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Case Report	1000	200	15	No tables	10 or total of 20 images
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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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Effect of Coronary Tortuosity on Exercise Stress Test

Koroner Tortiyozitenin Egzersiz Stres Testi Üzerindeki Etkisi

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ABSTRACT

Introduction: Coronary tortuosity (CT) is a common anatomical finding during coronary angiography (CA); however, its aetiology and clinical importance have not been clearly defined. We aimed to evaluate the effect of the presence or severity of CT and effect of the sigma-shaped right coronary artery (RCA) on the exercise stress test (EST).

Methods: The study included 175 patients who underwent CA due to cardiac symptoms and positive EST and had no obstructive coronary artery disease in a single centre between 2017 and 2018 June. The patients were divided into two groups: Group 1, patients with CT (n=88), and group 2, patients without CT (n=87). The patients were also categorised as low and moderate-to-high risk based on Duke treadmill score (DTS).

Results: The running distance and DTS were lower, and the rate of sigma-shaped RCA was higher in the CT group (p<0.006). The DTS was lower (p=0.024) in the presence of tortuosity in the left anterior descending coronary artery and negatively influenced as the number of coronary arteries affected by tortuosity increased (p<0.001). Based on the DTS score, patients with moderate-to-high risk have a higher number of vessels affected by tortuosity, involvement of left anterior descending coronary artery, and proportion of sigma-shaped RCA (p<0.001).

Conclusion: In the presence of CT, the rate of positivity is significantly higher, and the DTS is lower in the stress test.

Keywords: Coronary artery, Duke score, exercise stress test, sigma-shaped RCA, tortuosity

ÖZ

Amaç: Koroner tortiyozite (KT), koroner anjiyografi (KA) sırasında karşılaşılan yaygın bir anatomik bulgudur; ancak etiyolojisi ve klinik önemi net olarak tanımlanmamıştır. Biz de KT varlığı ve şiddeti ile sigma şekilli sağ koroner arter (SKA) varlığının egzersiz stres testi (EST) üzerine etkisini incelemeyi amaçladık.

Yöntemler: Çalışmaya 2017-2018 Haziran tarihleri arasında tek bir merkezde kardiyak semptomlar ve pozitif EST nedeniyle KA uygulanan ve obstrüktif koroner arter hastalığı bulunmayan 175 hasta dahil edildi. Hastalar iki gruba ayrıldı: Grup 1, KT'si olan hastalar (n=88) ve grup 2, KT'si olmayan hastalar (n=87). Ayrıca hastalar Duke koşu bandı skoruna (DTS) göre sınıflandırıldı.

Bulgular: KT grubunda koşma mesafesi ve DTS daha düşüktü ve sigma şeklindeki SKA oranı daha yüksekti (p<0,006). Sol ön inen koroner arterde KT varlığında DTS'nin daha düşük (p=0,024) olduğu ve tortiyoziteden etkilenen koroner arterlerin sayısı arttıkça DTS'nin olumsuz etkilendiği bulundu (p<0,001). DTS skoruna göre orta-yüksek risk grubunda olan hastalarda tortiyoziteden etkilenen damar sayısı ile sol ön inen koroner arter tutulumu ve sigma şekilli SKA oranı daha yüksekti (p<0,001).

Sonuç: KT varlığında, stres testinde pozitiflik oranı daha yüksektir ve DTS daha düşüktür.

Anahtar Kelimeler: Koroner arter, Duke skoru, egzersiz stres testi, sigma RCA, tortiyozite

Introduction

Coronary tortuosity (CT) is a common anatomical finding during coronary angiography (CA); however, its aetiology and clinical importance have not been clearly defined (1). CT has been shown to be associated with advanced age, hypertension, atherosclerosis and diabetes mellitus and to be more common in atherosclerotic arteries (2,3). Degeneration of elastin in the arterial wall and chronic vascular pressure load also play a significant role in the development of CT (4,5). Therefore, it has been suggested that the CT is an arterial remodelling caused by hypertension, that is, an adaptation of coronary arteries to hypertension (6). Besides, hypertension severity was an independent risk factor for CT in women (2).

Patients with CT often complain of chest pain during exercise and the pain disappears during rest (4). Although patients with severe CT and normal coronary arteries exhibit myocardial perfusion defects, the role

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of tortuosity in angina is not fully known (7). It has been suggested that myocardial blood flow reserves might be decreased in patients with ischaemia but not obstructive coronary artery disease, and severe CT may be a particularly important cause of ischaemia (8). As such, CT can not be considered as a completely benign coronary anomaly.

In practice, the exercise stress test (EST) is one of the most commonly used methods to evaluate ischaemia related to coronary artery disease. This study aimed to evaluate the effect of the presence or severity of CT and the effect of the sigma-shaped right coronary artery (RCA) linked to RCA tortuosity on the EST in patients who underwent CA after positive stress test and were found to have normal coronary anatomy during angiography.

Methods

Study Population

The study included patients who were admitted to our cardiology clinic because of chest pain, shortness of breath, or any angina equivalent and who were indicated for exercise tests and could exercise on a treadmill table. Subsequently, 175 patients who underwent CA due to positive EST but without coronary artery disease during angiography between June 2017 and June 2018 in our department were included. The patients were divided into group 1, patients with CT (n=88), and group 2, patients without CT as control group (n=87). Demographic data, laboratory findings and echocardiographic findings were recorded. Patients with chronic disease (chronic renal failure, malignancy, connective tissue disease), moderate-to-severe heart valve disease, active infection, previously known coronary artery disease, coronary artery ectasia, myocardial bridge, myocarditis or pericarditis, hypertrophic cardiomyopathy, or pulmonary hypertension were excluded. The study protocol was approved by the Necmettin Erbakan University Meram Faculty of Medicine Institutional Ethics Board (decision no: 89, date: 24.05.2019), and written informed consent was obtained from all patients.

Exercise Stress Test

The records were examined for the patients who were diagnosed with CT and underwent an EST using the Philips StressVue System (Philips Healthcare, Andover MA, USA). Blood pressure, heart rate and standard 12-lead electrocardiograms were recorded before the test, and the measurements were repeated intermittently. The patients' angina status and ST-segment deviations were examined. The maximum ST-segment deviation was measured at 80 ms after the J point. Patients were categorised based on the Duke treadmill score (DTS) as follows: low risk (DTS ≥+5), moderate risk (-10< DTS ≤+4) and high risk (DTS <-11) (9). Based on this risk assessment, the presence of tortuosity, RCA shape and the number of coronary arteries affected by tortuosity were compared.

The DTS was calculated using the following formula (10):

DTS= Exercise time-(5×ST deviation)-(4×Angina index).

Angina index was scored as 2, 1 and 0 for exercise restriction, without exercise restriction, and no pain, respectively.

Evaluation of Coronary Anatomy

Diagnostic CA was performed using the radial or femoral artery according to the operator's preference and patient's clinical characteristics. Angiographic images were recorded after intracoronary nitroglycerin administration based on the patient's blood pressure. The CA images were separately evaluated by two cardiologists; the patient's CT status and RCA shape were recorded.

Coronary Tortuosity and Right Coronary Artery Shape

CT was defined as the presence of more than three 45° deviations in the main coronary arteries [RCA or left anterior descending (LAD) and circumflex coronary arteries] at both systole and diastole (11). Sigma-shaped RCA was determined by two steps in the simple left anterior oblique projection-at 25°-35°-usually with no craniocaudal angulation. First, the two outermost points of the RCA were combined with an imaginary line, and the maximal arterial diameter was calculated. Second, the length between the imaginary line and coronary artery was measured. If the distance was longer than the maximal measured arterial diameter, it was categorised as sigma-shaped RCA. The RCA was considered C shaped if it did not meet the criteria of the sigma shape or had only one lateral point (12).

Statistical Analysis

SSPS® version 16.0 statistical package programme (SPSS Inc., Chicago, IL, United States) was used for statistical analyses. Quantitative variables fitting into normal distribution and categorical variables were presented as mean ± standard deviation and number and percentages, respectively. Normality of distribution was evaluated using the Kolmogorov-Smirnov test. The mean values of continuous variables were compared between independent groups using the Student t-test, One-Way ANOVA, or Kruskal-Wallis test as appropriate. The chi-squared test was performed to compare the study groups in terms of categorical variables. Statistical significance was determined for $p<0.05$.

Results

The mean age of the study population was 62.1±10 years; the majority of the participants were women (56.5%). The rate of female sex was higher in the CT group but not statistically significant. The rates of smoking and hypertension were significantly higher in the CT group (p=0.029 and p=0.043, respectively). No correlation was found between the number of tortuous coronary arteries and sex, age, smoking, diabetes mellitus, or hypertension (p>0.05). No significant difference in the haematological or biochemical findings was found between the two groups. Pulmonary arterial pressures and ejection fractions were similar; the left atrial diameter was significantly higher in patients with CT (p=0.038). Table 1 shows the patient's demographic and laboratory findings.

The stress test results showed that the running distance was lower in the CT group (p=0.004), which had a lower DTS (p<0.001). As expected, the rate of sigma-shaped RCA was higher in the CT group (p=0.005). In the subgroup analyses, 34.3% (n=60) of the total study population had sigma-shaped RCA, and the DTS was lower in these patients (p<0.001). The DTS was lower (p=0.024) in the presence of tortuosity in the LAD coronary artery and negatively influenced as the number of coronary

arteries affected by tortuosity increased (p<0.001). The rate of sigma-shaped RCA and the number of patients with tortuous arteries were higher in moderate-to-high risk group (p<0.001). The relationships between the CT status and EST results are shown in Tables 2 and 3.

Table 1. Demographic, clinical and laboratory characteristics of the study population

	Control group n=87	Tortuosity group n=88	p
Age (years)	61.4±10.6	61.7±10.8	0.841
Sex (female), n (%)	40 (45.9)	50 (56.8)	0.058
DM, n (%)	21 (24.1)	23 (26.1)	0.761
Hypertension, n (%)	47 (54)	60 (68)	0.043
Smoking, n (%)	20 (23)	35 (40)	0.029
LVEF (%)	59.2±4.1	58.6±3.7	0.300
LA diameter (cm)	3.47±0.32	3.78±0.31	0.038
Systolic PAB (mmHg)	27.5±3.8	28.3±4.7	0.276
Creatinine (mg/dL)	0.79±0.19	0.78±0.17	0.582
Hb (g/dL)	13.4±1.8	13.4±1.7	0.952
Platelet (10^3/mm^3)	254.3±59.7	255.3±60.0	0.917
Leukocyte (10^3/mm^3)	7.51±2.41	7.53±2.40	0.947
FBG (mg/dL)	103.3±25.9	108.2±33.2	0.288
LDL-C (mg/dL)	126.1±32.3	129.7±39.1	0.516
HDL-C (mg/dL)	41.8±9.6	41.2±11.4	0.722
Triglyceride (mg/dL)	155 (99,231)	154 (98,226)	0.884
Duke treadmill score (IQR)	1 (-2, 3)	-3 (-7, 0)	0.001
METs	10.6±2.04	9.55±2.71	0.004
Terminated HR, %	91.1±7.6	90.1±10.4	0.473
Sigma-shaped RCA, %	21 (24.1)	39 (44.3)	0.005

DM: Diabetes mellitus, LVEF: left ventricular ejection fraction, Hb: haemoglobin, FBG: fasting plasma glucose, Hg: haemoglobulin, LA: left atrium, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, PAB: pulmonary artery pressure, RCA: right coronary artery, HR: heart rate, METs: metabolic equivalents

Discussion

Our study showed that, in the presence of CT, the rate of false positivity was significantly higher, and the DTS was lower in patients with chest pain. Furthermore, the findings were more manifest as the number of vessels affected by tortuosity in coronary artery system increased, and the DTS tended to be lower in cases of LAD coronary artery involvement. The presence of RCA with sigma-shaped morphology was also shown to impact the exercise test negatively. Arterial tortuosity can be seen in various organ systems. Such tortuosities have been thought to be associated with genetic syndromes (13). However, ageing and hypertension have been known to be associated with tortuosity not only in the coronary arteries, but also in the cerebral, femoral and carotid arteries (14). Naturally, coronary arteries tend to be mildly more tortuous relative to other arterial systems to adapt to the cardiac cycle, that is, to be able to show flexion and extension (15). It has been speculated that the CT might cause angina during exercise and false-positive results in ESTs. Increasing the angle and number of bends has been suggested to cause a significant energy loss during blood flow and lead to ischaemia

Table 2. Duke scores according to right coronary artery type, left anterior descending artery involvement and severity of tortuosity

RCA type (study group)	**n (%)**	**Duke score**
C-shaped RCA	115 (65.7)	0 (-2, 2)
Sigma-shaped RCA	60 (34.3)	-4 (-8, 0)
p	-	<0.001
LAD involvement (tortuosity group)	**n (%)**	**Duke score**
Presence	76 (86.4)	-3 (-7, -1)
Absence	12 (13.6)	0 (-2.75, 1.75)
p	-	0.024
Severity of involvement (tortuosity group)	**n (%)**	**Duke score**
One vessel	23 (26.1)	1 (-2, 2)
Two vessels	40 (45.5)	-2 (-5, -1)
Three vessels	25 (28.4)	-9 (-9.5, -6.5)
p	-	<0.001*

RCA: Right coronary artery, LAD; left anterior descending artery, *for all groups

Table 3. Comparison of groups based on the treadmill Duke score

Study population (n=175)	**Low-risk group (n=101)**	**Intermediate and high-risk groups (n=74)**	**p**
Presence of coronary tortuosity (n/%)	24 (13.7)	64 (36.5)	0.0001
Sigma-shaped RCA (n/%)	17 (16.8)	43 (58.1)	0.0001
C-shaped RCA (n/%)	84 (83.1)	31 (41.8)	0.0001
Duke treadmill score (mean ± std)	7.96±2.70	-3.34±4.84	0.0001
Tortuosity group (n=88)	**Low risk group (n=24)**	**Intermediate and high-risk groups (n=64)**	**p**
LAD involvement (n/%)	15 (62.5)	61 (95.3)	0.002
Sigma-shaped RCA (n/%)	11 (45.8)	49 (76.5)	0.0001
Three vessels involvement (n/%)	4 (16.6)	21 (32.8)	0.019
Duke treadmill score (mean ± std)	6.47±3.14	-4.37±4.65	0.0001

RCA: Right coronary artery; LAD: left anterior descending artery, std: standard deviation

due to reduction in distal perfusion pressure in the coronary vascular bed (4). It is not yet known whether the reduction in distal perfusion pressure is significant and leads to myocardial ischaemia. In association with the decreased diastolic filling due to increased heart rate during emotional or physical stress, increased tortuosity can lead to ischaemic symptoms by further reducing blood flow in the distal coronary vascular bed or by increasing coronary vascular resistance (6,16,17) By contrast, the probability of acute coronary syndrome due to spontaneous coronary dissection and recurrence of dissection is higher in tortuous segments (18).

In studies investigating the relationship between atherosclerosis and tortuosity, the calcium score calculated by computed tomographic angiography was higher in tortuous coronary arteries (19), and the carotid intima-media thickness was increased in patients with CT (20). Likewise, the progression of atherosclerotic plaque has been suggested to intensify due to increased shear stress in the tortuous vessels, and the risk of consequential plaque rupture would be high (21). By contrast, in individuals with CT, atherosclerotic stenosis in the tortuous segment was less than that in the non-tortuous region, and CT might have a protective role against atherosclerosis-induced vascular obstruction (22). Despite these, long-term follow-up studies showed that the presence of CT has no effect on the development of major cardiovascular events (2).

Studies have shown that CT was associated with chronic stable angina, typically resulting in increased chest pain increased during exercise and decreased chest pain with rest, and leading to reversible perfusion defects in myocardial perfusion scintigraphy (8).

In an investigation of patients with ischaemia on myocardial perfusion scintigraphy but with normal CA, the presence of CT resulted in 7-times more ischaemia. In these patients, the rate of ischaemia detection in stress echocardiography was higher (8). In another study, most of the patients with chest pain but without obstructive coronary artery disease were women, and the rate of CT in women was two-folds higher than in males (7). Although the groups were age- and sex-matched in our study, female sex was more common in the CT group albeit not statistically significant. Similar to previous studies, the proportion of hypertensive patients was higher in the CT group (p=0.043). Therefore, blood pressure regulation might be an effective treatment for controlling angina in these patients. Moreover, increasing coronary perfusion by decreasing the heart rate and prolonging the diastolic phase might be effective in controlling angina in patients with high heart rate and hypertension.

The rate of CT was higher in patients who underwent CA due to a positive EST, which was frequently used in practice, but were not found to have coronary artery disease. In addition, the CT angles were more severe in patients with a positive EST (23). In the same study, the number of tortuous bends higher in the group with ischaemic changes. Another study based on the EST found that the rates of ST depression and the changes in T wave were higher in patients with CT, and the objective ischaemia findings correlated with the number of vessels affected by the tortuosity (24). In our study, the DTS decreased as the number of vessels affected by the tortuosity increased. Besides, the DTS was lower in patients with LAD coronary artery involvement. The moderate-to-high risk group has higher number of vessels affected by tortuosity, LAD coronary artery involvement, and proportion of sigma-shaped RCA.

Previous studies investigating the relationship between RCA morphology and atherosclerosis found that atherosclerotic plaque formation was more common in C-shaped RCA (10). The presence of C-shaped RCA has been reported as an independent predictor of the severity and extent of coronary artery disease (25). In support of these findings, the proportion of flow-mediated dilatation in the brachial artery in individuals with sigma-shaped RCA was better than that in those with C-shaped RCA (26). Given that the sigma-shaped RCA is a special naming for the CT, the protective effect of CT against atherosclerosis can be considered more predominant. By contrast, because the DTS was lower in the exercise tests of the CT group, endothelial dysfunction resulting from decreased coronary flow after stress might be worse in this group. More studies are needed to assess the relationship between CT and atherosclerotic plaque formation.

The study involved a relatively small number of patients. Moreover, because the number of high-risk patients based on the DTS was low (n=5), this group could not be considered separately. More comprehensive results could be obtained if myocardial perfusion scintigraphy was also performed. Likewise, the effect of the tortuosity on the distal flow could be evaluated more precisely if standard fractional flow reserve (FFR) was also measured. However, the rigidity of the FFR wire and the presence of CT could increase the likelihood of procedure-related complications in these patients.

Conclusion

The presence of CT might be a reason for a visit to the clinic due to recurrent angina. Controlling the risk factors in patients with positive EST and CT might be an effective approach to control angina. Further histopathological and molecular studies are needed to evaluate the relationship between CT and atherosclerosis.

Ethics

Ethics Committee Approval: The study protocol was approved by the Necmettin Erbakan University Meram Faculty of Medicine Institutional Ethics Board (decision no: 89, date: 24.05.2019).

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

Peer-review: Externally and internally peer-reviewed.

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Determination of Vestibulo-ocular Reflex Gain Normal Values in Children with Video Head Impuls Test

Çocuklarda Video Kafa İtme Testi ile Vestibülo-oküler Refleks Kazanç Normal Değerlerinin Belirlenmesi

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ABSTRACT

Introduction: Video head impuls test (vHIT) is used in the diagnosis of vestibular dysfunction. There is no study conducted on vHIT application and its results on children in our country. Our study aimed to examine vHIT tests in children with normal hearing function and to determine normal value ranges.

Methods: This study was made up of a total of 78 children under 16 years of age with normal hearing function. All children received vHIT and the values found were recorded.

Results: Of the 78 children participating in the study, 44 (56.4%) were boys and 34 (43.6%) were girls. There was no significant difference in the results of vHITs between the ages of 4-6, 7-9 and 10-12 in terms of mean left lateral, right lateral, left anterior, right posterior, left posterior and right anterior values ($p>0.05$ for each). However, in the analysis performed by combining 4-12 age groups, there was a significant difference between the ages of 4-12 and 12 years in terms of left posterior mean values ($p=0.012$).

Conclusion: When the findings of our study and combined reports were evaluated, it was observed that normal vestibulo-ocular reflex gain values should be determined in the paediatric population by the vHIT method. We consider that, paediatricians may use the findings of our study as guide for the evaluation of vestibular function in children. Extensive studies are needed to ensure that the normal value ranges reach a higher level of reliability.

Keywords: Child, vertigo, video head impuls test, vHIT, vestibulo-ocular reflex

ÖZ

Amaç: Video kafa itme testi (vHIT) vestibüler fonksiyon bozukluğu tanısında kullanılmaktadır. Ülkemizde çocuklar üzerinde vHIT uygulaması ve sonuçları ile ilgili bir çalışma henüz bulunmamaktadır. Çalışmamızda normal işitme fonksiyonuna sahip çocuklarda vHIT testlerinin irdelenmesi ve normal değer aralıklarının belirlenmesi amaçlanmıştır.

Yöntemler: Çalışmaya normal işitme fonksiyonuna sahip 16 yaş altı olan toplam 78 çocuk dahil edilmiştir. Tüm çocuklara vHIT uygulanmış ve bulunan değerler kaydedilmiştir.

Bulgular: Çalışmaya katılan çocukların 44'ü (%56,4) erkek, 34'ü (%43,6) kız idi. vHIT sonuçlarında 4-6, 7-9 ve 10-12 yaş grupları arasında ortalama sol lateral, sağ lateral, sol anterior, sağ posterior, sol posterior ve sağ anterior değerleri açılarından anlamlı fark yoktu (her biri için $p>0,05$). Ancak 4-12 yaş gruplar birleştirilerek yapılan analizde 4-12 yaş ile 12 üzeri yaş grubu arasında sol posterior ortalama değerleri açısından anlamlı fark saptandı ($p=0,012$).

Sonuç: Çalışmamız bulguları ile yayınlanmış raporlar birleştirilerek değerlendirildiğinde, pediatrik popülasyonda vHIT yöntemi ile normal vestibülo-oküler refleks kazanç değerlerinin belirlenmesi gerekliliği görülmüştür. Çalışmamız bulgularının pediatristlerce çocuklarda vestibüler fonksiyon değerlendirilmesinde yol gösterici olabileceği düşüncesindeyiz. Normal değer aralıklarının daha yüksek güvenilirlik düzeyine ulaşması için daha geniş çalışmalara gereksinim bulunmaktadır.

Anahtar Kelimeler: Çocuk, vertigo, video kafa itme testi, vHIT, vestibülo-oküler refleks

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Introduction

Dizziness is known as the feeling or illusion that the person or his environment is moving. Although the term vertigo is sometimes used instead of just dizziness, vertigo is defined as a sendrom presenting with several symptoms such as dizziness, nausea, vomiting and imbalance together (1-4).

Vertigo is caused by disorders in the pathway or structures between the vestibular nuclei of the brainstem and the vestibular apparatus in the inner ear. The vestibular apparatus consists of three semicircular canals (anterior, posterior and lateral), and two autolytic organs; utricle and saccule. Semicircular canals perceive angular motion changes and speed in all directions in the three-dimensional space, such as the head's rotation, bending and twisting motion. The utricle perceives linear head movements in the horizontal plane more often, while the saccule perceives linear head movements in the vertical plane mostly. In this way, balance is created. Dysfunctions in these structures cause the appearance of vertigo and/or an imbalance table (1,5-7).

Vestibulo-ocular reflex is a reflex that creates eye movements in response to the rotating movements of the head for the image to be focused and clarity. Semicircular canals detect changes in the head position and transmit alerts that will allow the eyes to shift in the same direction and opposite the head movement direction. In case of dysfunction, eye movement, that is nystagmus arises that are not synchronised with the change in head movement. Nystagmus is used in the diagnostic tests of vertigo (1,5-7).

Video head impuls test (vHIT) has been developed in the diagnosis of peripheral vertigo caused by disorders related to semicircular canals (8). In previous methods, the eye movements in nystagmus, which were received in response to sudden head push warnings in the clinical setting, were interpreted subjectively by the staff performing the application. However, in the vHIT method, using high resolution and fast shooting cameras, eye movements that occur reflexively against sudden pushes of the head in different planes can be measured objectively, clearly and numerically. In addition, this method can be easily applied near the patient (8-12).

The vHIT has been performed on adults for years, and normal ranges for adults have been established (13,14). In recent years, the applicability of this application on children has been investigated, and normal value ranges have been tried to be determined for these age group (15,16). However, there is no study conducted on vHIT application and its results on children in Turkey. Our study aimed to examine vHIT in children with normal hearing function, and to determine normal value ranges.

Methods

This was a retrospective study, approved by University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethical Committee with the number of 2239 (date: 27.04.2020). Medical records including audiovestibular test results were reviewed. Informed consent was obtained from parents of all patients.

Patients

A total of 78 patients under 16 years of age with normal hearing function and who had applied to our hospital's Otorhinolaryngology clinic for control were included in the study. The patients were divided into four groups as 4-6 years, 7-9 years, 10-12 years and over 12 years old (15).

Patients with a hearing or balance complaint or history, chronic disease, with long-term drug use and those with a head injury were not included in the study.

Tests

vHIT measurements were performed using the OTOsuite Vestibular software (Software Version: 3.00 Build 1007, Otometrics) and high-speed (250 Hz) infrared camera (EyeSee Cam™ system Interacoustics A/S, Denmark ™) mounted on special glasses (Type-1085 ICS impulse).

In the evaluation of the lateral semicircular canals, the head position was bent forward by 30 degrees, and head pushing movements were applied to the right and left at angles of 15 degrees, with the back of the jaw being fully grasped. In the vertical semicircular canals, the head thrust movement was applied by rotating the head position 45 degrees to the right or left in order to stimulate the vertical channels while the children were asked to be looking at the target points on both sides. At these stages, the test was completed by applying five head pushing movements for each channel, and vestibulo-ocular reflex gain values of six semicircular channels were determined.

Statistical Analysis

All statistical analyses in the study were done using SPSS 25.0 software (IBM SPSS, Chicago, IL, USA). Descriptive data are presented as numbers and percentages. In terms of categorical variables, comparisons between groups were made using Pearson's chi-square test and Fisher's Exact test. Whether the continuous variables are suitable for normal distribution was confirmed using the Kolmogorov-Smirnov test. The differences between the groups in terms of continuous variables were performed using the Student's t-test and the comparison of mean values between multiple groups was done by variance analysis. The results were evaluated within the 95% confidence interval and $p<0.05$ values were considered significant. Bonferroni correction was made where appropriate.

Results

Of the children participating in the study, 44 (56.4%) were boys and 34 (43.6%) were girls. Twelve (15.4) of the children were 4-6 years, 15 (19.2%) were 7-9 years, 16 (20.5%) were 10-12 years and 35 (44.9%) were over 12 years old. Gender distributions were similar between the groups ($p=0.384$) (Table 1).

Table 1. Sex distribution by age groups

Age groups (years)	Male	Female	Total
4-6	5	7	12
7-9	10	5	15
10-12	11	5	16
>12	18	17	35
Total	44	34	78
p=0.384			

There were no significant differences in the results of the vHITs among the ages of 4-6, 7-9 and 10-12 in terms of mean left lateral, right lateral, left anterior, right posterior, left posterior and right anterior values (p>0.05 for each). However, in the analysis performed by combining the 4-12 age groups, a significant difference was found between the 4-12 age group and the above 12 age group in terms of left posterior mean values (p=0.012) (Table 2). In Table 3, the mean ± standard deviation values for the 4-12 age range reported from different studies and the present study are shown.

Discussion

vHIT is a method that provides objective data regarding the vestibulo-ocular reflex. vHIT is the only method that can evaluate the anterior and posterior semicircular canals individually in both ears. It was also stated that the vHIT method was the most valuable method in the evaluation of the horizontal canal vestibulo-ocular reflex (1,8,17). It has been reported that the vHIT method is useful in differentiating central or peripheral causes of acute vertigo syndrome, it can evaluate at physiological and high frequencies, and it is being used more commonly in emergency departments (1). In addition, it has been stated that this method can be superior to other methods in terms of being a non-invasive method, providing high accuracy data, not being affected by middle and outer ear problems, evaluating the ears and semicircular canals separately, being easy and fast to apply and being applicable in children (1,5,8).

There are limited reports on the use of the vHIT in adults. In recent years, studies on the usability of the vHIT in children have been started (15-18,19). Ross and Helminski (19) reported that the re-applicability of the vHIT method in the child population is good. Those researchers also stated that the vHIT method provided reliable data in children, although their sensitivity and specificity regarding vestibular disorder were not high enough (19). Tozar et al. (16) found no significant difference in terms of mean vestibulo-ocular reflex gain values measured using the vHIT method in terms of the control group in children with otitis media and dizziness. Those researchers stated that symptoms of otitis media and dizziness did not result in the detection of vestibular disorders using the vHIT method (16). Nassif et al. (20) also found no significant difference in terms of the mean vestibulo-ocular reflex gain values measured using the vHIT method between the children with cochlear implants and the controls, but they stated that the number of patients was low. Zhou et al. (21) found that the vHIT test performed with a head tilt angle below 100° may not show the loss of function in the semicircular canal in most patients, and vHIT tests not exceeding the 150° angle may cause false negative results. However, these researchers stated that the 150° head angle could not be applied in children. Hülse et al. (22) reported that the

Table 2. Comparison between age groups in terms of mean ± standard deviation values of the vestibulo-ocular reflex gain obtained using the video head impuls test

Age groups	n	Lateral		Anterior		Posterior	
		Left	Right	Left	Right	Left	Right
4-6	12	0.93±0.08	1.01±0.12	0.79±0.13	0.88±0.1	0.83±0.1	0.73±0.09
7-9	15	0.91±0.06	0.95±0.08	0.85±0.15	0.79±0.14	0.79±0.12	0.78±0.11
10-12	16	0.92±0.07	0.95±0.06	0.77±0.17	0.87±0.15	0.81±0.14	0.7±0.14
p*		0.654	0.214	0.387	0.182	0.772	0.235
4-12	43	0.92±0.07	0.97±0.09	0.8±0.15	0.84±0.14	0.81±0.12	0.74±0.12
>12	35	0.92±0.1	0.99±0.1	0.83±0.12	0.82±0.17	0.74±0.12	0.75±0.12
p**		0.819	0.199	0.409	0.48	0.012	0.706

One-Way ANOVA method has been used. *This is an analysis between 4-6, 7-9 and 10-12 age groups. ** This is an analysis made between 4-12 and 12 years old groups

Table 3. Comparison between age groups in terms of mean ± standard deviation values of the vestibulo-ocular reflex gain obtained using the video head impuls test

Age groups	n	Lateral		Anterior		Posterior	
		Left	Right	Left	Right	Left	Right
Present study	43	0.92±0.07 (0.82-1.16)	0.97±0.09 (0.84-1.33)	0.8±0.15 (0.37-1.08)	0.84±0.14 (0.58-1.1)	0.81±0.12 (0.42-1.02)	0.74±0.12 (0.54-1.1)
Bachmann et al. (15)	30	0.96±0.09 (0.79-1.14)	1.04±0.09 (0.87-1.23)	0.80 ± 0.11 (0.58-1.02)	0.90 ± 0.19 (0.53-1.27)	0.91 ± 0.14 (0.65-1.18)	0.83±0.09 (0.65-1.01)
Tozar et al. (16)*	30	0.97 (0.73-1.35)	1.06±0.22	0.95 ± 0.22	0.86 (0.71-1.26)	0.95±0.23	0.95 (0.87-1.35)
Kidd et al.**	-	0.98±0.10 (0.82-1.14)	1.04±0.11 (0.85-1.21)	-	-	-	-

*Some data could not be reached, it covers the ages of 4-15. **Unpublished data; Kidd C, Byrd S, Riska K, Murnane O, Akin F. (2014) Intra-and inter-examiner reliability of the video head impulse test. http://icsimpulse.com/blog/wp-content/uploads/Inter-Intra-Reliability-VA-Mountain-Home.pdf

vHIT method was a sensitive and an effective test in children. Hamilton et al. (18) stated that the vHIT method was very effective and useful in determining the semicircular canal functions in children. These researchers also added that this method had many advantages over the gold standard rotary chair and caloric test methods. It was emphasised that there is need to conduct studies on determining the normal values of vHIT in children (17,18). These data show that although there are some limitations in the implementation of the vHIT method in children, it can be used to quantify semicircular canal functions in this population.

Tozar et al. (16) determined the normal values of the vestibulo-ocular reflex gain for children using the vHIT method in their studies. Bachmann et al. (15) also applied the vHIT method in children to determine the normal values of the vestibulo-ocular reflex gain. The researchers divided the participants into 4-6, 7-9 and 10-12 age groups, and could not find any difference between the groups in terms of the vHIT values. In our study, the vHIT method was used and vestibulo-ocular reflex gain normal values were determined for healthy children aged 4-12 years (Table 3). It is seen that the mean normal values of all these studies are very close to each other. Similarly, it is observed that the obtained minimum and maximum values are close to each other between the studies. These findings show that the normal values of the vestibulo-ocular reflex gain obtained for healthy children in our study are reliable to be used by clinicians.

It has been shown that there may be differences in vestibulo-ocular reflex gain values between children and adults (15). Bachmann et al. (15) found that some vHIT values were significantly higher in the child group in comparison to the adult groups included in the study. In our study, it was observed that there was a significant difference between the children groups and the group over the age of 12 in terms of the left posterior vestibulo-ocular reflex value. These differences between children and other groups indicate the need to establish a normal vestibulo-ocular reflex gain value table for healthy children apart from adults.

There were some limitations in our study. Considering the difficulty of applying the vHIT test, children under the age of 4 were not included in the study, in line with the recommendations of some previous studies (15,17). In parallel, in our study, vHIT normal values for the paediatric population between the ages of 4-12 were determined. Further investigations on younger age groups needs to be conducted.

Conclusion

When the findings of our study and combined reports were evaluated, it was observed that normal vestibulo-ocular reflex gain values should be determined in the paediatric population using the vHIT method. We consider that the findings of our study may be a guide for the evaluation of the vestibular function in children by paediatricians. Extensive studies are needed to ensure that the normal value ranges reach a higher level of reliability.

Ethics

Ethics Committee Approval: This was a retrospective study, approved by the Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 2239, date: 27.04.2020).

Informed Consent: Informed consent was obtained from parents of all patients.

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Comparison of the Haematological and Anaesthetic Complications of Multiple Pregnancy Cases

Çoğul Gebelik Olgularının Hematolojik ve Anestezik Komplikasyonlarının Karşılaştırılması

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ABSTRACT

Introduction: The frequency of caesarean delivery is increasing worldwide. Nowadays, multiple pregnancy rates are increasing significantly due to the prevalence of assisted reproductive techniques. The purpose of this retrospective study is to compare the haematological and anaesthesia complications of multiple and singleton pregnancies and to increase awareness among anaesthesiologists and obstetricians of complications that may occur during and after a caesarean section in multiple pregnancies.

Methods: Our study was carried out by retrospectively searching the anaesthesia forms and files of the American Society of Anesthesiology 1-2 group of patients, who underwent caesarean sections between January 2019 and January 2020 at the University of Health Sciences Turkey, İstanbul Training and Research Hospital Gynecology and Obstetrics Clinic. The cases were then divided into multiple (n=50) and singleton (n=63) pregnancies, and the haematological and anaesthesia complications were compared between the two groups.

Results: No statistically significant difference was found between the age, pre- and postoperative haematocrit (Hct) values, and Hct differences between singleton and twin pregnancies ($p>0.05$). The rate of bradycardia in twin pregnancies was found to be significantly lower than that in singleton pregnancies ($p<0.05$). There was no statistically significant difference in nausea-vomiting and hypotension rates between twin and singleton pregnancies ($p=0.26$).

Conclusion: Knowledge about complications associated with anaesthesia in patients with multiple pregnancies delivering by caesarean section in the world and our country is still insufficient. Based on our data, we recommend that anaesthesiologists and obstetricians work as a team and prepare for the operation in a planned approach, considering the hemodynamic changes occurring owing to twin pregnancies.

Keywords: Multiple pregnancy, spinal anaesthesia, hypotension, bradycardia, haematocrit

ÖZ

Amaç: Sezaryen doğum sıklığı dünya çapında giderek artmaktadır. Günümüzde, yardımcı üreme tekniklerinin yaygınlığından dolayı çoğul gebelik oranları önemli ölçüde artmaktadır. Bu retrospektif çalışmanın amacı çoğul ve tekil gebeliklerde hematoloji ve anestezi komplikasyonlarını retrospektif olarak karşılaştırmak ve anestezi ve kadın doğum hekimlerinin ikiz gebeliklerde sezaryen sırası ve sonrasında oluşabilecek komplikasyonları ile ilgili farkındalıklarını artırmaktır.

Yöntemler: Çalışmamız Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'nde, Ocak 2019 ve Ocak 2020 tarihleri arasında 18-45 yaş arası sezaryen operasyonu yapılan Amerikan Anesteziyoloji Derneği 1-2 grubuna giren hastaların anestezi formları ve dosyaları retrospektif taranarak gerçekleştirilmiştir. Olgular daha sonra çoğul (n=50) ve tekil (n=63) gebelik olarak ikiye ayrılarak gruplar arası hematolojik ve anestezi komplikasyonları karşılaştırılmıştır.

Bulgular: Tekiz ve ikiz gebeliklerde yaş, operasyon öncesi ve sonrası hematokrit (Hct) değerleri, Hct farkları arasında istatistiksel anlamlı fark bulunamamıştır ($p>0,05$). İkiz gebeliklerde bradikardi oranı tekiz gebeliklere göre istatistik anlamlı olarak düşük bulunmuştur ($p<0,05$). İkiz ve tekiz gebeliklerde bulantı-kusma ve hipotansiyon oranları arasında fark bulunmamıştır ($p=0,26$).

Sonuç: Türkiye'de ve dünyada sezaryen ile doğum yapılan çoğul gebelik hastalarında anestezi ile ilişkili komplikasyon görülme sıklığı ile ilgili çalışmalar halen yetersizdir. Verilerimizden yola çıkarak anestezi ve kadın doğum doktorlarının ekip olarak çalışması ve ikiz gebeliklere bağlı hemodinamik değişiklikleri göz önünde bulundurarak planlı ve hazır bir şekilde operasyon hazırlığı yapmalarını önermekteyiz.

Anahtar Kelimeler: Çoğul gebelik, spinal anestezi, hipotansiyon, bradikardi, hematokrit

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Introduction

The frequency of cesarean delivery is steadily increasing worldwide (1). Although cesarean section has become very safe over the years, it is still associated with high maternal and perinatal mortality and morbidity rates (2).

Selection of anesthesia method in cesarean section is determined according to the urgency of the procedure, the patient's current systemic problems, the request of the patient and the surgeon, and the experience of the anesthesiologist (3). In recent years, especially regional techniques have been used. Regional anesthesia has the advantages of patient comfort, the mother is awake and sees the baby at the time of birth, the fetus is not exposed to inhalation and intravenous anesthetics, and allows pain control after surgery. General anesthesia creates less hypotension and better cardiovascular stability by providing airway and respiratory safety with rapid induction in emergency procedures. However, it should be kept in mind that complications such as aspiration of gastric contents, failure of intubation, maternal hyperventilation, neonatal depression and bleeding due to uterine atony may occur during general anesthesia (4,5).

Nowadays, multiple pregnancy rates are increasing significantly due to the prevalence of assisted reproductive techniques. Since the physiological changes resulting from multiple pregnancies are different from singleton pregnancy, they are considered high-risk pregnancies. Some complications may occur in the prenatal period due to the increase in preterm delivery and the increase in the rate of maternal beta agonist use. Drugs used in multiple pregnancies may cause maternal tachycardia, hypokalemia and pulmonary edema. Multiple pregnancies increase the rate of cesarean delivery and intraoperative complications such as postpartum hemorrhage and hysterectomy.

Regional anesthesia, which is also preferred in twin pregnancies, may lead to more maternal hypotension, which may result from aortocaval compression, especially when compared to singleton pregnancy. However, some patients who have contraindications for regional anesthesia such as thrombocytopenia, coagulopathy or pulmonary edema may cause anesthesiologists to prefer general anesthesia for these patients.

Maternal risk factors are also high in multiple pregnancies. Anesthesia planning should be done earlier and in a planned manner in multiple pregnancies.

The aim of this retrospective study is to compare the hematology and anesthesia complications in multiple and singleton pregnancies retrospectively and to increase the awareness of anesthesiologists and obstetricians about the complications that may occur during and after cesarean section in twin pregnancies.

Methods

Our study was carried out by retrospectively scanning the anesthesia forms and files of patients in the American Society of Anesthesiology (ASA) 1-2 group who underwent cesarean section between January 2019 and January 2020 at the University of Health Sciences Turkey, İstanbul Training and Research Hospital Gynecology and Obstetrics Clinic. The cases were then divided into two groups as multiple (n=50) and singleton (n=63) pregnancies, and the hematological and anesthetic complications were compared between the groups.

Patient's age, gestational week, chorioosinity if twin pregnancy, emergency or elective, anesthesia method applied, whether oxytocin and transamine was administered, whether atony was performed, whether blood products were needed, whether there was a decrease in preoperative postop hemogram values, complications in the mother (hypotension, the development of bradycardia, bleeding, nausea-vomiting) has been recorded.

Exclusion criteria; ASA 3-4 patients.

In both groups, 1.5 mL/kg of crystalloid fluid was first administered in addition to colloid fluid in hypotension (mean arterial blood pressure below 60 mmHg) following anesthesia. Ephedrine hydrochloride (5-10 mg; IV) was administered in case of persistence of hypotension.

Patients with bradycardia (heart rate falling below 50 beats per minute) were administered 0.5 mg atropine sulphate IV.

Statistical Analysis

In the evaluation of the data, besides descriptive statistical methods (mean, standard deviation), Student t-test was used by considering normal distribution in comparison of the groups. Chi-square test was used to determine the statistical significance among the groups with bradycardia, nausea-vomiting and hypotension. Significance levels were determined by finding p-values suitable for these tests. $P<0.05$ was considered significant.

Our study has the permission of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 2175, date: 07.02.2020). Since our study was retrospective, written consent could not be obtained from the patients.

Results

As shown in Table 1, no statistically significant difference was found between age, haematocrit (Hct) values before and after surgery and Hct differences in singleton and twin pregnancies ($p>0.05$). Pregnancy week of twin pregnancies was found to be statistically significantly lower than singleton pregnancies ($p<0.05$).

As shown in Table 2, the bradycardia rate in twin pregnancies was found to be statistically significantly lower compared to singleton pregnancies ($p<0.05$). There was no difference between the rate of nausea and vomiting in twin and singleton pregnancies ($p=0.9$). There was no difference between the rate of hypotension in twin and singleton pregnancies ($p=0.26$). ASA 2 twin pregnancy rate was statistically significantly higher than ASA 2 singleton pregnancies ($p<0.05$). No statistically significant difference was found between the two groups in the rates of emergency, elective cesarean section and regional, and general anesthesia.

Differences in Hct before and after surgery in monochorionic twin pregnancy (n=7), dichorionic twin pregnancy (n=43) patients are 4.24 g/dL and 3.84 g/dL, respectively. No difference was found between Hct

differences before and after surgery in monochorionic and dichorionic twin pregnancies (p=0.24). In twin pregnancies, the proportion of patients given additional oxytocic agent was found to be 50%. In singleton pregnancies, the proportion of patients given additional oxytocic agent was 23%.

Discussion

Studies on the differences in hemodynamic changes during cesarean between twin and singleton pregnancies are insufficient. In our study, as shown in Table 1, no difference was found between pre- and postoperative Hct rates in twin and singleton pregnancies. Hyperdynamic circulation is more in twin pregnancies than in singleton pregnancies. Left ventricular systolic function and mean arterial pressure in twin pregnancies are affected more than singleton pregnancies after the 20th week (6). In many studies, high maternal cardiac output and low peripheral resistance have been shown in twin pregnancies (7). However, high blood loss is correlated with no difference in expected twin pregnancy, high hemodynamic parameters at the beginning of twin pregnancy reach their lowest level in the middle of pregnancy, and then being equivalent to a single pregnancy (8). This hypothesis was supported by the fact that maternal hemodynamic parameters were found equivalent for each singleton and twin pregnancies during and immediately after cesarean in the study conducted by Lavie et al. (8).

Emergency cesarean brings the risk of blood transfusion. In our study, 67% of single pregnancies and 70% of twin pregnancies were caesarean sections in emergency conditions. In the study conducted by Kolås et al. (9), the prevalence of excessive blood loss differed between elective (2.1%) and emergency (3.3%) cesarean deliveries. While maternal factors, chronic maternal diseases, conditions related to pregnancy and birth, placenta previa and transverse arrival are risk factors for blood loss in elective operations, placenta previa, placental abruption, intervention to full cervical dilatation and high body mass index were risk factors for blood loss in emergency operations. Although the rate of emergency cesarean section is higher in twin pregnancies, we think that no statistically significant difference can be detected under favour of the early and planned obstetric approach.

In a study conducted by Blickstein et al. (10), hemoglobin values in the first and second trimester were found to be low in twin pregnancies, no difference was found between hemoglobin values in single and twin pregnancies during the third trimester. In our study, there was no statistically significant difference between age, Hct values before and after surgery and Hct differences in single and twin pregnancies (Table 1). In our study, we believe that the reason for the high rate of use of additional oxytoxic agents in twin pregnancies is increased obstetric complications such as premature birth, placenta previa and detachment placenta.

The most common obstetric complication associated with twin pregnancies is preterm birth. In the literature, this rate has been reported at 50% and is 12 times higher than single pregnancies (11). In our study, similarly, the week of pregnancy of twin pregnancies is lower than that of single pregnancies. Mikami et al. (12) also found that the week of pregnancy at birth in the twin pregnancy group was statistically significantly lower than in the single pregnancy group.

Table 1. General data of caesarean section patients

	Single pregnancy (n=63)	Twin pregnancy (n=50)	p
Age (year)	27.8	30	0.20
Preoperation Hct (g/dL)	33.9	32.7	0.21
Postoperation Hct (g/dL)	29.3	28.8	0.18
Hct difference (g/dL)	5.3	3.83	0.18
Pregnancy week	38.1	34.3	<0.05

No statistically significant differences were found between age, Hct values before and after surgery and Hct differences in single and twin pregnancies (p>0.05). Pregnancy week of twin pregnancies is statistically significantly lower than single pregnancies (p<0.05). Hct: Hematocrit

Table 2. Anesthesia data of caesarean section patients

	Single pregnancy (n=63) (%)	Twin pregnancy (n=50) (%)	p
ASA 1	18 (28%)	8 (16%)	>0.05
ASA 2	45 (72%)	42 (84%)	>0.05
Emergency caesarean section	42 (67%)	35 (70%)	>0.05
Elective caesarean section	21 (33%)	15 (30%)	>0.05
Regional anesthesia	51 (80%)	43 (86%)	>0.05
General anesthesia	12 (28%)	7 (14%)	>0.05
Nausea-vomiting	30 (47%)	25 (50%)	>0.05
Hypotension	42 (66%)	30 (60%)	>0.05
Bradycardia	32 (50%)	7 (14%)	>0.05

In twin pregnancies, ASA 2 score was statistically significantly higher than single pregnancies and bradycardia rate was statistically significantly lower than single pregnancies (p<0.05), ASA: American Society of Anesthesiology

Although spinal anesthesia is generally accepted as safer and appropriate in multiple pregnancies (13), they are more prone to severe hypotension than patients with singleton pregnancy in the literature (14,15). In our study, contrary to the literature, no difference was found between the rate of hypotension in twin and singleton pregnancies (Table 2). Although it seems surprising that our results differ from the literature, in fact, there are very few data supporting the severity of hypotension in multiple pregnancies when the literature is searched. Although Jawan et al. (16) found more cephalic spinal anesthesia spread in twin pregnancies; they found the incidence of hypotension similar to that of singleton pregnancies. Similar to our study, Ngan Kee et al.'s (17) study revealed that there was no difference between single and multiple pregnancies in terms of hypotension, vasopressor need, nausea and vomiting in cesarean deliveries undergoing spinal anesthesia. They concluded that although aortocaval compression is higher in multiple pregnancies, its effect may decrease as the blood volume and cardiac output are increased more, and there is no potential for more hypotension development in multiple pregnancies compared to singleton pregnancies (17). In a study conducted by Behforouz et al. (18), epidural anesthesia was applied to 2 quadruplet, 19 triplet and 31 singleton pregnancies, and the incidence of developing hypotension was found to be similar in singleton and multiple pregnancies. It was observed that the need for Ringer's lactate and total dose of ephedrine was higher in singleton pregnancies with the initiation of the block. This is due to the decreased risk of hypotension due to the increase in blood volume and cardiac output more in multiple pregnancies than singleton pregnancies.

In our study, the rate of bradycardia was found to be statistically high in singleton pregnancies (Figure 1). Bradycardia is caused by sympathetic blockade. The blockade of cardiovascular fibers from T1 to T4 is part of the bradycardia trigger mechanism. In parallel with our results, Pereira et al. (19) found that the rate of development of sinus bradycardia was higher in ASA 1 patients. We think that this can be explained by the high rate of ASA 2 twin pregnancy patients in our study. Since there was no statistically significant difference in the rates of hypotension of our patients, there was no statistically significant difference in the rate of nausea-vomiting between the groups, as expected.

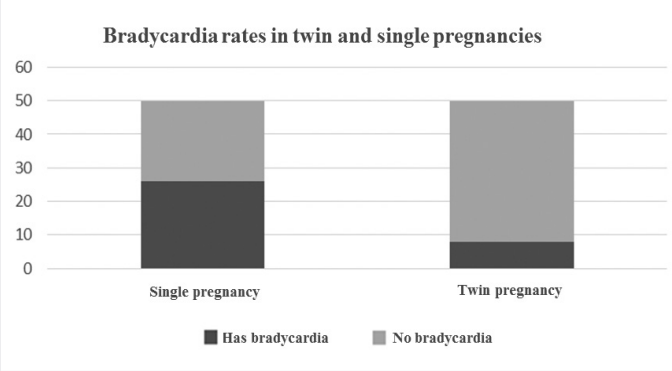

Figure 1. Bradycardia rates in twin and singleton pregnancies

A statistically significant difference was found between bradycardia rates in twin and single pregnancies ($p<0.05$).

Conclusion

In cesarean sections, spinal anesthesia is the preferred anesthesia technique due to its rapid onset of action, reliability, superior postoperative pain control and lower mortality rates when compared with general anesthesia. However, it is predicted that the most important complication is maternal hypotension, which may result from more aortocaval compression in multiple pregnancies, especially when compared with singleton pregnancies.

In Turkey and around the world, studies on the incidence of complications associated with anesthesia in patients with multiple pregnancies delivered by cesarean section are still insufficient. In our study, we identified the complications that may arise from postpartum anesthesia techniques. Based on our data, we recommend that anesthesiologists and obstetricians work as a team and prepare for the operation in a planned and ready manner, considering the hemodynamic changes due to twin pregnancies.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 2175, date: 07.02.2020).

Informed Consent: The study was retrospective, written consent could not be obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - B.Ş.K.; Concept - B.Ş.K.; Design - N.A.; Data Collection or Processing - A.G.F.; Analysis or Interpretation - N.A.; Literature Search - B.Ş.K.; Writing - B.Ş.K.

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Effect of Postpartum Depression and Anxiety on Infant Development at 12 Months: A One-year Follow-up Study

Postpartum Depresyon ve Anksiyetenin Çocuğun 12. Aydaki Gelişimi Üzerine Etkisi: Bir Yıllık İzlem Çalışması

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ABSTRACT

Introduction: To evaluate the effect of maternal postpartum depression (PPD) and anxiety disorder (AD) during the postnatal first year on infant development at 12 months.

Methods: This prospective study was conducted at the well child follow-up clinic. A total of 113 mother-infant pairs were included in the study. In the postnatal first month, face-to-face interviews were conducted with mothers in order to complete the questionnaire. At the end of postnatal 1, 3, 6 and 12 months, the Edinburgh Postpartum Depression scale (EPDS) and Beck Anxiety scale (BAS) were administered to mothers. Those who scored ≥13 points in EPDS and/or ≥8 in BAS underwent psychiatric interviews and the structured clinical interview for the DSM-IV scale was performed. Infant development was evaluated at 12 months using the Denver-II Developmental Screening test and Guide for Monitoring Child Development.

Results: The study was completed with 91 mother-infant pairs. Among the mothers, 23.1% (n=21) had a personal history of psychiatric disorder while 15.4% (n=14) had a family history of psychiatric disorders. The prevalence of PPD and AD was determined to be 10.9% and 25.2%, respectively. We found that the children of mothers with PPD had a higher prevalence of developmental delay in the domain of play at 12 months (p=0.048), while the children of mothers with AD had a higher prevalence of developmental delay in the domain of relating (p=0.049).

Conclusion: PPD and AD affect not only mothers but also their children. Physicians conducting paediatric follow-up should evaluate maternal mental health and refer mothers for professional help if necessary.

Keywords: Postpartum depression, anxiety disorder, child development, perinatal mental disorders

ÖZ

Amaç: Doğum sonrası ilk yılda annelerin postpartum depresyon (PPD) ve anksiyete bozukluğunun (AB) çocuğun 12. aydaki gelişimi üzerine etkisini değerlendirmektir.

Yöntemler: Bu prospektif çalışma sağlam çocuk izlem polikliniğinde yapıldı. Yüz on üç anne-çocuk ikilisi çalışmaya katıldı. Doğum sonrası birinci ay sonunda annelerle yüz yüze kişisel bilgi anket formu dolduruldu. Postnatal 1., 3., 6. ve 12. ay sonunda annelere Edinburg Postpartum Depresyon ölçeği (EPDÖ) ve Beck Anksiyete ölçeği (BAÖ) verildi. EPDÖ puanı ≥13 ve/veya BAÖ puanı ≥8 olanlarla psikiyatrik görüşme yapıldı ve Ruhsal Bozuklukların Tanısal ve Sayımsal El Kitabı'na (DSM-IV) dayalı yapılandırılmış psikiyatrik görüşme ölçeği uygulandı. Çocukların gelişimi düzeltilmiş 12. ay sonunda Denver-II Gelişimsel Tarama testi ve Gelişimi İzleme ve Destekleme Rehberi ile değerlendirildi.

Bulgular: Çalışma birinci yıl sonunda düzenli takipleri yapılan 91 anne-bebek ikilisiyle tamamlandı. Annelerin %23,1'inin (n=21) öz geçmişinde, %15,4'ünün (n=14) soy geçmişinde psikiyatrik hastalık öyküsü vardı. PPD sıklığı %10,9 ve AB sıklığı %25,2 olarak saptandı. PPD'li annelerin çocuklarının 12. ay oyun alanındaki gelişimlerinin (p=0,048), AB olan annelerin çocuklarının ise ilişki alanındaki gelişimlerinin (p=0,049) gecikmeli olma sıklığı diğerlerine göre daha fazlaydı.

Sonuç: PPD ve AB sadece anneleri değil aynı zamanda çocuklarını da etkileyen bir durumdur. Bu nedenle çocuk sağlığı izlemi yapan hekimler, çocukların takibini yaparken annelerin ruhsal durumunu değerlendirmeli ve gerekirse uzman desteğine yönlendirmelidir.

Anahtar Kelimeler: Postpartum depresyon, anksiyete bozukluğu, çocuk gelişimi, perinatal zihinsel bozukluklar

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Introduction

Pregnancy and the postpartum period constitute a high-risk stage in women's lives in terms of developing mental disorders (1). Postpartum depression (PPD) is a common complication of pregnancy with a reported prevalence in western societies of 10%-15% and in Turkey of 15.4%-51.3% (2,3). It is defined as a depression attack occurring within 4 weeks after birth (4). Studies have reported that this period may last for up to one year (3).

Postnatal anxiety disorders (AD) are more common than depression (5). They may occur alone or in combination with PPD (6). It has also been reported that mothers with PPD have a higher possibility of developing AD in the postnatal period (6,7).

Parental mental health has a significant impact on infant development (1). Particularly, it was reported that chronic PPD disrupted mother-child interactions and led to cognitive, social, emotional and behavioural problems in children (1,8,9). However, due to varied sociocultural structures across different societies, maternal mental disorders may have different effects on children. Although many studies have been conducted in Turkey to investigate the prevalence of PPD and related factors, only few studies have evaluated the effect of PPD on infant development (3,4,10).

Therefore, this study aimed to evaluate the effect of PPD and AD on infant development at 12 months in Turkey.

Methods

This prospective cohort study was conducted at Şişli Hamidiye Etfal Training and Research Hospital between September 2015 and December 2016. The participants were informed about the study, and their oral and written consents were obtained. A total of 113 mothers who accepted to participate were included. Approval was obtained from the Ethics Committee of Şişli Hamidiye Etfal Training and Research Hospital (decision no: 536, date: 04.08.2015).

In the aforementioned hospital, the follow-up of children begins at the well child follow-up clinic at the end of the first postnatal month and continues periodically until the age of six years, assessing the growth and development of infants and providing recommendations to families in order to support such growth and development.

Mothers who applied to the well child clinic between 1st September 2015 and 31st December 2015 with infants chronologically at postnatal one month, and who did not fulfil the exclusion criteria were randomly invited to the study. One of the researchers conducted a face-to-face interview with each participating mother in order to complete the personal information questionnaire developed for this study.

This questionnaire was developed by two paediatricians and one psychiatrist using the current studies in the literature. The questionnaire consisted of a total of 44 questions including maternal sociodemographic characteristics (age, education, socio-economic status, number of live births, etc), PPD risk factors (maternal personal history of psychiatric disorder, whether the pregnancy was planned or not, relationship with spouse, etc) and information about birth and the infant (gender, gestation week, birth weight, mode of delivery, etc).

After completing the personal information questionnaire, the mothers were handed the Edinburgh Postpartum Depression scale (EPDS) and Beck Anxiety scale (BAS) to be completed in order to screen for PPD and anxiety. The completed scales were cross-checked by the researcher upon submission in order to have the blank questions completed.

The EPDS and BAS were performed on the mothers at the end of postnatal 1, 3, 6 and 12 months of their infants. In each of these four screenings, an EPDS score of ≥13 and a BAS score of ≥8 were considered as the risk group and psychiatric examinations of the mothers falling into this group were planned for diagnosis. The mothers were evaluated by the same two psychiatrists in the study team with a focus on depression and AD. For diagnostic evaluation, structured interviews based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) were conducted. The Structured Clinical Interview for DSM-IV (SCID-I) scale was performed. For those mothers who were diagnosed with PPD and/or anxiety in SCID-I, a follow-up process was initiated by the psychiatrist researchers.

The Denver-II Developmental Screening test and the Guide for Monitoring Child Development (GMCD) were administered in order to assess the infants' development at the end of the corrected 12 months. We determined whether the infants' development was age appropriate and if not, which domains were delayed. The assessments were conducted by the same researcher.

Exclusion Criteria

Mothers with native language other than Turkish, illiterate mothers, with physical disorders complicating child care, infants with congenital anomalies, risky birth history (infants born at gestation week <35, perinatal asphyxia or neonatal resuscitation) or infants hospitalized in the neonatal intensive care within the first one month were excluded from the study.

Scales Used in the Assessment of Maternal Depression and Anxiety

The EPDS: It is the most common self-reported scale used for screening depression in the postpartum period, which is a four-point Likert-type scale consisting of a total of ten questions. The lowest possible score is zero and the highest is 30. The Turkish adaptation was made by Engindeniz et al. (11) with a cut-off score of ≥13.

The BAS: It is a Likert-type self-assessment scale with 21 symptom categories each having 4 choices. Each item is worth 0 to 3 points evaluated as follows: 8-15 points: Mild anxiety, 16-25 points: Moderate anxiety, 26-63 points: Severe anxiety. The Turkish validity and reliability were conducted by Ulusoy et al. (12).

The Structured Clinical Interview Scale - The Clinician Version for DSM-IV Axis I Diagnoses: It is a clinical interview structured by First et al. (13) for DSM-IV Axis I disorders. The Turkish validity and reliability have been completed (14).

Scales Used in the Assessment of Infant Development

The Denver-II Developmental Screening Test: It is a screening test used for assessing the development of children aged 0 to 72 months. The test form consists of four sections devoted to the developmental domains

of personal-social, language, fine motor and gross motor skills. It was adapted and standardised into Turkish by Yalaz et al. (15).

The GMCD: It is a guide developed to prevent developmental problems and to direct the respective process towards early diagnosis and interventions. It is performed on children aged 0 to 42 months enabling the assessment and monitoring of the developmental domains of expressive and receptive language, gross and fine motor skills, play, relating and self-help. It was developed, internationally standardised and verified by Ozturk Ertem et al. (16). It is one of the few tools that possess adequate psychometric and feasibility criteria for use in low- and middle-income countries (17).

Statistical Analysis

SPSS 16.0 for Windows programme was used for statistical analysis. Descriptive statistics were expressed as counts and percentages for categorical variables. Rate comparisons were performed using the chi-square analysis in independent groups. The statistical alpha significance level was taken as $p<0.05$.

Results

The study was initiated with 113 mother-infant pairs, and completed at the end of the first year with 91 mother-infant pairs under regular follow-up. The study flow chart is shown in Figure 1. The maternal mean age was 30.5±5.7 years and the maternal mean duration of education was 10.6±4.9 years. Among the participants, 15.4% (n=14) had a family history of psychiatric disorder. In addition, 23.1% (n=21) of the mothers reported a personal history of psychiatric problem, whereas 4.4% (n=4) reported a psychiatric problem experiences in the previous pregnancy. The sociodemographic data of the participants is shown in Table 1.

During the one-year follow-up period, 48 mothers (52.7%) scored high in the screening tests performed for PPD and anxiety, and were classified as the risk group. Fifteen of the mothers in the risk group were not diagnosed with any disorder and were classified as the healthy group along with those mothers who scored low in the scales, altogether making 58 mothers (63.7%) not diagnosed by SCID-I. Also, 33 of the participating mothers (36.3%) were diagnosed by SCID-I, namely 10 (10.9%) were diagnosed with PPD and 23 (25.2%) were diagnosed with AD (Figure 1).

According to the DENVER test, no differences were detected in the development at 12 months of the children whose mothers had PPD, AD or no disorders in the domains of personal-social, language, fine and gross motor skills (p=0.224, p=0.677, p=0.389, p=0.519, respectively). The DENVER test results are shown in Table 2.

According to the GMCD, no differences were detected in the development at 12 months of the children whose mothers had PPD, AD or no disorders in the domains of expressive language, receptive language, motor skills and self-help (p=0.710, p=0.220, p=0.401, p=0.647, respectively). On the other hand, differences were found in the development at 12 months of children whose mothers were in these three groups in terms of the play and relating domains. In the group of mothers with PPD, there were more children who had developmental delay in the domain of play (p=0.048). Among the children of mothers with AD, there were more children with delayed development in the domain of relating (p=0.049). These children's development at 12 months assessed according to the GMCD is shown in Table 3.

Discussion

In this study, the prevalence of maternal PPD and anxiety was 10.9% and 25.2%, respectively. These rates were similar to those of the previous studies. It is estimated that in low-and middle-income countries, perinatal mental disorders, predominantly consisting of PPD and anxiety, are observed in one sixth of pregnant women and one fifth of women in the postnatal period (9). In a study conducted in Pakistan, the prevalence of PPD was reported as 24%-56% in women (18). On the other hand, in a study conducted among Pakistani women living

Table 1. Distribution of the sociodemographic data of the participants

	Mean ± standard deviation
Maternal age, years	30.5±5.7
Maternal duration of education, years	10.6±4.9
Monthly income, Turkish lira	3.018±2.725
Number of living children, n	2*
Infant's gestation week	38.2±1.6
Infant's birth weight, kg	3,156±1,656
	n, %
Sex	
Male	41 (45.1)
Female	50 (54.9)
Maternal employment status	
Employed	28 (30.8)
Housewife	63 (69.2)
Family type	
Nuclear	72 (79.1)
Extended	19 (20.9)
Family history of psychiatric disorder	
Yes	14 (15.4)
No	77 (84.6)
Personal history of psychiatric disorder	
Yes	21 (23.1)
No	70 (76.9)
Maternal history of psychiatric problem in previous pregnancy	
Yes	4 (4.4)
No	87 (95.6)
Relationship with spouse	
Good	71 (78)
Mediocre	18 (19.8)
Bad	2 (2.2)
Was the pregnancy planned?	
Yes	61 (67)
No	30 (33)

*: Median value provided for the number of living children

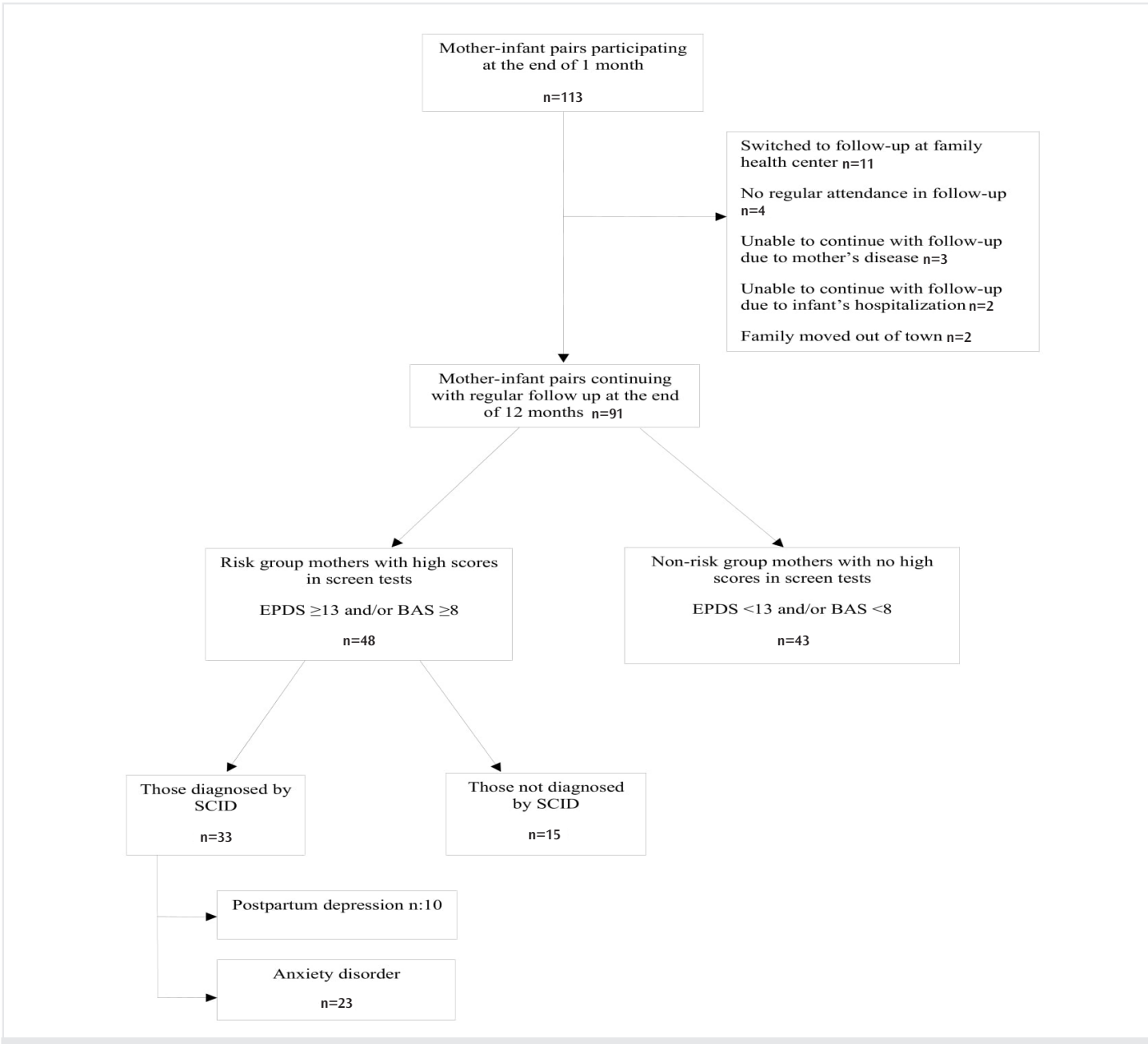

Figure 1. Study flow chart

EPDS: Edinburgh Postpartum Depression scale, BAS: Beck Anxiety scale, SCID: The structured clinical interview for DSM-IV

Table 2. Effect of postpartum depression and anxiety on infant development at 12 months DENVER results

DENVER developmental domains		Postpartum depression n=10	Anxiety disorder n=23	Those not diagnosed by SCID n=58	p
Personal-social	Pass	10	22	58	0.224
	Fail	0	1	0	
Language	Pass	10	22	57	0.677
	Fail	0	1	1	
Fine motor	Pass	9	23	55	0.389
	Fail	1	0	3	
Gross motor	Pass	9	21	56	0.519
	Fail	1	2	2	

SCID: The structured clinical interview for DSM-IV

Table 3. Effect of postpartum depression and anxiety on infant development at 12 months GMCD results

GMCD developmental domains		Postpartum depression n=10	Anxiety disorder n=23	Those not diagnosed by SCID n=58	p
Expressive language	Age appropriate	8	16	45	0.710
	Delayed	2	7	13	
Receptive language	Age appropriate	8	20	55	0.220
	Delayed	2	3	3	
Gross- fine motor skills	Age appropriate	8	21	54	0.401
	Delayed	2	2	4	
Relating	Age appropriate	10	21	58	0.049
	Delayed	0	2	0	
Play	Age appropriate	6	18	52	0.048
	Delayed	4	5	6	
Self-help	Age appropriate	9	22	56	0.647
	Delayed	1	1	2	

GMCD: Guide for monitoring child development, SCID: The structured clinical interview for DSM-IV

in England, the PPD prevalence was determined as approximately 17% (19). In Egypt, the rate of depression and/or anxiety in the postnatal period was reported as 32.8% (7). In Canada, this rate was found to be 17% for anxiety and 4.8% for depression (20). The studies conducted in Turkey report various results depending on the cultural characteristics of the region of study, the postnatal timing of the study and the method used (3,4). The number of studies based on SCID are limited, and PPD prevalence has been determined as 6.3%-16.8% (21,22).

In the present study, we found that the prevalence of developmental delay at 12 months in the domain of play was higher in the children of mothers with PPD compared to those without depression. Regarding the children of mothers with AD, it was observed that the prevalence of developmental delay at 12 months in the domain of relating was higher. This may be due to the fact that such mothers may be unable to spare time to playing with their children or to provide the stimulants appropriate to support their children's development and the challenges in mother-child interaction. In a study on this matter, it was determined that mothers suffering from depression were less likely play to with their babies, show picture books or talk to them compared to mothers without depression (23).

In this study, we did not find any differences in the development at 12 months of the children whose mothers had PPD, AD or no disorders in terms of the domains of expressive language, receptive language, gross motor skills, fine motor skills and self-help. There are many studies in this regard in the literature; however, only one study was previously conducted in Turkey regarding this matter. In a study analysing the effect of PPD on breastfeeding and infant development, Salgın et al. (10) performed the EDB scale to 100 mothers three times in the first six months. However, at the end of 15 months, only 55 infants could be reached to perform the DENVER test. There was no statistically significant difference in the children of mothers with or without depression as a result of the DENVER test conducted at 15 months.

In a systematic review, it has been reported that maternal postnatal stress contributes to delayed cognitive and socio-emotional development in infants (24). Black et al. (8) reported that the infants of mothers with PPD attain lower levels of cognitive, motor and orientation/engagement skills at 6-12 months compared to those without PPD. A study conducted in Bangladesh reported developmental delays at 6-8 months in the motor skills of infants whose mothers had depression at 2-3 months postpartum (25). Another study conducted in Greece reported that infants with mothers suffering from PPD scored lower points in fine motor development at 18 months than the children of those without PPD (26). Another study analysing the effect of PPD and anxiety on infant development indicated that infants with mothers suffering from depression had developmental delays in cognitive, fine-gross motor and language domains in comparison to the children of those without depression. The aforementioned study also determined that mother's depression predisposes the child to approximately a 6-fold risk of being delayed in terms of emotional development (18).

The development a child's vocabulary is affected by various factors such as an interactive and stimulating environment, socio-economic status and relationship with parents (18). Quevedo et al. (27) determined that in the postnatal period, the children of mothers who had undergone depression stood a higher risk of developmental delay in the language domain at 12 months. Further, it was also reported that the duration of maternal depression was related to developmental delays in language (27,28).

Studies have reported that maternal AD is correlated with infant socio-emotional development and behavioural difficulties (1). Babies of socially anxious mothers may develop similar behaviour such as fear and avoiding strangers (1). It has also been determined that antenatal anxiety is influential not only during infancy but also at school age manifested by lower success in exams and disrupted executive functions (29,30).

It has been reported that in case of high socio-economic status, availability of social support and short-termed maternal mental disorder, the effect on children is lower (1). In a study conducted on Pakistani mothers and children living in England, the BAYLEY III development scale was performed on the infants at 6 months. This study found that the only infant developmental domain significantly correlated with PPD is adaptive behaviour (communication, play, self-direction and social skills) (19). The results of the aforementioned study are similar to those of our study. In the present study, one of the reasons why infant developmental domains other than play and relating were unaffected by maternal depression and AD may be that the study was conducted at a Well Child Clinic. Each visit involves recommendations given to mothers to support infant growth and development. In this way, before any developmental delay in children can occur, families are already aware of the significance of social support to be provided to mothers.

The strengths of this study consist of the fact that this was a prospective study, which followed-up the mother-child pairs for one year; the mothers were assessed for PPD and anxiety at four time points during this period, and the diagnosis for PPD and AD was made using the SCID-I performed by a psychiatrist instead of self-assessment reports.

The limitation of this study is that there were more mothers at the beginning of the study, but the sample group diminished as the mothers did not regularly participate in the follow-up or completely discontinued it.

Conclusion

In the present study, the prevalence of maternal PPD was found as 10.9% and anxiety as 25.2%. It was determined that the children of mothers with PPD had a higher prevalence of developmental delay in the domain of play at 12 months whereas the children of mothers with AD had a higher prevalence of developmental delay in the domain of relating. According to this study, maternal depression and AD affect not only the mothers themselves but also their children. Therefore, assessing maternal mental health in paediatric follow-up especially during the first year is crucial for optimal child development. Developmental delays in children may be prevented by providing early diagnosis and appropriate support to those mothers suffering from mental health issues.

Ethics

Ethics Committee Approval: Approval was obtained from the ethics committee of Şişli Hamidiye Etfal Training and Research Hospital (decision no: 536, date: 04.08.2015).

Informed Consent: The participants were informed about the study, and their oral and written consents were obtained.

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Evaluation of Atrial Conduction Times and Epicardial Adipose Tissue Thickness in Patients with Ankylosing Spondylitis

Ankilozan Spondilit Hastalarında Atriyal İleti Sürelerinin ve Epikardiyal Yağ Dokusu Kalınlığının Değerlendirilmesi

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ABSTRACT

Introduction: In this study, we aimed to evaluate whether atrial electromechanical delay (EMD) and epicardial adipose tissue (EAT) thickness differed between ankylosing spondylitis (AS) patients and healthy subjects.

Methods: This prospective, cross-sectional study included 43 consecutive AS patients followed up in the Physical Medicine and Rehabilitation Department of the University of Health Sciences Turkey, İstanbul Training and Research Hospital, between June 2019 and January 2020. The control group consisted of 42 age-and gender-matched healthy participants. The PA atrial EMD was accepted as the beginning of the P wave on the electrocardiograph and the begining of late diastolic wave (Am wave) on the tissue Doppler obtained by transthoracic echocardiography, and all EMD parameters, including lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and right ventricular tricuspid annulus (tricuspid PA), were calculated. The thickness of EAT was obtained from the thickest part of the right ventricular free wall at the end of diastole in the parasternal long axis window.

Results: In AS patients, tissue Doppler measurements of PA lateral, PA septal and PA tricuspid were longer than the measurements in the control group. In addition, EAT thickness was significantly higher in AS patients than in the control group. There was a moderate correlation between interatrial EMD and C-reactive protein ($r=0.445$, $p<0.001$) and EAT thickness ($r=0.451$, $p<0.001$).

Conclusion: In this study, interatrial EMD and intraatrial EMD were significantly higher in AS patients. In addition, the thickness of EAD was significantly greater in patients with AS. These findings suggest a higher tendency toward coronary artery disease and atrial fibrillation in patients with AS.

Keywords: Ankylosing spondylitis, electromechanical delay, epicardial adipose tissue, atrial fibrillation

ÖZ

Amaç: Bu çalışmada, ankilozan spondilit (AS) hastaları ile tamamen sağlıklı kişiler arasında atriyal elektromekanik gecikme (EMG) ve epikardiyal yağ dokusu (EYD) kalınlığı bakımından fark olup olamadığını değerlendirmeyi amaçladık.

Yöntemler: Bu prospektif kesitsel çalışmaya, Haziran 2019-Ocak 2020 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi Fiziksel Tıp ve Rehabilitasyon bölümünde takip edilen 43 ardışık AS hastası dahil edildi. Kontrol grubu, yaş ve cinsiyete göre eşleştirilen 42 sağlıklı katılımcıdan oluşuyordu. PA atriyal EMG elektrokardiyografide P dalgasının başlangıcı ve transtorasik ekokardiyografik ile elde edilen geç diyastolik dalga (Am dalgası) başlangıcı olarak kabul edildi ve tüm EMG parametreleri olan lateral mitral anulus PA, septal mitral anulus PA ve sağ ventrikül triküspit anulus PA hesaplandı. EYD kalınlığı, parasternal uzun eksen penceresindeki diyastolün sonundaki sağ ventrikül serbest duvarının en kalın kısmından elde edildi.

Bulgular: AS hastalarında PA lateral, PA septal ve PA triküspit doku Doppler ölçümleri kontrol grubuna göre daha uzundu. Ek olarak, AS hastalarında EYD kalınlığı kontrol grubuna göre anlamlı olarak daha yüksekti. İnteratriyal EMG ile C-reaktif protein ($r=0,445$, $p<0,001$) ve EYD kalınlığı ($r=0,451$, $p<0,001$) arasında orta derecede bir korelasyon vardı.

Sonuç: Bu çalışmada, AS hastalarında interatriyal EMG ve intraatriyal EMG AS hastalarında anlamlı derecede yüksekti. Ayrıca, EYD kalınlığı AS hastalarında anlamlı olarak daha fazlaydı. Bu bulgular, AS'li hastalarda koroner arter hastalığı ve atriyal fibrilasyon eğiliminin daha yüksek olduğunu gösterebilir.

Anahtar Kelimeler: Ankilozan spondilit, elektromekanik gecikme, epikardiyal yağ dokusu, atriyal fibrilasyon

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory joint disease that mainly affects the sacroiliac joints and axial skeleton (1). Extra-articular involvement in AS includes cardiovascular involvement findings such as aortic valve regurgitation, aortic root pathologies, and transmission disorders (2). In addition to AS patients, increased cardiovascular morbidity and mortality have been reported compared to the general population. Although the reason for this increase is not known exactly, the idea that chronic inflammation and autoimmunity play a role comes to the fore (3).

Atrial fibrillation (AF) is the most common type of cardiac arrhythmia that causes increased mortality. The various pathophysiological mechanisms that lead to AF include structural and electrical abnormalities, tissue remodeling, and inflammation (4). Previous studies have shown that prolonged atrial transmission time or electromechanical delay (EMD) may predispose to AF in chronic inflammatory diseases such as systemic sclerosis, psoriasis vulgaris (5,6). The gold standard in the evaluation of atrial transmission time is invasively applied electrophysiological studies. Another simple and non-interventional method can be obtained by measuring the time (PA) from the beginning of the P wave in electrocardiography (ECG) to the beginning of the Doppler A wave on transthoracic echocardiography (TTE) (7). Inter and intraatrial EMD can be evaluated using this method.

Epicardial adipose tissue (EAT) located between the myocardium and visceral pericardium is the actual visceral adipose tissue of the heart. EAT is a metabolically active tissue and a source of various local inflammatory mediators. Echocardiography can be used as the most appropriate low-cost and non-radiation imaging method to evaluate EAT. Many studies have shown an association between EAT and the development of atherosclerotic cardiovascular diseases, metabolic syndrome, and AF, including coronary artery disease (CAD) (8,9). In this study, we aimed to evaluate whether there was a difference in atrial EMD and EAT thickness between AS patients with a complex inflammatory structure and fully healthy people.

Methods

Data Collection

Fourty three consecutive patients with AS who were followed in the University of Health Sciences Turkey, İstanbul Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation between June 2019 and January 2020 were included in this prospective, cross-sectional study. The control group of 42 healthy participants was matched with the patient group in terms of age and gender. All patients enrolled in the study met the modified New York criteria for AS. The exclusion criteria in the study are as follows; atherosclerotic cardiovascular disease, left ventricular (LV) systolic or diastolic (> grade II) dysfunction, moderate-to-severe heart valve disorder, diabetes mellitus, thyroid dysfunction, chronic lung disease, poor display quality, conduction abnormalities and/or the presence of branch block in ECG, electrolyte disorder, the use of antiaritmic and/or antipsychotic medication. Key clinical features such as age, gender and body mass index (BMI), duration of disease and drugs used in treatment for all patients were recorded. For each patient, pain conditions, movement restrictions and disease activity were assessed by using Bath Ankylosing Spondylitis Disease Activity index, Bath Ankylosing Spondylitis Functional index and chest expansion (Table 1).

This forward-looking, cross-sectional study protocol has been approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 1849, date: 24.05.2019). A written informed consent form was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Transthoracic Echocardiography Evaluation

TTE examinations were performed in all patients with echocardiography device using 5-1 MHz S5-1 ultrasound probe (EPIQ 7; Philips Medical Systems, Bothell, WA, USA) in accordance with the standards of the

Table 1. Clinical features and laboratory findings of patients in the ankylosing spondylitis and control group

	AS patient group (n=43)	Control group (n=42)	p
Age, years	42.8±9.2	41.5±8.9	0.491
Male Gender, n (%)	31 (72.1)	30 (71.4)	0.946
BMI, kg/m^2	27.3±4.9	28.5±4.3	0.261
Smoking, n (%)	24 (55.8)	18 (42.9)	0.232
Heart rate, pulse/min	77.3±10.2	74.6±9.0	0.215
Duration of disease, year	9.19±5.54	-	-
NSAID use, n (%)	17 (39.5)	-	-
Sulfasalazine use, n (%)	13 (30.2)	-	-
Anti-TNF-alfa use, n (%)	20 (46.5)	-	-
BASMI	7.84±2.22	-	-
BASDAI	2.91±1.86	-	-
BASFI	2.03±2.34	-	-
Chest expansion, cm	4.23±0.86	-	-
Leucocyte, 10^3 u/L	7.98±2.2	7.16±1.8	0.068
Hemoglobin, g/dL	13.9±1.6	14.3±1.6	0.213
Thrombocyte, 10^3 u/L	254.6±64.5	244.0±56.8	0.425
Fasting blood glucose, mg/dL	96.0±19.4	94.4±16.6	0.848
Blood urea nitrogen, mg/dL	31.2±11.4	28.6±7.0	0.286
Creatinine, mg/dL	0.77±0.35	0.75±0.16	0.520
Total cholesterol, mg/dL	194.7±29.1	198.1±40.6	0.653
LDL cholesterol, mg/dL	122.8±25.3	123.6±33.6	0.899
HDL cholesterol, mg/dL	47.9±10.8	46.1±12.4	0.341
Triglyceride, mg/dL	119.8±61.1	142.3±83.7	0.305
ESR, mm/hr	15.5±13.6	11.3±12.2	0.067
CRP, mg/dL	7.28±9.49	3.53±5.96	<0.001
ASDAS-ESR	2.30±0.81	-	
ASDAS-CRP	2.38±0.77	-	

Nominal variables (%) and continuous variables presented frequently are shown as mean ± standard deviation.

AS: Ankylosing spondylitis, BMI: body mass index, NSAID: non-steroid antiinflammatory drugs, TNF: tumor necrosis factor, BASMI: Bath Ankylosing Spondylitis Metrology index, BASDAI: Bath Ankylosing Spondylitis Disease Activity index, BASFI: Bath Ankylosing Spondylitis Functional index, LDL: low density lipoprotein, HDL: high density lipoprotein, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASDAS: ankylosing spondylitis disease activity score

American Echocardiography Association. During the examination, D2 derivation ECG was recorded continuously and the average of 3 consecutive measurements was calculated.

Conventional Echocardiography Measurements

From the parasternal long axis view window, LV end-systolic diameter, end-diastolic diameter, interventricular septum, posterior wall thickness, left atrial anteroposterior diameter, aortic root and ascending aortic diameter were measured by M-mode echocardiography. LV ejection fraction was measured by the Simpson's method. Left and right atrium mediolateral and apicobasal diameters as well as left and right atrium areas were measured from the apical-4 space window. In pulsed wave Doppler echocardiographic examination, the sample volume was placed at the tip of the mitral valve and the mitral early diastolic filling rate (E), late diastolic filling rate (A), E/A ratio and deceleration time were measured from the apical 4-chamber image. Systolic movement of the tricuspid valve annular plane towards the apex was measured by placing the M-mode cursor at the junction point of the tricuspid valve and the free wall of the right ventricle in the apical 4-chamber view.

Tissue Doppler Parameters

Tissue Doppler evaluation was performed with the same device, using a spectral pulse Doppler signal filter at a Nyquist limit of 15-20 cm/sec, with an optimal gain. The monitor flow rate was adjusted to 50-100 mm/s to optimize the image of myocardial velocities. A pulse Doppler volume sample from the apical 4 gap window was taken from the systolic volume (SV) lateral mitral ring, septal mitral ring, and right ventricular tricuspid ring, and peak systolic (Sm), peak early diastolic (Em), and peak late diastolic (Am) velocities were measured from these samples.

Electromechanical Delay Measurement

The time between the onset of the P wave on the superficial ECG and the onset of the tissue Doppler late diastolic wave (Am wave) was defined as PA atrial EMD (atrial conduction time), and all atrial EMDs were measured from lateral mitral annulus (lateral PA), septal mitral annulus (septal PA) and right tricuspid annulus (tricuspid PA) (Figure 1). The difference between the PA durations measured from the SV lateral mitral annulus (ML) and the right ventricular tricuspid annulus (TL) regions was defined as interatrial EMD, the difference between the PA durations measured from SV lateral mitral annulus and septal mitral annulus (MS) was defined as intra-left atrial EMD, the difference between the PA durations measured from septal mitral annulus and right ventricular tricuspid annulus was defined as intra-right atrial EMD.

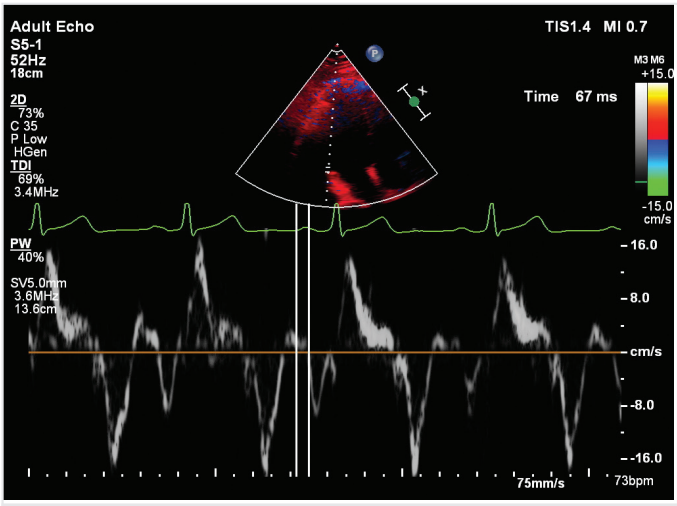

Figure 1. Evaluation of atrial conduction times with Doppler echocardiography

Epicardial Adipose Tissue Thickness

EAT thickness was obtained from the thickest part at the end of the diastole from the right ventricular free wall in the parasternal long axis window (Figure 2).

Laboratory Analysis

Blood values of the patients including erythrocyte sedimentation rate, C-reactive protein (CRP) and lipid values were obtained after 8 hours of fasting. The hematology analyzer (Beckman Coulter LH 780, FL, USA) was used to obtain the results of the full blood samples, while the CRP was measured using a biochemical analyzer (Beckman Coulter AU 680).

Statistical Analysis

SPSS statistical software version 22.0 (IBM, Chicago, IL, USA) was used to analyze the data. Kolmogorov-Smirnov tests were used to test whether the data was normal distribution. Mean ± standard deviation was used to express quantitative variables, while categorical variables were expressed in numbers and percentages. When comparing two groups for numerical variables, independent t-tests were used if there was a normal distribution. If there was no normal distribution, Mann-Whitney U tests were used. Chi-square tests were used to evaluate differences in categorical variables. Spearman correlation analysis was used to show the relationships between continuous variables. The power analysis of the study was evaluated using the G*power 3.1 program. The power of the study was 0.956 and the effect size was 1.413. $P<0.05$ was found to be statistically significant.

Results

Fourty three AS patients and age and gender matched 42 healthy control subjects were included in our study. Clinical characteristics and laboratory findings for AS patients and healthy people and various

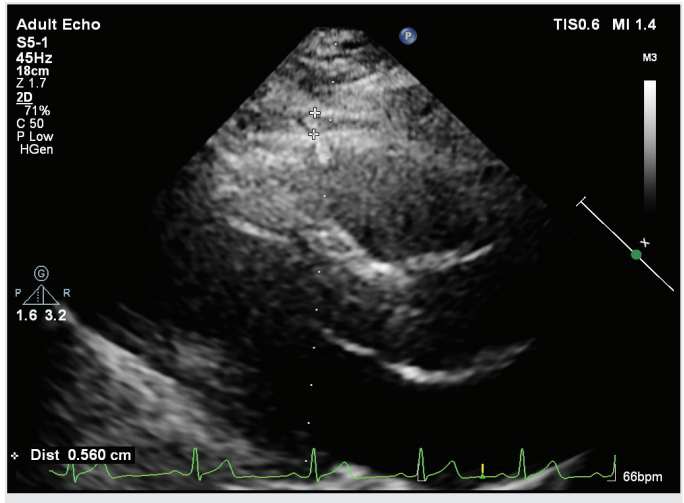

Figure 2. Evaluation of epicardial adipose tissue thickness by echocardiography

disease activity parameters of AS patients are given in Table 1. In terms of laboratory findings, CRP was significantly higher in AS patients ($p<0.05$). Other laboratory parameters were similar between groups.

Analysis of Conventional Echocardiographic and Tissue Doppler Parameters

There was no significant difference between many conventional echocardiographic parameters in which the diameter and functions of the right and left spaces were evaluated and tissue Doppler parameters (Table 2). However, diameters and volumes of the right and left atria were significantly higher and septal annulus systolic myocardial velocity (Sm) was significantly lower in AS patients.

Atrial Electromechanical Delay and Epicardial Adipose Tissue Thickness

Doppler tissue measurements showed that PA lateral, PA septal and PA tricuspid in AS patients were more elongated than the control group ($p<0.05$ for each). With all Doppler findings indicating EMD, EAT thickness was significantly higher in AS patients than in the control group (Table 3).

Correlation Between Electromechanical Delay, Epicardial Adipose Tissue, Echocardiographic Parameters and Working Variables

A significant moderate correlation was found between interatrial EMD and CRP ($r=0.445$, $p<0.001$) and EAT thickness ($r=0.451$, $p<0.001$). Atria dimensions and correlation results between BMI and interatrial EMD are given in Table 4.

Table 2. Echocardiographic findings of ankylosing spondylitis and control group patients

	AS patient group (n=43)	Control group (n=42)	p
Conventional echocardiography			
LV EF, %	64.60±2.95	64.67±2.47	0.961
Ascending aorta diameter, mm	3.19±0.36	3.23±0.33	0.587
Sinus of valsalva diameter, mm	3.24±0.30	3.29±0.29	0.293
Aortic root width, mm	2.14±0.16	2.15±0.17	0.676
LV end-diastolic diameter, mm	4.57±0.29	4.61±0.27	0.534
LV end-systole diameter, mm	2.68±0.27	2.69±0.24	0.961
Interventricular septum, mm	0.94±0.09	0.94±0.09	0.970
Posterior wall, mm	0.92±0.09	0.93±0.09	0.993
LA AP diameter, mm	3.55±0.28	3.41±0.23	0.008
LA ML diameter, mm	4.01±0.33	3.85±0.30	0.018
LA AB diameter, mm	5.03±0.40	4.79±0.30	0.003
LA volume, mL	17.10±2.41	15.42±1.61	<0.001
RA ML diameter, mm	3.61±0.38	3.49±0.25	0.035
RA AB diameter, mm	4.58±0.43	4.34±0.34	0.007
RA volume, mL	14.14±2.53	12.91±1.62	0.010
Mitral early (E) diastolic flow rate, cm/s	73.77±15.76	78.31±12.76	0.148
Mitral late (A) diastolic flow rate, cm/s	66.53±16.06	63.88±14.40	0.425
E/A	1.15±0.31	1.26±0.26	0.086
Deceleration time, ms	210.28±29.79	210.14±41.11	0.986
TAPSE, cm	2.63±0.15	2.68±0.18	0.133
Tissue Doppler parameters			
Lateral annulus Sm, cm/s	11.03±1.62	11.35±2.27	0.467
Lateral annulus Em, cm/s	13.82±3.20	14.44±2.42	0.316
Lateral annulus Am, cm/s	11.10±2.90	10.46±2.30	0.264
Septal annulus Sm, cm/s	8.12±1.01	9.05±1.46	0.002
Septal annulus Em, cm/s	10.45±2.12	11.30±2.11	0.070
Septal annulus Am, cm/s	9.86±1.91	9.46±2.03	0.354
Tricuspid annulus Sm, cm/s	14.01±1.57	14.32±1.62	0.377
Tricuspid annulus Em, cm/s	13.56±3.39	13.50±2.56	0.931
Tricuspid annulus Am, cm/s	13.97±2.96	14.79±2.69	0.183

Continuous variables are presented as mean ± standard deviation.

LV: Left ventricle, EF: ejection fraction, LA: left atrium, AP: anteroposterior, ML: mediolateral, AB: apicobasal, RA: right atrium, TAPSE: systolic displacement of the tricuspid valve in the annular plane, Sm: systolic myocardial velocity, Em: early diastolic myocardial velocity, Am: late diastolic myocardial rate, AS: ankylosing spondylitis

Table 3. Atrial electromechanical delay times and epicardial adipose tissue thickness findings of patients in the ankylosing spondylitis and control groups

	AS patient group (n=43)	Control group (n=42)	p
PA lateral, ms	60.07±6.62	52.14±4.51	<0.001
PA septal, ms	48.95±5.39	43.12±2.88	<0.001
PA tricuspid, ms	39.86±4.02	37.60±2.74	0.002
Interatrial EMD, ms	20.21±4.25	14.55±3.74	<0.001
İntra LA EMD, ms	11.12±2.80	9.02±2.94	0.001
İntra RA EMD, ms	9.09±2.62	5.52±1.93	<0.001
Epicardial fat tissue thickness, cm	0.46±0.15	0.33±0.12	<0.001

Continuous variables are presented as mean ± standard deviation.

PA: The duration from the onset of the P wave on electrocardiography to the onset of the A wave on echocardiography, EMD: electromechanical delay, LA: left atrial, RA: right atrial, AS: ankylosing spondylitis

Table 4. Correlation between electromechanical delay, epicardial adipose tissue, echocardiographic parameters and study variables

	Interatrial EMD, ms	
	r	p
Age, years	0.156	0.155
BMI, kg/m^2	0.236	0.036
CRP, mg/dL	0.445	<0.001
LA AP diameter, mm	0.520	<0.001
LA ML diameter, mm	0.214	0.051
LA AB diameter, mm	0.460	<0.001
LA volume, mL	0.407	<0.001
RA ML diameter, mm	0.135	0.219
RA AB diameter, mm	0.406	<0.001
RA volume, mL	0.367	0.001
EAT	0.451	<0.001

BMI: Body mass index, CRP: C-reactive protein, LA: left atrium, AP: anteroposterior, ML: mediolateral, AB: apicobasal, RA: right atrium, EAT: epicardial adipose tissue, EMD: electromechanical delay

Discussion

In our study, atrial EMD and EAT thickness were evaluated in patients with AS, and three main findings were as follows: 1) Interatrial EMD and intraatrial EMD were significantly higher in AS patients; 2) EAT thickness was significantly greater in AS patients; 3) there was a significant correlation between interatrial EMD and CRP, atrial sizes and EAT.

Although AS primarily affects the axial skeleton, it is a systemic chronic inflammatory rheumatic disease affecting extra skeletal tissues such as ophthalmologic, cardiac and neurological. Cardiac complications occur especially after a long illness period (2,10). Cardiovascular complications seen in 5-10% of patients are aortic root diseases, diastolic dysfunction, intracardiac transmission disorders, myocardial fibrosis and more rarely arrhythmia. It is also recently reported a trend towards increased subclinical atherosclerosis in patients with AS without clinical evidence of cardiac involvement. Fibrosis in the atrial tissue that arises as a result of inflammation may also contribute to conduction abnormalities and impairment of atrial mechanical function in patients with AS (3,11). However, recent studies have shown that there is a relationship between chronic inflammation and the development of AF, and infiltration by inflammatory cells in the atrial tissue has been observed in AF patients (12). It has been reported that atrial conduction disorders due to electrophysiological and electromechanical abnormalities increase the risk of developing AF (4). In addition, it has been shown in recent studies that prolonged intraatrial and interatrial electromechanical conduction times increase the risk of AF (13,14). In this study, we observed that intraatrial and interatrial conduction times increased in AS patients. Although there is still no clear evidence, it has been suggested that AS patients may be at high risk for developing AF as a result of increased chronic inflammation and myocardial fibrosis.

EAT, located between myocardium and visceral pericardium, is a type of visceral adipose tissue. EAT secretes a wide variety of active biological molecules that regulate vascular smooth muscle contraction. Paracrine effects arise from its proximity to adventitia and extravascular bed (15). TTE provides non-invasive evaluation of EAT. EAT is thought to play an important role in CAD and AF pathogenesis (8,9). In a study conducted, it was shown that EAT is associated with hypertension, atherosclerosis and coronary heart disease (16). It has been shown by Yamashita et al. (17) that there is relationship between increased EAT thickness measured on computed tomography and especially left anterior descending and right coronary artery coronary plaque load. There are also studies explaining the relationship between EAT and the development and severity of AF. In the Framingham Heart Study, it was shown that higher pericardial fat volume was associated with approximately 40% higher AF rates, even after adjusting for risk factors such as age, myocardial infarction, heart failure, BMI, and gender associated with AF (18). Batal et al. (19) reported that increased EAT thickness is an important predictor of AF load independent of age, BMI, or left atrial area, and that patients with permanent AF have a significantly thicker EAT than patients with paroxysmal AF or without AF. Another study showed that EAT was associated with AF even after adding other risk factors, and that every 10 mL increase in EAT volume increased AF rates by 13% (20). In addition, the association of EAT with recurrence after AF catheter ablation has been demonstrated. It has been shown that in patients with increased EAT, recurrence is observed earlier after the ablation procedure and EAT independently predicts the presence, severity and recurrence of AF (21). All these evidences show that there is a close relationship between

EAT and CAD and AF. In our study, we observed significantly increased EAT thickness in AS patients. Our study had the following limitations. First, the main limitation was that there were a limited number of cases included in the study and that it was done in a single center. Therefore, multi-center studies involving large number of subjects are needed to validate the results of our study. Second, methods such as cardiac magnetic resonance or computed tomography for atrial remodeling and EAT evaluation were not used in this study. Therefore, it may be necessary to evaluate EAT and atrial remodeling with these methods in AS patients. Third, since a limited number of patients were included in the study, independent variables could not be evaluated by multiple analyses. Finally, the mean follow-up period of AS cases included in the study was relatively short. Since this time is not sufficient to show the development of AF and CAD, longer studies are required.

Conclusion

In this study, it has been shown that there is a prolongation in atrial EMG, that predicts AF in AS patients and an increase in EAT thickness, which also causes the development of CAD and AF. In addition, a significant positive correlation was found between interatrial and intraatrial EMD and EAT. These results suggest that it may cause increased CAD and AF development in AS patients. Therefore, AS patients should be followed closely in terms of cardiac involvement.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 1849, date: 24.05.2019).

Informed Consent: A written informed consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

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Predictors of Complex Aortic Plaques in Patients Undergoing Transoesophageal Echocardiography

Transözefajiyal Ekokardiyografik İnceleme Yapılan Hastalarda Kompleks Aort Plaklarının Öngördürücüleri

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ABSTRACT

Introduction: Atrial fibrillation (AF) is one of the most important causes of ischaemic stroke according to the TOAST classification. The CHA_2DS_2-VASc score is a widely used scoring system for estimating systemic thromboembolism in patients with non-valvular AF. TOAST classification indicates that an ischaemic stroke may also be due to large artery atherosclerosis. Since some of the atherosclerotic risk factors also occur in the CHA_2DS_2-VASc scoring system, we hypothesised that this scoring system can also predict the presence of complex aortic plaques and their stroke risk.

Methods: We retrospectively investigated 551 patients who underwent transthoracic echocardiography and subsequent transoesophageal echocardiography (TEE). Baseline characteristics of the patients were recorded, and the CHA_2DS_2-VASc score was calculated before the TEE examination. Aortic plaques are classified as complex when they are protruding more than 4 mm, mobile or have irregular boundaries.

Results: Among 551 patients, 110 complex aortic plaques (CAPs) were detected. Considering all the patients, higher CHA_2DS_2-VASc score [odds ratio (OR): 2.905], increasing age (OR: 1.056), and male (OR: 3.008) were significantly associated with CAP. CHA_2DS_2-VASc score was even more significantly associated with CAP in patients with a previous stroke [p<0.001, OR: 16.754 (4.196-66.894), confidence interval (CI): 95%]. After excluding complicated aortic plaques from the calculation, higher CHA_2DS_2-VASc score in patients with AF was also associated with the presence of CAPs (p<0.001, OR: 3.379 1.848-6.179, CI: 95%).

Conclusion: Although the CHA_2DS_2-VASc score has been validated to estimate thromboembolic risk in patients with non-valvular AF, the results of this study show that a high CHA_2DS_2-VASc score may also indicate an increased risk for CAP in patients with both sinus and non-valvular-AF rhythm.

Keywords: Complex aortic plaques, CHA_2DS_2-VASc score, ischaemic stroke

ÖZ

Amaç: Atriyal fibrilasyon (AF) TOAST sınıflamasına göre iskemik inmenin önemli bir nedenidir. CHA_2DS_2-VASc skor non-valvüler AF'li hastalarda iskemik stroke ve tromboemboli riskini belirlemek için sıklıkla kullanılan bir skorlama sistemidir. Bunun yanı sıra TOAST sınıflamasında, büyük arter aterosklerozu kardiyoembolizm gibi iskemik inmenin ayrı bir sınıfıdır. Biz bu çalışmamızda CHA_2DS_2-VASc skorunun kompleks aortik plaklar (KAP) ile olan ilişkisini incelemeyi amaçladık.

Yöntemler: Retrospektif olarak transtorasik ve sonrasında transözefajiyal ekokardiyografi (TÖE) uygulanmış 551 hasta analiz edildi. Hastaların demografik ve klinik özellikleri kaydedildi. CHA_2DS_2-VASc skoru TÖE incelemesi öncesinde hesaplandı. 4 mm'den büyük, hareket eden veya düzensiz sınırları olan plaklar KAP olarak kabul edildi.

Bulgular: Beş yüz elli bir hasta dahil edildi ve 110 KAP saptandı. Tüm hastalar göz önüne alındığında CHA_2DS_2-VASc skoru [olasılık oranı (OR): 2,905], yaş (OR: 1,056) ve ve erkek cinsiyet (OR: 3,008) anlamlı bir şekilde KAP ile ilişkili saptandı. Buna ek olarak daha önce iskemik inme geçiren [p<0,001, OR: 16,754 (4,196-66,894), güven aralığı (GA) %95] veya AF'li hastalarda da (p<0,001, OR: 3,379 1,848-6,179, GA: %95) KAP CHA_2DS_2-VASc skoru ile ilişkili saptandı.

Sonuç: Her ne kadar CHA2DS2-VASc skoru non-valvüler AF hastalarında tromboembolik riski hesaplamak için geliştirilmiş olsa da, bu çalışmanın sonucu CHA2DS2-VASc skorunun hem sinüs hem de AF ritmindeki hastalarda artmış KAP riskine işaret edeceğini de göstermiştir.

Anahtar Kelimeler: Kompleks aort plakları, CHA_2DS_2-VASc skoru, iskemik inme

Presented in: This study has been presented in the 2017 European Society of Cardiology congress.

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Introduction

Ischaemic stroke is one of the leading causes of mortality and morbidity worldwide and it is related to multiple underlying aetiologies. Although the trial of ORG 10172 in acute stroke treatment (TOAST) ischaemic stroke classification has divided ischaemic strokes into five subgroups according to the underlying aetiology, the underlying aetiologies cannot be definitely diagnosed in the majority of the cases (1).

Cardioembolism is assumed to be the underlying cause in 30% of ischaemic strokes. Previous studies have demonstrated that the CHA_2DS_2-VASc score predicts cardioembolic stroke particularly in patients with non-valvular atrial fibrillation (NV-AF). Moreover, some studies suggested that it might also predict stroke risk even in patients with sinus rhythm (2-4). Current literature suggests that an increment in the CHA_2DS_2-VASc score is related to a higher stroke risk due to left atrial (LA) abnormalities, which create a favourable milieu for thrombus formation (5). Most of the risk factors that make up the CHA_2DS_2-VASc score are also traditional risk factors for atherosclerosis; therefore, an increased CHA_2DS_2-VASc score may also imply a higher atherosclerotic burden. Overwhelming evidence in the literature suggests that the presence of aortic atheroma plaques predicts future ischaemic stroke, especially when the thickness exceeds 4 mm. Sugioka et al. (6) have demonstrated a significant relationship between $CHADS_2$ score and complex aortic plaques (CAP). Since the CHA_2DS_2-VASc score predicts ischaemic stroke modestly better than the CHADS score (1), regardless of the underlying rhythm, we aimed to investigate the relationship between the CHA_2DS_2-VASc score and CAP.

Methods

Study Population

We retrospectively analysed 651 patients who underwent transoesophageal echocardiography (TEE) between January 2016 and January 2018 in our university clinic. Twenty-one patients were excluded due to the lack of prior transthoracic echocardiographic (TTE) data and 79 patients were excluded due to the absence of clinical variables. Finally, 551 patients (267 men and 284 women) were included in the analysis. The study protocol was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (decision no: 51436, date: 07.02.2018) and patients were included after their informed consent was obtained.

Patients' demographic characteristics such as age, sex and medical history including diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), peripheral arterial disease, ischaemic stroke and AF were recorded.

CHA_2DS_2-VASc score was calculated according to the recommendations of the current guidelines. In brief, one point was given for the history of heart failure, presence of diabetes, HT, age between 65 and 75 years, female sex, vascular disease and two points for age >75 years and history of previous stroke. History of myocardial infarction, symptomatic peripheral arterial disease and the presence of CAPs were considered to be vascular diseases as recommended.

Echocardiographic Data

TTE was performed prior to the TEE examination of each patient in accordance with the American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines. TEE was performed for various clinical indications such as infective endocarditis, assessment of valvular diseases or identification of the aetiology of an ischaemic stroke. TTE and TEE findings that were suggested as potential sources of cardioembolism according to the TOAST classification were collected. In the TOAST trial, cardiac abnormalities, which are prone to be the source of embolism, were divided into two groups: high risk and medium risk.

TEE was performed to all the patients using a commercially available ultrasound imaging system with a 3-D matrix array transoesophageal transducer (Philips Medical systems, IE33, Andover, MA, USA and probe X7-2t). The thoracic aorta was screened when the probe was withdrawn gradually from the descending aorta after the routine assessment of the cardiac structures. Aortic plaques were considered complex if the plaque protruded more than 4 mm from intima to the lumen in the horizontal plane and perpendicular to the arterial wall. We also considered plaques as complex if the plaque had a mobile component or an ulceration. Plaque ulceration was defined as a 2 mm indentation of the plaque surface towards the arterial wall.

Statistical Analysis

SPSS version 20 (SPSS Inc., Chicago, IL, USA) was used for the data analysis. MedCalc Statistical Software version 18 (MedCalc Software bvba, Ostend, Belgium) was used for building the graphics. Data are presented as (i) mean ± standard deviation for continuous variables and (ii) counts with percentages for categorical variables. Normality of distribution for continuous variables was analysed using the Shapiro-Wilk test. Depending on the distribution pattern, independent samples t-test or Mann-Whitney U test was used for group comparisons of the continuous variables. Chi-square test or Fischer's Exact test was performed for the group comparisons of categorical variables as appropriate. Univariate and multivariate logistic regression analyses were used to assess the possible association among demographic, clinical, imaging findings, CHA_2DS_2-VASc scores and the presence of CAPs. Variables with $p<0.05$ in the univariate logistic regression were included in the multivariate logistic regression. Age, sex, HT, stroke, DM and CAD were included in the multivariate analysis regardless of their statistical significance in the univariate analysis. The statistical significance threshold in the multivariate analyses was adjusted using Bonferroni correction. Cochran-Armitage test was performed to test the trend between CHA_2DS_2-VASc scores and the prevalence of CAP. Unless otherwise stated, $p<0.05$ indicated statistical significance.

Results

Patients Demographics

The characteristics of all the 551 patients are shown in Table 1. Mean age was 55±18 years, and 49.1% of the patients were men. The prevalence of AF was high (33.4%). A total of 167 (30.3%) patients had a recent or previous ischaemic stroke. Echocardiographic findings that were supposed to be a potential source of cardioembolism according to TOAST classification are also shown in Table 1.

Potential Cardiac Source of Embolism

Fifty-two patients had LA/left atrial appendage (LAA) thrombi, three had left ventricular (LV) thrombi, 28 had a LV akinetic segment, three had an atrial myxoma, 97 had a diagnosis of dilated cardiomyopathy and 46 patients had a mitral stenosis with respect to the high risk for cardioembolism according to the TOAST classification. In addition, 184 patients had AF, of which 36 patients possessed a CHA_2DS_2-VASc score of 2, and CAP was detected in three of these 36 patients with AF. Therefore, the patients were deemed to have a high risk for future thromboembolism.

Table 1. Demographic and echocardiographic characteristics of all patients

	Value (n=551)
Age	55±18
Gender	
Female	284 (51.5%)
Male	267 (48.5%)
HT	266 (48.3%)
Stroke	167 (30.3%)
DM	114 (20.7%)
CAD	106 (19.2%)
Atrial fibrillation	184 (33.4%)
LVEF	54±8
LA diameter	41±8
LAA thrombus	47 (8.5%)
LAA SEC	92 (16.7%)
LAA velocity	60±24
CAP	74 (18.3%)
PFO	93 (16.9%)
ASD	38 (6.9%)
ASA	34 (6.2%)
LV thrombus	3 (0.5%)
Dilated CM	97 (17.6%)
Akinetic segment presence	28 (5.1%)
LA thrombus	5 (0.9%)
Myxoma	2 (0.4%)
IE	28 (5.1%)
MR	443 (80.4%)
MR grade	
Mild	200 (36.3%)
Moderate	166 (30.1%)
Moderate to severe	39 (7.1%)
Severe	38 (6.9%)
MS	46 (8.3%)
MS grade	
Mild	27 (4.9%)
Moderate	16 (2.9%)
Severe	3 (0.5%)
MVP	19 (3.4%)
MAC	7 (1.3%)
CHA_2DS_2-VASc score	2±2

HT: Hypertension, DM: diabetes mellitus, CAD: coronary artery disease, LVEF: left ventricular ejection fraction, LA: left atrial, LAA: left atrial appendage, SEC: spontaneous echo contrast, CAP: complex aortic plaque, PFO: patent foramen ovale, ASD: atrial septal defect, ASA: atrial septal aneurysm, LV: left ventricle, CM: cardiomyopathy, IE: infective endocarditis, MR: mitral regurgitation, MS: mitral stenosis, MVP: mitral valve prolapse, MAC: mitral annular calcification

Complex Aortic Plaques

Patients were divided into two groups according to the presence or absence of CAP. CAP were detected in a total of 110 patients*. In univariate analyses, there was a statistically significant difference between the groups with respect to age ($p<0.001$), HT ($p<0.001$), CAD ($p<0.001$), DM ($p=0.003$) and AF ($p<0.001$). Mean CHA_2DS_2-VASc score was significantly higher in patients with CAP (2±1 in patients without CAP and 4±1 in patients with CAP, $p<0.001$). After multivariate analyses, male sex ($p<0.001$) and age ($p=0.001$) were independently associated with the presence of CAP. As expected, CHA_2DS_2-VASc score was also independently associated with the presence of CAP [$p<0.001$, odds ratio (OR): 2.905 (1.906-4.428), confidence interval (CI): 95%] (Table 2). Trend analyses of CHA_2DS_2-VASc score and presence of CAP demonstrated a significant linear relationship, which is depicted in Figures 1, 2 and 3.

The Relationship Between Cardiac Rhythm and Complex Aortic Plaques

Among the 551 patients, 184 patients had AF and AF patients had a higher percentage of CAP (28.1% vs 54.5%). Although there was a significant difference in the univariate analyses ($p<0.001$), AF was not independently associated with the presence of CAP in the multivariate analyses ($p=0.307$). CHA_2DS_2-VASc score was also significantly associated with CAP both in the univariate and multivariate analyses [$p<0.001$ and OR: 3.379 (1.848-6.179), CI: 95%]. Among the cases with sinus rhythm, 50 of them had CAPs. Although age, HT, DM, CAD, LV ejection fraction and CHA_2DS_2-VASc score were significant in the univariate analysis, only CHA_2DS_2-VASc score was independently associated with the presence of CAP after the multivariate analysis [$p<0.001$, 3.021 (1.620-5.623), CI: 95%] (Table 3).

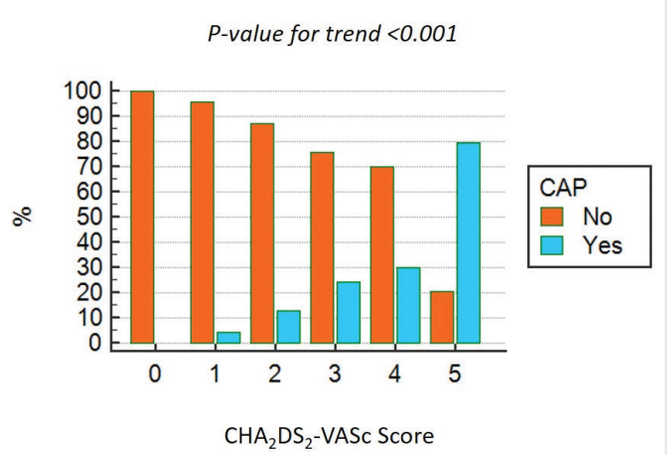

Figure 1. Trend analysis for CHA_2DS_2-VASc-VASc score and CAP in all patients
CAP: Complex aortic plaque

Table 2. Group comparisons along with univariate and multivariate logistic regression analyses in all patients with or without complex aortic plaque

	Group comparisons			Univariate logistic regression		Multivariate logistic regression	
	CAP- (n=441)	CAP+ (n=110)	p	OR (95% CI)	p	OR (95% CI)	p
Age	51±17	71±10	<0.001	1.117 (1.091-1.144)	<0.001	1.056 (1.023-1.090)	0.001
Male	209 (47.4%)	58 (57.2%)	0.338	1.238 (0.815-1.881)	0.317	3.008 (1.526-5.391)	0.001
HT	180 (40.8%)	86 (78.2%)	<0.001	5.196 (3.181-8.487)	<0.001	0.609 (0.279-1.331)	0.214
Stroke	131 (29.7%)	36 (32.7%)	0.563	1.151 (0.736-1.801)	0.537	0.425 (0.188-0.960)	0.039
DM	76 (17.2%)	32 (34.5%)	<0.001	2.535 (1.593-4.032)	<0.001	0.533 (0.260-1.094)	0.086
CAD	65 (14.7%)	41 (37.3%)	<0.001	3.437 (2.153-5.487)	<0.001	0.409 (0.193-0.869)	0.020
AF	124 (28.1%)	60 (54.5%)	<0.001	3.068 (1.998-4.711)	<0.001	0.697 (0.348-1.394)	0.307
LVEF	55±7	51±10	<0.001	0.946 (0.924-0.968)	<0.001	1.015 (0.972-1.059)	0.506
LA diameter	40±8	43±6	<0.001	1.041 (1.015-1.068)	0.002	0.952 (0.909-0.997)	0.038
LAA thrombus	28 (6.3%)	19 (17.3%)	<0.001	3.080 (1.648-5.755)	<0.001	2-202 (0.881-5.503)	0.091
LAA spontaneous echo contrast	48 (14.5%)	27 (36.5%)	<0.001	2.775 (1.698-4.536)	<0.001	0.968 (0.454-2.066)	0.934
LAA velocity	63±23	50±23	<0.001	0.976 (0.966-0.986)	<0.001	0.991 (0.977-1.006)	0.231
PFO	81 (18.4%)	12 (10.9%)	0.065	0.544 (0.285-1.038)	0.065	-	-
ASD	32 (7.3%)	6 (5.5%)	0.674	0.737(0.300-1.810)	0.506	-	-
ASA	30 (6.8%)	4 (3.6%)	0.272	0.517 (0.178-1.500)	0.225	-	-
LV thrombus	2 (0.5%)	1 (0.9%)	0.488	2.014 (0.181-22.412)	0.569	-	-
Dilated CM	68 (15.4%)	29 (26.4%)	0.011	1.964 (1.195–3.227)	0.008	2.003 (0.835-4.803)	0.120
Akinetic segment	10 (3.0%)	5 (6.8%)	0.125	1.161 (0.979-1.375)	0.136	-	-
Akinetic segment number	4±2	5±3	0.561	1.192 (0.716-1.983)	0.500	-	-
LA thrombus	4 (0.9%)	1 (0.9%)	0.998	1.002 (0.111-9.058)	0.998	-	-
LA SEC	59 (13.4%)	33 (30%)	<0.001				
Myxoma	2 (0.5%)	0	0.479	-	0.999	-	-
IE	24 (5.4%)	4 (3.6%)	0.627	0.254 (0.223-1.980)	<0.001	1.308(0.482-3.555)	0.598
MR	342 (77.6%)	101 (91.8%)	<0.001	3.249 (1.585-6.658)	-	-	-
MS	37 (8.4%)	9 (8.9 %)	0.944	0.973 (0.455-2.081)	0.944	-	-
MVP	18 (4.1%)	1 (0.9%)	0.103	0.216 (0.028-1.633)	0.137	-	-
MAC	5 (1.1%)	2 (1.8%)	0.566	1.615 (0.309-8.436)	0.570	-	-
CHA_2DS_2-VASc score	2±1	4±1	<0.001	2.537 (2.114-3.046)	<0.001	2.905 (1.906-4.428)	<0.001

HT: Hypertension, DM: diabetes mellitus, CAD: coronary artery disease, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LA: left atrium, LAA: left atrial appendage, CAP: complex aortic plaque, PFO: patent foramen ovale, ASD: atrial septal defect, ASA: atrial septal aneurysm, LV: left ventricle, CM: cardiomyopathy, IE: infective endocarditis, MR: mitral regurgitation; MS: mitral stenosis, MVP: mitral valve prolapse, MAC: mitral annular calcification, OR: odds ratio, CI: confidence interval, LA SEC: left atrial spontaneous echo contrast

When the stroke patients were analysed according to presence of CAP, AF was found to be significantly more frequent in CAPs (+) patients.

Discussion

Our study demonstrated that the CHA_2DS_2-VASc score is strongly correlated with the presence of CAPs regardless of the underlying rhythm and that as the CHA_2DS_2-VASc score increased, the possibility of CAP detection also increased. After adjustment for atherosclerotic risk factors, LA abnormalities and cardiac rhythm, CHA_2DS_2-VASc score was still independently and significantly associated with the presence of CAPs. Moreover, trend analyses between CHA_2DS_2-VASc score and CAPs revealed that every 1 point increase in CHA_2DS_2-VASc score was significantly associated with an increased risk of the presence of CAPs. Although the CHA_2DS_2-VASc score was primarily developed to estimate the stroke risk in patients with NV-AF, current studies suggest that these scores might also predict the future stroke risk even in patients without AF. This may be explained by the fact that most of the parameters included in the CHA_2DS_2-VASc scoring system are also the risk factors for stroke (7). Therefore, concomitance of a high CHA_2DS_2-VASc score, CAPs and stroke should be expected and the findings of our study provide evidence for this concomitance.

Although the aetiology and treatment modalities of ischaemic stroke are well defined in the literature, the precise cause of the ischaemic event in a particular patient cannot be established in most stroke cases (8). The TOAST classification system divides strokes into five subgroups according to the cause: cardioembolism, large artery atherosclerosis, small-vessel occlusion, stroke of other determined aetiology and stroke of undetermined aetiology. Strokes have an undetermined aetiology

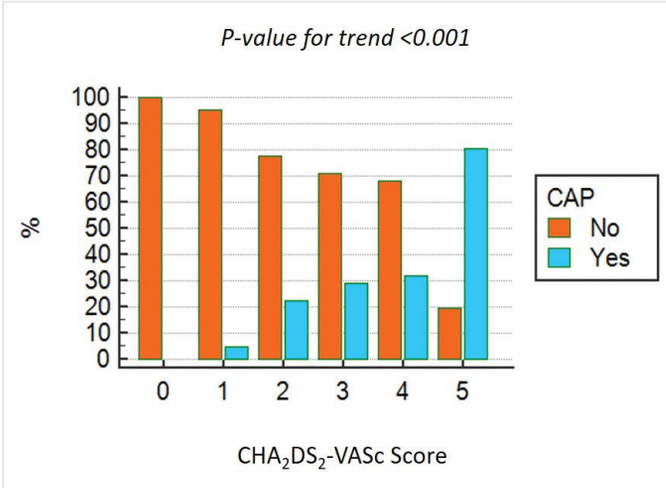

Figure 2. Trend analysis for CHA_2DS_2-VASc score and CAP in patients with atrial fibrillation

CAP: Complex aortic plaque

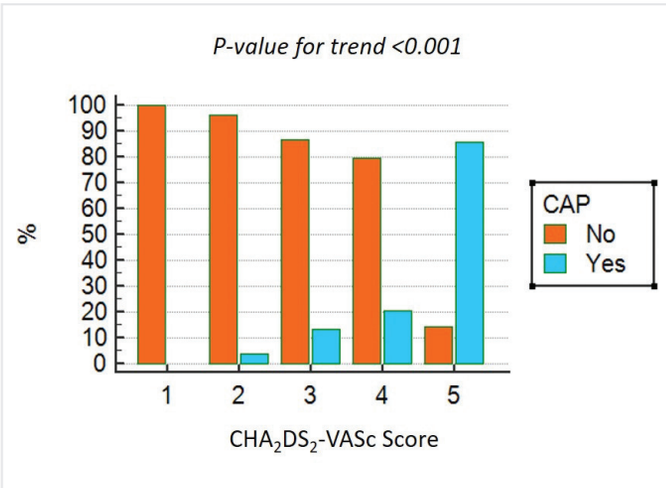

Figure 3. Trend analysis for CHA_2DS_2-VASc-VASc score and CAP patients with stroke

CAP: Complex aortic plaque

Table 3. Group comparisons along with univariate and multivariate logistic regression analyses in patients with atrial fibrillation

	Group comparisons			Univariate logistic regression		Multivariate logistic regression	
	AF+ & CAP- (n=124)	AF+ & CAP+ (n=60)	p	OR (95% CI)	p	OR (95% CI)	p
Age	61±11	75±8	<0.001	1.147 (1.094-1.202)	<0.001	1.032 (0.995-1.070)	0.089
Male	65 (52.4%)	33 (55.0%)	0.755	1.109 (0.598-2.060)	0.742	3.655 (1.453-9.199)	0.006
HT	80 (64.5%)	51 (85.0%)	0.005	3.117 (1.403-6.925)	0.005	0.530 (0184-1.521)	0.238
Stroke	24 (19.4%)	14 (23.3%)	0.299	1.268 (0.601-2.674)	0.553	0.112 (0.016-0.787)	0.028
DM	35 (28.3%)	20 (33.3%)	0.496	1.271 (0.654-2.470)	0.478	0.548 (0.188-0.1596)	0.270
CAD	36 (29.0%)	28 (46.7%)	0.021	2.139 (1.130-4.050)	0.020	0.518 (0.181-1.484)	0.221
LVEF	52±9	48±10	0.016	0.985 (0.955-1.015)	0.327	-	-
LA diameter	47±10	46±7	0.806	0.990 (0.952-1.029)	0.599	-	-
LAA thrombus	23 (18.5%)	16 (26.7%)	0.249	1.597 (0.770-3.313)	0.209	-	-
LAA SEC	43 (34.7%)	28 (46.7%)	0.109	1.648 (0.880-3.088)	0.119	-	-
LAA velocity	52±23	42±21	0.013	0.982 (0.967-0.998)	0.025	0.996 (0.979–1.013)	0.659
PFO	20 (16.1%)	4 (6.7%)	0.101	0.371 (0.121-1.140)	0.084	-	-
ASD	5 (4%)	1 (1.7%)	0.397	0.403 (0.046-3.532)	0.412	-	-
ASA	6 (4.8%)	1 (1.7%)	0.292	0.333 (0.039-2.833)	0.314	-	-
LV thrombus	2 (1.6%)	0	1.000	-	-	-	-
Dilated CM	39 (31.5%)	19 (31.7%)	0.326	1.010 (0.520-1.960)	0.977	-	-
Akinetic segment	7 (7.4%)	4 (8.9%)	0.747	0.968 (0.777-1.204)	0.767	-	-
Akinetic segment diameter	4±2	5±3	1.000	1.046 (0.596-1.834)	0.876	-	-
LA thrombus	1 (0.8%)	1 (1.7%)	0.598	2.085 (0.128-33.912)	0.606	-	-
Myxoma	1 (0.8%)	0	1.000	-	-	-	-
IE	0	0	-	-	-	-	-
MR	115 (92.7%)	57 (95.0%)	0.754	1.487 (0.388-5.705)	0.563	-	-
MS	10 (8.1%)	6 (10.0%)	0.781	1.267 (0.438-3.666)	0.463	-	-
MVP	1(0.8%)	1 (1.7%)	0.598	2.085 (0.128-33.912)	0.606	-	-
MAC	1 (0.8%)	1 (1.7%)	0.598	2.085 (0.128-33.912)	0.606	-	-
CHA_2DS_2-VASc score	3±1	5±1	<0.001	2.192 (1.662-2.892)	<0.001	3.379 (1.848-6.179)	<0.001

HT: Hypertension, DM: diabetes mellitus, CAD: coronary artery disease, AF: atrial fibrillation, LVEF: left ventricular ejection fraction, LA: left atrium, LAA: left atrial appendage, SEC: spontaneous echo contrast, CAP: complex aortic plaque, PFO: patent foramen ovale, ASD: atrial septal defect, ASA: atrial septal aneurysm, LV: left ventricle, CM: cardiomyopathy, IE: infective endocarditis, MS: mitral stenosis, MR: mitral regurgitation, MVP: mitral valve prolapse, MAC: mitral annular calcification, OR: odds ratio, CI: confidence interval

when the underlying cause cannot be established or more than one possible aetiologies are detected (1). In our study, we demonstrated that 39% of patients had at least two possible sources of embolism. Since the suggested strategy of treatment differs between TOAST groups, it is essential to precisely decide on the aetiology of the stroke. This scope of view is also valuable in patients with AF. Both the American College of Cardiology/American Heart Association and European Society of Cardiology (ESC) (9,10) guidelines on the treatment of AF strongly recommend anticoagulation in patients with a higher stroke risk; however, it has been demonstrated in previous studies that statin is more beneficial than anticoagulation in patients with stroke due to the CAPs. Di Tullio et al. (11) compared acetylsalicylic acid therapy with anticoagulation in patients with a previous stroke and aortic arch atherosclerosis. There was no difference between the groups in terms of recurrent stroke and death; however, in that study, although statin therapy was not given routinely to all patients, statin treatment was associated with improved outcomes with respect to recurrent stroke and death. In the light of these previous studies and ours, it would be fairly reasonable to administer statin therapy in patients with stroke and CAP regardless of antithrombotic therapies.

Sugioka et al. (6) demonstrated that the CHADS score is associated with the presence of CAPs, which is concordant with our findings. Although the CHADS score was used to estimate the stroke risk, current guidelines recommend the use of the CHA_2DS_2-VASc score, which has a modestly higher predictive ability for stroke. Sugioka had also shown a higher prevalence of CAPs in patients with AF. Although in our study, the univariate analysis suggested the same in our study, after adjustment for possible confounders, multivariate analyses have revealed that there is no independent association between CAPs and cardiac rhythm. Since most of the risk factors of AF and atherosclerosis are overlapping, one can expect the co-occurrence of AF and CAPs. However, there is no evidence in the literature regarding the accelerated atherosclerosis in AF patients, which is the case in our study as well.

Yang et al. (12) have also demonstrated a significant relationship between CHA_2DS_2-VASc score and CAPs. In that study, they concluded that the concomitance of AF and CAP may increase the risk of stroke by different mechanisms. In our study, 60 out of 184 AF patients had CAPs (32.6%), which eventually increased each patient's CHA_2DS_2-VASc score. There were 19 patients with a CHA_2DS_2-VASc score of 2. Among these patients, the score of two patients was 1 before the TEE examination and 1 point added as a result of the presence of CAPs, and consequently anticoagulation was indicated. Contrariwise to Yang et al. (12), there was a higher number of patients with CAP in our study (8.2% vs 19.9%). This may be explained by the higher CHA_2DS_2-VASc scores of the patients in our study (1.75±1.61 vs 2±2). Beside the CHA_2DS_2-VASc score, ESC considers the Turkish population as a very high-risk population for atherosclerosis (13). This may also explain the higher prevalence of CAP in our study.

Impact on the Treatment Strategy

In our study, 36 patients had AF with a CHA_2DS_2-VASc score of 2. Among these, three patients were considered as having an intermediate risk for stroke before the TEE examination; eventually, the presence of CAP increased their CHA_2DS_2-VASc score and anticoagulant therapy was finally indicated. Among those with a previous stroke, 38 patients had AF (22.7%). If AF was considered as the primary underlying aetiology, anticoagulant therapy could be sufficient. However, 14 of 38 patients had CAP, which could well also be the obscure underlying aetiology. In conclusion, 14/167 (8.38%) patients with stroke were detected to possess multiple sources of embolism, which requires both anticoagulant and statin therapies.

The major limitation of our study is its retrospective design. We included patients who underwent TEE examinations within the last 16 months; therefore, it did not reflect the effect of treatment on any patient. Another limitation of our study is that it as a single centre study, which is the reason for the relatively small number of patients with AF or stroke. Furthermore, we did not make mention of the clinical consequences of CAPs in our study population.

Since it was previously well defined in the literature that CAPs were associated with ischaemic stroke, patients with AF and high CHA_2DS_2-VASc scores need to be treated with statins in addition to the anticoagulant therapy. Future studies are needed to evaluate the value of statin therapy in patients with a high ischaemic stroke risk.

Conclusion

Although the CHA_2DS_2-VASc score predicts ischaemic stroke in patients with NV-AF, it is also useful for the prediction of CAPs, which are related to the ischaemic stroke in the literature.

Ethics

Ethics Committee Approval: The study was approved by the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee (decision no: 51436, date: 07.02.2018).

Informed Consent: Patients were included after their informed consent was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - E.D., C.E., E.Y., D.K., M.S.B.; Concept - E.D., B.K., B.Ko., U.R.; Design - E.D., B.K., C.E., B.Ko., D.K., M.S.B.; Data Collection or Processing - E.D., E.Y., U.R., Z.Ö.; Analysis or Interpretation - E.D., B.K.A., U.R., M.S.B., Z.Ö.; Literature Search - E.D., C.E., B.K.A., B.Ko., E.Y., Z.Ö.; Writing - E.D., B.K., B.K.A., D.K.

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Short- and Mid-term Effects of Acute Coronary Syndromes on Smoking Behaviour, Factors Affecting Smoking Status and the Family Physicians' Role After Discharge

Akut Koroner Sendromların Sigara İçme Davranışları Üzerine Kısa ve Orta Vadeli Etkileri, Taburculuk Sonrası Sigara İçme Durumunu Etkileyen Faktörler ve Aile Hekimlerinin Rolü

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ABSTRACT

Introduction: Cigarette smoking is one of the most important preventable risk factors for atherosclerotic diseases. This study aims to assess the smoking behaviour after acute coronary syndrome (ACS) and aims to delineate the factors affecting smoking status after discharge.

Methods: The Fagerström Test for Nicotine Dependence score, the sociodemographic status of patients, types of ACS and applied treatment methods were recorded. The Gensini scoring system was used to evaluate the extent and severity of coronary artery disease. Patients were reached via phone calls in the first, third and sixth month after discharge to assess their smoking status, their reasons for relapse and any recurrences of their diseases.

Results: Forty-five percent of patients were treated for ST-elevated myocardial infarction, and 43.2% (n=48) had high or very high levels of dependence. Patients who had early symptoms had a higher rate of quitting smoking (p=0.009). Only 78.4% had thought of quitting smoking after discharge. Seventy-four (66.6%) patients underwent catheter-based interventions. The rates of relapse were 20.8% (n=15), 42.6% (n=32) and 53.9% (n=41) at the end of the first, third and sixth month after discharge, respectively. Gensini scores seemed to be higher among patients who had quit smoking (p<0.05). Patients who have received medical treatment had a higher rate of smoking than before the end of six months (p<0.05). Only 28.8% (n=32) of patients stated that they had received information about smoking cessation from their family

ÖZ

Amaç: Sigara içmek aterosklerotik hastalıklar için önlenebilir en önemli risk faktörlerinden biridir. Bu çalışmada, akut koroner sendrom (AKS) sonrası sigara içme davranışı ile taburculuk sonrası sigara içme durumunu etkileyen faktörler değerlendirildi.

Yöntemler: Hastalara ait, Fagerström Nikotin Bağımlılığı testi skoru, hastaların sosyodemografik durumu, AKS tipleri ve uygulanan tedavi yöntemleri kaydedildi. Koroner arter hastalığının yaygınlığını ve şiddetini değerlendirmek için Gensini skorlama sistemi kullanıldı. Hastalara taburcu olduktan bir, üç ve altı ay sonra, sigara içme durumlarını, yeniden başlama nedenlerini, hastalıklarının nükslerini değerlendirmek için telefon görüşmeleri yoluyla ulaşıldı.

Bulgular: Hastaların %45'i ST yükselmeli miyokard enfarktüsü nedeniyle tedavi edildi ve %43,2'sinde (n=48) yüksek veya çok yüksek bağımlılık düzeyleri vardı. Erken semptomlarla başvuran hastaların sigarayı bırakma oranı daha yüksekti (p=0,009). Sadece %78,4'ü taburcu olduktan sonra sigarayı bırakmayı düşünmüştü. Hastaların 74'üne (%66,6) kateter bazlı girişim uygulandı. Sigara içmeye yeniden başlama oranları taburcu olduktan sonraki 1., 3. ve 6. ayların sonunda sırasıyla %20,8 (n=15), %42,6 (n=32) ve %53,9 (n=41) idi. Gensini skoru, sigarayı bırakanlarda daha yüksek olma eğilimindeydi (p>0,05). Medikal takip kararı verilen hastalarda 6. ayın sonunda sigara içme oranı daha yüksekti (p<0,05). Hastaların sadece %28,8'i (n=32) aile hekimlerinden sigara

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physician and 3.6% (n=4) of patients have applied to a smoking cessation unit.

Conclusion: Smoking cessation rates of patients who have suffered an ACS were low and rates of cigarette consumption in the following periods tended to increase. Family physicians should take a more active role in this topic in Turkey.

Keywords: Acute coronary syndrome, primary care, smoking, smoking cessation, preventive cardiology

bırakma hakkında bilgi aldığını ve %3,6'sı (n=4) sigara bırakma polikliniğine başvurduklarını belirtmiştir.

Sonuç: AKS geçiren hastaların sigara bırakma oranları düşüktür ve takip eden dönemlerde sigara tüketim oranları artma eğilimindedir. Türkiye'de, aile hekimleri bu konuda daha aktif rol almalıdır.

Anahtar Kelimeler: Akut koroner sendrom, birinci basamak, sigara, sigara bırakma, koruyucu kardiyoloji

Introduction

Due to the rise of industrialisation and the resulting increase in city populations, contagious diseases and nutritional disorders are being replaced by chronic conditions such as cardiovascular diseases and cancer. Despite advances in the treatment of cardiovascular diseases, they rank first among the causes of mortality according to the World Health Organization data (1,2). Acute myocardial infarction (AMI) is an important problem of public health as it manifests during productive years, can result in sudden death and has variable complications. The most well-known cause of coronary artery disease is atherosclerosis (3). Atherosclerosis is considered a multifactorial disease in which every step involves chronic inflammation and each underlying factor contributes to the inflammatory process (4).

Cigarette smoking is one of the most important preventable risk factors for atherosclerotic diseases (5). With several effects, cigarette use leads to destabilisation of the atherosclerotic plaque and, therefore, acute coronary syndromes (ACS) (6). In patients who quit smoking before or after coronary interventions or coronary artery by-pass surgery, AMI and mortality rates are reportedly lower (7). However, during quitting cigarette smoking, several mental and physiological changes occur since smoking typically induces psychological and physical addiction (8-10). On days 1-3 after quitting smoking, withdrawal symptoms reach their peak and subside in the fourth week. For some people, they may linger for six months. It is of paramount importance to intervene at these time points to prevent relapse (11).

Our aim in this study is to assess how patients' smoking behaviour is affected when being discharged after coronary angiography for ACS and the factors that affect those who continue smoking after discharge. Another aim is to highlight the role of smoking cessation centres and family physicians that form the preventive medicine basis in this process, beginning with patients' hospitalisation for an ACS.

Methods

Our study was designed as a prospective and descriptive study. One hundred and eleven actively smoking patients who underwent coronary angiography for an ACS at the Ankara Numune Training and Research Hospital, Cardiology Clinic between June 2016 and August 2016, were included in the study. On admission, patients received questions about their sociodemographic features, disease conditions, risk factors, smoking behaviour and their levels of motivation for quitting smoking. The Fagerström Test for Nicotine Dependence (FTND) that consisted of six questions was utilised to quantify patients' cigarette addiction. The scores of this test were classified into five groups: patients with a score of 0-2 were considered to have "very low", scores of 3-4 were "low", a score of 5 was "intermediate", scores of 6-7 were "high", scores of 8-10 were "very high" levels of dependence (12). The routine workup data, electrocardiographic findings, the history of interventions due to coronary artery disease, the number of days of hospitalisation per patient were noted. The Gensini scoring system was used to evaluate the extent and severity of coronary artery disease. This score was calculated by considering the level and the regional anatomic significance of the stenosis. This method defines a narrowing of the lumen of the coronary arteries as 1 for 1% to 25% stenosis, 2 for 26% to 50% stenosis, 4 for 51% to 75% stenosis, 8 for 76% to 90% stenosis, 16 for 91% to 99% stenosis and 32 for total occlusion. The score is then multiplied by a factor that represents the importance of the lesion's location in the coronary artery system. Those with Gensini scores over 20 were noted to have severe coronary artery disease, whereas those with scores of 20 or lower were noted to have mild-moderate coronary artery disease (13-15). There are several scoring systems to quantify the angiographic coronary artery disease burden. We preferred to evaluate the extensiveness of atherosclerosis with the Gensini score system because it is one of the most widely used systems according to the literature (15). Patients were reached via phone calls in the first, third and sixth month after discharge to assess their smoking status, their reasons for relapse, any recurrences of their diseases, whether they have received any advice for quitting and whether they had applied to a smoking cessation centre. The study received ethical review and approval from Ankara Numune Training and Research Hospital Local Ethics Committee with the decision number E-15/460 (date: 26.03.2015). Our study was consistent with the Declaration of Helsinki. Written consent was obtained from all participants.

Statistical Analysis

SPSS for Windows 18 package programme was used for the statistical analysis. Descriptive statistics were depicted as mean ± standard deviation or median [interquartile range (IQR)] or minimum-maximum values for continuous variables, and as the number of cases (n) and percentages (%) for categorical variables. The normality distribution was evaluated using the Kolmogorov-Smirnov test. Baseline characteristics were compared with the independent sample t-test, Mann-Whitney U test, chi-square test or a One-Way analysis of variance (ANOVA). The mean values of continuous variables were compared between groups using the t-test, One-Way ANOVA test or Kruskal-Wallis test. The chi-square test was performed to compare the differences between

categorical variables. An ANOVA was used for the analysis of parameters with multiple variables. A p-value of less than 0.05 was considered statistically significant.

Results

The study included 111 patients with a mean age of 53±9.8 years, among which 105 (94.6%) were males. First, it was found that 36% of participants had a history of coronary artery disease, and 45% of the study population was treated with ST-elevated myocardial infarction. Also, we have shown that most patients lived in city centres (75.7%), had at least a primary-school education (45.9%) and most patients were in the low-middle income category (71.2%). Of study patients, 63.1% (n=70) thought smoking influenced their current ailment whereas 11.7% (n=13) did not. Basic demographic features of the study population are summarised in Table 1. Regarding smoking behaviour, the mean smoking duration was 35.2±14.9 pack-years, the mean cigarette consumption was 37±19.9 cigarettes/day, and the FTND showed that 43.2% (n=48) of patients had high or very high levels of dependence. Tables 2 and 3 summarise the smoking history of the study population.

The most frequent complaint about admission to a hospital was chest pain (77.5%, n=86), whereas 13.5% (n=15) were admitted with atypical symptoms. Fifty-eight patients (52.3%) were admitted within an hour after the onset of their complaints. The mean duration of hospital stay was 2.3±1.59 days. The mean ejection fraction after discharge from the hospital was 53%±11%. Twelve patients (10.8%) had an ejection fraction of 35% or lower. The average Gensini score of patients was noted as 42.5±29.41; 75.6% (n=84) patients had a Gensini score higher than 20 (extensive coronary artery disease). Seventy-four (66.6%) of patients underwent catheter-based interventions (balloon angioplasty, bare-metal stent implantation, drug-eluting stent implantation), whereas 26.1% (n=29) received medical treatment and 7.2% (n=8) underwent coronary artery by-pass surgery.

Table 1. Basal and characteristic features of the study population

Variable	n (%)
Diabetes mellitus	24 (21.6)
Hypertension	34 (30.6)
Hyperlipidaemia	31 (27.9)
Family history	63 (56.8)
Sedentary lifestyle	78 (70.3)
Alcohol use	23 (20.7)
Chronic obstructive pulmonary disease	10 (9)
Peripheral artery disease	6 (5.4)
Cerebrovascular disease	5 (4.5)
Malignancy	5 (4.5)
Marital status (married)	91 (82)
The presence of coronary artery disease	40 (36)
Previous acute coronary syndrome	2 (1.8)
Diagnostic coronary angiography	9 (8.1)
Stent implantation after coronary angiography	19 (17.1)
By-pass surgery after coronary angiography	7 (6.3)
Previous coronary artery by-pass surgery and stent	3 (2.7)

At the end of six months, the rate of visiting a family physician for any reason was 48.6% (n=54); 59.3% (n=32) received information from their family physician on smoking cessation. The optimistic thoughts of patients on the effectiveness of this information given at the first, third and sixth month gradually ceded. At six months, 40.7% of patients had positive thoughts about smoking cessation information (p=0.043). A small group of patients (3.6%, n=4) had applied to a smoking cessation unit by the sixth month after discharge. Table 3 summarises patients' smoking status after discharge. The rates of re-starting smoking are also shown in Figure 1.

Table 2. Smoking behaviour of the study population

Variable	%
Daily cigarette consumption	
10 cigarettes or less	9.9
Between 11-20 cigarettes	13.5
21 cigarettes or more	76.6
Age at which smoking commenced	
15 years and under	37.8
16 years and over	62.1
Having tried smoking cessation at any time	69.4
Longest duration of smoking cessation (months, mean ± SD)	13.46±27.92
Having joined a smoking cessation programme	8.1
Psychological support	22.2
Nicotine replacement therapy	-
Drug therapy	44.4
Personal attempt	22.2
Smoking status of family members	45.9
Spouse	58.8
Parent	3.9
Children	35.2
Siblings	1.9
Smoking place of family members	
Inside the house	43.1
Outside the house/balcony	56.9
Thoughts of quitting smoking after discharge from the hospital	78.4
Knowledge about smoking cessation centre	55.9
Postdischarge thoughts of getting help from a smoking cessation centre	61.3
Fagerström nicotine dependence test	
Very low level	15.3
Low level	27.9
Intermediate level	13.5
High level	20.7
Very high level	22.5
Number of patients that claim to have quit smoking at the time of discharge	64

SD: Standard deviation

The comparison of the clinical and demographic features of smoking and non-smoking patients at the end of the sixth month after discharge is shown in Table 4. We found that there was no statistically significant difference between patients who quit smoking and those that did not in terms of age, gender, mean monthly income, occupation, antidepressant use, the presence of known risk factors for coronary artery disease (diabetes mellitus, hypertension, hyperlipidaemia, positive family history) and the presence of any combinations of these risk factors at the time of discharge (p>0.05). In addition, in the first and third months, the level of education (p=0.001) and the ratio of patients who had an ST-elevated myocardial infarction (p=0.001) were higher among those that quit smoking than those that did not. At the end of six months, these distributions were similar among smokers and patients who had quit smoking. Those that applied with early symptoms had a higher rate of quitting smoking at all three time points (p=0.009). Likewise, those that quit smoking by the end of the first or the third month after their discharge from the hospital had a longer non-hospitalised period (p=0.001). However, by the end of the sixth month, a period of non-hospitalisation was similar in both groups (p=0.169). Thoughts of smoking were more prevalent among patients who quit smoking at all time points than those who continued to smoke (p<0.001). Attempts at quitting were also more frequent among these patients in the first three months (p=0.014), but this association lost statistical significance in the sixth month (p=0.855). Patients who had a long history of smoking had a higher rate of quitting by the end of the first and third months

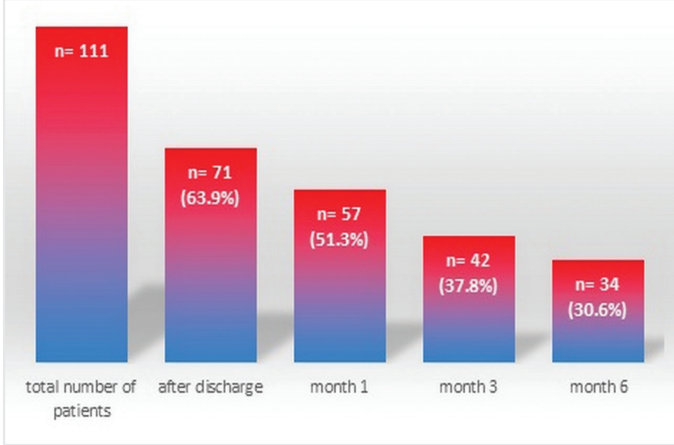

Figure 1. The number of patients who quit smoking after discharge

Table 3. Smoking behaviour of the study population after hospitalisation

Variable	Month 1 after discharge (%)	Month 3 after discharge (%)	Month 6 after discharge (%)
Number of patients that applied to a smoking cessation centre after discharge	1.8	1.8	3.6
Psychological support	0.9	0.9	1.8
NRT	-	-	-
Drug therapy	-	0.9	1.8
Having benefited from a smoking cessation centre	100	50	25
Reason for re-starting smoking			
Wish to smoke	66.6	50	41.4
Stressful event	13.3	31.2	29.2
Rough familial situation	13.3	15.6	24.3
Due to being fired	6.6	3.1	2.4
Influenced by family members	-	-	2.4
Total amount of time spent without smoking			
Never quit	-	-	32.4
<1 month	-	-	21.6
1-3 months	-	-	10.8
3-6 months	-	-	6.3
Did not smoke for 6 months	-	-	28.8
Number of cigarettes/day for those that kept smoking			
10 or less	46.2	43.4	44.1
Between 10 and 20	51.8	52.1	49.3
Between 21 and 30	-	1.4	3.8
31 or more	1.8	2.8	2.5
Smoking status of family members	43.2	41.4	38.7
Inside the house	37.5	39.1	34.8
Outside of house/balcony	62.5	60.9	65.2
Re-hospitalisation after discharge for an ACS	0.9	1.8	10.8

ACS: Acute Coronary syndrome, NRT: nicotine replacement therapy

Table 4. Comparison of the clinical and demographic features of smoking and non-smoking patients at the end of six months

Variable (%)	Smokers (n= 77)	Non-smokers (n=34)	p
Timing of seeking medical help (from the onset of chest pain)			
In 60 minutes	45.4	67.6	0.009
In 120 minutes	12.9	2.9	
In 12 hours	11.6	5.8	
After 12 hours	29.7	23.5	
Total number of cigarettes consumed per day (before hospitalisation)			
10 and less	6.4	17.6	0.007
Between 10 and 19	11.6	17.6	
Between 20 and 30	53.2	55.8	
30 and more	28.5	8.8	
Considering smoking cessation during hospitalisation	72.7	91.1	0.030
Fagerström nicotine dependence test			
Very low level	10.3	26.4	0.097
Low level	29.8	23.5	
Intermediate level	12.9	14.7	
High level	20.5	20.5	
Very high level	25.9	14.7	
Gensini score (mean ± SD)	41.40±29.1	45.07±29	0.466
Time to discharge/hospitalisation duration (days, mean ± SD)	2.19±1.44	2.64±1.87	0.187
Reason for admission into the hospital (%)			
STEMI	40.2	55.8	0.233
NSTEMI	35	23.8	
USAP	24.6	20.5	
Coronary intervention (%)			
Percutaneous coronary intervention	63.4	73.4	0.012
Coronary by-pass surgery	5.2	11.7	
Drug treatment	31.1	14.7	

*NSTEMI: Non-ST segment elevation myocardial infarction, STEMI: ST-segment elevation myocardial infarction, USAP: unstable angina pectoris, SD: standard deviation

(p=0.026), whereas at the end of six months, rates were similar (p=0.067). Also, patients with chronic obstructive pulmonary disease (COPD) had a higher smoking rate after six months (p=0.001). Although smoking rates among marital status and occupational groups were statistically similar in the first three months, by the end of six months, rates of re-starting smoking were higher among singles and widows (p=0.036) and actively working civil servants and workers (p=0.048). We did not find an effect on patients' primary complaint on smoking cessation (p=0.450).

Discussion

The present study demonstrates that an important fraction of patients who suffer from an ACS start smoking again during the short-term follow-up after discharge for various reasons. Furthermore, our study is noteworthy for showing how family physicians, usually the cornerstone of preventive medicine, have a minor influence on encouraging and helping smoking cessation in this group of patients.

Cigarette smoking remains an important public health problem both in our country and worldwide. It has been reported in previous studies to increase disease risk for all cardiovascular conditions, such as ischaemic stroke, peripheral artery disease, aortic aneurysm and cardiac vascular disease (16-19). The cardiovascular risk abates rapidly after smoking cessation and, in 10-15 years, almost reaches that of a person that has never smoked (20-23). Hence, for people with diagnoses of coronary artery disease, or those that go through an episode of an ACS, smoking cessation is just as necessary as the proper implementation of medical treatment to lower morbidity and mortality. Several factors have been revealed that are involved in smoking initiation or cessation. A previously published study has demonstrated that there was no significant association between smoking cessation and age, education level or the presence of a smoker among core family members. However, male gender and being married had positive predictive value (24). Despite the wide range of distribution over gender, our study shows that gender does not have a significant association with smoking cessation (p=0.92).

Another important result of our study is that in the early stages, marital status does not have a significant effect on smoking cessation. However, at the end of six months, single or widowed patients had a higher rate of re-starting smoking. Previous studies have shown that increased cardiovascular mortality in widows in a year after the passing of a spouse was a considerable sign of psychosocial stress (25). These points to the significance of family support for cases of ACS, and a similar conclusion can also be reached from our data despite the relatively low number of subjects (26). As the most paramount and continuous source of motivation and support is the family itself, the behaviour and attitude of family members can be thought to act as an effective means of protection from cardiovascular diseases. In addition, our study has demonstrated that education level may influence smoking cessation behaviour at the time of discharge. However, at the first, third and sixth month, it has no predictive role in smoking cessation.

Another interesting finding made by the present study also found a lack of association between early stage smoking cessation behaviour and the presence of additional disease conditions (cerebrovascular events, peripheral artery disease, COPD and other conditions). Another striking result was a statistically significant tendency of COPD patients to keep smoking during the first, third and sixth month after discharge. A similar study conducted in ACS patients similarly mentions that patients with cigarette-related lung diseases tended to keep smoking at the three month-follow-up (27). It may be inferred that ACS itself may not have an impact big enough to quit smoking in patients with a prior diagnosis of cardiovascular disease and COPD. On the other hand, occupational groups that do not seem to influence smoking cessation behaviour at the time of discharge and early stages after discharge tend to gain importance at the sixth-month follow-up as those who actively work at the time they are influenced regarding their smoking behaviour. This finding may indicate that smoking behaviour is affected dramatically by the social environment.

Another topic of discussion arises from the finding that symptoms at the time of applying for hospital admission in patients with ACS have no role in smoking cessation behaviour at either early or late stages of follow-up. Patients who seek medical help soon after the onset of symptoms tended to have higher rates of smoking cessation at the time of discharge. However, this association gradually lost statistical significance at the end of six months post-discharge. This result indicates a time-dependent loss of the deterrent effect of symptoms experienced during the early phases. On the other hand, patients who seek help early may have better self-care in general, and those who were admitted later may be relatively more negligent of their health issues in their daily lives. This difference might contribute to the lack of smoking cessation behaviour. Physicians may help these patients by delivering reminders during follow-ups in a manner that will not induce psychological trauma while considering the possibility of developing post-traumatic stress disorder. In addition, at the time of discharge and in the first and third months, smoking cessation rates were higher in patients with ST-elevated myocardial infarction, which presents as a more urgent clinical event. However, at the end of six months, no statistically significant difference was detected among the groups. This may, as was pointed out above, reflect the lack of constraint for continuing their daily lives after discharge from the hospital. Re-starting smoking, while normalising daily life functions, especially for those who are actively working post-discharge, may have accounted for this result. In our study, Gensini scores that express the severity of coronary artery disease and higher numbers of stents did not display a statistically significant relationship with smoking cessation behaviour.

Despite including occlusion percentages in a manner that can be comprehended, angiography reports given to patients after angiography did not have a substantial effect on smoking cessation. It may be inferred that not only visual, but verbal suggestions that include detailed information can yield a stronger influence for smoking cessation during the early stages. The advice and warnings given by the cardiologist that intervene first can have the most substantial influence in the early stages. It was demonstrated that 77.2% of family physicians question the smoking/tobacco use status of their patients, yet only 25.6% of them and 8.4% of nurses provide advice about smoking cessation (28). Our study shows the rate of receiving advice from the health centre that rendered the first diagnosis, including family physicians, was 77.5%. Although this rate seems high, the fact that not all patients receive simple smoking-related advice is a deficit of paramount importance. It can be considered a lack of attention on the physician's part that the number of patients referred to a smoking cessation centre is low (3.6% at the end of six months). Özşahin et al. (29) have stated that the two most important factors in quitting smoking are health problems and anti-smoking media campaigns. The same study showed that the third most important reason to quit smoking was physician advice. More attention on the part of physicians can yield more poignant results, along with effectively adding smoking cessation as primary protection into physician education programmes.

In addition to the data described above, patients who had duration of hospitalisation and those that underwent interventional treatments had more significant quitting behaviour during the first three time periods. However, this difference diminished at the end of the sixth month. This reduction may be explained by the condition at presentation, the psychologic status of the patient after an interventional procedure and the exposure to other patients with more severe conditions during their stay in intensive care units. Another point that warrants attention is the lower than expected rate of family physician visits during the six-month period. These rates are 15.3%, 45% and 48.6% at the end of the first, third and sixth month, respectively. The ratios of patients stating that they have received smoking cessation advice from their family physicians during these visits are 58.8%, 58% and 59.3%, respectively. Almost one of two physicians made no suggestions about quitting smoking. The role of family physicians is very important in smoking cessation counselling. This data may demonstrate that in the primary care setting where preventive medicine has its basis, this subject is not adequately addressed. We may say that family physicians are not properly involved in the fight against tobacco smoking in our country. The lack of data on why patients visited their family physicians can be counted as a limitation of the present study. It may be more effective for relevant institutions to send patients directly to the family physicians after ACS so that the doctor-patient relationship can be formed earlier.

For this reason, educational and training programmes on the fight against smoking should be organised for family physicians. It was shown that patients who implemented lifestyle changes had a significant increase in both physical and mental components of life quality (30). The rates of explaining lifestyle changes to patients by physicians were low in our study, despite the vital importance of such advice. Although it may not be easy to assess a behavioural change for smoking in a short time after ACS, our results demonstrated that there is inadequate patient compliance, and there are deficiencies in the family physician-patient relationship.

Both physicians and other healthcare staff are informed about the harmful effects of smoking and smoking cessation methods. However, not only the amount of information but attitude gains importance at this point. The most significant attitude on this subject is being a "role model". When considering how physicians and other healthcare workers can act as role examples, it is of paramount importance that they do not smoke (28). Furthermore, the first step in the fight against tobacco dependence is a "brief physician intervention" that is described as "the verbal summarisation of the indications of smoking cessation using medical terms and information about the harmful effects of smoking". These are short communications that can be used by all physicians in any setting (31). Especially in clinics that are interested in illness due to smoking like cardiology, teams of the medical staff that reach hospitalised patients and deliver "short motivational visits" can yield more favourable results.

Conclusion

In conclusion, the smoking cessation rate of patients who suffered an ACS is low, and rates of cigarette consumption during the periods that follow tend to soar. A multidisciplinary cooperative effort involving all physicians, especially family physicians and cardiologists, is required at times when patients attempt quitting smoking or start smoking again. In addition, it should be considered that family physicians in Turkey need to take a more active role in this regard.

Ethics

Ethics Committee Approval: The study received ethical review and approval from Ankara Numune Training and Research Hospital Local Ethics Committee (decision no: E-15/460, date: 26.03.2015).

Informed Consent: Written consent was obtained from all participants.

Peer-review: Externally and internally peer-reviewed.

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Microsurgical and Functional Linguistic Anatomy of Cerebral Basal Ganglia

Serebral Bazal Ganglionların Mikrocerrahi Anatomisi ve Dil Üretimi ile İlişkisi

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ABSTRACT

Introduction: The central core of the cerebral hemispheres is located on the medial side of the insular cortex. It is made up of basal ganglia and white matter tracts. The basal ganglia and their white matter connections serve important motor, sensorial, psychological, endocrinological and cognitive functions. Insular gliomas and other deeply located lesions can cause severe morbidity by affecting the basal ganglia and their connections. Hence, a thorough understanding of the anatomy of that area is needed for surgical planning on the insular area.

Methods: We dissected and photographed the insular cortex and basal ganglia in five human cadavers via white matter dissection techniques from lateral to medial side.

Results: The structures and connections of the insular cortex and basal ganglia are documented and presented with their functional correlations during the dissections.

Conclusion: Our results will guide the strategy and planning of surgery for the insula and basal ganglia. Additionally, they will be helpful in the follow-up and prediction of morbidities of lesions located in that area.

Keywords: Insula, basal ganglion, white matter, grey matter

ÖZ

Amaç: Serebral hemisferlerin derin santral bölgesi; bazal ganglionlar (subkortikal gri maddeler) ve kompleks ak madde liflerinden oluşur ve insular korteksin hemen mediyalinde yer alır. Bazal ganglionlar sahip olduğu ak madde lif bağlantıları sayesinde motor ve sensöriyal, duygu, endokrin düzenleme, kognisyon gibi fonksiyonlarda önemli rol oynar. Özellikle insular gliomalar ve derin yerleşimli lezyonlara bağlı, bazal ganglionların ve bağlantılarının zarar görmesi ciddi morbiditeye sebep olur. Bu nedenle bu bölgenin mikrocerrahi anatomisinin iyi bilinmesi, insuler bölgeye yapılacak cerrahinin planlanmasında ve cerrahi stratejide çok büyük öneme sahiptir.

Yöntemler: Beş adet insan kadavrasında, lateralden mediyale doğru olacak şekilde, insular korteks ve tüm bazal ganglion yapıları ak madde diseksiyon yöntemleri kullanılarak bağlantılarıyla beraber ortaya kondu ve fotoğraflandı.

Bulgular: İnsular korteksin uzaklaştırılması sonrası, ak madde bağlantıları, bazal ganglionlar ile bağlantıları ve fonksiyonel korelasyonları tarif edilip, görsel olarak dokümante edildi.

Sonuç: Araştırmamızın sonuçları, santral bölge ve bazal ganglion lezyonlarının, gerek takibinde, gerek cerrahisinde ve morbidite öngörüsünde yardımcı olacaktır.

Anahtar Kelimeler: İnsula, bazal ganglion, ak madde, boz madde

Introduction

The deep central-basal ganglia region of the cerebral hemisphere consists of subcortical areas of gray matter and complex white matter fibers. This region is also called central cor and is localized between the insula cortex in the lateral and the ventricle in the medial (1). Although it is relatively small in size, it has a wide range of sensory, motor, emotional and cognitive functions thanks to its wide afferent connection network. Anatomically, this structure includes the extreme capsule, claustrum, external capsule, lentiform nucleus (putamen + globus pallidus), internal capsule, caudate nucleus and thalamus.

From the perspective of neurosurgery, the surgery of this region is very difficult and the possibility of morbidity is high, due to its location deep in the cerebral hemispheres and the complex network of white matter fibers passing through and around it.

However, as the recent clinical studies and the increase in the number of these studies show; Factors such as the development of new approach

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concepts, studies of white matter anatomy, and the gradual development of diffusion tensor imaging magnetic resonance imaging technique, which enables us to view and evaluate white matter pathways in detail, have increased the possibility of wide resection and survival rates in this region surgery, while also reducing the risk of morbidity (2-10). In this region surgery, the concept of planning and foresight is now established according to the anatomical location of the lesion within the insular cortex and basal ganglia. Various degrees of speech and language disorders are common in central core lesions and surgery. In this study, we aimed to show both the basal ganglia structures from lateral to medial, and the relationship of these structures with all fiber bundles that contribute to language production.

Methods

Cadaver dissections of this study were performed in the neuroanatomy laboratories of Virginia University (USA). Five postmortem human brain specialties were kept in a 10% formalin solution for at least 1 month in accordance with the Klingler method, and then arachnoid, pia mater and vascular structures were removed under the operating microscope. Between dissections, specimens were stored in 10% formalin solution and at +4 °C. Dissections were performed under Zeiss microscope at x4 and x40 magnification, using a microsurgery set (edentulous forceps, Rhoton dissector, metal spatula, microhook) and aspirator.

The cerebral cortex was decorticated with the help of an aspirator and spatula. A lateral to medial dissection was performed on specimens. On the lateral faces of the specimens, short association fibers (U fibers) were removed and long major association fibers were reached. The insula was decorticated and all basal ganglia structures from lateral to medial were exposed.

Each stage was documented by photographing Canon EOS 550 camera with 18-55 and 100 lenses.

Our study does not require patient and Ethics Committee approval, as it is an anatomical laboratory study in a cadaver. The study was conducted in accordance with the principles of the Helsinki Declaration, 2013 (11).

Statistical Analysis

In our study, the relationship between basal ganglia and white matter was revealed by anatomical dissection techniques, visualized and documented by photographic techniques and then described. In our research, no measurements or comparisons were made that required statistical analysis.

Results

Insular Cortex and Basal Ganglia Structures

The surface of the insular cortex faces laterally and is bordered by the anterior, inferior, and superior posterior limitan sulcus. It is divided into two main parts, anterior and posterior, by the central insular sulcus. In the anterior part, which is wide, there are three short gyrus (anterior, middle, posterior) separated by two sulcus, and in the posterior part there are two long gyrus (anterior, posterior) separated by a single sulcus (Figures 1A, B). In the projection of the midpoint of the posterior short gyrus, the genus of the internal capsule and the foramen Monro are located. The central insular sulcus is parallel and aligned with the cerebral central sulcus that separates the frontal and parietal lobes. The insular apex is the highest area laterally above the insular convexity and is located in the lower part of the middle short gyrus. Short insular gyri join at the insular pole; long insular gyri join at the limen insula. The insular pole is located between the anterior limiting sulcus and the central insular sulcus.

Extreme capsule;it arises by decortication of the insular cortex (Figure 1C). It consists of short association fibers that provide the connection between the insular gyri and opercular gyri that extend into the sylvian fissure. It is responsible for the non-articular functions of speech (12).

External capsule; it consists of the ventral external capsule, fronto-occipital fascicle (FOF) and uncinate fascicle (UF) fibers. External outer capsule consists of dorsal claustrum fibers distributed in the frontal, parietal and occipital regions (Figure 1D).

Claustrum; it is the structure that emerges when the extreme capsule starts to be taken. Parabolic curve drawn from the middle short insular gyrus towards the midpoint of the posterior long insular gyrus; it divides the claustrum and the external capsule into two: dorsal claustrum and ventral claustrum. Ventral (anteroinferior) klaustrum; it is located within the UF and FOF and consists of gray matter. The dorsal claustrum forms the dorsal external capsule fibers, distributing to the frontal parietal and occipital regions. The claustrocortical system plays a role in the integration of visual, somatosensory and motor information, thanks to its wide distribution from the front of the supplementary motor area to the posterior parietal area (Figure 1E).

Putamen; it occurs after the external capsule is removed (Figure 1E). Together with the caudate nucleus it forms the dorsal striatum. After the putamen is taken medially, the globus pallidus externa is reached (Figure 1F).

Internal capsule; after the medial globus pallidus is removed, all internal capsule fibers are exposed (Figures 1F, G). The anterior branch of the internal capsule is located between the lentiform nucleus (putamen + globus pallidus) and the head of the caudate nucleus. It consists of anterior thalamic peduncle and frontopontin fibers. The internal capsule genus contains connective fibers and superior thalamic fibers that extend between the presentral cortex and the brainstem. Foramen Monro is found in the projection of the genu. The posterior branch of the internal capsule contains corticospinal tract, superior thalamic peduncle (thalamopostcentral part), corticopontine and corticotegmental fibers. The retrolenticular part of the internal capsule contains parietopontine, occipitopontine and posterior thalamic peduncle fiber bundles. Optical radiation fibers are also found within the posterior thalamic fiber bundles.

Caudate nucleus; it is seen with the thalamus after lifting the internal capsule and corona radiata from lateral to medial (Figure 1H). The head of the caudate nucleus is on the lateral wall of the frontal horn, its body is lateral to the body of the lateral ventricle and atrium, its tail is on the roof of the temporal horn. The caudate nucleus is “C” shaped and the thalamus is located inside the caudate nucleus.

White Matter Fibers Including in Basal Ganglion Structures or Having Close Anatomical Relationship

Superior longitudinal fascicle (SLF); it is the main association fiber bundle containing high cortical functions in the frontotemporoparietal region. It has been tractographically examined in three sections. SLF-I; lies under the superior frontal gyrus, SLF-II; under the middle frontal gyrus and under the inferior frontal gyrus of SLF-III (Figures 2A, B). Located in the parietal operculum in the suprasylvian area, SLF-III connects the supramarginal gyrus with the pars opercularis. SLF-III is involved in phonological processing (working memory) (9). Stimulation of SLF-III in the dominant hemisphere can cause speech articulation problems such as dysarthria and anarthria. In the non-dominant hemisphere, SLF-III is related to visual-spatial attention, prosody (prosody) and music processing (13,14).

Arcuate fascicle (AF); it connects motor (Broca's area) and sensory (Wernicke's area) language centers. It is divided into two as dorsal and ventral segments (Figure 2A). The ventral segment is ventral to the dorsal segment in the suprasylvian area, but is located anterior to the dorsal segment in the infrasylvian region.

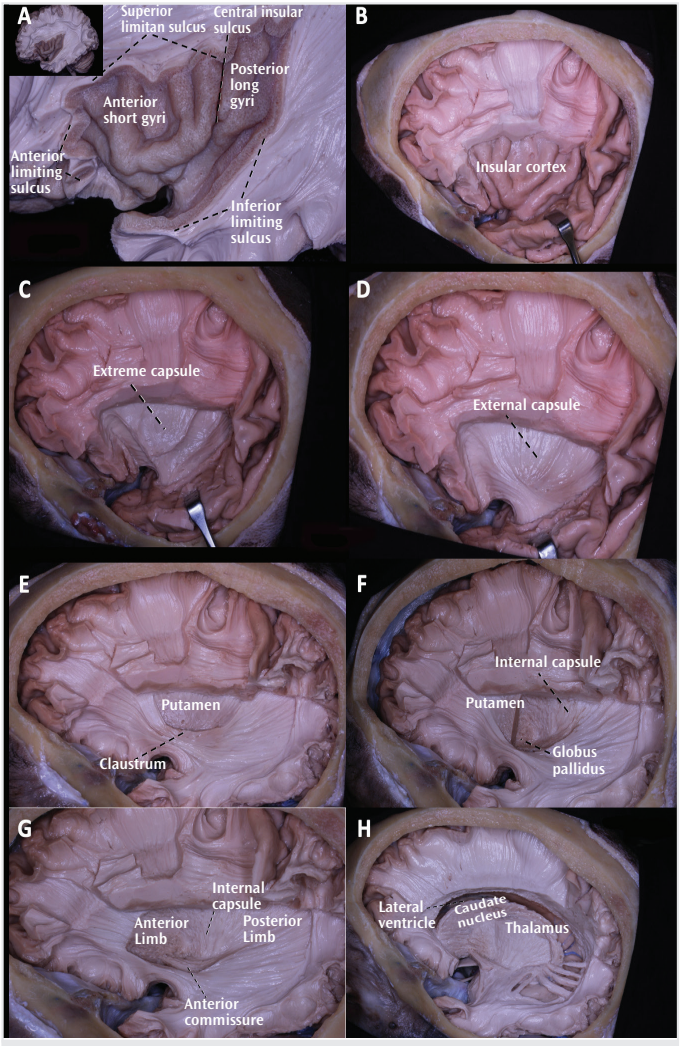

Figure 1. In the left cerebral hemisphere, the appearance of the insular cortex and basal ganglia structures from the lateral

The ventral segment starts from the middle and posterior parts of the superior temporal gyrus and the middle part of the middle temporal gyrus; it passes from the lower part of the supramarginal gyrus and anteriorly medial to the SLF-III in the frontoparietal operculum, and ends in the inferior frontal pars opercularis. The dorsal segment starts from the posterior part of the middle and inferior temporal gyrus and passes through the lower part of the angular gyrus and then runs forward slightly ventrally from the ventral of SLF-II to the middle and inferior frontal gyrus. The ventral segment of the AF is associated with phonological language processing, while the dorsal segment is associated with lexical and semantic language processing. The known classical AF model is equivalent to the ventral segment (15).

Middle longitudinal fascicle; it is located within the superior temporal gyrus. It extends between the Superior temporal gyrus and the inferior parietal lobule (especially the angular gyrus) (Figure 2B). This bundle of fibers, extending from the Inferior parietal lobule (especially the angular gyrus) to the superior temporal gyrus, is thought to play a role in the functions of language in the dominant hemisphere and attention in the non-dominant hemisphere.

Inferior longitudinal fascicle (ILF); it is located in the inferior temporal gyrus by anatomical definition and connects the temporal pole to the dorsolateral occipital cortex (Figure 2B). ILF has been shown to functionally play a secondary role in the inferior fronto-occipital fascicule in the "ventral semantic pathway" associated with the tongue regions in the anterior and middle temporal region.

Inferior fronto-occipital fascicle (IFOF); it connects the frontal and occipital regions. Starting from the prefrontal cortex, it proceeds just above the UF at the level of the limene insula and blends into the extreme and external capsule fibers (Figure 2C) (9,16). It extends posteriorly along the lateral walls of the temporal and occipital horns and ends in the occipital lobe. Together with the FOF and the ILF, it forms the semantic ventral pathway, and as a result of its intraoperative stimulation, semantic (semantic) parafhasia is observed (9).

UF; in the temporal region, it originates from the cortical nucleus of the amygdala and anterior temporal region in front of the temporal horn and moves forward from the inferior of the lentiform nucleus and IFOF at the level of the limen insula to the lateral orbitofrontal area (Figure 2C). It has been reported that the UF is responsible for posttraumatic retrograde amnesia (17). In the subgenual area, the UF, which is thought to be part of the ventral limbic pathway, meets with the fibers of the cingulum, which is considered the dorsal limbic pathway (18). Disconnection can cause behavioral disorder (19).

Frontostriatal tract (FST); it originates from the supplementary motor complex [especially the pre-supplementary motor area (SMA)], turns inferiorly and passes through the medial of the superior limiting sulcus and ends in the caudate nucleus, putamen, and external capsule structures (Figure 2D). The projection is the fiber bundle. With its stimulation in the dominant hemisphere, there is a problem in initiating speech.

Frontal aslant tract (FAT); it originates from the supplementary motor complex, progresses obliquely to the inferior and superficially within

the inferior frontal gyrus and ends in the pars opercularis (Figure 2D). It takes part in initiating speech and speaking fluently in the dominant hemisphere.

Discussion

Insular glioma surgery has always been challenging for neurosurgeons due to the complex shape and organization of the insular cortex, the functional importance of the insula, its medial white matter structures and its close relationship with the internal carotid artery, middle cerebral artery, and lenticulostriate vessels. Therefore, until recently, insular gliomas were considered too dangerous for surgical treatment, with an unacceptably high rate of postoperative morbidity. Especially in recent years, in addition to the previous surgical approach-based neuroanatomical studies, the detailed demonstration of the anatomical structures from the insular cortex to the medial with white matter dissection technique and the increase in the studies and documentation on this subject have enabled us to have a better understanding of the central core anatomy (10,20). In addition to this information, molecular

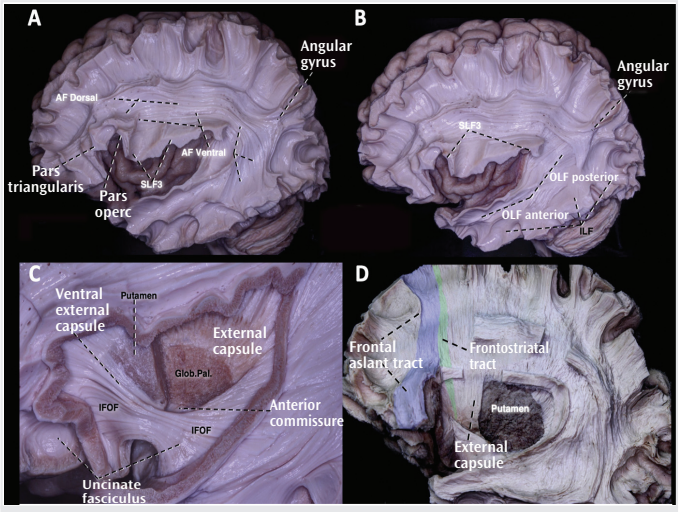

Figure 2. In the left cerebral hemisphere, the appearance of the relationship of basal ganglia and white matter fibers from the lateral

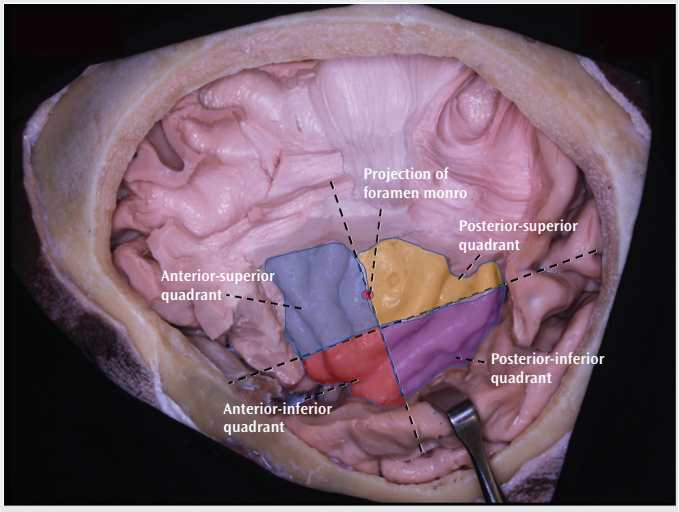

Figure 3. Sanai et al. (8), a lateral view in the left cerebral hemisphere of the separation of insular tumors according to four different quadrants

categorization studies of insular glioma that have increased in recent years and the widespread use of awake insular glioma surgery increase the success of total or subtotal excision of the tumor in insular glioma surgery, while decreasing surgical morbidity and increasing the progression-free survival rate for all patients.

In addition to the pathological features of the lesion, the location of the lesion in the central core and its spread to its immediate surroundings are important in order to increase survival, decrease loss of function and predict survival in patients with insular glioma. Very few of insula-derived gliomas are completely located in the insula (2,3,21,22). Also, depending on where the glioma originates in the insula, surgical approach and anatomical considerations may vary. Therefore, it is difficult to establish a common terminology when discussing insular gliomas. Yaşargil first classified insular tumors according to their localization, based on his large series. Accordingly, he proposed a classification system based on whether the lesion was included in the insula (type 3), part of the insula (type 3A), or the adjacent operculum (type 3B). In this classification system, insular lesions containing one or both of the paralimbic orbitofrontal and temporopolar areas were classified as type 5A or type 5b, respectively. In addition to this classification, Sanai et al. (8) have created their own classification in order to evaluate proximity to functional areas and predict and plan the possibility of wide resection. According to this classification, the insular cortex is divided into four main regions by a line drawn perpendicular to the sylvian fissure from the foramen Monro (Figure 3). With this classification, they revealed predictions about survival, perioperative morbidity and malign transformation after extensive resection, according to anatomical localization and spread of central Cor-placed tumors. Most insular gliomas are not confined to a single region or only within the central core boundaries. Zone 1 (anterior-superior) predominantly localized tumors are adjacent to the frontal operculum due to their anatomical neighborhood. Zone 2 (posterior-superior) tumors are important anatomical structures in terms of invasion of the presentral gyrus, primary motor cortex and parietal operculum. Zone 3 (posterior-inferior) localized tumors can often invade medial temporal structures, Heschl gyrus is an important cortical neighborhood. Frontobasal and temporal pole invasion can be seen frequently in tumors with zone 4 (anterior-inferior) localization due to their close neighborhood. Anatomical and clinical studies conducted in recent years have shown that damage to subcortical white matter tracts causes more severe clinical deterioration than damage to cortical structures and has a lower chance of recovery (23-26). The central core is sensitive because it contains large projection fiber junctions under the insular cortex and is closely adjacent to important association links in the perisylvian region.

In the medial invasion of central cor anterior-superior tumors, the anterior leg of the internal capsule, putamen and caudate head within the central core may be damaged. Due to the close proximity of the pars opercularis and triangularis in the frontal lobe, various speech disorders can be seen in the tumors of this region due to the damage of Broca and its connections. Also known as motor aphasia, the patient's speech is laborious and often slow, with pauses between words much more frequent than the words themselves. In classical Broca's aphasia, extensive damage involving the Broca area (BA44 and BA45 in the left

inferior frontal gyrus) and the surrounding frontal areas (BA6, BA8, BA9, BA10, BA46 and BA47) as well as the underlying white matter and adjacent central core structures seen (27). In our dissections, we saw that the FAT fibers started from the SMA and ended in the Broca area. In the dominant hemisphere, due to Broca's damage, there may be a damage at the end of the FAT fibers, and this may cause impairment in speaking initiation and fluency in the tumors of this region. Wernicke aphasia, known as sensory aphasia, usually develops as a result of damage to the posterior region (BA22) of the left auditory association cortex (posterior part of the superior temporal gyrus). Often BA37, BA39, BA40 or all three are involved (27). The central core can often be damaged due to its anatomical proximity with posterior-inferior tumors. In conduction (conduction) aphasia, patients can understand simple sentences and make intelligible sentences. However, they cannot repeat sentences word for word, they cannot properly place phonemes. It occurs in subcortical deep-seated lesions in the localisation of the AF connecting the Wernicke and Broca areas. In particular, conduction-type aphasia can be observed due to damage to central Cor tumors located in the anterior superior (zone 1) and posterior superior (zone 2) adjacent to the parietal and frontal operculum, where the AF proceeds under it. SLF-III fibers are the most superficial association fiber bundle within the parietal operculum and runs forward along the parietal operculum. It is closely related to the superior-anterior and superior-posterior quadrants. Anarthria and dysarthria may develop due to the injury of SLF-III fibers in the dominant hemisphere due to invasion of these two region lesions. In the non-dominant hemisphere, prosody (prosody) and music processing may be problematic. Unlike other association fibers involved in language production, the only fiber bundle included in the central core structure is IFOF. The density of the fiber bundle is mostly located in the anterior-superior and posterior-inferior regions within four defined regions, and semantic parafasia may develop in lesions related to these regions or in interventions performed in these regions due to IFOF damage (9). Patients have difficulty naming what they see. UF fibers are also the only projection fiber bundles that are for dilution and whose termination is in putamen, while FST is located in cor and is found in language production. FST fibers originate from the SMA complex like FAT fibers and the two fiber bundles are located very closely inferiorly. While FAT is superficial in the pars opercularis, FST fibers run under the superior limiting sulcus and end in the anterior part of the external capsule, striatum and internal capsule structures. While responsible for voluntary movements in both hemispheres, it plays a role in initiating speech in the dominant hemisphere. Therefore, in the dominant hemisphere, anterior-superior quadrant lesions, when deep central core structures are affected, language production may be impaired in the patient. As in IFOF, FST fibers can also be affected only in lesions located in the central core and not invading the environment.

Conclusion

In this anatomical study, we have made a detailed description of the insular cortex and central cortical cortical and subcortical structures. We wanted to specifically mention the close relationship with white matter fiber bundles that contribute to language production. We believe that if we have mastered the knowledge of central core and white matter fiber pathways anatomy, we can foresee what kind of language disorder the lesion may cause, according to the anatomical location of the lesion in the central core, we can better plan the surgery and the surgical success will be higher.

Ethics

Ethics Committee Approval: Our study does not require Ethics Committee approval, as it is an anatomical laboratory study in a cadaver. The study was conducted in accordance with the principles of the Helsinki Declaration, 2013.

Informed Consent: Our study does not require patient, as it is an anatomical laboratory study in a cadaver.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.G., M.Ç., B.B., K.Y.; Concept - M.G., B.B., K.Y.; Design - M.G., B.B., K.Y.; Data Collection or Processing - M.G., M.Ç., B.B., K.Y.; Analysis or Interpretation - M.G., M.Ç., B.B., K.Y.; Literature Search - M.G., M.Ç., B.B., K.Y.; Writing - M.G., M.Ç., B.B., K.Y.

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The Effect of Primary Tumour Resection on Prognosis in Emergency-operated Liver Metastatic Colon Cancer

Acil Ameliyat Edilen Karaciğer Metastatik Kolon Kanserinde; Primer Tümör Rezeksiyonun Prognoz Üzerine Etkisi

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ABSTRACT

Introduction: Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths in western societies. It is also the third cause of cancer-related deaths in male and female populations in the world. In population-based studies, 25%-30% of CRC patients are faced with liver metastasis at some point in their disease. Colon and rectal cancers most frequently metastasise to the liver and lungs. This study, which was carried out in patients who were operated due to acute complications of liver metastatic CRC; aimed to investigate the effects of primary tumour removal on mortality, morbidity, and survival.

Methods: Patients with colon or rectal cancer with liver metastases who applied to the University of Health Sciences Turkey, İstanbul Training and Research Hospital Emergency Service between 2011 and 2016 and were urgently operated were included in the study.

Results: A total of 59 patients were evaluated. There were 30 (50.8%) male and 29 (49.2%) female patients. The ages of the participants ranged from 24 to 86 years, with a median age of 65 (24-86) years. Primary tumour resection was performed in 37 (62.7%) patients during emergency surgery, whereas resection was not performed in 22 (37.3%) patients. The postoperative survival of the patients is minimum 1 month and maximum 60 months. The files of patients with a survival of more than sixty months were not followed after the 60th month. Twenty-three patients never received chemotherapy and thirty-six patients were operated during chemotherapy treatment. The hospitalization period of 44 (74.6%) patients was more than 10 days, and the hospitalization period of 15 (25.4%) patients was 10 days or less. When we take 24 months as a basis for the survival of the patients, the number of patients with 24 months or more survival is 23 (39%) and the number of patients with survival below 24 months is 36 (61%). When the 24-month survival "cut off" value was taken, the independent data of the patients were evaluated individually in terms of prognosis and whether it was significant ($p>0.05$).

ÖZ

Amaç: Kolorektal kanser (CRC) batı toplumlarında kanser ile ilişkili ölümlerde en önde gelen sebeplerdendir ve dünyada kansere bağlı ölümlerin erkek ve kadında üçüncü nedenidir. Toplum bazlı çalışmalarda CRC hastalarının %25-30'u hastalıklarının bir döneminde karaciğer metastazı ile karşı karşıya kalmaktadır. Kolon ve rektum kanserleri en sık karaciğer ve akciğere metastaz yapmaktadır. Bu çalışmanın amacı karaciğer metastatik CRC'nin acil komplikasyonları nedeniyle ameliyat edilen hastalarda; primer tümörün çıkarılmasının mortalite, morbidite ve sürviye etkisini araştırmaktır.

Yöntemler: 2011-2016 yılları arasında Sağlık Bilimleri Üniversitesi, İstanbul Eğitim ve Araştırma Hastanesi Acil Servisi'ne başvuran karaciğer metastatik kolon veya rektum kanseri hastalarından acil ameliyat edilen hastalar çalışmaya dahil edilmiştir.

Bulgular: Toplam incelenen hasta sayısı 59'dur. Erkek hasta sayısı 30 (%50,8), kadın hasta sayısı 29'dur (%49,2). Minimum yaş 24 iken maksimum yaş 86 ve medyan yaş değeri 65'tir (24-86). Otuz yedi (%62,7) hastada acil operasyon sırasında primer tümör rezeksiyonu yapılırken, 22 (%37,3) hastada rezeksiyon yapılmamıştır. Hastaların operasyon sonrası yaşam süresi minimum 1 ay, maksimum 60 aydır. Altmış aydan fazla yaşam süresi olan hastaların dosya takibi 60. aydan sonra yapılmamıştır. Yirmi üç hasta hiç kemoterapi almamışken 36 hasta kemoterapi tedavisi sırasında ameliyat edilmiştir. Kırk dört (%74,6) hastanın hastanede yatış süresi 10 günden fazla iken 15 (%25,4) hastanın hastanede kalış süresi 10 gün ve daha azdır. Hastaların yaşam süresi için 24 ayı baz aldığımızda 24 ay ve üzeri survisi olan hasta sayısı 23 (%39) iken 24 ay altında survi süresi olan hasta sayısı 36 (%61)'dır. Yirmi dört aylık survi "cut off" değer alındığı zaman hastaların bağımsız verileri tek tek prognoz açısından 24 aya göre değerlendirilmiş ve anlamlı olup olmadığı incelenmiştir. Yaşam süresi 24 ay altı

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Conclusion: Metastatic CRC patients are generally in the advanced age group. Many of these patients also have additional pathologies. Performing primary tumour resection contributes significantly to the average life expectancy in urgently-operated metastatic CRC patients. Still, this is a difficult surgical procedure; the best decision should be made during surgery, with several factors such as the general condition of the patient, additional pathologies, the experience of the surgeon, and whether the tumour is resectable being taken into consideration.

Keywords: Colorectal cancer, metastasis, liver, survey

ve üstü olan grupta hastaların yaşları anlamlı (p>0,05) farklılık göstermemiştir.

Sonuç: Metastatik CRC hastaları genelde ileri yaş gurubundadır. Bu hastaların birçoğunda ek patolojiler de mevcuttur. Acil opere edilen metastatik CRC hastalarında primer tümör rezeksiyonu yapmak ortalama yaşam süresine anlamlı katkı sağlamaktadır. Yine de bu ameliyat zor bir operasyondur; hastanın genel durumu ek patolojileri cerrahın tecrübesi ve tümörün rezektabl olup olmaması gibi değişken faktörlerle en iyi karar ameliyat esnasında verilmelidir.

Anahtar Kelimeler: Kolon kanseri, metastaz, karaciğer, survi

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related death in western societies. It is also the third cause of cancer-related death in both male and female populations in the world (1). In population-based studies, 25%-30% of CRC patients are faced with liver metastasis at some point in their disease (2). Colon and rectal cancers most frequently metastasise to the liver and lungs (3). Haematogenous spread through the portal vein is most commonly affects the liver (4). Recent studies show an increase in liver metastasis in colon cancers in recent years (3). Despite all developments in the field of surgery and oncology, only 25% of patients with liver metastases of colon cancer (CRCLM) are cured (5). Only 10%-25% of CRC patients have a resectable liver metastases at the time of diagnosis (6). The only known cure for this patient group is oncological surgery. The order of surgical and oncological treatment in CRCLM patients correlated with: the size and number of liver metastases, the presence or not in both lobes, the residual liver volume after surgery, the presence or absence of other comorbidities. In addition, the order of treatment to be given is affected by ileus, bleeding, or perforation caused by colon cancer. Although there is no clear consensus on this multifactorial situation, many surgeons prefer short chemotherapy treatment if there are no emergencies such as ileus, bleeding, perforation etc for CRCLM patients, after which they proceed to the surgery. After primary tumour resection, if liver metastasis is not suitable for resection, the patient continues chemotherapy (7,8). In this study, we compared the prognosis of patients who were admitted to the emergency department with an acute complication of CRC requiring emergency surgery, such as intestinal obstruction, bleeding, and perforation with liver metastasis, who underwent primary tumour resection during emergency surgery and who were placed on chemotherapy without resection of the primary tumour.

Methods

Patients with colon or rectal cancer with liver metastases who visited the emergency service between 2011 and 2016 and were operated urgently were included in the study. The files of the patients were analysed retrospectively. Demographic data, performance or not of tumour resection, commencement or not of neo-adjuvant chemotherapy, duration of hospital stay, and post-operative survival were analysed. The first patient included in the study was operated in February 2011, the last patient was operated in November 2015, and the 5-year survival of the patients from the date of surgery was evaluated. The effects of the previously-mentioned independent data on prognosis were compared.

This study, which is a retrospective analysis of CRC patients, was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 2420, date: 12.06.2020). Written informed consent was obtained from all cases.

Statistical Analysis

In the descriptive statistics of the data, mean, standard deviation, median, lowest value, highest value, frequency, and ratio values were used. The distribution of variables was measured by the Kolmogorov-Smirnov test. Mann-Whitney's U test was used to analyse quantitative independent data. The chi-square test was used in the analysis of qualitative independent data. Fischer's Exact test was used when the chi-square test conditions were not met. SPSS 26.0 software was used in the analysis.

Results

We evaluated 59 patients; 30 (50.8%) males and 29 (49.2%) females. The ages of the participants ranged from 24-86 years, with a median age of 65 (24-86) years. Primary tumour resection was performed in 37 (62.7%) patients during emergency surgery, whereas resection was not performed in 22 (37.3%) patients. The postoperative survival of the patients ranged from 1-60 months. Patients with a survival of more than 60 months were not followed up after the 60th month. While 23 patients never received chemotherapy, 36 were operated while they were on chemotherapy. The hospitalisation period of 44 (74.6%) patients was more than 10 days, while that of 15 (25.4%) patients was 10 days or less (Table 1). When we consider 24 months as the reference for the post-operative survival of the patients, the number of patients with a survival of 24 months or more is 23 (39%), while the number of patients with a survival below 24 months is 36 (61%). When the 24 month survival was taken as the cut-off value, the independent data of the patients were evaluated individually for 24 months in terms of prognosis and statistical significance was also determined.

There was no statistically significant difference (p>0.05) in the ages of the patients in the group with a survival of less than 24 months and that with survival over 24 months after surgery. The preoperative albumin value did not differ significantly (p>0.05) in the group with a survival of less than 24 months and that with survival over 24 months after surgery.

Primary tumour resection rate was significantly lower ($p<0.05$) in the group with a postoperative survival of ≤24 months than in the group with a postoperative survival of >24 months after surgery. The degree of tumour differentiation did not differ significantly ($p>0.05$) between the two groups. The neoadjuvant chemotherapy treatment rate did not differ significantly ($p>0.05$) between the two groups. The distribution of metastasis location did not differ significantly ($p>0.05$) between the two groups. The duration of hospitalisation did not differ significantly ($p>0.05$) between the two groups.

As seen in Table 2, the number of patients who lived for at least 24 months after operation was higher in the group in which primary tumour excision was performed. The ages of the patients did not significantly differ ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days. There was no significant difference in gender distribution ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days. The preoperative albumin value did not differ significantly ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days. In the group with hospital stay was longer than 10 days, the survival time after surgery was significantly shorter ($p>0.05$) than that in the group with less than 10 days of hospital stay.

Primary tumour excision rate did not differ significantly ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days. The neoadjuvant chemotherapy treatment ratio did not differ significantly ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days. The distribution of metastasis location did not differ significantly ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days. The duration of hospitalisation did not differ significantly ($p>0.05$) between the group whose hospital stay was less 10 days and that whose hospital stay was more than 10 days (Table 3).

Discussion

CRC is the most common cancer of the gastrointestinal tract (9). It is the 3rd leading cause of mortality in men and women. In recent years, early diagnosis and risk management are possible with community screening programmes and advanced technological imaging methods (10). Despite all community screening programmes and advances in surgery and oncology, there is no significant reduction in the number of metastatic colon cancer patients. In 50%-60% of all CRC patients, liver metastasis will develop at some point in their lives (10,11).

The majority of CRCs are first diagnosed in emergency departments, where they present with acute complications of the disease such as intestinal obstruction, perforation and bleeding. These acute complications are often life-threatening emergencies and are managed through emergency surgery. The most important factors determining the prognosis after surgery are advanced age, existing comorbidities, and advanced tumour stage (12). However, whether or not intestinal obstruction is a sign of bad prognosis is controversial (13,14).

Table 1. Analysis of all patients' data

		Min-max	Median	Mean ± SD/n-%
Age		24.0-86.0	65.0	64.5±12.0
Gender	Female	-	-	29/49.2%
	Male	-	-	30/50.8%
Preop albumin		1.9-4.7	2.8	3.0±0.7
Survival after surgery, months		1.0-60.0	16.0	21.4±14.3
Primary tumour excision	(-)	-	-	22/37.3%
	(+)	-	-	37/62.7%
Tumour differentiation	Low	-	-	23/39.0%
	Moderate	-	-	23/39.0%
	Well	-	-	13/22.0%
Neoadjuvant chemotherapy treatment	(-)	-	-	36/61.0%
	(+)	-	-	23/39.0%
Liver metastasis location	Left	-	-	10/16.9%
	Right	-	-	30/50.8%
	Bilateral	-	-	19/32.2%
Duration of hospitalisation	≤10 days	-	-	15/25.4%
	>10 days	-	-	44/74.6%
Survival after surgery	≤24 months	-	-	36/61.0%
	>24 months	-	-	23/39.0%

SD: Standard deviation, min: minimum, max: maximum

Table 2. Analysis of patients' data according to postoperative survival

		Survival after surgery ≤24 months		Survival after surgery >24 months		p
		Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	
Age		63.7±14.3	66.0	65.7±7.4	65.0	0.864[m]
Gender	Female	18/50%	-	11/47.8%	-	0.274[X²]
	Male	17/47.2%	-	13/56.5%	-	
Preop albumin		3.1±0.7	3.1	2.8±0.6	2.7	0.239[m]
Primary tumour excision	(-)	20/55.6%	-	2/8.7%	-	0.000[X²]
	(+)	16/44.4%		21/91.3%		
Tumour differentiation	Low	18/50.0%	-	5/21.7%	-	0.054[X²]
	Moderate	13/36.1%		10/43.5%		
	Well	5/13.9%		8/34.8%		
Neoadjuvant chemotherapy	(-)	22/61.1%	-	14/60.9%	-	0.985[X²]
	(+)	14/38.9%		9/39.1%		
Liver metastasis location	Left	5/13.9%	-	5/21.7%	-	0.735[X²]
	Right	19/52.8%		11/47.8%		
	Bilateral	12/33.3%		7/30.4%		
Hospitalisation	≤10 days	11/30.6%	-	4/17.4%	-	0.257[X²]
	>10 days	25/69.4%		19/82.6%		

[m]Mann-Whitney U test, [X²]chi-square (Fischer Exact test), SD: standard deviation

Table 3. Analysis of patients' data according to length of stay in hospital

		Hospitalisation ≤10 days		Hospitalisation >10 days		p
		Mean ± SD/n-%	Median	Mean ± SD/n-%	Median	
Age		59.5±15.7	64.0	66.2±10.2	66.0	0.864[m]
Gender	Female	15	-	14	-	1.000[X²]
	Male	14	-	16	-	
Preop albumin		3.3±0.6	3.4	2.9±0.7	2.6	0.239[m]
Survival after surgery months		16.3±7.0	15.0	23.1±15.7	22.5	0.000[m]
Primary tumour excision	(-)	6/40.0%	-	16/36.4%	-	0.801[X²]
	(+)	9/60.0%	-	28/63.6%	-	
Tumour differentiation	Low	6/40.0%	-	17/38.6%	-	0.606[X²]
	Moderate	7/46.7%	-	16/36.4%	-	
	Well	2/13.3%	-	11/25.0%	-	
Neo-adjuvant chemotherapy	(-)	11/73.3%	-	25/56.8%	-	0.257[X²]
	(+)	4/26.7%	-	19/43.2%	-	

[m]Mann-Whitney U test, [X²]chi-square test (Fischer Exact test), SD: standard deviation

In a study by Ergun et al. (10), 252 patients with metastatic colon cancer were evaluated in terms of primary tumour resection, and demonstrated that performing primary tumour resection before chemotherapy has no survival benefit. As a result, they reported that it would be more appropriate to start treatment with chemotherapy and biological agents in asymptomatic metastatic patients, thus, they showed that patients would be affected less by the mortality and morbidity of the operation.

In a study by de Mestier et al. (15), primary tumour resection and immediate subsequent chemotherapy in patients with asymptomatic metastatic CRC was found to be superior in terms of the duration and quality of postoperative survival of the patients compared to chemotherapy alone. Louis recommends primary tumour resection in patients under the age of 70 who: do not have extrahepatic metastases, have less than two metastases in the liver, and have at least half of the liver intact without metastasis (15).

Simillis et al. (16) found that performing primary tumour resection and then initiating chemotherapy in patients with asymptomatic metastatic CRC was superior in terms of survival compared to direct chemotherapy in a large meta-analysis with 77 studies they examined (16). Nevertheless, they suggested starting with primary tumour resection in a multidisciplinary manner. They examined the patients in six groups and the average life expectancy of the group that did not receive any treatment was found to be 4.02 months. The mean life expectancy was 7.42 months in the group in which primary tumour resection

was performed and did not receive chemotherapy. In the groups that received chemotherapy and bevacizumab without primary tumour resection, the mean survival time was 14.3 months and 17.27 months, respectively. The mean survival was 21.52 months and 27.52 months in two separate groups in which primary tumour resection was performed and immediately followed by chemotherapy and bevacizumab, respectively (16). The results of this meta-analysis partially support the findings of our study.

As above, the number of such studies can be increased, and there are studies that suggest direct chemotherapy before primary tumour resection. The difference between our study and these studies is that patients had emergency surgery as a result of symptoms associated with the primary tumour and to compare whether to perform primary tumour resection during surgery.

CRCLM patients after or before diagnosis: It is a patient group with a high probability of emergency surgery due to reasons such as ileus, bleeding, and perforation. Performing primary tumour resection during emergency surgery might result in a longer hospital stay, a higher rate of mortality and morbidity and this delays in the patient's commencement of chemotherapy. In our study, there was no significant difference in terms of hospital stay between the group that underwent primary tumour resection and the group that did not. The survival time after surgery was significantly more in the primary tumour resection group.

Conclusion

Metastatic CRC patients are generally in the elderly population. Many of these patients also have additional comorbidities. Performing primary tumour resection contributes significantly to the average life expectancy in urgently-operated metastatic CRC patients. Still, this is a difficult surgical procedure. The best decision should be made during surgery, with several factors such as the general condition of the patient, additional comorbidities, the experience of the surgeon, and the resectability of the tumour being taken into consideration.

Ethics

Ethics Committee Approval: This study, which is a retrospective analysis of CRC patients, was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 2420, date:12.06.2020).

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

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The Effect of General and Spinal Anaesthesia on Pulmonary Function Tests in Geriatric Patients

Geriatrik Hastalarda Genel ve Spinal Anestezinin Solunum Fonksiyon Testleri Üzerine Etkisi

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ABSTRACT

Introduction: This study aimed to compare the effects of general and spinal anaesthesia on pulmonary function tests (PFT) in the postoperative period among patients aged ≥65 years.

Methods: This prospective study included a total of 60 patients aged ≥65 years with American Society of Anesthesiologists I-III. General anaesthesia was applied to group I while spinal anaesthesia was applied to group II. PFTs were performed in all the patients in the preoperative evaluation and were repeated at the 2nd and 24th postoperative hours. Comparison of the results was done both within and between the groups.

Results: A comparison between the groups showed that both in the preoperative and postoperative periods, forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), the ratio of FEV1 to FVC (FEV1/FVC, Tiffeneau ratio), forced expiratory flow between 25% and 75% of the FVC (FEF25-75), peak expiratory flow and forced expiratory time values were not statistically significant ($p>0.05$). However, when the patients were compared within the groups, a statistically significant decrease in FEV1 and FVC values was found in the postoperative spirometric measurements in both groups compared to the preoperative period ($p<0.05$).

Conclusion: General or spinal anaesthesia adversely affects PFTs in elderly patients.

Keywords: Elderly, general anaesthesia, spinal anaesthesia, pulmonary function tests

ÖZ

Amaç: Genel ve spinal anestezinin postoperatif dönemde 65 yaş ve üstü hastalarda solunum fonksiyon testleri (SFT) üzerine etkisinin incelenmesi amaçlanmıştır.

Yöntemler: Bu ileriye dönük çalışmada Amerikan Anesteziyoloji Derneği I ile III aralığında 65 yaş ve üstü toplam 60 hasta değerlendirilmiştir. Genel anestezi uygulanan hastalar grup I, spinal anestezi uygulananlar ise grup II olarak sınıflanlandırılmıştır. Tüm olgulara ameliyat öncesi ve ameliyat sonrası 2. ve 24. saatlerde SFT yapılmıştır. SFT sonuçları gruplar arasında analiz edilmiştir.

Bulgular: Birinci saniye zorlu ekspiratuvar volüm (FEV1), zorlu vital kapasite (FVC), birinci saniye zorlu ekspiratuvar volümün (FEV1'in FVC'ye) zorlu vital kapasiteye oranı (FEV1/FVC, Tiffeneau oranı) zorlu ekspirasyon ortası akım hızı (FEF25-75), tepe akım hızı, zorlu ekspiryum zamanı değerlerinde gruplar arasında istatistiksel olarak anlamlı farklılık saptanmadı ($p>0,05$). Bununla birlikte genel anestezi ve spinal anestezi uygulanan hastalar grup içi değerlendirildiğinde her iki grupta da FEV1 ve FVC değerlerinde preoperatif döneme göre postoperatif spirometrik ölçümlerde istatistiksel olarak anlamlı bir azalma gözlendi ($p<0,05$).

Sonuç: Yaşlı hastalarda genel veya spinal anestezi SFT'lerini benzer şekilde olumsuz etkilemektedir.

Anahtar Kelimeler: Yaşlı, genel anestezi, spinal anestezi, solunum fonksiyon testleri

Introduction

Ageing is a physiological process affected by multiple factors such as lifestyle, environment, genetics, social environment, work environment and chronic diseases. It involves changes in physiological functions that occur over time without any particular disease. According to the World Health Organization, people aged ≥65 years are defined as "old" while people aged ≥80 years as "late elderly". Life expectancy in our country has been extended similar to that of the rest of the world. The elderly population is increasing along with related diseases that increase with ageing and require surgery. Accordingly, surgery and anaesthesia applications in elderly patients are becoming increasingly frequent (1,2).

With ageing, major changes are observed in all systems. One of the most obvious changes occurs in the respiratory system. The risk of

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perioperative pulmonary complications increases due to changes in the lung structure, lung mechanics and pulmonary blood flow in the elderly (3). Therefore, pulmonary function tests (PFT) can be an important assessment tool for predicting postoperative pulmonary complications. They provide more objective data than medical history and physical examination in demonstrating the presence and severity of respiratory dysfunction in patients to undergo surgery (4). In addition to the changing physiology, the anaesthesia techniques to be used are highly important in elderly patients with planned surgery. The effects of different anaesthesia methods on the respiratory function of elderly patients vary and their superiority to each other is controversial (5-7).

To our knowledge, there is a limited number of publications in the literature that compare the effects of general anaesthesia and spinal anaesthesia on PFTs (8,9). Therefore, this study aimed to compare the effects of general and spinal anaesthesia on PFTs in elderly patients with planned extremity surgery.

Methods

The study was approved by the Ethics Committee of Gaziosmanpaşa University, Gaziosmanpaşa (13-KAEK-236) and was registered as a clinical trial at ClinicalTrials.gov (http://www.clinicaltrials.gov) with the identification number NCT03399201 (decision no: 83116987-036, date: 27.01.2014). In addition, informed consent was obtained from each patient. The study included 60 patients aged ≥65 years with American Society of Anesthesiology (ASA) scores I-III, and who were to undergo general or spinal anaesthesia in the Research and Application Center of the Faculty of Medicine at Gaziosmanpaşa University between February and December 2018.

Patients with contraindications for spinal anaesthesia, those with known respiratory diseases or obesity (body mass index >30 kg/m^2) or those whose surgery was in a position other than the supine position were excluded. Patients randomised using the closed envelope technique were divided into two groups: Group I (general anaesthesia) (n=30) and group II (spinal anaesthesia) (n=30). In all patients, venous vascular access was performed from the back of the hand or the antecubital fossa with a 20 gauge (G) branule in the operation room. Electrocardiogram (ECG), peripheral oxygen saturation and non-invasive blood pressure monitoring were performed using a bedside monitor (GE Datex-Ohmeda F-CM1-05 Anesthesia Monitor, Helsinki, Finland). Patients in group I were pre-oxygenated through spontaneous breathing, with the mask containing 100% O_2 and fresh gas flow at 5 L/min for three minutes. Induction was performed with 1-2 mcg/kg fentanyl and 5-7 mg/kg thiopental. After achieving muscle relaxation with 0.6 mg/kg rocuronium, the patients were intubated with an appropriate diameter endotracheal tube. In the maintenance anaesthesia, 1 minimum alveolar concentration sevoflurane and 50% O_2-air mixture was used. The mode of mechanical ventilation in the anaesthesia machine (GE-Datex-Ohmeda S/5 Avance, USA) was the "synchronized intermittent mandatory ventilation mode" with a tidal volume of 7-10 mL/kg, breathing frequency of 12/min, I: E ratio of 1:2 and positive end-expiratory pressure of 4-5 cm H_2O. At the end of the surgery, the patients were extubated with neostigmine at 0.03 mg/kg IV and atropine at 0.01 mg/kg IV to restore the neuromuscular blockage. In group II, 12.5 mg (2.5 mL) of 0.5% hyperbaric bupivacaine was applied in the sitting position using a 25 G atraumatic spinal needle (Egemen® spinal needle, Egemen International, Turkey) from the L3-4 or L4-5 range, with a midline spinal puncture. After the spinal anaesthesia, the sensory block level was determined by a pin-prick test. The loss of stinging/pain sensation to a needle tip was evaluated down the middle clavicular line. The T6-8 levels were the sufficient sensory block levels for the surgery. The surgery was started when the block reached these levels. The patients were given 3 L/min oxygen by nasal cannula during the surgery.

In the preoperative evaluation, all the patients were explained how the PFT was performed and the same practitioner performed the tests when the patients' numerical pain score was three and below. PFTs were performed in the sitting position using a portable spirometry device (Spirodoc class IIA/Roma Italy) before the surgery, and at the postoperative 2nd and 24th hours. Forced expiratory volume in the first second (FEV1), forced vital capacity (FVC), the ratio of FEV1 to FVC (FEV1/FVC, Tiffeneau ratio), forced expiratory flow between 25% and 75% of the FVC (FEF25-75), peak expiratory flow (PEF) and forced expiratory time (FET) values were recorded as well as the demographic information and duration of the surgery.

Statistical Analysis

All the data were evaluated using the software Statistical Package for Social Sciences 20.0 (SPSS Inc. Chicago, IL). P<0.05 was accepted as statistically significant. The Kolmogorov-Smirnov test was used to evaluate the compliance of the data to a normal distribution. Descriptive data are presented as mean (standard deviation) for normally distributed data and as median for non-normally distribution data. The distance between quarters is presented as 25th and 75th percentiles, and categorical data are presented as number (frequency). The categorical data were compared using Pearson's chi-square test or Fisher's Exact chi-square test. The independent t-test was used to compare the groups when the continuous data was normally distributed, and the Mann-Whitney U test was used to compare the groups when the continuous data was not normally distributed. Analysis of Variance was used to compare repeated measurements. Bonferroni-corrected multiple comparisons were used to determine the different groups. Friedman's test was used for repeated measurements that did not fit the normal distribution. Dunn's test with Bonferroni correction was applied to determine different groups. It was used as a multiple comparison test.

Results

There was no statistically significant difference between the groups in terms of demographic data, sex, duration of operation, smoking and ASA score (Table 1) (p>0.05). FEV1, FVC, FEV1/FVC, FEF25-75 and PEF values were compared among the patients included in the study. There was no significant difference in the preoperative period, at the postoperative 2nd hour and 24th hour in the intergroup evaluation (Table 2) (p>0.05). According to the comparison within the groups, the FEV1 value decreased significantly in both groups over time. There was a significant difference in FEV1 at the basal-postoperative 2nd hour (p=0.002) and 24th hour (p=0.004) in group I; in FEV1 at the basal-postoperative 24th hour (p=0.001) in group II (Figure 1). We found a statistically significant

decrease in FVC over time in both groups. The difference in FVC was as follows: with regard to the basal-postoperative 2nd hour (p=0.035) and 24th hour (p=0.011) values in group I, and the basal-postoperative 2nd hour (p=0.007) and 24th hour (p=0.001) values in group II (Figure 2).

Discussion

Due to developments in the field of health and advances in social life, the number and proportion of the elderly in the total population are steadily increasing. Depending on the increase in the elderly population and the diseases requiring surgery with ageing, it is predicted that surgery and anaesthesia applications will be more frequent in the future. The respiratory system among other systems experiences the most changes with ageing (10). A study evaluating the effect of ageing on pulmonary function parameters demonstrated a progressive decrease in PFT parameters with ageing in patients >60 years (11). Studies to determine spirometric reference values in the elderly have associated the following with a decrease in spirometric values: in addition to known respiratory system diseases, the use of cardiac glycoside, beta-blockers, diuretics, theophylline and diabetic drugs; smoking for more than five packs per year; conditions such as exertional dyspnoea, hypertension,

Table 1. Demographic data and operation times

	Group I (n=30)	Group II (n=30)	p*
Age (years) median (lower limit - upper limit)	70 (65-82)	67.5 (65-93)	0.32[a]
Sex (M/F) n	10/20	11/19	0.79[b]
Length (cm) mean ± SD	160.87±7.11	162.83±8.40	0.33[c]
Weight (kg) mean ± SD	78.4±14.78	78.10±12.23	0.93[c]
Operation duration (min) median (lower limit - upper limit)	145 (75-250)	126 (90-225)	0.096[a]
ASA (I/II/III) n	4/11/15	2/15/13	0.86[a]
Smoking (yes/no)	10/20	8/22	0.56[b]

*Comparison between groups, [a]Mann-Whitney U test, [b]Pearson's chi-square test, [c]Independent t-test
SD: Standard deviation, ASA: American Society of Anesthesiology, M: male, F: female, min: minute

Table 2. Preoperative and postoperative pulmonary function test measurements

	Group I (n=30)	Group II (n=30)	p
FEV1			
Preoperative median (lower limit-upper limit)	1.86 (1.12-3.33)	1.91 (1.12-2.91)	0.78[a]
2nd hour median (lower limit-upper limit)	1.58 (0.93-3.14)	1.67 (0.83-3.24)	0.37[a]
24th hour median (lower limit-upper limit)	1.54 (1.14-3.35)	1.61 (0.90-3.00)	0.81[a]
FVC			
Preoperative median (lower limit-upper limit)	2.39 (1.12-4.62)	2.45 (1.12-3.58)	0.80[a]
2nd hour median (lower limit-upper limit)	1.97 (0.93-3.88)	2.28 (1.10-3.60)	0.68[a]
24nd hour median (lower limit-upper limit)	1.93 (1.21-4.15)	2.06 (1.24-3.35)	0.24[a]
FEF25-75			
Preoperative median (lower limit-upper limit)	1.79 (1.00-3.83)	1.98 (1.01-5.09)	0.64[a]
2nd hour median (lower limit-upper limit)	1.85 (0.76-3.33)	2.01 (0.72-4.75)	0.35[a]
24th hour median (lower limit-upper limit)	1.95 (1.04-3.51)	1.85 (0.59-4.58)	0.68[a]
PEF			
Preoperative median (lower limit-upper limit)	3.68 (1.94-6.91)	3.66 (1.34-8.77)	0.85[a]
2nd hour median (lower limit-upper limit)	3.33 (1.82-6.97)	3.69 (1.87-9.84)	0.12[a]
24th hour median (lower limit-upper limit)	3.51 (1.67-7.21)	3.51 (1.45-9.84)	0.61[a]
FET			
Preoperative median (lower limit-upper limit)	4.07 (0.93-6.52)	3.84 (0.63-6.28)	0.93[a]
2nd hour median (lower limit-upper limit)	3.12 (0.86-6.50)	3.43 (1.27-9.71)	0.24[a]
24th hour median (lower limit-upper limit)	3.38 (0.95-6.12)	3.92 (2.06-7.01)	0.29[a]
FEV1/FVC			
Preoperative median (lower limit-upper limit)	0.78 (0.54-1.00)	0.81 (0.51-1.00)	0.45[a]
2nd hour median (lower limit-upper limit)	0.79 (0.57-1.00)	0.82 (0.58-1.05)	0.13[a]
24th hour median (lower limit-upper limit)	0.82 (0.59-1.44)	0.80 (0.51-0.90)	0.30[a]

[a]Mann-Whitney U test, FEV1: volume in the first second, FVC: forced vital capacity, FEF25-75: forced expiratory flow between 25% and 75% of FVC, PEF: peak expiratory flow, FET: forced expiratory time, FEV1/FVC: the ratio of forced expiratory FEV1 to FVC

major ECG anomalies, previous history of thoracic surgery and evidence of pretibial oedema (12,13). In our study, preoperative FEV1 and FVC values were lower compared to those of studies conducted to determine spirometric reference values in the elderly. Our study excluded cases with primary lung disease. However, 90% of our study population had accompanying conditions that are known to result in a decrease in PFTs such as hypertension, diabetes and beta-blocker use. This may have contributed to the lower PFT values. With advanced age, smoking, immobilisation and the supine position cause the closing capacity to be higher than the functional residual capacity (FRC), which results in atelectasis (8). Our study group included orthopaedic patients who were elderly and with limited mobilisation. This may have caused spirometric measurements to be low due to a possible underlying atelectasis.

Anaesthesia methods used during surgery have their advantages and disadvantages when compared with each other. General anaesthesia reduces regional ventilation by lowering the FRC. As the FRC approaches the closing capacity, small airways collapse, atelectasis occurs and perioperative atelectasis worsens underlying chronic lung diseases (14,15). Several studies in the literature have shown a statistically

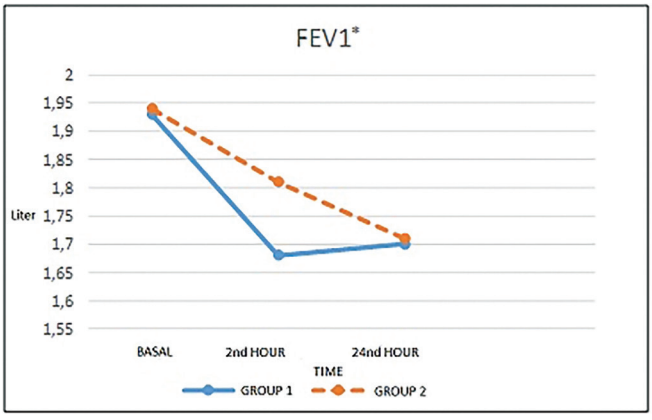

Figure 1. Comparison of volume in the first second mean values within and between the groups

FEV1: Volume in the first second

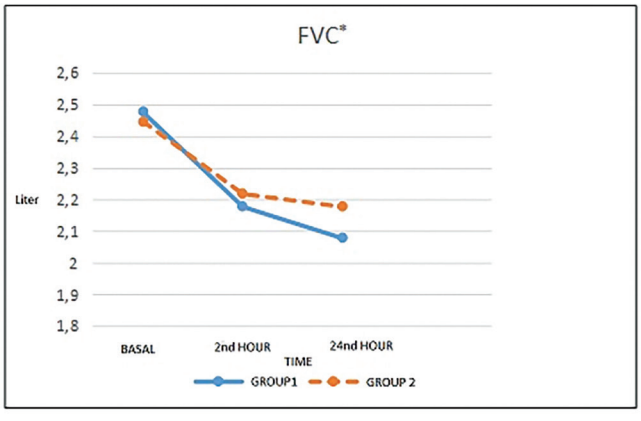

Figure 2. Comparison of forced vital capacity mean values within and between the groups

FVC: Forced vital capacity

significant decrease in the postoperative spirometric values of patients who underwent general anaesthesia compared to the preoperative period (16-19). Similarly, we observed a statistically significant decrease in FEV1 and FVC values in the postoperative period compared to the preoperative period in group I patients, while no significant difference was found in FEV1/FVC, FEF25-75, PEF and FET values. It is compatible with the spirometric restriction that the FEV1/FVC ratio is normal while FEV1 and FVC are low. This measurement occurs in cases of true restriction, mixed obstruction-restriction or non-specific ventilation pattern, and the diagnosis is made through a detailed evaluation (20). The result of our spirometric measurements suggests that the development of atelectasis due to general anaesthesia in our cases highlights a restrictive type postoperative respiratory dysfunction and requires detailed evaluation.

Spinal anaesthesia can also have negative effects on pulmonary function parameters. Studies evaluating the respiratory functions before and after the intervention in surgeries with spinal anaesthesia found a statistically significant decrease in spirometric values in the postoperative period compared to the preoperative period (21-23). Oğurlu et al. (1) evaluated 50 patients to examine the effects of spinal anaesthesia on PFTs. They reported a statistically significant decrease in basal FVC, FEV1 and FEF25-75 values in patients (in the 60-85 age group) with spinal anaesthesia above the thoracic 6th (T6) level in the postoperative 40th minute compared to the preoperative period. However, the mean FVC, FEV1 and FEF25-75 values were lower in the 40th minute postoperatively compared to the preoperative period in patients with a spinal anaesthesia level below the T6 level, albeit not significant. Similar to the literature data, our study found a statistically significant decrease in the postoperative FEV1 and FVC values of group II patients compared to the preoperative period (1,21-23). In the same group, there was no statistically significant difference in the mean FEF25-75, PEF, FET values and FEV1/FVC ratio at the 2nd and 24th postoperative hours compared to the preoperative period. In spinal anaesthesia, the level of the motor block above the T6 level affects the accessory expiratory muscles, causing a decrease in vital capacity and FVC. The lack of ventilation caused by this situation and the supine position may lead to atelectasis (8). We think that a restrictive type of respiratory dysfunction occurred after spinal anaesthesia, similar to that in group I.

There is a very limited number of publications in the literature that compares the effects of regional and general anaesthesia on pulmonary functions. Ungern-Sternberg et al. (8) recorded the basal spirometric values of patients by examining the effects of general and spinal anaesthesia on perioperative spirometric values in 84 patients aged between 22-84 years, with a planned gynaecological surgery. Then, by applying the preferred anaesthesia technique, they repeated the spirometric measurement at the 20th minute, 1st hour, 2nd hour and 3rd hour postoperatively. A statistically significant decrease was recorded in all values after premedication compared to the basal values in both groups. There was also a decrease in all postoperative values, and this decrease was statistically significant in the general anaesthesia group compared to the spinal anaesthesia group. Another study examined 100 cases between 39-47 years of age to compare the effects of spinal and general anaesthesia on pulmonary functions. PFTs showed a statistically

significant decrease in the general anaesthesia group in the postoperative period compared to those who received spinal anaesthesia. In addition, when the preoperative and postoperative values were compared, there was a statistically significant decrease in the postoperative values in both anaesthesia groups compared to the preoperative period (9). In our study, the spirometric values of both groups were significantly decreased in terms of the FEV1 and FVC in the postoperative period compared to the preoperative period. However, we did not find a statistically significant difference between group I and group II. Since the preoperative spirometric values of our patients were lower than the reference values, we may not be able to show the difference between the groups that may occur in the postoperative period compared to the preoperative period. In addition, the decrease in both groups in the postoperative period compared to the preoperative period may be due to the increase in the closing capacity that occurs with ageing, and the decrease in the FRC due to the supine position and anaesthesia effect, both contributing to the development of atelectasis.

The limitations of our study were as follows: The number of cases was small. The condition of the lungs before and after the surgery could not be evaluated by computed tomography, chest radiography or ultrasound. The absence of a lung disease was based only on a verbal declaration. Preoperative spirometric values were lower than the reference values.

Conclusion

We found that the preoperative PFTs of elderly patients with planned extremity surgery are quite low compared to those reported in the literature. Both anaesthesia methods led to a similar decrease in PFTs. Although new studies are needed to confirm the results, we think that a preoperative examination of the respiratory system, a good evaluation of respiratory functions and lung capacity may be much more beneficial compared to the choice of the anaesthesia technique in the anaesthesia management of elderly patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Gaziosmanpaşa University, Gaziosmanpaşa (13-KAEK-236) and was registered as a clinical trial at ClinicalTrials.gov (http://www.clinicaltrials.gov) with the identification number NCT03399201 (decision no: 83116987-036 date: 27.01.2014).

Informed Consent: Informed consent was obtained from each patient.

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Comparative Evaluation of Three Different Treatment Approaches for Intertrochanteric Fracture in Advanced Age Patients

İleri Yaş Hastalarda İntertrokanterik Kırık için Üç Farklı Tedavi Yaklaşımının Karşılaştırmalı Değerlendirilmesi

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ABSTRACT

Introduction: Considering the general condition of elderly patients, it is important to treat intertrochanteric fracture along with early rehabilitation interventions. We compared the mortality and clinical outcomes among the factors of Ender nailing, proximal femoral nailing (PFN) and hemiarthroplasty in patients aged >90 years with intertrochanteric fractures.

Methods: We retrospectively evaluated the medical records of 78 patients aged >90 years who were diagnosed with intertrochanteric fracture and treated during 1997-2016 at our clinic. The patients were earlier treated with Ender nailing (n=16), PFN (n=32) and hemiarthroplasty (n=30). The mean age of the patients was 93.3 years (range: 90-104); 14 of them were men and 64 women. All patients were mobile before their fracture. The preoperative American Society Anaesthesiologists (ASA) score and the postoperative hospital stay duration, survival, mobilisation and mobilisation time were evaluated.

Results: Among the 78 patients, 60 (76.9%) eventually died and 18 (23.1%) survived. The mean survivals after surgery were 30.5, 27.2 and 21.7 months in the Ender, PFN and hemiarthroplasty groups, respectively. The overall death rates were 62.5% (n=10), 62.5% (n=20) and 100% (n=30) in the Ender, PFN and hemiarthroplasty groups, respectively. No significant difference was noted in the ASA score. The mean postoperative hospital stay durations were 8.2, 9.4 and 7.6 days in the Ender, PFN and hemiarthroplasty groups, respectively. The mean mobilisation days were 36, 4.3 and 4.8 days in the Ender, PFN and hemiarthroplasty groups, respectively. Six (37.5%) patients in the Ender, 5 (16.6%) in the hemiarthroplasty and 5 (15.6%) in the PFN groups could not walk. The Ender group was mobilised significantly late (p<0.001).

Conclusion: Although PFN is accepted as the gold standard for treating intertrochanteric fractures, different treatment

ÖZ

Amaç: Yaşlı hastaların genel durumu göz önüne alındığında, intertrokanterik kırığın erken rehabilitasyon müdahaleleri ile birlikte tedavi edilmesi önemlidir. Bu çalışmada Ender çivileme, proksimal femoral çivileme (PFN) ve hemiartroplasti ile tedavi edilen intertrokanterik kırıklı 90 yaş üstü hastaların mortalite ve klinik sonuçları karşılaştırdık.

Yöntemler: 1997-2016 yılları arasında kliniğimizde tedavi edilen 90 yaş üstü intertrokanterik kırık tanılı hastaların dosyaları retrospektif olarak incelendi. Ender çivisi ile 16, hemiartroplasti ile 30, PFN ile 32 toplam 78 hastanın tedavi edildiği saptandı. Hastaların yaş ortalaması 93,3 yıl (aralık: 90-104) idi ve hastaların 14'ü erkek, 64'ü kadındı. Bütün hastalar kırık öncesi yürüyebiliyordu. Hastaların preoperative Amerikan Toplumu Anestezistleri (ASA) skoru ve postoperative hastanede kalış süresi, postop yaşam süresi, mobilizasyonu ve mobilizasyon süresi değerlendirildi.

Bulgular: Hastalardan altmışının (%76,9) öldüğü, on sekizinin (%23,1) sağ olduğu saptandı. Ender grubunun %62,5'i (n=10) PFN grubunun %62,5'i (n=20) hemiartroplasti grubunun %100'ü (n=30) öldüğü tespit edildi. Gruplar arasında ASA skoru açısında anlamlı fark saptanmadı. Postoperatif hastaneden kalış süreleri karşılaştırıldığında; Ender grubu 8,2 gün, PFN grubu 9,4 gün ve hemiartroplasti grubu 7,6 gün olarak saptandı. Hastaların postop mobilizasyonları karşılaştırıldığında; Ender grubu ortalama 36 günde, hemiartroplasti grubu 4,8 günde, PFN grubu 4,3 günde yürüdüğü saptandı. Ender grubunda 6 (%37,5) hasta, hemiartroplasti grubunda 5 (%16,6) hasta, PFN grubunda 5 (%15,6) hastanın yürüyemediği saptandı. Ender grubu anlamlı olarak geç mobilize oldu (p<0,001).

Sonuç: PFN intertrokanterik kırıklar için altın standart kabul edilse de özellikle ileri yaş, osteoporotik, birden fazla ek hastalığı olan düşkün hastalarda farklı tedaviler uygulanabilir.

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options can be used, especially in patients with advanced age, osteoporotic and in those presenting with multiple comorbidities. In this study, we found that the patients treated with Ender nail had lower mortality.

Keywords: Very old patients, more than 90 years, proximal femur nail, hemiarthroplasty, Ender nail

Bu çalışmamızda Ender çivisi ile tedavi edilen hastaların daha düşük mortalitesi olduğunu saptadık.

Anahtar Kelimeler: İleri yaş hasta, 90 yaş üstü, proksimal femur çivisi, parsiyel protez, Ender çivisi

Introduction

Hip fracture is a particularly common injury in older individuals, and a past study has reported that the risk of hip fractures is 15-fold greater in individuals aged >90 years when compared with the corresponding risk in individuals aged <65 years (1). The risk of intertrochanteric hip fractures is considered to increase with an increase in the age owing to osteoporosis; therefore, such fractures can form a significant cause of morbidity and mortality in patients of advanced age, and they are known to affect the function and life of patients aged >90 years (2). The treatment of intertrochanteric fractures is extremely important, particularly in elderly patients, and early rehabilitation should be targeted to facilitate better improvement in the general condition of the patients.

Various treatment methods have been described in the literature for intertrochanteric hip fractures in elderly patients. For instance, proximal femoral nailing (PFN) and dynamic hip screws are frequently preferred for osteosynthesis. However, hemiarthroplasty is preferred to prevent non-union complications and to achieve early mobilisation, particularly in elderly (1,2).

However, the most appropriate treatment of intertrochanteric fractures in elderly patients remains unclear. The present study aimed to compare patient mortality and clinical outcomes among the factors of Ender nailing, PFN and hemiarthroplasty in patients with intertrochanteric fractures and of age >90 years.

Methods

The study design was approved by the Institutional Review Board of İstanbul University Faculty of Medicine (date: 27.07.2020, decision no: 124567). We retrospectively reviewed the medical records of all patients who were treated for intertrochanteric femur fracture during 1997-2016. Overall, 935 patients with intertrochanteric femur fracture were retrospectively investigated in this study. The medical histories and radiographic images of these patients were assessed using the data obtained from their respective medical registration files. The procedures were explained in detail to the patients, and written informed consent was obtained from them. The Social Security Administration Death Master File (Social Security Death index) was used to determine death and the date of death of the deceased patients.

In this study, the patient inclusion criteria were diagnosis with intertrochanteric femur fracture, age >90 years and past treatment with PFN, Ender nailing or hemiarthroplasty. The patient exclusion criteria were as follows: (i) diagnosis with reverse intertrochanteric femur fracture, treatment with dynamic hip screw, pathological fracture, high-energy hip fractures or hip fractures as a result of direct blunt trauma and femoral neck fractures.

According to the treatment approach employed, the patients were divided into Ender nailing, PFN and hemiarthroplasty groups. All patients were capable of ambulation before the fracture. We evaluated the preoperative American Society of Anaesthesiologists (ASA) score, the length of postoperative hospital stay duration, postoperative survival, complications and postoperative mobilisation by reviewing the hospital records and interviewing the patients and their relatives. The data obtained were compared among the treatment groups.

Statistical Analysis

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 software for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistical methods were used to evaluate study data. Normality of distribution was tested using the Shapiro-Wilk test. The data were compared by One-Way ANOVA, with the statistical significance set at $p<0.05$. For comparisons among the three groups, Tukey's range test was used among the post-hoc tests.

Results

Our study included 78 patients; of them, 16 were included in the Ender nailing group, 32 in the PFN group and 30 in the hemiarthroplasty group (Figures 1-3). The mean patient age was 93.3 years (age range: 90-104 years) and their mean ASA score was 3.1 (range: 2-4). At least one comorbidity was detected in all patients. Among the patients, 62 had hypertension, 28 had chronic heart diseases and 23 had dementia or Alzheimer's disease (Table 1).

The mean survival durations after surgery were 30.5 months (range: 1-89 months) in the Ender nailing group, 27.2 months (range: 0.4-75.7 months) in the PFN group and 21.7 months (range: 0.6-84.9 months) in the hemiarthroplasty group. Of the 78 patients, 60 (76.9%) eventually died, while 18 (23.1%) survived. The overall death rates in the respective groups were 62.5% (n=10), 62.5% (n=20) and 100% (n=30) in the Ender, PFN and hemiarthroplasty groups, respectively.

The death rates at 1-month were 12.5% (n=2), 9.4% (n=3) and 16.7% (n=5) in the Ender nailing, PFN and hemiarthroplasty groups, respectively. No difference was noted in the 1-month survival rate among the groups (p=0.67). The death rates at 1-year were 25% (n=4) in the Ender nailing group, 18.7% (n=6) in the PFN group and 33.3% (n=10) in the hemiarthroplasty group. No difference was noted in the 1-year survival rate among the groups (p=0.40). The 5-year death rates were 61.3% (n=8) in the Ender nailing group, 75.5% (n=20) in the PFN group and 86.7% (n=26) in the hemiarthroplasty group. In addition, the 5-year

survival rates were 38.7% in the Ender nailing group, 24.5% in the PFN group and 13.3% in the hemiarthroplasty group. The 5-year survival rate was significantly different among the groups (p=0.007; Figure 4).

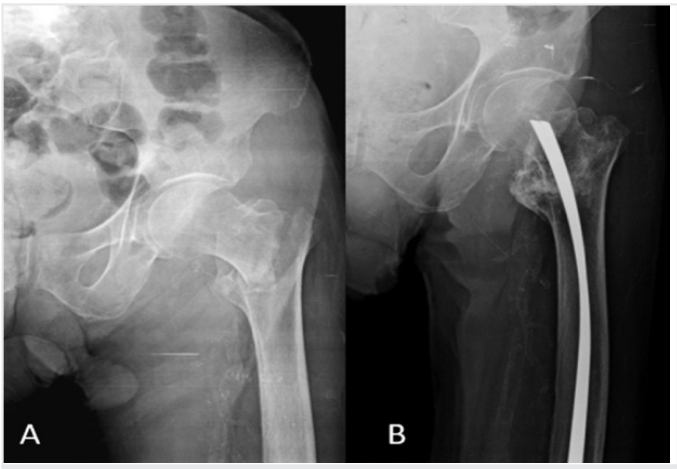

Figure 1. A 96-year-old woman with an intertrochanteric fracture being treated with Ender nailing

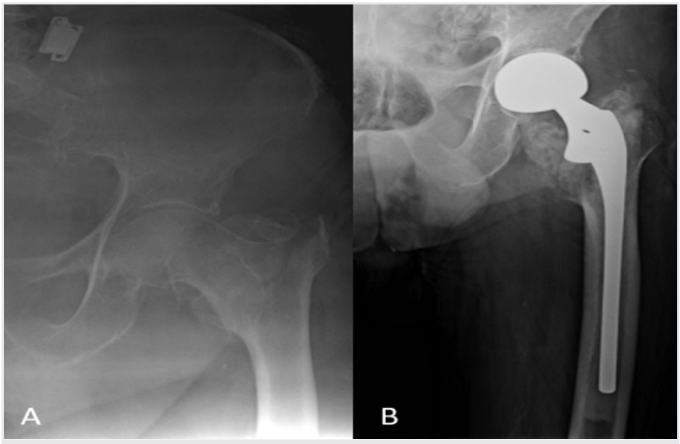

Figure 2. A 91-year-old woman with an intertrochanteric fracture being treated with proximal femoral nailing

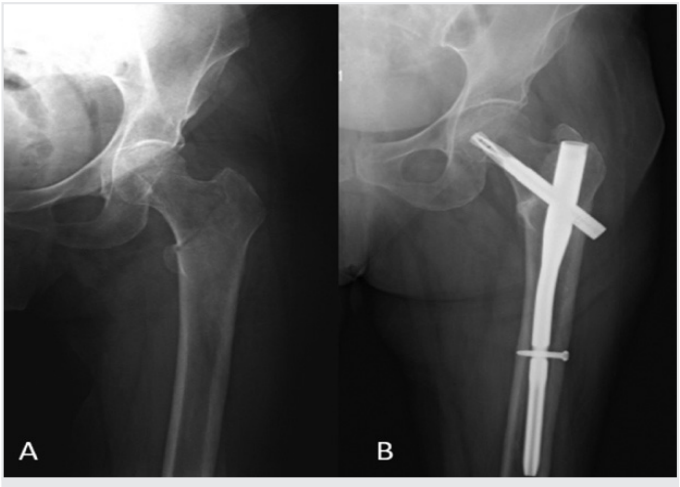

Figure 3. A 93-year-old man with an intertrochanteric fracture being treated with hemiarthroplasty

The lengths of hospital stay were 8.2 days (range: 3-18 days) in the Ender nailing group, 9.4 days (range: 2-73 days) in the PFN group and 7.6 days (range: 3-22 days) in the hemiarthroplasty group. No difference was noted in the length of hospital stay among the groups (p=0.78).

Patient mobilisation was attempted after a mean of 36 days (range: 3-150 days) in the Ender nailing group, 4.3 days (range: 2-10 days) in the PFN group and 4.8 days (range: 2-12 days) in the hemiarthroplasty group. Patient mobilisation could not be performed in 37.5% (n=6) of

Table 1. The distribution of the American Society Anaesthesiologists scores and comorbidities in the study patients

	Ender	Hemiarthroplasty	PFN	Overall n (%)
ASA Scores				
ASA 2	6	7	7	25
ASA 3	5	13	12	38.4
ASA 4	5	10	13	35.8
Comorbidities				
Hypertension	14	22	26	62
Chronic heart disease	4	12	12	28
Dementia or alzheimer	4	9	10	23
Cancer	3	2	4	9
Diabetes mellitus	4	1	4	9
Parkinson disease	2	1	2	5
Hypothyroidism	2	2	1	5
Epilepsy	1	1	1	3
Chronic kidney disease	0	3	2	5
Asthma	1	0	3	4

ASA: American Society Anaesthesiologists, PFN: Proximal femoral nailing

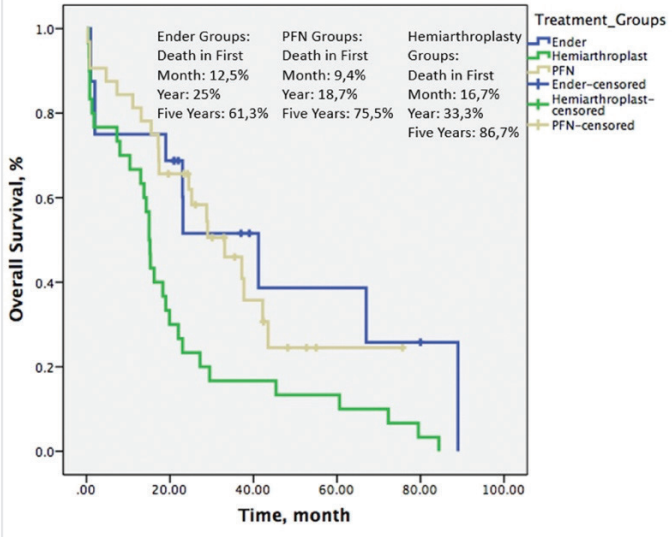

Figure 4. Comparison of the survival rate among the Ender nailing, proximal femoral nailing and hemiarthroplasty groups.

the patients in the Ender nailing group, 15.6% (n=5) of the patients in the PFN group and 16.6% (n=5) of the patients in the hemiarthroplasty group. Although no significant difference was noted in patient mobilisation between the PFN and hemiarthroplasty groups (p=0.99), significant differences were identified between the Ender nailing group and both the PFN (p<0.001) and hemiarthroplasty (p<0.001) groups (Table 2).

In the Ender nailing group, 6, 4 and 5 patients had an ASA score of 2, 3 and 4, respectively. In the PFN group, 7, 12 and 14 patients had an ASA score of 2, 3 and 4, respectively. In the hemiarthroplasty group, 7, 13 and 10 patients had an ASA score of 2, 3 and 4, respectively (Table 1). However, no differences were noted in the ASA scores among the groups (p=0.40).

In the Ender nailing group, implant failure was detected in 2 patients and an extra Ender nail was inserted in 1 patient owing to mechanical insufficiency. PFN revision was performed in 1 patient with implant failure on day 17. In another patient, removal of the implant led to implant failure, requiring conservative treatment. In the PFN group, implant failure was detected in 1 patient, but no surgical intervention could be performed because the patient's general condition had deteriorated. In the hemiarthroplasty group, no complication arose that required revision.

Discussion

The global human population is ageing; accordingly, it is assumed that orthopaedic surgeons would encounter increasing number of elderly patients with hip fractures in the future. In parallel, the number of extremely elderly patients with intertrochanteric fractures will increase in the future. The main characteristic of this patient group is the presence of comorbidities that significantly increases morbidity and mortality (3,4). However, to prevent morbidities, such as from pulmonary embolism, infection and decubitus ulcers, patients with intertrochanteric hip fractures should be mobilised with surgery as soon as possible.

Intertrochanteric fractures may cause death, unless they are treated surgically (5). Therefore, intertrochanteric fractures are preferably treated via surgical interventions if the surgical risks are not very high for the patient. Diverse operative devices have been developed for the treatment of intertrochanteric fractures; however, there is no device available without any ensuing complications (6). In the present study, we considered the techniques of Ender nailing, PFN and hemiarthroplasty as treatment interventions.

Table 2. The clinical data and mortality rates of the all groups.

	Ender	Hemiarthroplasty	PFN
Hospital stay (day)	8.2 (3-13)	7.6 (3-22)	9.4 (2-73)
Dependent/mobile	6/10	5/25	5/27
Mobility time (day)	36 (3-150)	4.8 (2-12)	4.3 (2-10)
Follow-up (months)	30.5 (12-89)	21.7 (12-84.9)	27.2 (12-75)
Death/living	10/6	30/30	20/12
Mortality			
In first month	2 (12.5%)	5 (16.7%)	3 (9.4%)
In first year	4 (25%)	10 (33.3%)	6 (18.7%)
In five years	8 (61.3%)	26 (86.7%)	20 (75.5%)

PFN: Proximal femoral nailing

Ender nailing has been frequently used previously as an intramedullary nailing option. Presently, orthopaedic surgeons prefer PFN to intramedullary fixation for the treatment of intertrochanteric fractures owing to the lack of rotational stability with the Ender nailing technique (7-9). Nonetheless, Ender nailing is a minimally invasive intervention associated with relatively less surgical stress and only a few complications (10).

Hemiarthroplasty is preferred because the reoperation risk is lower with this approach than with osteosynthesis options and also because the application of this approach enables early mobilisation. However, the disadvantages include a relatively long duration of surgery and high blood loss. The opinion related to hemiarthroplasty for treating intertrochanteric fractures has evolved over time. Although good outcomes have been reported by some authors, advanced age and serious osteoporosis has been reported to restrict the indications for hemiarthroplasty with the emergence of the intramedullary fixation technique (11,12). Kesmezacar et al. (13) reported that hemiarthroplasty with shorter survival and greater mortality does not offer any advantage over internal fixation, which is the only benefit of earlier weight bearing. A past prospective, randomised study comparing hemiarthroplasty with intramedullary fixation devices reported superior clinical outcomes with PFN, although the functional outcomes were similar across the methods (14).

Mortality generally occurs within the first 6 months of getting intertrochanteric fractures (15). Past studies have demonstrated that advanced age alone can increase the risk of mortality (16,17). In addition, comorbidities have significant effect on the chances of mortality. Aharanoff et al. (18) reported that the postoperative mortality rates were higher among patients with preoperative ASA scores of 3-4 than among those with ASA scores of 1-2.

In the present study, assessment of the mortality rates based on the surgical approaches employed showed no differences in the 1-month and 1-year mortality rates among the groups. However, the 5-year survival rate was significantly higher with Ender nailing than with the other approaches. Kesmezacar et al. (13) reported that the frequency of death was higher and the mean postoperative survival time was shorter with hemiarthroplasty than with osteosynthesis; however, these differences were not statistically significant. Although some studies found that arthroplasty for hip fractures was associated with a high mortality rate (19,20), others have reported that arthroplasty does not increase the mortality rate (21).

In our study, no significant differences were noted in the complications and hospital stay durations among the groups. With regard to mobilisation, we found that patients who underwent Ender nailing experienced late mobilisation. Moreover, the time until mobilisation had no effect on mortality and 20% of the patients did not even achieve mobilisation. The Ender nailing group included 6 bed-dependent patients, the hemiarthroplasty group included 5 and the PFN group included 5. Holt et al. (22) reported that 36% of the patients (from 50

patients) with hip fractures aged >95 years were bed-dependent after surgery; this value is higher than that recorded in the present study (22).

We noted that the preferred treatment option had no significant effect on the length of hospital stay. Holt et al. (22) found that the mean length of hospital stay was 12 days for 50 patients aged >95 years.

The present study has some limitations. First, this study had a retrospective design and relatively small number of cases. Second, we did not evaluate the functional status postoperatively for compare among the groups. Third, ın this study, we did not evaluate the stability of fracture pattern and not classy them. Lastly, other factors affecting mortality, such as postoperative stay in intensive care unit or postoperative delirium were not investigated.

Conclusion

Although PFN is regarded as the gold standard for the treatment of intertrochanteric femur fractures, different treatment options can be considered based on the osteoporotic bone structure, presence of coexisting diseases and the possibility of early mobilisation in patients with advanced age. In this study, we found that patients treated with Ender nail showed a lower rate of mortality.

Ethics

Ethics Committee Approval: The study design was approved by the Institutional Review Board of İstanbul University Faculty of Medicine (date: 27.07.2020, decision no: 124567).

Informed Consent: The study retrospectively reviewed the medical records of all patients who were treated for intertrochanteric femur fracture during 1997-2016.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - S.S.; Concept - Ö.N.E.; Design - S.B.; Data Collection or Processing - S.B.; Analysis or Interpretation - S.S.; Literature Search - Ö.N.E.; Writing - S.B.

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

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Evaluation of the Relationship Between Initial Lymphocyte Count and Molecular Response to Imatinib Therapy in Chronic Myeloid Leukaemia Patients

Kronik Miyeloid Lösemi Hastalarında Tanı Anı Lenfosit Sayısı ve İmatinib Moleküler Yanıtının Değerlendirilmesi

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ABSTRACT

Introduction: Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm characterised by the overproduction of haematopoietic cells in the granulocytic series, involving translocation of chromosomes 9 and 22. The first tyrosine kinase inhibitor, imatinib, used in the treatment of CML, represents one of the most successful targeted therapies marking a new era in the treatment of CML. Many scoring systems such as the Hasford and Sokal systems have been developed to stratify CML patients into risk categories, and to predict patient outcome. We aimed to evaluate the relationship between blood lymphocyte count (BLC) at diagnosis and molecular response to imatinib therapy as a prognostic factor.

Methods: A total of 108 chronic phase CML patients diagnosed between January 2010 and January 2020 were evaluated. Patient characteristics, laboratory results, BLC and response to treatment were recorded.

Results: The median BLC was 4,665/mm^3 and patients were divided into two groups according to the median BLC as ≤4,665/mm^3 and >4,665/mm^3. The responses at 3, 6, 12 month and the final status of patients, namely achievement of major molecular response or not, did not differ between the two groups of patients.

Conclusion: The introduction of new therapeutic options in CML necessitates improvement in existing risk scoring systems. No direct relationship was found between the initial BLC and imatinib response in CML. However this is the first study exploring the role of BLC at diagnosis in CML patients receiving imatinib, and further studies that look into lymphocyte subgroups as well as bone marrow lymphocyte count at diagnosis might allow a more precise evaluation about the contribution of lymphocyte count to risk assessment in CML patients.

Keywords: Imatinib, lymphocyte, molecular response, optimal, warning, failure

ÖZ

Amaç: Kronik miyeloid lösemi (KML), 9 ve 22. kromozomların translokasyonu ve granülositik serideki olgun hücrelerin aşırı üretimi ile karakterize miyeloproliferatif bir neoplazmdır. İlk tirozin kinaz inhibitörü olan imatinib, KML tedavisinde yeni bir döneme işaret eden, en başarılı hedefe yönelik tedavilerden birini temsil eder. KML prognoz ve tedavi yanıtının belirlenmesi amacıyla Hasford veya Sokal gibi birçok skorlama sistemi ve risk faktörü geliştirilmiştir. Tanıda mutlak lenfosit sayısı (MLS) ile imatinib moleküler yanıt arasındaki ilişkiyi prognostik bir faktör olarak değerlendirmeyi amaçladık.

Yöntemler: Ocak 2010 ile Ocak 2020 arasında tanı konulan 108 kronik faz KML hastası incelendi. Hasta özellikleri, laboratuvar sonuçları, MLS ve tedaviye yanıt kaydedildi.

Bulgular: Medyan MLS 4.665/mm^3 idi ve hastalar medyan MLS'ye göre ≤4.665/mm^3 ve >4.665/mm^3 olmak üzere iki gruba ayrıldı. Üç, 6, 12. ay yanıtları ve majör moleküler yanıtı olan veya olmayan hastaların son durumları iki grup arasında farklılık göstermedi.

Sonuç: KML'ye yeni terapötik seçeneklerin dahil edilmesi, risk skorlama sistemlerinin iyileştirilmesini gerektirmektedir. Başlangıçtaki MLS ile KML'deki imatinib yanıtı arasında doğrudan bir ilişki bulunmamıştır. Ancak bu, imatinib alan KML hastalarında MLS'nin tanıdaki rolünü araştıran ilk çalışmadır. Ayrıca tanıdaki lenfosit alt gruplarının ve kemik iliği lenfosit sayısının araştırılması, KML hastalarında lenfosit sayısının risk değerlendirmesine katkısı hakkında daha kesin bir değerlendirmeyi mümkün kılabilir.

Anahtar Kelimeler: İmatinib, lenfosit, moleküler yanıt, optimal, uyarı, yetmezlik

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Introduction

Chronic myeloid leukaemia (CML), which is characterised by the overproduction of haematopoietic cells, is included in the group of chronic myeloproliferative neoplasms. Although the disease has three distinct clinical phases, namely, chronic phase, accelerated phase and blast phase, most CML patients are diagnosed in the chronic phase (1,2). CML is one of the first conditions linked to a specific chromosomal anomaly caused by a reciprocal translocation between chromosomes 9 and 22. The abnormal chromosome, designated as the Philadelphia (Ph) chromosome forms when a part of chromosome 9 and a part of chromosome 22 break and switch positions. The altered chromosome 22 is referred to as the Ph chromosome. The *breakpoint cluster region (BCR)-Abelson (ABL)* gene which forms on chromosome 22 (Ph chromosome), is the product of fusion of the *ABL* oncogene from chromosome 9q34 with the BCR on chromosome 22q11.2, i.e. t(9;22)(q34;q11.2), leading to the generation of a 210 kDa (p210) molecular weight protein. This oncoprotein exhibits increased tyrosine kinase activity which is responsible for the development of the leukemic phenotype in CML (2,3).

Tyrosine kinases play a vital role in diverse biological processes like cell growth, differentiation and apoptosis through mediating the signalling cascades (4). Imatinib, the first tyrosine kinase inhibitor (TKI) used in the treatment of CML, represents one of the most successful targeted therapies marking a new era in CML treatment (5). Despite the high rates of haematological, cytogenetic and molecular response obtained with imatinib, some CML patients using imatinib, require a switch to another TKI either due to an insufficient response or loss of response to treatment, or drug side effects. Evaluation of response in CML patients receiving TKI is based on the International scale (IS) which is expressed and reported as BCR-ABL 1% on a log scale standard approach and this evaluation is recommended to be performed at 3, 6, 12 months following treatment initiation, and every 3-6 months thereafter. (6)

Many scoring systems and risk factors have been employed to select the most appropriate therapeutic option to obtain a speedy and effective response for various diseases. Accordingly, we aimed to evaluate the association between the blood lymphocyte count (BLC) at diagnosis and molecular response to imatinib therapy.

Methods

In this study, 108 chronic phase CML patients, who were diagnosed and followed up at University of Health Sciences Turkey, İstanbul Training and Research Hospital Clinic of Hematology between January 2010 and January 2020, were analysed retrospectively. Patient characteristics including age, gender, white blood cell (WBC) count; BLC, blood neutrophil count, haemoglobin (Hb) level; platelet (PLT) count, presence of splenomegaly and/or hepatomegaly, and response to treatment were recorded from the files of the patients. The response was evaluated according to the European Leukaemia Net (ELN) 2020 recommendations (6). The BCR-ABL levels in peripheral blood were obtained using polymerase chain reaction based on the IS. The responses were grouped as optimal, warning, or failure at 3 months, 6 months and 12 months after the start of imatinib. In addition, instances of switching from imatinib to dasatinib or nilotinib were also noted. According to their final response status, patients were ultimately divided into two groups: patients with major molecular response and patients with no response. The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 988, date: 14.04.2017). Informed consent was obtained from all of our patients to participate in this study.

Statistical Analysis

SPSS 24 programme was used for statistical evaluation. Data was described as numbers and percentage or median and range, when appropriate. $\chi 2$ Fisher's Exact test was used for evaluating categorical values and Mann-Whitney U test for continuous values in patient groups. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

Results

The clinical data of 108 CML patients at diagnosis is summarised in Table 1. The median age of the patients was 45 (range: 17-80); with 49 (45.3%) female and 59 (54.7%) male. The median Hb value was 11.9 (range: 6.5-16.6), PLT count was 374,500x10^3/µL (range: 89,000-1,820,000), WBC was 54,925/mm^3 (range: 3,950-286,300), neutrophil count was 41,875/mm^3 (range: 1,430-264,400), BLC was 4,665/mm^3 (range: 1,229-14,550). Fifty-four (50%) of the patients had splenomegaly and 33 (30.6%) had hepatomegaly (Table 1).

The median follow-up period was 60.2 (range: 6.1-150.2) months. At 3 months, 81 (75%) patients had optimal response, 10 (9.3%) patients had warning response and 17 (15.7%) patients had treatment failure.

Table 1. Patient characteristics

Characteristics	**n=108**
Gender, n (%)	
Female	49 (45.4%)
Male	59 (54.6%)
Age, years, median (range)	45 (17-80)
WBC (/mm^3), median (range)	54,925 (3,950-286,300)
Neutrophil (/mm^3), median (range)	41,875 (1,430-264,400)
Lymphocyte (/mm^3), median (range)	4,665 (1229-14,550)
Hb (g/dL), median (range)	11.9 (6.5-16.6)
Plt (×10^3/mm^3), median (range)	374,500 (89,000-1,820,000)
Hepatomegaly, n (%)	
Yes	33 (30.6%)
No	75 (69.4%)
Splenomegaly, n (%)	
Yes	54 (50%)
No	54 (50%)
Follow-up duration, months, median (range)	60.2 (6.1-150.2)
Switch of imatinib, n (%)	37 (34.3%)
TKI switching to dasatinib, n (%)	17 (15.7%)
TKI switching to nilotinib, n (%)	20 (18.5%)
Last response status: MMR, n (%)	97 (89.8%)
No response, n (%)	10 (9.3%)

WBC: White blood cell, Hb: haemoglobin, Plt: platelet, TKI: tyrosine kinase inhibitor, MMR: major molecular response

At 6 months 82 (75.9%) patients had optimal response, 8 (7.4%) patients had warning response and 18 (16.6%) patients had treatment failure. At 12 months 80 (74%) patients had optimal response, 1 (0.9%) patient had warning response and 26 (25.9%) patients had treatment failure. As final response, major molecular response (MMR) was detected in 97 (89.8%) patients and 10 (9.3%) patients had no response (Table 2).

Imatinib was switched to a second line TKI in 37 (34.3%) patients. Twenty (18.5%) patients were switched to nilotinib because of grade 3 skin toxicity in three patients, grade 4 myalgia in one patient and response failure in 16 patients. Seventeen patients were switched to dasatinib due to grade 4 skin toxicity in five patients, grade 3-4 nausea and vomiting in one patient and response failure in 11 patients (Table 1).

The median BLC was 4,665/mm^3 (range: 1,229-14,550) and the patients were divided into two groups according to the median BLC as ≤4,665/mm^3 and >4,665/mm^3. Both groups included 54 (50%) patients each. The responses at 3 months, 6 months, 12 months did not differ between the groups with lymphocyte count ≤4,665/mm^3 and >4,665/mm^3 (p>0.05) (Table 3). Regarding the final status of the patients, whether a MMR was achieved or not, the results in the two groups were comparable (p>0.05) (Table 3).

Discussion

Risk stratification and personalised treatment have increasingly become the mainstay in the management of various diseases. Although the approval of TKIs targeting BCR-ABL has provided a personalised therapeutic option for CML, especially in the chronic phase, risk identification is still essential for a minority of CML patients who show insufficient response to treatment. Three classical risk scoring systems have been described to predict the course of CML: the Sokal score, the Hasford score and European Treatment and Outcome Study (EUTOS) metrics (7-9). While the Hasford and the Sokal risk scoring systems were developed prior to the use of TKIs, EUTOS risk scoring system was evolved based on the use of imatinib, but not the 2nd generation TKIs. With the introduction of new therapeutic options in CML, the risk scoring systems had to be improved. Actually, the ELN recommended using the new EUTOS Long Term Survival score which is calculated based on patient age, spleen size, peripheral blood blast and PLT count. The major issues in this scoring system include problems in the standardisation of spleen size and the fact that it consists of only four parameters. However, a more objective risk assignment becomes important in terms of preference of either a first generation TKI imatinib or a second generation TKI as first line therapy, especially in countries such as Turkey where imatinib is generally chosen as first line TKI therapy for CML patients. From this viewpoint, we evaluated BLC at diagnosis in patients receiving imatinib and did not find any relationship between the BLC and molecular response to imatinib.

The association between the lymphocyte count and imatinib response was first evaluated by Mustjoki et al. (10) in 37 CML patients. The lymphocyte count in the bone marrow at 3 months and 6 months of imatinib treatment increased significantly in patients responding to therapy. Also early bone marrow lymphocytosis during imatinib therapy was found to be a predictor of optimal response in these patients. However such an outcome could not be verified with BLC since it was observed that there was little or no correlation between bone marrow lymphocyte counts and BLC. This inconsistency between the BLC and bone marrow lymphocyte count could thus explain the results (no relationship of BLC to molecular response in CML) in our study. As another point in contrast, we investigated the BLC at diagnosis, but the effects of lymphocytosis occurring post-TKI treatment seems more prominent in the earlier study.

In our study, we did not investigate the status of lymphocyte subgroups, which might have been more informative in elucidating the role of BLC

Table 2. Response of patients to imatinib therapy

	n=108
3 months optimal, n (%)	81 (75%)
3 months warning, n (%)	10 (9.3%)
3 months failure, n (%)	17 (15.7%)
6 months optimal, n (%)	82 (75.9%)
6 months warning, n (%)	8 (7.4%)
6 months failure, n (%)	18 (16.6%)
12 months optimal, n (%)	80 (74%)
12 months warning, n (%)	1 (0.9%)
12 months failure, n (%)	26 (25.9%)

Table 3. Comparison of response to the imatinib therapy in patients with blood lymphocyte count ≤4,665/mm^3 and >4,665/mm^3

	≤4,665/mm^3 n=54	>4,665/mm^3 n=54	p
3 months optimal, n (%)	41 (38%)	40 (37%)	
3 months warning, n (%)	2 (1.9%)	8 (7.4%)	0.079
3 months failure, n (%)	10 (9.3%)	9 (90%)	
6 months optimal, n (%)	41 (38%)	41 (37.9%)	
6 months warning, n (%)	2 (1.9%)	6 (5.5%)	0.236
6 months failure, n (%)	11 (10.2%)	7 (6.5%)	
12 months optimal, n (%)	40 (37.4%)	40 (37.4%)	
12 months warning, n (%)	1 (0.9%)	0 (0%)	0.564
12 months failure, n (%)	12 (11.2%)	14 (13.1%)	

in prognosis of CML. In CML patients, especially those receiving dasatinib, proliferation of CD8+, natural killer (NK) and NK/T-like cells has been well established and associated with long lasting treatment response (11-13). In addition, before the TKI era, Kreutzman et al. (13) showed that CML patients treated with interferon (IFN)-alpha had increased numbers of NK-cells and clonal γδ (+) T-cells when they had a long lasting response. de Castro et al. (14) showed that there was an increase in the percentage of CD8/FasL+, DR/CD3+, DQ/CD3+, CD34/Fas+, DR/CD56+, CD56/FasL+ cells and of IFN-gamma- and IL-2-producing lymphocytes and an increase in NK cytotoxicity in CML patients receiving IFN-alpha, who achieved complete haematological remission.

Conclusion

No direct relationship was found between the initial BLC and molecular response to imatinib therapy in CML patients. However this is the first study exploring the role of BLC at diagnosis in CML patients receiving imatinib. The limitations of this study include the retrospective nature of the study and the relatively low number of patients. Additionally, investigation of lymphocyte subgroups and bone marrow lymphocyte count at diagnosis (not undertaken in this study) could allow a more precise evaluation about the contribution of lymphocyte count in the risk assessment in CML patients treated with imatinib.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Turkey, İstanbul Training and Research Hospital Ethics Committee (decision no: 988, date: 14.04.2017).

Informed Consent: Informed consent was obtained from all of our patients to participate in this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices- İ.S., V.C.Ç.; Concept - M.H.D., İ.S.; Design - M.H.D., İ.S.; Data Collection or Processing - İ.S., V.C.Ç.; Analysis or Interpretation - İ.S.; Literature Search- İ.S.; Writing - İ.S., M.H.D., E.S.

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A New Biochemical Marker for the Differential Diagnosis of Epileptic Seizure Types: Ischaemia-modified Albumin

Epileptik Nöbet Tiplerinin Ayırıcı Tanısında Yeni Biyokimyasal Belirteç: İskemi Modifiye Albümin

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ABSTRACT

Introduction: This study aimed to evaluate the changes in ischaemia-modified albumin (IMA) levels in different types of hypoxia-associated epileptic seizures.

Methods: A total of 80 patients admitted to the Neurology Outpatient Clinic in Ankara Numune Training and Research Hospital and 103 controls were included in the study. The patients were divided into two groups in terms of the seizure type, including seizures with partial and secondary generalisation and primary generalised seizures. Additionally, patients were classified in terms of the duration between the initial diagnosis and admission. The levels of IMA, albumin and uric acid were analysed by spectrophotometry and comparisons between the groups were performed.

Results: IMA levels and IMA/Albumin index values were higher in the patient group than in the control group ($p<0.05$; $p<0.01$, respectively). Regarding the evaluation of the seizure types, IMA and IMA/Albumin index levels were mainly higher in patients with primary generalised seizures ($p<0.05$). Moreover, these parameters were significantly increased in proportion to the duration of diagnosis.

Conclusion: IMA and IMA/Albumin index may enable clinicians to differentiate the types of epilepsy.

Keywords: Albumin, epileptic seizures, uric acid

ÖZ

Amaç: Bu çalışmanın amacı, hipoksi ile ilişkili farklı epileptik nöbet tiplerinde iskemi-modifiye albümin (İMA) seviyelerindeki değişiklikleri araştırmaktır.

Yöntemler: Çalışmaya Ankara Numune Eğitim ve Araştırma Hastanesi Nöroloji Polikliniği'ne başvuran toplam 103 kişi kontrol, 80 hasta dahil edildi. Hastalar parsiyel ve sekonder jeneralize nöbet ve primer jeneralize nöbet olmak üzere iki gruba ayrıldı. Ayrıca, hastalar ilk tanı ve başvuru arasındaki süre açısından sınıflandırıldı. İMA, albümin, ürik asit düzeyleri spektrofotometrik olarak analiz edildi ve gruplar arasında karşılaştırmalar yapıldı.

Bulgular: Hasta grubunda İMA düzeyleri ve İMA/Albümin indeks değerleri kontrol grubundan daha yüksekti (sırasıyla, $p<0,05$; $p<0,01$). Nöbet tiplerinin değerlendirildiğinde primer jeneralize nöbeti olan hastalarda İMA ve İMA/albümin düzeyleri anlamlı olarak yüksek bulundu ($p<0,05$). Ayrıca, bu parametreler tanı alındığı dönemde önemli ölçüde artmıştır.

Sonuç: Sonuç olarak, İMA ve İMA/Albümin indeksi klinisyenlerin epilepsi türlerini ayırt etmelerine yardımcı olabilir.

Anahtar Kelimeler: Albümin, epileptik nöbet, ürik asit

Introduction

Epilepsy is a chronic neurological disease that requires long-term treatment. Numerous studies have focused on the role of oxidative stress in the pathogenesis of atherosclerosis and some psychiatric and neurodegenerative disorders (1).

In comparison to antioxidant levels, an increase in the formation of free radicals is regarded as an important contributing factor to the pathogenesis of various diseases caused by oxidative injury (2,3). Free radicals can play a role in the exacerbation of some types of seizure. The most investigated oxidative damage markers have been lipid peroxidation end products, protein carbonyl groups and nitric oxide. Animal studies using seizure models have provided evidence of increased oxidative stress (elevated lipid peroxidation and protein carbonylation) after seizures (4).

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Oxidative stress due to Reactive Oxygen Substance formation plays a role in ischaemia- and reperfusion-induced neuronal damage. In addition, plasma antioxidant activity can be an essential component in protecting against neuronal impairments induced by stroke-related oxidative stress (5). Ischaemia-modified albumin (IMA) is considered as a comparatively new biomarker for ischaemia as it has been extensively investigated in various types of ischaemic disorders (6). This biomarker is a variant of the metabolic protein produced in acute ischaemic situations as a result of the reduction in the albumin binding capacity for transition metals such as cobalt, nickel and copper (7-9). While ischaemia and reperfusion occur, the modification that changes the binding capacity of albumin to transition metals can also occur as a result of oxidative stress (10,11). Secondary physiological changes (including hypotension, hypoxia, hypoglycaemia and hyperthermia) that occur as the length of epileptic seizures increases contribute to injury both in the brain and other organs (12).

The recent finding that ischaemia causes changes in serum albumin structure has facilitated the development of a new marker for ischaemia. The last amino acid terminal in the albumin structure has the ability to bind heavy metals such as copper, nickel and cobalt. Factors such as hypoxia, acidosis and free radical damage occurring during ischaemia lead to the reduced binding of these metals to the N-terminus of albumin. This albumin with an altered structure is described as IMA. For the biochemical analysis of various diseases such as ischaemic heart disease, deep vein thrombosis, pulmonary embolism, mesenteric ischaemia and cerebrovascular events, the aforementioned protein level was investigated and its level was found to be above the normal level (9,13). Anaerobic metabolism resulting from decreased blood supply in the hypoxic ischaemic region leads to the formation of free oxygen radicals through the reduction of free metals and the catalytic effect of the superoxide dismutase enzyme, which results in increased IMA levels in the blood.

Animal studies have shown that the use of antioxidants in addition to anticonvulsants led to both a decrease in oxidative stress and frequency of seizures. The complex mechanism of epileptogenesis still remains unclear. However, factors causing neuronal death, which is a key element, may play an important role in the disease progression. Indeed, oxidative stress due to free radicals has been shown to cause mitochondrial dysfunction and cell death. In addition, this study aimed to evaluate the oxidative stress in patients with epilepsy who are not using any antiepileptic drug (AED) and the effects of AEDs in those taking a monodrug or multidrug therapy (14).

This study aimed to evaluate the changes in plasma IMA levels in two types of epileptic episodes in an age- and sex-matched control group.

Methods

A total of 80 patients admitted to Ankara Numune Training and Research Hospital Clinic of Neurology and 103 controls were included in the study. The patients were classified into two groups in terms of the seizure type, including seizures with partial and secondary generalisation and primary generalised seizures. Furthermore, the time interval between the initial diagnosis and admission time was categorised.

The controls consisted of 47 (45.6%) males (47.6±8.3 years) and 56 (54.4%) females (42.7±7.6 years) (Table 1) while the epilepsy patients consisting of 38 males (47.5%) (49.3±9.4) and 42 females (52.5%) (47.2±8.3 years) (Table 1). While 10% of the patients were untreated, 52.5% of them were receiving a monotherapy (24.6% carbamazepine, 42.6% phenytoin, 14.8% valproate, 18% others) and 37.5% were receiving a polytherapy (Table 2). The demographics and epilepsy profiles of the participants are shown in Table 2. IMA, albumin and uric acid levels were analysed using spectrophotometric methods. Ankara Numune Training and Research Hospital Ethics Committee with protocol number: 17-1439 (date: 05.07.2017). Informed volunteer consent was obtained from each patient.

Measurement of Serum Ischaemia-modified Albumin Levels

Serum IMA levels were measured using the colorimetric method described by Bar-Or et al. (8). In this method, 200 µL serum was added into 50 µL cobalt chloride solution 0.1% (w/v) and stirred gently for 10 minutes for sufficient albumin-cobalt binding reaction to occur. Then, 50 µL of dithiothreitol (1.5 mg/mL H_2O) was added as a colouring agent. After 2 minutes of incubation, 1.0 mL of 0.9% NaCl was added to terminate the reaction. The colour change was then measured at 470 nm using a spectrophotometer (Hitachi U-2900 Spectrophotometer). Measurement results were reported as Absorbance Unit. Serum albumin was detected with the Bromcresol-Green method in a calibrated and well controlled autoanalyser. IMA/Albumin index and albumin-adjusted IMA were calculated using the following equations:

IMA/Albumin index = IMA/Albumin

Albumin-adjusted IMA = (Albumin/Median of Albumin) × IMA

Statistical Analysis

Statistical analysis was conducted using SPSS version 20 and MS Excel. The continuous variables are presented as mean ± standard deviation, while categorical data are presented as percentages. The differences between two continuous variables was analysed by Student's Unpaired t-test, while ANOVA test was preferred for the detection of the differences between different groups. The relationship between the variables were assessed by Pearson's correlation coefficient. A p value of <0.05 was considered statistically significant.

Results

Eighty patients with epilepsy and 103 healthy controls, who were matched in terms of age and sex, were included in this study. Serum IMA, uric acid and albumin values are shown in Tables 1 and 2. Compared to the control group, a highly significant increase in the serum IMA levels ($p<0.05$) of patients with acute epilepsy was detected, while there was a significant decrease in endogenous antioxidants such as uric acid ($p<0.05$) and albumin ($p<0.05$) in epileptic patients. Furthermore, a significant negative correlation between serum IMA and serum uric acid ($r=-0.237$, $p<0.05$) was detected. IMA levels were negatively correlated but not statistically significant between treatment groups and disease duration ($r=-0.40$, $p>0.05$; $r=-0.168$, $p>0.05$, respectively).

IMA levels, IMA/Albumin index and Albumin-adjusted IMA values were higher in the patient group compared to the control group ($p<0.05$; $p<0.01$; $p<0.05$, respectively) (Table 1). In terms of seizure types, IMA, IMA/Albumin index and Albumin-adjusted IMA levels were significantly higher in patients with primary generalised seizures ($p<0.05$) (Table 2). In addition, IMA levels were significantly increased in proportion to the duration of the diagnosis. It was detected that the median duration of disease in the patient group was 7 (1-13) years. There was no difference between genders in terms of the disease duration.

Discussion

Anaerobic metabolism resulting from decreased blood supply in the hypoxic ischaemic region leads to the formation of free oxygen radicals by the reduction of free metals and catalytic effect of the superoxide dismutase enzyme, which results in increased blood IMA levels.

Many investigations have demonstrated that the formation of free radicals, which lead to oxidative stress, plays a significant role in the pathogenesis of epileptic diseases. Various factors make brain tissue susceptible to the detrimental impact of free radicals. Cerebral cell membrane lipids are particularly abundant in polyunsaturated fatty acid side chains, which are extremely sensitive to free radical damage (15,16). IMA, formerly investigated in patients with acute chest pain, is a non-specific tissue ischaemia marker that has been shown to increase spontaneously in epileptic patients (13).

Table 1. Serum IMA, uric acid and albumin values in the patient and control groups

	Patients (n=80)	Control (n=103)	p
Male (N, %)	38 (47.5)	47 (45.6)	0.051
IMA (ABSU)	0.668±0.135	0.597±0.183	0.027
IMA/albumin	0.162±0.038	0.128±0.045	0.005
Albumin-adjusted IMA	0.654±0.137	0.585±0.144	0.025
Albumin (g/dL)	4.11±0.43	4.65±0.37	0.023
Uric acid (mg/dL)	4.19±0.83	4.77±1.06	0.042

IMA: Ischaemia-modified albumin, ABSU: Absorbance Unit

Particularly, in patients with hypoalbuminemia, IMA/Albumin index and albumin-adjusted IMA levels are more valuable than IMA levels. Therefore, we included these parameters in our study. The albumin levels were decreased in the patient group compared to the control group.

According to the results of most previous studies involving patients receiving treatment, it was not shown that oxidative stress was due to epilepsy or AEDs. On the other hand, some studies comparing treated and untreated patients showed no difference (17-19). According to the results of these studies as well as those of our study, the role of AEDs in increasing oxidative stress is not significant. These outcomes have therapeutic consequences.

Although this study contributes to the current literature data, a more thorough investigation is required to understand the mechanism of epilepsy in order to offer newer methods of disease modification. Furthermore, it was concluded in this study that elevated IMA levels with increased severity and duration of epilepsy have the potential to help clinicians in determining the type of epilepsy.

As a limitation, this study was performed among cases with no markers of hypoxia following seizure (no acidosis, oxygen saturation >90%). In addition, acute phase proteins were not measured.

Conclusion

Oxidative markers were found to be increased in the epileptic patients in this study. The finding that the AEDs did not affect the oxidative markers indicates that the oxidative stress was caused by seizures. However, the underlying mechanism of epileptogenesis is still unknown. Although new AEDs have been identified, most of them are refractory to therapy. Therefore, it is necessary to have new treatment modalities, including AEDs with a potential supplementary antioxidant therapy. In addition to the inclusion of new results in the current literature, more detailed studies are required to analyse the mechanism of epilepsy.

We can conclude that IMA is a simple, non-invasive approach to evaluate the oxidative stress in clinical practice, although without other inflammatory markers, IMA alone may not inform physicians about the

Table 2. Serum IMA, uric acid and albumin values in the patient groups

	Primary generalised seizure (n=42)	Partial and secondary generalised seizures (n=30)	p
IMA (ABSU)	0.694±0.107	0.623±0.093	0.041
IMA/albumin	0.172±0.054	0.151±0.038	0.029
Albumin-adjusted IMA	0.678±0.112	0.612±0.108	0.038
Albumin (g/dL)	4.09±0.33	4.14±0.42	0.414
Uric acid (mg/dL)	4.11±0.76	4.43±0.91	0.047
Duration of diagnoses, years [Median (min-max)]	13 (2-48)	10 (2-50)	0.822
Therapy			
None (n, %)	1 (2.3)	2 (7.1)	0.020
Received monotherapy (n, %)	7 (16.3)	12 (42.9)	-
Received polytherapy (n, %)	35 (81.4)	14 (50)	-

IMA: Ischaemia-modified albumin, ABSU: Absorbance Unit, min: minimum, max: maximum

inflammatory state. However, IMA, IMA/Albumin index and Albumin-adjusted IMA may help clinicians to differentiate the types of epilepsies.

Ethics

Ethics Committee Approval: The study was approved by the Ankara Numune Training and Research Hospital Ethics Committee with protocol number: 17-1439 (date: 05.07.2017).

Informed Consent: Informed volunteer consent was obtained from each patient.

Peer-review: Externally peer-reviewed.

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Successful Management of Uterovaginal Prolapse During the Second Trimester of Pregnancy Using Vaginal Pessary: A Case Report

Gebeliğin İkinci Döneminde Gözlenen Uterus Prolapsusun Pesser Halkası ile Başarılı Yönetimi: Olgu Sunumu

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ABSTRACT

Pelvic organ prolapse rarely occurs during pregnancy. Its aetiology is not well understood and it can complicate pregnancy. A 36-year-old multigravida patient developed uterovaginal prolapse in the second trimester of her pregnancy and was managed successfully with the pessaries ring. There are conservative approaches and surgical options in the treatment of prolapse. Pessary ring is a safe treatment option and should be considered before surgical options in the treatment of pelvic organ prolapse.

Keywords: Pelvic organ prolapse, pregnancy, pessaries, pelvic floor

ÖZ

Gebelik sırasında uterin prolapsus nadiren gözükür. Etiyolojisi tam olarak bilinmemektedir. Gebelikte gözlenen prolapsus gebeliği komplike hale getirebilir. Otuz altı yaşında multipar hastanın, gebeliğinin 2. trimesterında total uterin prolapsus gelişmiş olup pesser halkası ile sorunsuz tedavi edilmiştir. Prolapsus tedavisinde konservatif yaklaşımlar ve cerrahi seçenekler vardır. Pesser halkası güvenli bir tedavi seçeneğidir. Prolapsus tedavisinde cerrahi seçeneklerden önce pesser halkası akılda tutulmalıdır.

Anahtar Kelimeler: Uterus prolapsus, gebelik, vajinal ilaçlar, pelvik taban

Introduction

Pelvic organ prolapse (POP) is a common disorder affecting up to 30% of ageing women. However, uterine prolapse during pregnancy is rare and has an incidence of 1 per 10,000-15,000 deliveries (1,2). Uterine prolapse may complicate pregnancy by causing patient discomfort, cervical ulceration, urinary and genital tract infections, abortion, foeto-maternal sepsis and maternal death. Its management depends on the gestational age and experience and varies from a conservative approach to a laparotomic or minimally invasive treatment (3).

The pessary ring is generally preferred in the non-surgical treatment of uterine prolapse during pregnancy. Pessaries-have different shapes and sizes (such as Ring, Gehrung, Gellhorn, Shaatz, Donut, Cube, Inflatoball etc), and the silicone ring pessary is more comfortable for self- insertion and removal (4).

Herein, we present a case of uterovaginal prolapse complicating a 16-week pregnancy, which was managed successfully using a vaginal pessary.

Case Report

A 36-year-old multigravida woman presented to the obstetrics clinic with cervical prolapse in the 16th week of gestation (Figure 1). This was her third pregnancy and she had two previous vaginal deliveries without any complications. In addition, she had no complaints during her previous pregnancies, and had no history of POP, constipation, chronic cough or pelvic trauma. On transvaginal ultrasound, the cervical length was 45 mm and the entire cervix was observed to be outside of the vulva. The cervical mucosa was oedematous and ulcerated. POP was classified as follows: uterine prolapse POP-Q 4. After repositioning the uterus with a pessary ring, we found a cystocele POP-Q 1. Her cervical prolapse was successfully restored to the pelvic cavity in the supine position. An obstetric ultrasonography was performed and a live, apparently normal, 16 weeks +3 days foetus was seen. The amniotic fluid index measurement was also normal.

Antibiotherapy (amoxicillin-clavulanate 1000 mg treatment for one week) was started for the cervicovaginal infection. Vaginal pessary was

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recommended to prevent uterine prolapse. A silicone ring-shaped size 11 (0-13) vaginal pessary was inserted into the vagina (Figure 2). Once the pessary ring was inserted, the cervix remained intravaginal and the patient had no urinary retention complaint. She was advised to continue her routine daily activities and bed rest was not recommended. The patient was monitored weekly and the vaginal pessary was removed, cleaned and re-inserted at each control visit. The prolapse resolved spontaneously POP-Q 1 in the 24th week and the patient did not use the pessary again. The antepartum follow-up was normal and no further complications occurred during pregnancy. There was no vaginal or cervical ulceration and the old cervical ulcerations healed with the help of the vaginal pessary.

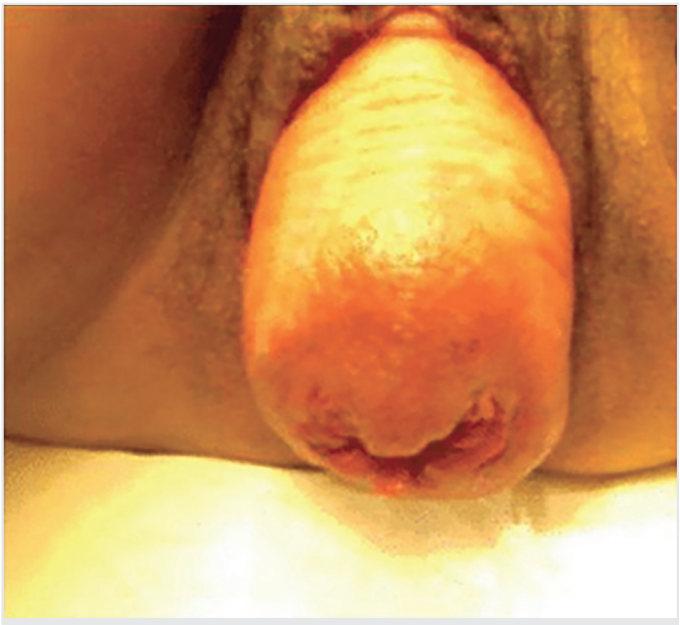

Figure 1. Uterovaginal prolapse at 16 weeks of gestation

Figure 2. The silicone ring pessary

The patient had a spontaneous vaginal delivery at 40 weeks +4 days of a healthy baby weighing 3,800 gr, length 50 cm, and the APGAR scores at the first and fifth minutes were 7 and 8, respectively. After birth, no POP was observed and the patient was discharged with no complications. No problems were encountered during the puerperal period. A further examination at three months postpartum showed no evidence of any prolapse.

Informed consent was obtained from the patient.

Discussion

Although POP occurs with ageing, it is very rare during pregnancy. Many risk factors are associated with the development of prolapse during pregnancy. Parity, ethnicity, delivery type, the interval between consecutive pregnancies, connective tissue diseases, increased strain on the support of the uterus, physiologic changes of pregnancy and past history of prolapse are among the most common risk factors (5). In this case, cervical prolapse occurred in the second trimester of pregnancy. We think that hormonal changes, especially progesterone and relaxin, lead to the growth and softening of the cervix.

POP during pregnancy can cause antepartum, intrapartum and puerperal complications. Antepartum complications can result in abortion, urinary and genital tract infections, acute urinary retention, preterm labour and even maternal death. Major intrapartum complications include an inability to attain adequate cervical dilatation, cervical laceration, obstructive labour, hysterorrhexis at the lower uterine segment, foetal death and maternal morbidity. Puerperal infection and postpartum haemorrhage due to uterine atony are common consequences of uterine prolapse after delivery (3).

The management strategies vary depending on the clinical conditions and experience. In the literature, there are two different types of management approaches, including conservative and surgical management (3,4). Conservative management consists of gynaecological hygiene and bed rest in a slight Trendelenburg position (5). In addition, vaginal pessaries can be used in POP and be easily applied. Common complications of vaginal pessaries include vaginal discharge, odour, mucosal erosion and abrasions of the vagina and urinary retention (4). In this patient, we preferred the pessary ring and did not encounter any of these complications. The pessary ring size was no: 11 and perfectly fitted into the patient. She learned how to use the pessary by herself and perfectly adapted to the procedure. Therefore, selection of the size and shape of the ring and the patient's compatibility affects the success of the procedure.

In general, any surgery during pregnancy can lead to both foetal and maternal morbidity. Cases that were managed with abdominal laparotomic and laparoscopic methods have been reported in the literature. Particularly, for women who do not desire future pregnancies, concomitant caesarean hysterectomy with abdominal sacrocolpopexy may be a good option. Currently, the surgical approach for prolapse using laparoscopy is widely used and laparoscopic uterine suspension surgeries have been reported across the globe. However, the success of the laparoscopy depends on the surgeon, and procedure should be performed in experienced hands, since several failed laparoscopic

uterine suspension cases have been encountered (6). Treatment strategies should aim to improve foeto-maternal health and patient comfort. In this case, we successfully managed the uterine prolapse with a silicone pessary ring and avoided all complications.

In conclusion, POP rarely occurs during pregnancy; however, it may complicate pregnancy. Pessary rings are an effective and a reliable method for treatment and should be considered before surgical alternatives.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - Ç.H.; Concept - B.K.E.; Design - B.K.E.; Data Collection or Processing - B.K.E.; Analysis or Interpretation - Ç.H.; Literature Search - Ç.H.; Writing- B.K.E.

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Methaemoglobinemia Developing Following Lidocain Use

Lidokain Kullanımı Sonrası Gelişen Methemoglobinemi

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ABSTRACT

Methaemoglobinemia is a severe haematological disease occurring when haemoglobin Fe^{+2} is oxidised to Fe^{+3}, and characterised by cyanosis due to inability to transport sufficient oxygen to the tissues. Our case report is a 1-year-old Syrian girl administered local lidocaine for analgesic purposes due to burns who later developed methaemoglobinemia and was treated in our paediatric intensive care unit.

Keywords: Methaemoglobinemia, lidocaine, methylene blue, cyanosis

ÖZ

Methemoglobinemi, iki değerli hemoglobin demirinin okside olup üç değerli duruma geçmesiyle oluşan ve dokulara yeterli oksijen taşınamaması nedeniyle siyanoz ile karakterize olan ciddi bir hematolojik hastalıktır. Burada, yanık nedeniyle analjezik amaçlı lokal lidokain uygulanan, methemoglobinemi gelişen ve çocuk yoğun bakım ünitemizde tedavi edilen 1 yaşında Suriye'li kız hasta sunulmuştur.

Anahtar Kelimeler: Methemoglobinemi, lidokain, metilen mavisi, siyanoz

Introduction

Methaemoglobin results from oxidation of haemoglobin (Hgb) that needs to be in the ferrous (Fe^{+2}) form in order to transport oxygen to the ferric (Fe^{+3}) form. The methaemoglobin reductase system permits iron to be stored in a reduced state in the erythrocyte. It may occur in association with congenital or acquired causes. Congenitally, it occurs in the presence of deficiencies of glucose-6-p dehydrogenase, cytochrome b5 and nicotinamide adenine dinucleotide (NADH) diaphorase, which permit methaemoglobin reduction in the organism, and in the presence of abnormal Hgb. Of the total Hgb, methaemoglobin represents 1% and does not exceed 2-3% under physiological conditions. It appears when the balance between oxidation and reduction is compromised in the presence of increased oxidants, decreased reduction capacity or abnormal Hgb. Exposure to chemical agents or drugs (amyl nitrate, nitroglycerine, dapsone, phenacetin, phenytoin, primaquine, sulfonamides and local anaesthetics) is the most common cause of acquired methaemoglobinemia (1,2).

High amounts of nitric oxide are released in patients with sepsis. The nitric oxide that forms is converted into methaemoglobin or nitrate. Septic patients have reported higher levels of methaemoglobin compared to nonseptic patients (3).

We reported a 1-year-old girl, administered local lidocaine for analgesic purposes due to burns who later developed methaemoglobinemia and was treated in our paediatric intensive care unit (PICU).

Case Report

A 1-year-old refugee girl who suffered feet burns from hot water and developed cyanosis following application of lidocaine-containing ointment was transferred to our PICU. We learnt she had no previous symptoms, and that peripheral cyanosis had developed 2 hours after ointment application, 12 hours after hot water poured on her feet. Family consent was obtained and she was admitted to the PICU. At physical examination, blood pressure was 90/50 mmHg, heart rate was 160 bpm and respiration rate 43/ minute. The patient was agitated, and perioral and peripheral cyanosis were present. The burn area covered 10% of the lower extremities. Oxygen saturation measured using a pulse oximeter was 65%. Arterial blood gas examination was performed while 80% oxygen was administered using a high flow nasal cannula, pH was measured at 7.39, pO_2 at 110 mmHg, pCO_2 at 41 mmHg, HCO_3 at 24.3 mEq/l, SaO_2 at 98% and methaemoglobin levels at 12%. At complete blood count, Hgb was 12 g/dL, white blood cell: 7,400 mm^3 and platelet: 319,000/mm^3. Posterior-anterior chest radiography was normal, and no pathology was determined at echocardiography. Glucose-6-phosphat dehydrogenase levels were within normal limits. Methaemoglobinemia was suspected, and ascorbic acid therapy at 300 mg/kg was administered intravenous (IV). Methylene blue obtained from another institution was subsequently administered IV at a dose of 1.5 mg/kg. Cyanosis decreased on the 3rd hour of treatment and subsequently resolved entirely. Methaemoglobin levels decreased consecutively to 5.8% and 2.9% (Table 1). Oxygen saturation measured using a pulse oximeter increased, and

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oxygen therapy was discontinued. The patient's general condition was good and clinical findings had improved, and the patient was transferred to the paediatric department.

Discussion

The presence of abnormal Hgb must be investigated once congenital heart diseases and respiratory diseases have been excluded in patients with cyanosis and desaturation. Cyanosis despite normal PaO_2 levels in arterial blood gas, and cyanosis failing to resolve despite oxygen therapy is an important finding in cases of methaemoglobinemia (4). In our case too, although PaO_2 was 120 mmHg, SaO_2 98% and SpO_2 65%, no clinical response to oxygen therapy was achieved.

Under normal conditions, blood methaemoglobin levels are 1-2%. Since methaemoglobin reductase activity and fetal Hgb are more easily oxidised in the first 3 months of life, there is a higher risk of development of methaemoglobinemia in association with toxic substances (5).

Cyanosis frequently develops when methaemoglobin levels are 10-20%. Respiratory difficulty, dizziness, headache, tachycardia, lethargy, nausea and vomiting due to tissue hypoxia may be observed at levels of 30% or above, and lethargy, stupor and syncope at levels above 55%. Higher levels may lead to cardiac arrhythmias and circulatory insufficiency. Level above 70% are fatal unless treated (6). Although our patient's methaemoglobin level was 12%, agitation, tachypnea, and perioral and peripheral cyanosis were present. Higher methaemoglobin levels are reported as necessary for tachypnea and tachycardia in the literature. We thought that these findings might have been due to agitation.

Blood turns chocolate-brown in colour in case of high methaemoglobin concentrations. Our patient's blood had a characteristic chocolate-brown colour too. Treatment must be initiated when methaemoglobin levels exceed 20% and the patient is symptomatic, or if levels exceed 30% and the patient is asymptomatic. Treatment may also be initiated at lower level in cases of anaemia and cardiopulmonary problems. Methylene blue is administered IV at a dose of 2 mg/kg in infants, 1.5 mg/kg in children and 1 mg/kg in adults. Methaemoglobin levels generally decrease to below 10% within 30 min. The dose may be repeated hourly. Paradoxically, however, a dose greater than 7 mg/kg^{-1} is not recommended since this can trigger methaemoglobinemia. Methylene blue must not be used in Glucose-6-phosphate dehydrogenase (G6PD) deficiency (7). Our patient's G6PD levels were normal. Methylene blue was administered IV at a dose of 1.5 mg/kg^{-1} due to agitation, tachycardia, tachypnea and cyanosis despite methaemoglobin levels of 12%. Sulfhemoglobinemia, G6PD deficiency, congenital NADPH Met-Hb reductase deficiency and, rarely, toxins must be considered at differential diagnosis in cases that do not respond to methylene blue therapy (8). Ascorbic acid therapy is more used long-term and in oral form in congenital methaemoglobinemias. Hyperbaric oxygen therapy and exchange transfusion may be required in patients with methaemoglobin levels exceeding 70% (9). Experimental studies have also investigated the use of N-acetylcysteine, cimetidine and ketoconazole in methaemoglobinemia (10).

Table 1. Changes in methaemoglobin, oxygen saturation and heart rate

	0 hour	3 hour	12 hour
Methaemoglobin level (%)	12	5.8	2.9
Oxygen saturation (%)	65	90	97
Heart rate (bpm)	160	142	121

Conclusion

Methaemoglobinmia should be considered at differential diagnosis in cases developing cyanosis after local anaesthetic use, and care must be taken to ensure that methylene blue suitable for IV use is available in centres where these agents are frequently employed.

Ethics

Informed Consent: Family consent was obtained and she was admitted to the PICU.

Peer-review: Externally and internally peer-reviewed.

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

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