothelial damage may be a result of systemic disorders such as hyperlipidemia or hypertension, but may also be secondary to blunt mechanical trauma (7).

There is a possibility of obstruction of the pudendal artery and common penile artery in patients with ED due to pelvic fracture. Although renal vascularization methods, usually used in the occlusion of penile arteries mostly due

to trauma are difficult procedures, they are quite effective when administered in an appropriate patient. Virag et al. (4) first described the revascularization of the deep dorsal vein in 1980. Furlow et al. (8) modified the dorsal vein revascularization. Later in 1986, Hauri (9) further developed the revascularization technique and described a new method by anastomosing the inferior epigastric artery to the deep dorsal vein. Kawanishi et al. (10) reported a 5-year efficacy of 65.5% in patients with penile revascularization. In addition to conventional microvascular surgery, different techniques have been described for penis revascularization, including small vessel angioplasty, such as stenting or stroking and revascularization of larger donor vessels. (11). In our patient who had arteriogenic ED after trauma-related injury, we performed a modified Furlow-Fisher technique for revascularization surgery. This technique was effective due to raising in patient's IIEF score from 5 to 22 and peak systolic flow from 18 to 31. Despite invasive preoperative evaluations such as, duplex Doppler ultrasound, dynamic cavernosometry, selective internal pudendal arteriography and the long and difficult surgical procedure revascularization surgery is highly effective in particularly selected young patients. Patients with arteriogenic ED after pelvic trauma, revascularization surgery should be kept in mind and it should be applied in appropriate patients for effective results.

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YAZARLARA BİLGİLENDİRME

BİLİMSEL SORUMLULUK

Bilimsel yayıncılık standartları açısından, gönderilecek makaleler, Uluslararası Tıbbi Dergi Editörler Kurulu (ICMJE), Dünya Tıbbi Editörler Birliği (WAME) ve Yayın Etik Kurulu (COPE) kriterlerine uygun olarak hazırlanmalıdır.

- Gönderilecek makalelerde araştırma ve yayın etiğine uyulması zorunludur. Makalelerin sorumluluğu yazarlarına aittir.
- Makalelerin daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmaması gerekir.
- Değerlendirme sürecinin başlaması için makaleler, tüm yazarlar tarafından imzalanmış Telif Hakkı Devir Formu ile birlikte gönderilmelidir. Yazar sıralaması için Telif Hakkı Devir Formu'ndaki imza sırası dikkate alınır.
- Sorumlu yazar, tüm yazarlar adına makalenin son halinin sorumluluğunu taşır.

ETİK SORUMLULUK

- "İnsan" öğesini içeren tüm çalışmalarda Helsinki Deklerasyonu Prensipleri'ne (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uygunluk aranır. Bu tip çalışmalarda yazarların, GEREÇ VE YÖNTEMLER bölümünde çalışmayı bu prensiplere uygun olarak yaptıklarını, kurumlarının etik kurullarından onay ve çalışmaya katılmış insanlardan "bilgilendirilmiş olur" (informed consent) aldıklarını belirtmeleri gerekmektedir.
- Çalışmada "Hayvan" öğesi kullanılmış ise yazarların, GEREÇ VE YÖNTEMLER bölümünde Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmeleri gerekmektedir.
- Olgu sunumlarında hastalardan "bilgilendirilmiş olur" (informed consent) alınmalıdır.
- Etik kurul onay bilgisi GEREÇ ve YÖNTEMLER bölümünde kurul adı, onay tarihi ve sayısı ile birlikte belirtilmelidir.
- Eğer çalışmada direkt-indirekt ticari bağlantı veya maddi destek veren kurum mevcut ise yazarlar; kullanılan ticari ürün, ilaç, firma vb. ile ticari hiçbir ilişkisinin olmadığını veya varsa nasıl bir ilişkisinin olduğunu (konsültan, diğer anlaşmalar), editöre sunum sayfasında belirtmelidirler.
- Yazarlar çalışma ile ilgili kişisel ve finansal tüm ilişkilerin bildirilmesinden sorumludur. Makalenin başvurusu ve/veya değerlendirmesi ile ilişkili herhangi bir çıkar çatışması olup olmadığının açıkça beyan edilmesi gerekmektedir.
- Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır.

BAŞVURU DOSYALARI

Makaleler aşağıda belirtilen şekilde ayrı dosyalar halinde sisteme yüklenmelidir.

Telif Hakkı Devir Formu: Başvuru sırasında sistemden alınacak Telif Hakkı Devir Formu tüm yazarlar tarafından makaledeki yazar sıralamasına uygun şekilde imzalanmış olmalıdır.

Başvuru Mektubu: Makalenin türü, daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmadığı, varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu kuruluşların yazarlarla olan ilişkileri (yoksa olmadığı) belirtilmelidir. Makalenin konusuyla ilgili olarak önerilen, yazarlarla ve kurumlarıyla ilgisi olmayan en az iki hakemin adları, akademik unvanları, kurumları, iletişim bilgileri ve e-posta adresleri yazılmalıdır. Editörlerin hakemleri seçme hakkı saklıdır.

Başlık Sayfası: Makalenin başlığını (Türkçe ve İngilizce), 40 karakteri geçmeyen kısa başlık, tüm yazarların adlarını, akademik unvanlarını, ORCID® numaralarını, kurumlarını, e-posta adreslerini ve ayrıca sorumlu yazarın adını, yazışma adresini, telefon numarasını, e-posta adresini içermelidir. Makale daha önce bilimsel bir toplantıda sunulmuş ise toplantı adı, tarihi ve yeri (yoksa sunulmadığı) belirtilmelidir.

Ana Metin: Makalenin başlığı (Türkçe ve İngilizce), 40 karakteri geçmeyen kısa başlık, Öz (Türkçe ve İngilizce), Anahtar kelimeler (Türkçe ve İngilizce), Ana Metin (gönderilen makalenin türüne uygun olarak bölümlere ayrılmış), Kaynaklar, Tablolar ve Şekil açıklamaları yer almalıdır.

Etik Kurul Onay Belgesi: Tüm araştırma makaleleri için Etik Kurul Onay Belgesi ayrı bir dosya olarak yüklenmelidir.

Not: Makalede şekil, resim veya fotoğraf varsa bunların da her biri ayrı birer dosya olarak yüklenmelidir.

MAKALE TÜRÜNE GÖRE METİNDE KULLANILMASI GEREKEN BÖLÜMLER

Araştırma Makalesi
ÖZ (Türkçe ve İngilizce), GİRİŞ, GEREÇ VE YÖNTEMLER, BULGULAR, TARTIŞMA, SONUÇ, KAYNAKLAR
ÖZ/ABSTRACT 200-250 kelime arasında olmalıdır.
ÖZ, "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç" şeklinde yapılandırılmalıdır.
ABSTRACT, "Aim, Material and Methods, Results, Conclusion" şeklinde yapılandırılmalıdır.

Derleme (Sadece Davetli)
ÖZ (Türkçe ve İngilizce), GİRİŞ, Konu ile İlgili Alt Başlıklar, SONUÇ, KAYNAKLAR
ÖZ/ABSTRACT 150-200 kelime arasında olmalıdır.

Olgu Sunumu
ÖZ (Türkçe ve İngilizce), GİRİŞ, OLGU SUNUMU, TARTIŞMA, KAYNAKLAR
ÖZ/ABSTRACT 100-150 kelime arasında olmalıdır.

Diğer
Bu üç temel makale türü dışındaki (editöre mektup, editöryel yorum/tartışma vb.) yazıların hazırlanmasında da genel yazım kuralları geçerlidir. Bu tür yazılarda başlık ve öz bölümleri yoktur. Kaynak sayısı 5 ile sınırlıdır. İthaf olunan makale sayı ve tarih verilerek belirtilmelidir. Yazının sonunda yazarın ismi, kurumu ve adresi yer almalıdır. Mektuba cevap, editör veya makalenin yazarları tarafından, yine dergide yayınlanarak verilir.

YAZARLARA BİLGİLENDİRME

YAZIM KURALLARI
- Makaleler Microsoft Word® belgesi olarak hazırlanmalıdır.
- Sayfa kenarlarında 2,5 cm boşluk bırakılmalıdır.
- Sayfa numaraları sayfanın sağ alt köşesine yerleştirilmelidir.
- Tüm metinler 12 punto Times New Roman karakteri kullanılarak çift satır aralığı ile sola hizalanmış olarak yazılmalıdır.
- Türkçe makalelerde Türk Dil Kurumu'nun Türkçe sözlüğü (http://www.tdk.org.tr), ayrıca Türk Tıbbi Derneklerinin kendi alanlarına ait terimler sözlüğü esas alınmalıdır.

ANAHTAR KELİMELER
- Anahtar kelime sayısı en az 2 olmalı, kelimeler birbirlerinden noktalı virgül (;) ile ayrılmalıdır.
- Türkçe anahtar kelimeler Türkiye Bilim Terimleri (TBT)'ne (http://www.bilimterimleri.com), İngilizce anahtar kelimeler Medical Subject Headings (MESH)'e (http://www.nlm.nih.gov/mesh/MBrowser.html) uygun olarak verilmelidir.

İSTATİSTİKSEL YÖNTEMLER
- Tüm araştırma makaleleri biyoistatistik açıdan değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir. Bu makalelerde, GEREÇ VE YÖNTEMLER bölümünün son alt başlığı "İstatistiksel Analiz" olmalıdır.
- Bu bölümde çalışmada kullanılan istatistiksel yöntemler ne amaçla kullanıldığı belirtilerek yazılmalı, istatistiksel analiz için kullanılan paket programlar ve sürümleri belirtilmelidir.
- p değerleri ondalık üç basamaklı (p=0,038; p=0,810 vb.) olarak verilmelidir.
- Makalelerin biyoistatistik açıdan uygunluğunun kontrolü için ek bilgi www.icmje.org adresinden temin edilebilir.

KISALTMALAR
- Terim ilk kullanıldığında parantez içinde kısaltmayla birlikte açık olarak yazılmalı ve tüm metin boyunca aynı kısaltma kullanılmalıdır.
- Uluslararası kullanılan kısaltmalar Bilimsel Yazım Kurallarına uygun şekilde kullanılmalıdır.

TABLOLAR VE ŞEKİLLER
- Metinde ilgili cümlenin sonunda (Tablo 1) ve/veya (Şekil 1) şeklinde belirtilmelidir.
- Tablolar (başlıklarıyla birlikte) ve şekiller (açıklamalarıyla birlikte) kaynaklardan sonra ve her biri ayrı bir sayfada olacak şekilde metnin sonuna eklenmelidir.
- Tablo başlıkları tablo üstünde (Tablo 1. Tablo başlığı), şekil açıklamaları ise şeklin altında (Şekil 1. Şekil açıklaması), ilk harfleri büyük olacak şekilde yazılmalıdır.
- Tablolarda ve şekillerde kısaltma veya sembol kullanılmış ise altında dipnot olarak açıklanmalıdır.
- Şekiller ve fotoğraflar, .png, .jpg vb. formatta ve en az 300 dpi çözünürlükte ayrı dosyalar halinde yüklenmelidir.
- Şekil ve fotoğraf alt yazıları, son tablonun olduğu sayfadan sonra, ayrı bir sayfada sırasıyla verilmelidir.
- Daha önce basılmış şekil, resim, tablo, grafik vb. kullanılmış ise yazılı izin alınmalı ve açıklama olarak belirtilmelidir. Bu konudaki hukuki sorumluluk yazarlara aittir.

TEŞEKKÜR
- Eğer çıkar çatışması/çakışması, finansal destek, bağış ve diğer bütün editöryel (İngilizce/Türkçe değerlendirme) ve/veya teknik yardım varsa, bu bölümde, KAYNAKLAR bölümünden önce belirtilmelidir.

KAYNAKLAR
- Kaynaklar, kullanım sırasına göre numaralandırılmalı ve metin içinde ilgili cümlenin sonunda parantez içinde numaralarla (1) veya (1,2) veya (3-5) şeklinde verilmelidir.
- Kaynaklar dizini, metin içinde kaynakların kullanıldığı sıraya göre oluşturulmalıdır.
- Yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 6 yazar belirtildikten sonra "et al." (Türkçe makaleler için "ve ark.") eklenmelidir.
- Kongre bildirileri, kişisel deneyimler, basılmamış yayınlar, tezler ve internet adresleri kaynak olarak gösterilmemelidir.
- DOI tek kabul edilebilir online referanstır.

Makale:

Al-Habian A, Harikumar PE, Stocker CJ, Langlands K, Selway JL. Histochemical and immunohistochemical evaluation of mouse skin histology: comparison of fixation with neutral buffered formalin and alcoholic formalin. J Histotechnol. 2014;37(4):115-24.

Aho M, Irshad B, Ackerman SJ, Lewis M, Leddy R, Pope T, et al. Correlation of sonographic features of invasive ductal mammary carcinoma with age, tumor grade, and hormone-receptor status. J Clin Ultrasound. 2013;41(1):10-7.

Kitap:

Buckingham L. Molecular diagnostics: fundamentals, methods and clinical applications. 2nd ed. Philadelphia: F.A. Davis; 2012.

Kitap Bölümü:

Altobelli N. Airway management. In: Kacmarek R, Stoller JK, Heuer AJ, editors. Egan's fundamentals of respiratory care. 10th ed. St. Louis: Saunders Mosby; 2013. p.732-86.

AUTHOR GUIDELINES

SCIENTIFIC RESPONSIBILITY

In terms of scientific publishing standards, articles to be submitted should be prepared in accordance with the criteria of the International Committee of Medical Journal Editors (ICMJE), the World Association of Medical Editors (WAME) and the Committee of Publication Ethics (COPE).

- Complied with the research and publication ethics in articles to be submitted is an obligatory. The responsibility of the articles belongs to the authors.
- Articles are required to have not been published in anywhere previously, and/or are not in the evaluation process for publication.
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- Compliance with The Principles of Helsinki Declaration (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) is required in all studies including "human" factor. In this kind of studies, authors must state that they perform the study in compliance with these principles, they have taken the approval from ethics committee of their institution and the "informed consent" from people participating the study, in the MATERIAL AND METHODS section.
- If "animal" factor was used in the study, authors must state that they have protected the animal rights in line with the principles of Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf) and they have taken the approval from ethics committee of their institution, in the MATERIAL AND METHODS section.
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- If there is a direct-indirect commercial connection or an institution giving financial support in the study, authors must state that they have no commercial relationship with the commercial product, medicine, company etc. used, or if any, what kind of a relationship they have (consultant, other agreements), in the cover letter to the editor.
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ABSTRACT (English and Turkish), INTRODUCTION, MATERIAL AND METHODS, RESULTS, DISCUSSION, CONCLUSION, REFERENCES

ÖZ/ABSTRACT should be between 200-250 words.

ÖZ, should be structured as "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç".

ABSTRACT should be structured as "Aim, Material and Methods, Results, Conclusion".

Review (Invited Only)

ABSTRACT (English and Turkish), INTRODUCTION, Subtitles Related to the Subject, CONCLUSION, REFERENCES

ÖZ/ABSTRACT should be between 150-200 words.

Case Report

ABSTRACT (English and Turkish), INTRODUCTION, CASE REPORT, DISCUSSION, REFERENCES

ÖZ/ABSTRACT should be between 100-150 words.

Other

The general writing rules are applied for the preparation of the writings (letter to the editor, editorial comment/discussion, etc.) except these three basic types of article. There is no title and abstract sections in these writings. The number of references is limited to 5. The dedicated article should be specified by giving the number and date. The name, institution and address of the author should be included at the end of writing. Answer to the letter is given by the editor, or authors of the dedicated article, by publishing again in the journal.

AUTHOR GUIDELINES

WRITING RULES

- Articles should be prepared as Microsoft Word® document.
- The required margins are 2.5 cm on all sides.
- Page numbers should be placed to bottom right corner of pages.
- All texts must be typed with double-space as left-aligned using 12 point Times New Roman font.
- In Turkish articles, the Turkish dictionary of the Turkish Language Association (http://www.tdk.org.tr) and also term glossary of Turkish Medical Associations' belonging their own field should be taken as basis.

KEYWORDS

- Number of the keywords must be at least 2, words should be separated from each other by a semicolon (;).
- Keywords in Turkish must be given in accordance with Türkiye Bilim Terimleri (TBT) (http://www.bilimterimleri.com), and keywords in English must be given in accordance with Medical Subject Headings (MESH) (http://www.nlm.nih.gov/mesh/MBrowser.html).

STATISTICAL METHODS

- All research articles should be assessed in terms of biostatistics and indicated with appropriate plan, analysis and report. In these articles last subtitle of the MATERIAL and METHODS section should be the “Statistical Analysis”.
- In this section, the statistical methods used in the study should be written by indicating the purpose of use, package programs and versions used for statistical analysis should be specified.
- p values should be given in three decimal digits (p=0.038; p=0.810 etc.).
- Further information to control the convenience of articles in terms of biostatistics, can obtained from www.icmje.org.

ABBREVIATIONS

- The term should be written in full words with the abbreviation in parenthesis where first mentioned, and the same abbreviation should be used throughout the entire text.
- Abbreviations used internationally should be used in accordance with the Scientific Writing Rules.

TABLES AND FIGURES

- Should be indicated at the end of the relevant sentence in the text as (Table 1) and/or (Figure 1).
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ACKNOWLEDGEMENT

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REFERENCES

- References should be numbered according to the order of use and stated with numbers in parentheses as (1) or (1,2) or (3-5) at the end of the relevant sentence in the text.
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- The conference papers, personal experiences, unpublished papers, theses and internet addresses should not be used as references.
- DOI is the only acceptable online reference.

Article:

Al-Habian A, Harikumar PE, Stocker CJ, Langlands K, Selway JL. Histochemical and immunohistochemical evaluation of mouse skin histology: comparison of fixation with neutral buffered formalin and alcoholic formalin. J Histotechnol. 2014;37(4):115-24.

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