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BAGCILAR MEDICAL BULLETIN
Bağcılar Tıp Bülteni

CONTENTS / İÇİNDEKİLER

ORIGINAL RESEARCHES / ARAŞTIRMALAR

CASE REPORTS / OLGU SUNUMLARI

ORIGINAL RESEARCH

Bagcilar Med Bull 2024;9(1):1-8
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A Novel Clinical Predictor of Metabolic Syndrome: Vascular Risk Age

Metabolik Sendromun Yeni Bir Klinik Belirleyicisi: Vasküler Risk Yaşı

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Abstract

Objective: Metabolic syndrome (MetS) promotes the development of diabetes mellitus (DM) and atherosclerotic cardiovascular disease (ASCVD). Predicting individuals who are at high risk for developing MetS is essential. Vascular risk age (VRA) is a clinical substitute for cardiovascular risk. In this study, we ascertained whether VRA is an indicator of MetS.

Method: This study involved 169 subjects (96 females, 73 males, aged 40-83 year) without any previous diagnosis of ASCVD or DM. MetS was diagnosed as stated by ATP III-2005 and IDF-2009. The SCORE2/SCORE2-OP 10-year fatal CVD risk and VRA were computed for all participants.

Results: The frequency of MetS based on the ATP III-2005 criteria was 40.2% overall, 39.6% in females, and 41.1% in males, while it was 47.9% in total, 43.8% in females, and 53.4% in males based on IDF-2009 criteria. VRA was significantly higher in cases with MetS in comparison to the cases without MetS (p<0.001), and it was associated with all components of MetS (WC, r=0.194, p=0.011; SBP, r=0.434, p<0.001; BDP, r=0.262, p=0.001; total-C, r=0.223, p=0.003; high-density lipoprotein-C, r=-0.307, p<0.001; TG, r=0.324, p<0.001; and FG, r=0.196, p=0.011). VRA was appeared to be a power-full predictor of MetS in area under the curve (AUC)-ROC curve analysis [AUC=0.658, 95% confidence interval (CI)= 0.576-0.740; for a cut-off of 54.0 years, Youden index=0.19, sensitivity=75.0%, and specificity of 45.0%], and logistic regression (odds ratio: 1.086, p=0.041, 95% CI=1.003-1.175).

Conclusion: VRA is an important and independent predictor of MetS and can be considered for clinical purposes.

Keywords: Atherosclerosis, atherosclerotic cardiovascular disease, diabetes mellitus, metabolic syndrome, vascular risk age

Öz

Amaç: Metabolik sendrom (MetS) varlığı diabetes mellitus (DM) ve aterosklerotik kardiyovasküler hastalık (ASKVH) oluşumunu tetikler. MetS gelişimi açısından yüksek risk altında olan bireylerin öngörülmesi önemlidir. Vasküler risk yaşı (VRA) kardiyovasküler riskin klinik bir göstergesidir. Bu çalışmada, VRA'nın MetS'nin bir göstergesi olup olmadığını tespit etmeyi amaçladık.

Yöntem: Çalışmaya daha önce ASKVH ve DM tanısı olmayan 169 kişi (96 kadın, 73 erkek, yaşları 40-83) dahil edildi. ATP III-2005 ve IDF-2009 kriterleri aracılığıyla MetS tanısı koyuldu. SCORE2/SCORE2-OP 10 yıllık ölümcül KVH riski ve VRA tüm katılımcılar için hesaplandı.

Bulgular: ATP III kriterlerine göre MetS sıklığı tüm popülasyonda %40,2, kadınlarda %39,6 ve erkeklerde %41,1 olarak saptanırken, IDF-2009 kriterlerine göre tüm popülasyonda %47,9, kadınlarda %43,8 ve erkeklerde 53,4 olarak saptandı. VRA MetS saptanan bireylerde MetS saptanmayan bireylere göre anlamlı olarak yüksek saptandı (p<0,001). Ayrıca VRA ile tüm MetS komponentleri arasında ilişki saptandı (WC, r=0,194, p=0,011; SBP, r=0,434, p<0,001; BDP, r=0,262, p=0,001; total-C, r=0,223, p=0,003; yüksek yoğunluklu lipoprotein-C, r=-0,307, p<0,001; TG, r=0,324, p<0,001; ve FPG, r=0,196, p=0,011). Eğri altında kalan (AUC)-ROC analizinde VRA'nın MetS'nin güçlü bir öngörücüsü olduğu görüldü [AUC=0,658, %95 güven aralığı (CI)=0,576-0,740; for a cut-off of 54,0 yaş, Youden indeks=0,19, sensitivite=%75,0, and spesifik %45,0], and logistic regresyon (olasılık oranı: 1,086, p=0,041, %95, CI=1,003-1,175).

Sonuç: VRA, MetS'ninn önemli ve bağımsız bir belirleyicisidir ve klinik amaçlarla düşünülebilir.

Anahtar kelimeler: Ateroskleroz, aterosklerotik kardiyovasküler hastalık, diyabet, metabolik sendrom, vasküler risk yaşı

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality worldwide (1,2). Hyperlipidemia, increased blood pressure, insulin resistance, visceral adiposity, and prothrombotic and proinflammatory states are risk factors for ASCVD. Conditions in which these risk factors are observed together are called metabolic syndrome (MetS) (3).

However, the frequency of MetS varies among different nations; approximately one-fourth of the community has MetS. Frequency ranges of 11.6-26.3% in Europe, 13.6-36.3% in the Middle East, and 18.8-43.0% in America have been reported (3). MetS is more prevalent in Turkey than in the United States, Korea, China, and Japan (3,4). A recent meta-analysis conducted by Abacı et al. (4) revealed that the rate of MetS in Turkey was 32.9% and 43.3%, based on IDF and ATP III criteria, respectively.

MetS is classified among the considerable risk factors for the development of type 2 diabetes mellitus and ASCVD (2,3). Thus, diagnosing MetS is an essential clinical implication in terms of these devastating diseases. MetS is diagnosed based on high blood pressure, high blood sugar, low high-density lipoprotein (HDL) level, high TG level, and waist circumference measurement. Age, race, weight, postmenopausal status, smoking, low income, sugar-based diet, and immobility are linked to MetS (5,6). Beyond these traditional risk factors, additional cardiovascular risk concepts such as metabolic age and vascular risk age (VRA) may predict the development of cardiometabolic diseases (7,8). VRA may be an alternative method of demonstrating cardiovascular risk. In other words, it is an expression of endothelial dysfunction and consequently atherosclerosis. VRA can assist individuals in shared preventive decision making.

Subjects with MetS are generally in the asymptomatic preclinical stages of atherosclerosis (1-8). In individuals with MetS, paying attention to the VRA can be essential in informing and shaping the clinician-patient discussion, detection of early atherosclerosis indicators, and primary prevention therapies. VRA in the setting of MetS is not introduced yet. In our study, we investigated whether VRA can be treated as a decisive factor of MetS.

Materials and Methods

Individuals who presented to the check-up clinics were eligible for this cross-sectional study. Subjects who were older than 18 years and who consented to participate were included in this study. Individuals with active infection, pregnancy, diabetes mellitus, renal disease with a GFR <60 mL/min/1.73 m^2, coronary heart disease, and heart failure were not included. Guidelines proposed in the Declaration of Helsinki were taken into account at all stages of the study. This study was authorized by a Clinical Research Ethics Committee of Kırklareli University (3/2022.K-42, date: 20.05.2022). Informed consent was obtained from all participants.

MetS diagnosis: The National Cholesterol Education Program Adult Treatment Panel III-2005 (ATP III) (9) and the International Diabetes Federation-2009 (IDF) (2) were used to diagnose MetS. The presence of any three of the following five criteria established the diagnosis of MetsS (1-Waist circumference ≥102 cm in men and ≥88 cm in females according to the ATP III, and ≥94 cm in men and ≥80 cm in females based of IDF-2009. 2-Triglycerides ≥150 mg/dL, 3-HDL cholesterol <40 mg/dL in males and <50 mg/dL in females, 4-Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure, 5-Fasting plasma glucose ≥100 mg/dL or drug treatment for elevated blood glucose). In the statistical analysis, we used only the ATP-III criteria as these are adjacent to the recommendations of the Turkish Society of Endocrinology and Metabolism in the context of the WC.

SCORE2/SCORE2-OP and VRA estimation: For participants aged 40-69 years, the high-risk countries SCORE2 (10) and for participants >70 years, the high-risk countries SCORE2-OP risk charts (11) were used to calculate the SCORE2/SCORE2-OP and VRA. Age, gender, current smoking status, total-C, HDL-C, non-HDL-C, and systolic BP levels were considered during the calculations.

To determine the VRA, the evaluated risk score was compared with the age at which risk was similar but all other risk factors were at optimum levels. For example, a 53-year-old smoker with an SBP of 170 mmHg, HDL-C 38 mg/dL, and total-C level of 270 mg/dL has a cardiovascular risk estimate of 21% according to the SCORE2 table for high-risk countries. The VRA of this person would be 76 years. Normally, a 76-year-old man with optimum risk factors (e.g. not smoking, a systolic blood pressure of 120 mmHg, and normal cholesterol levels) has 21% risk of CVD.

Anthropometrics: The weight, height, and WC information of the subjects were obtained. BMI and waist-to-height circumference were also calculated. WC was measured horizontally around the body at the upper border of the iliac crest in the standing position with a relaxed abdomen and arms at the sides.

Biochemical analysis: Venous blood was obtained after 12 h of fasting for measurement of the HbA1c, fasting glucose, and lipid panel. LDL-C was measured directly by a colorimetric method, other blood tests were performed using standard methods, and the same blood sample was used for all analyses. Non-HDL-C was counted asfollows: total cholesterol HDL-C=non-HDL-C.

Statistical Analysis

A histogram with a bell curve and one-sample Kolmogorov-Smirnov tests were used to assess the distribution. Mean ± standard deviation or median (interquartile range) was used to present continuous variables, and numbers and percentages were used to present categorical variables. We classified the participants into two groups according to their gender. Variations in baseline clinical characteristics between groups were evaluated by Mann-Whitney U and independent-samples t-test for continuous variables and the chi-square test for categorical variables. The Wilcoxon signed-rank test was applied to compare the chronologic and VRAs of the entire study population and subgroups. We performed Pearson correlation analysis to investigate the association of age surrogates with anthropometric parameters, MetS components, and SCORE2/SOCRE2-OP. In addition, ROC analysis was used to determine the predictability of VRA for MetS. Finally, we used logistic regression and tested several models to determine which factors better explained the probability of participants exhibiting MetS. The ultimate model comprised gender, chronologic age, VRA, and body mass index (BMI). We also presented odds ratios and 95% confidence intervals (CI) to measure the change in the probability of MetS when the value of an estimator increases by one unit. The primary endpoint of this study was to determine whether VRA could act as an explanatory variable of MetS. Sample size (n) was calculated using the single proportion population formula ($n=Z^2\ p\ (1-p)/d^2$, $n=1.96^2\ 0.43\ (0.57)/0.08^2$, n=148) where p; shows the prevalence of MetS in the population, which was reported as 43.3% according to the ATP III criteria (4), dis precision (8%), and Zis the statistic for a level of confidence, which equals 1.96 for a 95% CI. Based on this information, the sample size was determined to be 148 participants. Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS) (Inc., Chicago, Illinois, USA). Differences at the 2-sided p<0.05 level were considered statistically significant.

Results

From May 2021 to March 2022, 169 participants (females; 96, males; 73, aged; 40-83 years, with MetS: 68, without MetS: 101) were recruited for the study. In our analysis, the incidence of MetS as specified by the ATP III-2005 criteria was 40.2% overall, 39.6% in females, and 41.1% in males, whereas it was 47.9% in total, 43.8% in females, and 53.4% in males based on the IDF-2009 criteria. Table 1 shows the baseline characteristics for the entire sample and compares them with the MetS groups. The mean height, total-C, and LDL-C, along with the frequency of female gender and current smoking state, were not significantly different across the groups. Similarly, no significant difference was observed between the groups according to the median chronologic age. However, individuals with MetS were more likely to have a higher mean weight (p<0.001), MBI (p<0.001), WC (p<0.001), WHR (p<0.001), SBP (p<0.001) HDL (p<0.001), non-HDL-C (p=0.001), fasting glucose (p<0.001) and HbA1c (p<0.001). In addition, the median VRA (p<0.001), DBP (p<0.001), TG (p<0.001), and SCORE2/SCORE2-OP (p<0.001) along with the frequency of HT (p<0.001) and MetS-IDF2009 (p<0.001) were higher in participants with MetS. In contrast, the mean HDL-C (p<0.001) was higher in persons without MetS.

Our results also revealed that chronologic age was significantly correlated with VRA (p<0.001), WHR (p=0.003), height (p=0.019), SBP (p=0.006), FG (p=0.007) and SCORE2/SCORE2-OP (r=0.652, p<0.001). Contrast weight, height, BMI, WC, DBP, total-C, HDL-C, non-HDL-C, LDL-C, TG, and HbA1c were not significantly correlated with chronologic age. VRA was significantly correlated with weight (p=0.039), BMI (p=0.021), WC (p=0.011), WHR (p=0.031), SBP (p<0.001), BDP (p=0.001), total-C (p=0.003), HDL-C (p<0.001), non-HDL-C (p<0.001), LDL-C (p=0.001), TG (p<0.001), FG (p=0.011) and SCORE2/SCORE2-OP (r=0.995, p<0.001). Whereas, VRA was not correlated significantly with height and HbA1c. Our analysis showed that VRA was associated with almost all variables, including all constituents of MetS, as highlighted in Table 2.

ROC analysis was used to determine the predictability of the VRA for MetS (Table 3, Figure 1). VRA was a good predictor for MetS in the entire study population [area under the curve (AUC)=0.658, 95% CI 0.576-0.740), and a cut-off of 54.0 years was determined using a significant Youden index (Youden index=0.25, sensitivity=75.0%, and specificity of 45.0%). More significant results were determined when the data were specified to females. VRA was a better predictor for MetS in the female gender than in the entire

Table 1. General characteristics of the study subjects

	Entire sample	With MetS n=68	Without MetS n=101	p
Female n, %	96 (56.8%)	38 (55.9%)	58 (57.4%)	0.843
Male n, %	73 (43.2%)	30 (44.1%)	43 (42.6%)	0.843
Chronological age (year)	51 (40-83)*	53 (40-76)*	50 (40-83)*	0.126
Vascular risk age (year)	55 (40-80)*	56 (45-80)*	51 (40-80)*	<0.001
Weight (kg)	79.23±15.71	86.73±15.53	74.18±13.75	<0.001
Height (cm)	166.89±9.67	166.34±10.10	167.26±9.38	0.546
BMI (kg/cm^2)	28.42±5.05	31.35±4.96	26.45±4.07	<0.001
WC (cm)	95.86±12.24	102.65±9.92	91.29±11.56	<0.001
WHR	0.58±0.08	0.62±0.07	0.55±0.07	<0.001
SBP (mmHg)	126.36±14.96	133.88±15	121.29±12.69	<0.001
DBP (mmHg)	80 (60-100)*	85 (60-100)*	75 (60-92)*	<0.001
Total-C (mg/dL)	215.34±37.91	219.75±39.86	212.38±36.44	0.216
HDL-C (mg/dL)	58.05±16.94	50.12±11.87	63.39±17.79	<0.001
Non-HDL-C (mg/dL)	157.30±38.52	169.63±37.74	148.99±36.94	0.001
LDL-C (mg/dL)	139.74±30.88	144.28±30.46	136.68±30.93	0.117
TG (mg/dL)	120 (38-485)*	169 (41-485)*	102 (38-341)*	<0.001
Fasting glucose	97.41±10.08	102.01±10.64	94.31±8.40	<0.001
HbA1c	5.75±0.47	5.9±0.56	5.64±0.36	<0.001
SCORE2/SCORE2-OP %	4 (1-28)*	5 (1-26)*	3 (1-28)*	<0.001
Hypertension (%)	37 (21.9%)	28 (41.2%)	9 (9.8%)	<0.001
Current smoking n (%)	57 (33.7%)	18 (26.5%)	39 (38.6%)	0.102

* Data are presented as median and minimum-maximum;±, standard deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, WC: Waist circumference, WHR: Waist-to-height ratio, HDL: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Total-C: Total cholesterol, HbA1c: Hemoglobin A1c, MetS: Metabolic syndrome, SCORE2/SCORE2-OP: Systemic coronary risk evaluation2-older person, TG: Triglyceride

Table 2. Association of vascular risk age with anthropometric parameters, components of metabolic syndrome, and SCORE2/SCORE2-OP

	Chronological age (year)	p	Vascular risk age (year)	p
Chronological age (year)	1		0.683	<0.001
Vascular risk age (year)	0.683	<0.001	1	
Weight (kg)	-0.003	0.973	0.159	0.039
Height (cm)	-0.180	0.019	0.047	0.540
Body mass index (kg/cm^2)	0.143	0.063	0.178	0.021
Waist circumference (cm)	0.132	0.086	0.194	0.011
Waist-to-height ratio	0.225	0.003	0.166	0.031
Systolic blood pressure (mmHg)	0.210	0.006	0.434	<0.001
Diastolic blood pressure (mmHg)	0.108	0.163	0.262	0.001
Total-C (mg/dL)	0.081	0.293	0.223	0.003
HDL-C (mg/dL)	0.047	0.547	-0.30	<0.001
Non-HDL-C (mg/dL)	0.028	0.715	0.343	<0.001
LDL-C (mg/dL)	0.047	0.546	0.259	0.001
Triglyceride (mg/dL)	0.025	0.746	0.324	<0.001
Fasting glucose	0.207	0.007	0.196	0.011
HbA1c	0.116	0.133	0.046	0.551
SCORE2/SCORE2-OP %	0.652	<0.001	0.995	<0.001

HDL: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, Total-C: Total cholesterol, HbA1c: Hemoglobin A1c, SCORE2/SCORE2-OP: Systemic coronary risk evaluation2-older person

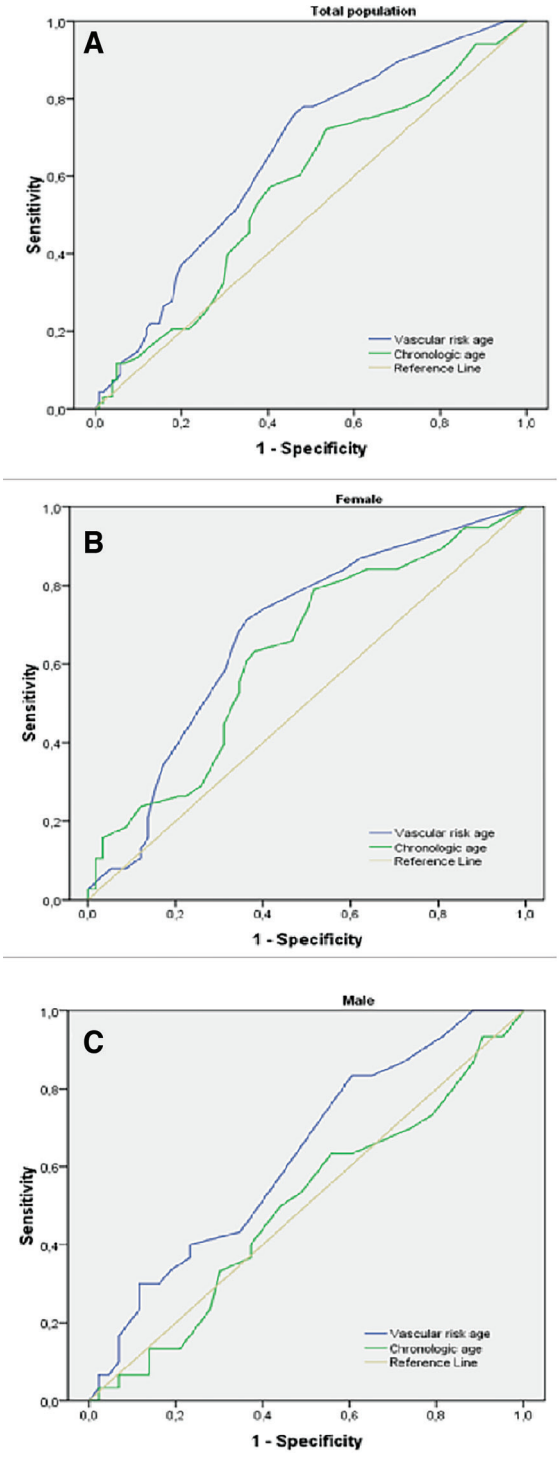

Figure 1. "Subjects with MetS are more accurately predicted by vascular risk age than chronologic age. (A) ROC curve was produced and AUC was computed to establish vascular risk-age (blue line) and chronological age (green line) predictability for metabolic syndrome. Subsequently, the cohort was re-analyzed as was ranked by sex into females (B) and males (C). The reference line (yellow line) matches no predictability (AUC=0.500).''

AUC: Area under the curve, MetS: Metabolic syndrome

study population (AUC=0.677, 95% CI 0.568-0.786), and a cut-off of 55.5 years was determined using a significant Youden index (Youden index=0.31, sensitivity=68.4%, and specificity of 65.0%). In comparison with the chronologic age, VRA was a significantly better predictor of MetS, particularly in the female gender.

In addition, we performed logistic regression analysis to evaluate the role of gender, chronologic age, VRA, BMI, WC, fasting glucose, and non-HDL-C levels in terms of the probability of MetS. The full model including all seven predictors was statistically significant [X^2 (7, n=169 = 73,318, p<0.001)], indicating that the model was able to discriminate between the presence and absence of MetS. In general, 35.2% (Cox and Snell R square) to 47.6% (Nagelkerke R square) variance in MetS status was explained by the entire model, and 81.1% of the cases were correctly classified. As demonstrated in Table 4, VRA was an important predictor of MetS in this sample, with an odds ratio of (OR: 1.086, p=0.041). This suggests that for each one-year increase in VRA the odds of presenting MetS increases by a factor of 1.086. In addition, fasting glucose was a significant predictor of MetS (OR: 1.082, p=0.001). This indicates that for each 1 mg/dL increase in fasting glucose, the odds of having MetS increases by a factor of 1.082.

Discussion

In this study, we found that individuals with MetS had an increased BMI, WC, WHR, SBP, DBP, non-HDL-C, TG, FG, HbA1c, and decreased HDL-C compared with individuals without MetS. Previous studies have revealed that increased body weight, insulin resistance, increased blood pressure, and atherogenic dyslipidemia participate in the development of MetS (1-5). In this context, our results are consistent with previously published data. Differing from previous reports, in this work we mainly investigated whether VRA might significantly predict MetS. Therefore, individuals with MetS were divided into two groups on the basis of the sensitivity and specificity values of the chronologic age and the VRA, with a cut-off age of 54.0 years. This study mainly found that individuals with MetS had increased VRA and SCORE2/SCORE2-OP %. Furthermore, it was evident that VRA can significantly predict MetS in general and particularly in the female gender. Our analysis showed that the ROC-AUC of MetS in the entire study population increased from 0.569 in a model with chronological age to 0.658 in a model with SCORE2-based calculated VRA. Furthermore, AUC was even more

pronounced when the model was adjusted only for females (up to 0.677). In addition, our logistic regression model also supported us and showed an OR of 1.086 (p=0.041, 95% CI=1.003-1.175) for VRA in the prediction of MetS. As we all know, this is the first study showing the prediction of MetS by VRA.

VRA is a surrogate of an individual's excess cardiovascular risk, which is calculated using a risk prediction model such as Framingham or SCORE2/SOCRE2-OP (1,10,11). Furthermore, VRA can be investigated by additional methods, such as measurement of carotid intima-media thickness and plaque detection, coronary artery calcification, pulse wave velocity, and pulse wave analysis that reflect arterial stiffness (1,12,13). In the recently mentioned methods, VRA is the age at which the result of an imaging test would equal the population reference values. In all terms, VRA is considered to improve cardiovascular risk prediction models and may help in a better understanding of cardiovascular risk at the preclinical stages, particularly in young patients, as the long-term effects of high-risk factors can be disguised (1). In all respects, VRA is considered to improve cardiovascular risk prediction models and may aid a better understanding of cardiovascular risk, particularly in the preclinical stages in younger patients, as the long-term effects of high-risk factors may be obscured (1). Here, we used the recently recommended SCORE2/SCORE2-OP risk chart calibrated to the high-risk countries (including Turkey) for calculating fatal and non-fatal CVD events as well as VRA with regard to recognizing MetS. In almost all previous reports (1), the mean VRA is usually higher than chronological age, with the differences ranging from 1 to 26.5 years. Our findings were in agreement with these observations, as we found VRA to be significantly higher than chronologic age in the overall sample (p<0.001), subjects with MetS (p<0.001), and those without MetS (p=0.008).

Many reports have demonstrated older chronologic age as a predictor of MetS (14,15). However, using chronological age alone could cause misunderstanding of cardiometabolic risk because it excludes the subject's lifestyle, distribution of the adipose tissue, and accompanying diseases (16). Thus, risk scales, including chronologic age analysis, may cause underestimation of subjects in whom aggressive management of CV disease risk factors should be applied (17,18). In our sample, subjects diagnosed with MetS were not significantly older than subjects without MetS (p=0.126). In contrast, we showed that VRA was significantly higher in individuals with MetS

Table 3. Receiver operating characteristic analysis of the entire study population and gender-specific values

Variables	AUC	Std. error	p	95% CI	Cut-off	sensitivity	Specificity	J-index
Entire population vascular risk age	0.658	0.042	<0.001	0.576-0.740	54.0	75.0	45.0	0.19
Chronologic age	0.569	0.045	0.126	0.481-0.657	54.0	46.0	65.0	0.09
Females								
Vascular risk age	0.677	0.056	0.004	0.568-0.786	54.0	68.4	65.0	0.27
Chronologic age	0.629	0.058	0.034	0.515-0.742	54.0	52.0	65.0	0.13
Males								
Vascular risk age	0.627	0.066	0.067	0.498-0.755	54.0	83.0	0.43	0.00
Chronologic age	0.495	0.069	0.942	0.359-0.631	54.0	43.0	0.60	-0.035

AUC: Area under the curve, CI: Confidence interval, J-index: Youden index

Table 4. Predictors of metabolic syndrome based on the logistic regression model

Predictors	B	S.E.	Wald	df	P	Odds ratio	95% CI for EXP (B)	
							Lower	Upper
Gender (F=1, M=0)	0.812	0.481	2.851	1	0.091	2.252	0.878	5.777
Age (year)	-0.061	0.039	2.433	1	0.119	0.941	0.871	1.016
Vascular risk age (year)	0.082	0.040	4.187	1	0.041	1.086	1.003	1.175
BMI (kg/m^2)	0.120	0.081	2.199	1	0.138	1.128	0.962	1.323
WC	0.054	0.034	2.465	1	0.116	1.056	0.987	1.129
Fasting glucose	0.079	0.023	11.460	1	0.001	1.082	1.034	1.133
Non-HDL-C	0.011	0.006	3.284	1	0.070	1.011	0.999	1.022
Constant	-20.332	3.445	34.841	1	<0.001	<0.001		

BMI: Body mass index, B: Unstandardized regression weight Wald, Wald statistic test, df: Degrees of freedom, 95% CI for EXP(B): 95% Confidence interval for the odds ratio, WC: Waist circumference, Non-HDL-C: Non-HDL-C

than in those without MetS (p<0.001). In addition, rather than chronologic age, VRA was an independent predictor of MetS. The increase in the prevalence of MS based on age is significantly influenced by the high frequency of metabolic risk factors developed at the oldest age, in particular, >65 years (19). Our sample was free of high-risk features such as CVD and DM along with a higher number of young individuals (overall median age=51 years), which may explain the equivalence of age in subjects with and without MetS.

Previous papers have reported that the female gender was more likely to develop MetS (16). Contrary to the latter study, which enrolled only Brazilian patientswas assessed a cross-section of the Turkish population (Caucasian ethnicity) and demonstrated no significant difference in the frequency of MetS regarding gender. In this context, our findings were consistent with recent domestic population reports (4).

Hyperlipidemia is one of the main triggers of atherosclerosis, which manifests in its early form as coronary artery calcification or increased carotid IMT, which have been proposed as surrogates of VRA (20). In this regard, our results indicate that VRA is in excellent correlation with all components of the lipid panel, as previously published works experienced (1,2,9). This association may explain the higher atherosclerotic features of VRA in subjects with MetS. However, chronologic age was not associated with any lipid parameter.

Increased BMI and WC and cigaret smoking are other potential factors contributing to both a high VRA and MetS development (1,16). Our findings also complement this idea, with the exception of cigaret smoking. Our results revealed that VRA is significantly associated with BMI and WC. This interrelationship may account for the hazardous characterization of both MetS and increased VRA.

High fasting glucose and insulin resistance are the main features of MS (2). Consistent with general acceptance, our logistic regression results showed that fasting blood glucose was an independent predictor of MS (2,4,5).

This is the first study to investigate VRA age in the context of MetS. Our results demonstrated that VRA is a novel clinical marker of risk for MetS. In this analysis, we used complete data on SCORE2/SCORE2-OP charts and MetS criteria. In addition, we tested vascular risk of prediction of MetS through several statistical analyses (logistic regression and AUC-ROC curve analysis). The present study has some limitations as well; it was a cross-sectional work, done in a single center, included only a Turkish sample (Caucasian ethnicity), the sample was entirely above 40 years of age, and individuals with DM and ASCVD were not included in the study, which could cause a miscalculation of the incidence of MetS.

Conclusion

Our analysis showed that VRA is a significant clinical predictor of MetS. In clinical evaluation, paying attention to the VRA may help in the early detection of MetS, the precursor of ASCVD and DM. Thus, it contributes to an effective clinician-patient discussion regarding primary prevention treatments. However, to evaluate the diagnostic and prognostic value of VRA in the context of MetS, prospective studies are needed.

Ethics

Ethics Committee Approval: This study was authorized by a Clinical Research Ethics Committee of Kırklareli University (3/2022.K-42, date: 20.05.2022).

Informed Consent: Informed consent was obtained from all participants

Authorship Contributions

Surgical and Medical Practices: A.N., R.Ç.G., S.S., Ö.Ş., Concept: A.N., D.E.A., S.S., Design: A.N., D.E.A., R.Ç.G., Ö.Ş., Data Collection or Processing: A.N., D.E.A., R.Ç.G., S.S., Analysis or Interpretation: A.N., S.S., Ö.Ş., Literature Search: D.E.A., R.Ç.G., S.S., Ö.Ş., Writing: A.N., D.E.A., R.Ç.G., S.S., Ö.Ş.

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ORIGINAL RESEARCH

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Evaluation of Neutrophil/Lymphocyte and Thrombocyte/Lymphocyte Ratios in Cases of Preterm Premature Rupture of Membranes

Preterm Prematür Membran Rüptürü Olgularında Nötrofil/Lenfosit ve Trombosit/Lenfosit Oranlarının Değerlendirilmesi

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Abstract

Objective: There is no daily practical method for the diagnosis and follow-up of premature rupture of membranes (PPROM). In this study, we examined the association between PPROM and platelet/lymphocyte (PLR) and neutrophil/lymphocyte (NLR) ratios.

Method: Eighty women with a diagnosis of PPROM between the 24th and 34th weeks of gestation were included in the study. Eighty-three women without membrane rupture between the same gestational weeks constituted the control group. Information about the women included in the study was collected retrospectively from hospital medical records. For each patient, gravida, parity, age, week of gestation, week of birth, and mode of delivery were examined. To evaluate perinatal outcomes, sex, 1st and 5th minute Apgar scores, birth weight, and neonatal death were examined. The patients' white blood cells, lymphocyte neutrophil, and platelet counts, PLR, NLR ratios, hemoglobin, and C-reactive protein values were examined.

Results: The mean NLR of the PPROM group was 30.96±2.55 [mean ± standard deviation (SD)] and mean PLR was 148.06±72.18 (mean ± SD). In the control group, these values were calculated as 30.91±2.43 (mean ± SD) and 126.74±45.85 (mean ± SD), respectively. Both rates were higher in the PPROM group (p=0.026).

Conclusion: PLR and NLR ratios were higher in the study group. Therefore, PLR and NLR can be used in the management of PPROM.

Keywords: Neutrophol/lymphocyte ratio, platelet/lymphocyte ratio, preterm premature rupture of fetal membranes

Öz

Amaç: Preterm prematür membran rüptürü (PPROM) tanı ve takibinde günlük pratik bir yöntem bulunmamaktadır. Biz çalışmamızda PPROM ile platelet/lenfosit (PLR) ve nötrofil/lenfosit (NLR) oranları arasındaki ilişkiyi incelemeyi amaçladık.

Yöntem: PPROM tanısı alan 24-34 gebelik haftaları arasında olan 80 kadın çalışmaya dahil edildi. Kontrol grubunu ise aynı haftalar arasındaki 83 sağlıklı gebe oluşturdu. Çalışmaya katılan kadınlara ait bilgiler retrospektif olarak hastanenin tıbbi kayıtlarından elde edildi. Her hastanın yaşı, gravidası, paritesi, gebelik haftası, doğum haftası ve doğum şekli incelendi. Perinatal sonuçları değerlendirmek için cinsiyet, 1. ve 5. dakika Apgar skorları, doğum ağırlığı ve yenidoğan ölümü incelendi. Hastaların beyaz kan hücresi, lenfosit, nötrofil ve trombosit sayıları, nötrofil/lenfosit, trombosit/lenfosit oranları ve hemoglobin, C-reaktif protein değerlerine bakıldı.

Bulgular: PPROM grubunun ortalama NLR'si 30,96±2,55 [ortalama ± standart sapma (SS)] ve ortalama PLR'si 148,06±72,18 (ortalama ± SS) idi. Kontrol grubunda ise bu değerler sırasıyla 30,91±2,43 (ortalama ± SS) ve 126,74±45,85 (ortalama ± SS) olarak hesaplandı. Her iki oran da PPROM grubunda daha yüksekti (p=0,026).

Sonuç: PLR ve NLR oranları çalışma grubunda anlamlı derecede yüksekti. Bu nedenle PPROM'nin yönetiminde NLR ve PLR kullanılabilir.

Anahtar kelimeler: Nötrofil/lenfosit oranı, platelet/lenfosit oranı, preterm prematür membran rüptürü

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Introduction

Premature rupture of membranes (PPROM) is the loss of amniotic fluid due to damage to the chorioamniotic membranes before labor begins. If this condition occurs before the 37th week of pregnancy, it is referred to as preterm PPROM (1). The week of gestation at birth is inversely proportional to neonatal morbidity and mortality (2). Although the main causes of preterm birth include PPROM, preterm birth due to maternal or fetal indications, and multiple pregnancies, the cause of some preterm births cannot be explained. PPROM causes 30-35% of all preterm births (3). Preterm birth is the most frequently observed cause of neonatal morbidity and mortality. Approximately 560,000 preterm births occur in the USA every year, and approximately 150,000 preterm births are complicated by PPROM (2). PPROM has a complex pathophysiology that includes inflammation and oxidative stress. Although there are many factors that increase the risk of PPROM, the reason for this is not fully understood.

Fetal membranes act as a barrier against the ascending infection. When fetal membranes are damaged, both the mother and fetus are at risk of infection and other complications. Major maternal complications include chorioamnionitis, placental abruption, and cord prolapse. In PPROM, intraamniotic infection develops at a rate of 13-60% and postpartum endometritis develops at a rate of 2-13% (4). The most important factor in neonatal complications is the gestational age. Polymicrobial intraamniotic infection, which occurs in 15-30% of patients with PPROM, has been associated with 3-20% neonatal death and intraventricular hemorrhage (IVH). Severe oligohydramnios that develop in PPROM cause an increase in the incidence of cord compression at birth and unreliable fetal tests, leading to a further increase in the risk of birth by cesarean section. Factors such as infection and cord accidents carry a 1-2% risk of intrauterine fetal death (5). Although respiratory distress syndrome is the leading complication of PPROM, necrotizing enterocolitis, IVH, and sepsis are other important causes of morbidity (6).

The clinical evaluation and management approach for patients with PPROM is controversial. Management is based on the assessment of gestational age, relative risks of delivery, and possible complications of the expectant approach (1). Although tests such as the fern test, nitrazine test, and Amnisure are available to confirm the diagnosis of PPROM, no method is available to reliably predict PPROM (3). Many studies have been conducted to evaluate fetal well-being by measuring inflammatory mediators in amniotic fluid and cervicovaginal secretions and maternal blood. There is still no practical method suitable for daily monitoring. The use of markers such as C-reactive protein (CRP) and white blood cell count remains controversial. Complete blood count is a cheap and simple laboratory test. It has been shown in many studies that platelet increase in peripheral blood is associated with inflammatory conditions, various malignancies, and infections. Recently, platelet/lymphocyte (PLR) and neutrophil/lymphocyte (NLR) ratios have been identified as new markers associated with poor outcomes in various pathological conditions (7). The goal of this study was to evaluate the usability of PLR and NLR ratios as markers for the diagnosis and follow-up of PPROM.

Materials and Methods

Between April 2017 and April 2021, 196 patients between 24 and 34 weeks of gestation at the University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital Gynecology and Obstetrics Clinic were included in the study. Twenty of these patients were excluded from the study because of chronic hypertension and preeclampsia, 10 because of diabetes mellitus, and 3 because of active systemic infection. Eighty women diagnosed with PPROM formed the study group, and 83 healthy women between 24 and 34 weeks of gestation who were not diagnosed with PPROM formed the control group.

Data on the patients were obtained by retrospectively scanning the patient files and the hospital electronic information system. Patients with maternal chronic diseases, such as diabetes mellitus, hypertension, and preeclampsia, were not included in the study because they may affect the neutrophil, lymphocyte, and platelet values investigated. For each patient, age, gravida, parity, week of gestation, week of birth, and mode of delivery were examined. To evaluate perinatal outcomes, birth weights, gender, 1st and 5th minute Apgar scores, and neonatal mortality were examined. The patients' white blood cell, neutrophil, lymphocyte, and platelet counts, neutrophil/lymphocyte, PLR ratios, hemoglobin, and CRP values were examined. Laboratory values during hospitalization were included in the study to ensure that the treatments applied did not change the data.

Statistical Analysis

In the evaluation of the data, in addition to descriptive statistical methods [mean, standard deviation (SD), median, interquartile range], the distribution of the variables was examined using the Shapiro-Wilk normality test. The independent t-test was used to compare pairwise groups of

variables with normal distribution, and the Mann-Whitney U test was used to compare pairwise groups of variables that did not show a normal distribution. The chi-square test was used to compare qualitative data. Univariate and multivariate logistic regression analyses were performed to separate the effective factors in the presence of PPROM. For the differential diagnosis of the presence of PPROM, the areas under the ROC curve were calculated, and the sensitivity, specificity, positive predictive value, negative predictive value, and predictive value of the variables were determined. The results were evaluated at a significance level of $p<0.05$.

Results

In total, 163 patients were examined in our study. Eighty three patients constituted the control group and 80 patients constituted the PPROM group. The mean maternal age was 27.43±6.71 (mean ± SD) in the PPROM group and 27.99±5.79 (mean ± SD) in the control group. It was not found that there was a difference in groups in gravida and parity values. The mean gestational week in the PPROM group was 30.91±2.5 (mean ± SD). In addition to the mean week of birth being significantly lower in the study group (p=0.001), cesarean deliveries were more frequent in this group (p=0.0001). The 1st and 5th minute Apgar scores and average newborn weight were observed to be lower in the PPROM group (p=0.0001) (Table 1).

No significant difference was found when the hemoglobin, platelet, lymphocyte, and CRP values were examined. The mean leukocyte count was 11.49±3.04 (mean ± SD) in the PPROM group and 10.34±1.77 (mean ± SD) in the control group, and this difference was significant (p=0.004). While the mean neutrophil count of the study group was 8.93±2.87 (mean ± SD), it was calculated as 7.66±1.79 (mean ± SD) and similarly, this difference was also significant (p=0.001) (Table 2).

Table 1. Baseline demographic features and distribution of patients between PPROM (-) and PPROM (+)

		PPROM (-)		PPROM (+)		p
Age	Mean ± SD	27.99±5.79		27.43±6.71		0.574
Gravidity	Mean ± SD	2.32±1.44		2.62±1.66		0.330
	Median (IQR)	2 (1-3)		2 (1-4)		
Parity	Mean ± SD	0.98±1.11		1.15±1.34		0.666
	Median (IQR)	1 (0-1)		1 (0-2)		
Gestation week	Mean ± SD	30.96±2.43		30.91±2.5		0.899
Birth week	Mean ± SD	36.17±2.75		32.07±2.69		0.0001
Type of birth	**Vaginal**	43	53.09%	26	32.10%	**0.007**
	C/S	38	46.91%	55	67.90%	
Birth weight	Mean ± SD	2820.74±629.73		1925.63±593.41		**0.0001**
Gender	**Boy**	44	54.32%	43	53.09%	0.875
	Girl	37	45.68%	38	46.91%	
1st minute Apgar score	Mean ± SD	7.36±1		6.38±1.39		**0.0001**
5st minute Apgar score	Mean ± SD	8.72±0.76		8.07±1.1		**0.0001**

PPROM: Premature rupture of membranes, SD: Standard deviation, IQR: Interquartile range

Table 2. Laboratory values of the patients

		PPROM (-)	PPROM (+)	p
Hemoglobin	Mean ± SD	11.18±1.47	11.31±1.3	0.575
Leukocyte	Mean ± SD	10.34±1.77	11.49±3.04	**0.004**
Platelet	Mean ± SD	226.8±54.49	235.1±63.37	0.373
Neutrophil	Mean ± SD	7.66±1.79	8.93±2.87	**0.001**
Lymphocyte	Mean ± SD	1.92±0.58	1.91±1.09	0.416
	Median (IQR)	1.8 (1.5-2.28)	1.82 (1.28-2.32)	
CRP	Mean ± SD	9.75±13.5	17.68±35.93	
	Median (IQR)	6.49 (3.07-10.11)	7.56 (4.06-15.11)	0.168

PPROM: Premature rupture of membranes, SD: Standard deviation, IQR: Interquartile range, CRP: C-reactive protein

When the NLR and PLR values of both groups were calculated, the mean NLR of the PPROM group was 30.96±2.55 (mean ± SD) and the mean PLR was 148.06±72.18 (mean ± SD). In the control group, these values were calculated as 30.91±2.43 (mean ± SD) and 126.74±45.85 (mean ± SD), respectively. Both rates were significantly higher in the PPROM group (p=0.026) (Table 3).

In the differential diagnosis of PPROM positivity, the area under the ROC curve of the NLR variable was 0.599 (0.519-0.675) and that of the PLR variable was 0.582 (0.502-0.659) (Figure 1).

While the cut-off value of the NLR variable was above 7.3, the sensitivity was determined to be 39.63, and the specificity was 95.06. When the cut-off value of the PLR variable was above 165, its sensitivity was 30.86 and its specificity was 87.65 (Table 4).

Discussion

PPROM is one of the most common causes of preterm birth, with serious maternal and fetal complications. Today, premature birth still has an important place in neonatal mortality and morbidity. Although the pathogenesis of PPROM is not clearly clear, factors such as maternal infection, genetic conditions, smoking, and maternal chronic diseases are blamed. The best method for detecting intrauterine infection is amniocentesis. However, amniocentesis is an invasive method and may result in various procedure-related complications, such as a 0.5% risk of fetal loss. Therefore, non-invasive methods are required. Different studies have shown that PLR and NLR have prognostic and predictive importance in various diseases, including preeclampsia and gynecological malignancies (8,9).

The major findings of our study are as follows: (1) The mean PLR, NLR, and cesarean deliveries were higher in the PPROM group (2). The 1st and 5th minute APGAR scores were lower in the PPROM group (3). There was not difference between the CRP values of both groups.

Toprak et al. (10) investigated the relationship between PPROM and PLR and NLR values in 96 pregnant patients with spontaneous preterm labor and 121 pregnant patients with PPROM. They did not detect any significant difference between the two groups in terms of age, gravida, parity, gestational week, and lymphocyte values, similar to our study. Again, in this study, they found that the mean NLR was higher in the PPROM group and that there was a relationship between the increase in PLR values and neonatal complications (10). In our study, we also found

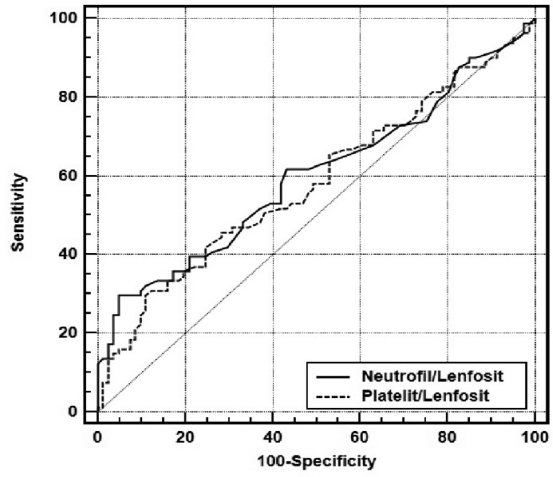

Figure 1. ROC curve in terms of NLR and PLR in the diagnosis of PPROM

PPROM: Premature rupture of membranes, NLR: Neutrophil/lymphocyte, PLR: Platelet/lymphocyte, ROC: Receiver operating characteristic

Table 3. NLR and PLR values of the patients

		PPROM (-)	PPROM (+)	p
NLR	Mean ± SD	30.91±2.43	30.96±2.55	**0.029**
	Median (IQR)	3.9 (3.25-5.15)	4.62 (3.2-7.9)	
PLR	Mean ± SD	126.74±45.85	148.06±72.18	**0.026**

PPROM: Premature rupture of membranes, SD: Standard deviation, IQR: Interquartile range, NLR: Neutrophil/lymphocyte, PLR: Platelet/lymphocyte

Table 4. NLR and PLR cut-off points

	Cut-off value	Sensitivity	Specificity	PCP	NCP	LR (+)
NLR	**>7.3**	39.63	95.06	85.7	57.5	4.00
PLR	**>165**	30.86	87.65	71.4	55.9	2.50

PCP: Positive predictive value, NCP: Negative predictive value, LR: Likelihood ratio, NLR: Neutrophil/lymphocyte, PLR: Platelet/lymphocyte

a lower Apgar score in preterm birth and newborns in the PPROM group and higher PLR and NLR values in the PPROM group.

Ekin et al. (11) investigated the risk factors associated with the latent period and perinatal outcomes in patients with PPROM. Maternal age, parity, mode of conception, maternal disease, PPROM history, previous cesarean section history, antenatal bleeding history, tobacco use, week of gestation with PPROM, amniotic fluid index, latent period, week of birth, and maternal blood parameters (CRP, platelet, leukocyte, lymphocyte and neutrophil) data. They calculated the NLR and PLR values. No differences were observed between the two groups regarding maternal age, fetal gender, tobacco use, and mode of conception. It was observed that there was an increased risk of abruptio placentae, emergency cesarean delivery, cord prolapse, and chorioamnionitis in the group with a latent period of over 72 h. They found that there was no relationship between the latent period and the NLR and PLR values between the groups (11).

Ozel et al. (12) found in their study that the mean NLR of patients diagnosed with PPROM was higher than that of the healthy group and the group with threatened preterm birth. They also stated that the predictive value of NLR was 5.14 (12). In our study, we calculated the predictive value of NLR to be 7.3.

Lakshmi and Sravani (13) examined the predictive values of PLR and NLR for PPROM. Researchers found that the mean hemoglobin value was lower and the neutrophil count, mean PLR, and NLR were higher in the PPROM group than in the control group. The mean birth weight in the PPROM group was also found to be lower. These results were similar to those of our study.

Conclusion

Consequently, in our study, we detected that PLR and NLR values were higher in patients diagnosed with PPROM. Therefore, PLR and NLR may be used as a cost-effective method in the diagnosis and follow-up of PPROM because they are non-invasive values that can be easily calculated by complete blood count. More studies are needed to determine the routine use of these parameters in the management of PPROM.

Ethics

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research. This study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul Prof. Dr. Cemil Taşcıoğlu City Hospital, with protocol number 48670771-514.10, on May 24, 2021.

Informed Consent: Our study is retrospective and was carried out on data processing data without using patient names.

Authorship Contributions

Concept: V.M., Y.Ö., Design: V.M., Y.Ö., Data Collection or Processing: Y.Ö., Y.K., Analysis or Interpretation: Y.Ö., D.Y.K., Drafting Manuscript: S.G., D.Y.K., Critical Revision of Manuscript: Y.Ö., Y.K., V.M., Final Approval and Accountability: Y.Ö., S.G., Y.K., D.Y.K., V.M., Technical or Material Support: Y.Ö., Y.K., Supervision: D.Y.K., S.G., Writing: Y.Ö., S.G., Y.K., D.Y.K., V.M.

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ORIGINAL RESEARCH

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Comparison of Non-alcoholic Fatty Liver Disease Indexes and Hepatic Ultrasonography as Predictors of Hepatosteatosis in Patients with Obesity

Obezitesi Olan Hastalarda Hepatosteatoz Belirteci Olarak Alkolik Olmayan Yağlı Karaciğer Hastalığı İndeksleri ve Hepatik Ultrasonografinin Karşılaştırılması

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Abstract

Objective: Obesity affects 60% of adults in Europe. Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent obesity consequences that increase cardiovascular and hepatic morbidity and mortality. Here; it was aimed to compare NAFLD indexes with hepatic ultrasonography (USG) and determine whether these indexes could be used as predictors of hepatosteatosis in patients with obesity.

Method: Eighty randomly chosen patients from our obesity center were included in the study. Patients ≥18 years-old, having files with all research parameters were included and having acute/chronic hepatic disease/malignancy, getting any kind of treatment for hepatosteatosis, having alcohol consumption above recommended amounts were excluded. All patients' age, gender, weight, height, body mass index (BMI), waist circumference, gasting blood glucose, high-density lipoprotein, triglyceride, low-density lipoprotein, insulin, alanine transaminase (ALT), aspartate aminotransferase, gamma-glutamyl transferase, hepatic USG results, accompanying diseases and medicines were recorded. Non-alcoholic fatty liver disease indexes: Hepatosteatosis index (HSI), visceral adiposity index (VAI), fatty liver index (FLI) and lipid accumulation product index (LAP) were calculated. Results were evaluated using SPSS program.

Results: Sixty-five female and 15 male, totally 80 people with obesity were included in the study. Mean age was 44.29±12.82 years in women and 38.27±12.88 years in men. In general population HS rates were: No hepatosteatosis 10%, first degree 17.05%, second degree: 58.75% and third degree: 13.75%. Weight, WC, ALT, diabetes mellitus, hypertension, being on medication for accompanying diseases and alcohol consumption within recommended rates were higher in HS(+) group when compared

Öz

Amaç: Obezite Avrupa'daki erişkinlerin %60'ını etkilemektedir. Non-alkolik yağlı karaciğer hastalığı (NAYKH) obezitenin en sık sonuçlarından biridir ve kardiyovasküler ve hepatik morbisite ve mortaliteyi artırır. Burda; NAYKH indekslerini hepatik ultrasonografi (USG) ile karşılaştırarak, obezitesi olan hastalarda bu indekslerin hepatosteatoz belirleyicisi olarak kullanılabilirliğinin belirlenmesi amaçlanmıştır.

Yöntem: Obezite merkezimizden random seçilen 80 hasta çalışmaya dahil edildi. ≥18 yaş olup tüm araştırma parametreleri dosyada mevcut olan hastalar çalışmaya alındı, akut/kronik karaciğer hastalığı/maliginitesi olanlar, hepatosteatoz için herhangi bir tedavi alanlar, önerilen dozlar üzerinde alkol kullanımı olanlar çalışmaya alınmadı. Hastaların yaş, cinsiyet, boy, kilo, vücut kitle indeksi (VKİ), bel çevresi, açlık kan şekeri, insülin, yüksek yoğunluklu lipoprotein, trigliserit, düşük yoğunluklu lipoprotein, alanin transaminaz (ALT), aspartat aminotransferaz, gama-glutamil transferaz, hepatik ultrasonografi sonuçları, eşlik eden hastalıkları ve kullandıkları ilaçlar kaydedildi. NAYKH indeksleri: Hepatosteatoz indeksi (HSİ), visseral adipozite indeks (VAİ), yağlı karaciğer indeksi (YKİ) ve lipid birikim ürünü indeksi (LBÜİ) hesaplandı. Sonuçlar SPSS ile değerlendirildi.

Bulgular: Obezitesi olan 65 kadın, 15 erkek, toplam 80 hasta çalışmaya dahil edildi. Kadın hastalarda yaş ortalaması 44,29±12,82 yıl ve erkek hastalarda 38,27±12,88 yıl olarak bulundu. Genel popülasyonda hepatosteatoz oranları şu şekildeydi: HS olmayan %10, birinci derece %17,05, ikinci derece %58,75 ve üçüncü derece %13,75. Kilo, BÇ, ALT, diabetes mellitus, hipertansiyon, ilaç kullanımı ve önerilen limitler dahilinde alkol kullanımı oranları HS(+) grupta HS(-) gruptan yüksekti.

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Abstract

to HS(-) group. When HS levels were compared with mean NAFLD index values, there was statistically significant difference for HSI mean group values. There was no statistically significant difference for other NAFLD indexes. There was a positive correlation between BMI and LAP, FLI and HSI. There was no significant correlation between BMI and VAI.

Conclusion: As NAFLD is a strong predictor of cardiometabolic morbidity and mortality, it is important to make a diagnosis before progression in people living with obesity and simple non-invasive screening/diagnostic tools are needed for this purpose. VAI, LAP, FLI, HSI are easily calculated scientific models that are found to be predicting NAFLD. Although we could only partially found this prediction, they could be used sufficiently after national validation studies that determine the cut-off values and help to achieve prevention of NAFLD-related complications with early diagnosis.

Keywords: NAFLD, NAFLD indexes, obesity

Öz

HS düzeyleri ortalama NAYKH indeks değerleriyle karşılaştırıldığında, HSİ ortalama grup değerlerinde istatistiksel olarak anlamlı fark vardı, diğer indekslerde ise fark bulunmadı. VKİ ile LBÜİ, YKİ ve HSİ arasında pozitif korelasyon mevcuttu, VKİ ve VAİ arasında anlamlı korelasyon yoktu.

Sonuç: NAYKH kardiyometabolik morbidite ve mortalitenin güçlü bir belirleyicisi olduğu için, obezitesi olan kişilerde progresyon öncesi tanı koymak önemlidir ve bu amaçla geliştirilmiş basit, non-invaziv tarama/tanı yöntemlerine ihtiyaç vardır. VAİ, LBÜİ, FLİ ve HSİ kolayca hesaplanarak NAYK'sini öngördüğü belirlenmiş olan bilimsel modellerdir. Biz çalışmamızda bu öngörüyü sadece kısmen gösterebilmiş olmamıza rağmen, bu indeksler ulusal validasyon çalışmalarıyla cut-off değerleri belirlenerek etkin bir şekilde kullanılabilirler ve erken tanı sayesinde NAYKH-ilişkili komplikasyonların engellenmesini sağlayabilirler.

Anahtar kelimeler: NAYKH, NAYKH indeksler, obezite

Introduction

Over the last decade, there has been an exponential increase in obesity and overweight prevalence worldwide, practically resulting in a global pandemic. Obesity affects 60% of adults in Europe. Obesogenic lifestyle choices, combined with environmental/hormonal/genetic factors, have resulted in major public health issues. Diabetes, metabolic syndrome, dyslipidemia, fatty liver disease, hypertension, ischemic heart disease, heart failure, stroke, chronic respiratory diseases, obstructive sleep apnea, musculoskeletal disorders, chronic organ failures, mental health problems, and even cancer rates have all increased as obesity complications (1-4).

Non-alcoholic fatty liver disease (NAFLD) is one of the most prevalent obesity consequences. NAFLD is characterized as excess fat accumulation in the liver and reflects the presence of steatosis in >5% of hepatocytes on histology. NAFLD is predicted to affect 19-30% of European individuals. NAFLD is strongly linked to insulin resistance, metabolic syndrome, type 2 diabetes mellitus (DM), and dyslipidemia, all of which are common in people living with obesity and increase the risk of cardiovascular morbidity and mortality. NAFLD can also cause hepatic cirrhosis and hepatocellular carcinoma, both of which increase the risk of hepatic disease mortality (4-6).

The diagnosis of NAFLD is made by radiological or histopathological findings after excluding conditions such as viral hepatitis, significant alcohol intake and medicines that can cause fatty changes. Non-invasive measurements include abdominal ultrasonography (USG), elastography, computed tomography and magnetic resonance imaging. Hepatic biopsy is the gold standard for diagnosis, but its invasiveness limits its availability (4-6). Omics-based biomarkers (metabolomics and lipidomics) and non-coding RNA seem to be promising for NAFLD diagnosis, but they still need validation with more detailed studies (7). Recently introduced NAFLD indexes fatty liver index (FLI), visceral adiposity index (VAI), hepatosteatosis index (HSI) lipid accumulation product index (LAP) that are calculated with standard formulations using simple patient data are suggested as practical screening/diagnostic tools for liver fat accumulation (8-11).

In this study, we compared NAFLD indexes with hepatic USG and determined whether these indexes could be used as predictors of hepatosteatosis in patients with obesity.

Materials and Methods

This was a retrospective, single-center, correlational study. Eighty randomly chosen patients from our obesity center according to inclusion/exclusion criteria were included in the study.

Inclusion criteria wereas follows: Being 18 years old and above, having a patient file in an obesity center, having the results of all research parameters and hepatic USG on file, and exclusion criteria wereas follows: Having acute/chronic hepatic disease, receiving any kind of treatment for hepatosteatosis, having malignancy, and alcohol consumption above recommended amounts (above 30 g/day in male and 20 g/day in female).

Because the patients were being followed in an obesity center, they were all prescribed a Mediterranean-style calorie deficit diet tailored to their body mass index

(BMI), gender, and accompanying diseases by a dietitian. They were also recommended to engage in 150 minutes of aerobic exercise per week, mainly involving walking or swimming if possible, and to perform resistance exercises twice a week as instructed by a physiotherapist. Alcohol consumption was present in 6 male patients (7.5%) who reported drinking socially once or twice a year at levels that were not above the recommended limit; thus, they did not need to be excluded.

All patients' age, gender, weight, height, BMI, fasting blood glucose, high-density lipoprotein, triglyceride, low-density lipoprotein, insulin, alanine transaminase (ALT), aspartate aminotransferase, gamma-glutamyl transferase, and hepatic USG results, accompanying diseases, and medicines if present were recorded. Non-alcoholic fatty liver disease indexes: VAI, lipid accumulation product index (LAP), FLI, and hepatosteatosis index (HSI) were calculated according to international standard formulations. Results were evaluated using the SPSS program.

Statistical Analysis

SPSS 23.0 was used for statistical analysis. Descriptive statistics are reported as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of variables was tested with the Kolmogorov-Smirnov test. Quantitative independent data analysis was performed using the Mann-Whitney U test and Kruskal-Wallis test. Categorical variable analysis was performed using the chi-square test. Qualitative independent data analysis was performed using the Pearson and Spearman correlation test. Statistical significance was set as $p<0.05$.

Ethics committee approval: Ethics committee approval was obtained for this study from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (05.03.2021/2764). All procedures performed in this study were in accordance with the 1964 Helsinki Declaration.

Results

Sixty-five females and 15 males, a total of 80 people with obesity, were included in the study. The mean age was 44±12 years in women and 38±12 years in men. Mean BMI was 40.7 kg/m^2±6.3 and WC 118.1±11.7 cm in women and 41.1±6.3 kg/m^2 and 130.9±9.9 9.9 cm in men.

In the general population, HS rates are: HS(-) 10%, 1st degree 17.05%, 2nd degree: 58.75%, and 3rd degree: 13.75%. Alcohol consumption and being on medication for accompanying diseases rates were higher in HS(+) group than in the HS(-) group. DM, HT, and other accompanying diseasesrates were higher in HS(+) group. Descriptive analyses of other clinical findings for men and women are listed in Table 1.

When HS levels were compared with mean NAFLD index values, there was a statistically significant difference for HSI mean group values ($p<0.05$). There was no statistically significant difference for the other NAFLD indexes (Table 2).

There was no statistically significant difference between HS(+) and HS(-) groups for VAI, LAP, FLI, and HSI mean values ($p>0.05$). Weight, WC, and ALT mean values were higher in HS(+) group than in the HS(-) group ($p<0.05$). There was a positive correlation between BMI and LAP and between FLI and HSI. There was no significant correlation between BMI and VAI (Table 3).

Discussion

NAFLD is one of the most common liver diseases, and its prevalence has been increasing concurrently with the global obesity epidemic (12). It has great clinical importance because of its hepatic and cardiometabolic consequences. Hepatic steatosis can develop into fibrosis, non-alcoholic steatohepatitis, and ultimately, cirrhosis, which can result in hepatocellular cancer. It is also strongly related to insulin resistance, which can cause several metabolic disturbances. NAFLD is found in 30-87% of patients with type 2 DM. Dyslipidemia, hypertension, inflammation, and atherosclerosis are also highly present in NAFLD.

Table 1. Comparison of VAI, LAP, FLI and HSI according to hepatic USG

	Hepatic USG												p
	No HS			1st degree HS			2nd degree HS			3rd degree HS			
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
VAI	3.2	±3.5	2.0	2.5	±1.1	2.3	3.4	±3.8	2.8	3.1	±1.6	2.7	0.528
LAP	97.9	±93.3	52.0	91.8	±45.1	75.2	127.1	±114.0	101.9	136.5	±62.4	140.7	0.072
FLI	80.7	±21.0	88.0	84.9	±18.9	93.0	93.7	±7.3	97.0	96.2	±5.2	97.0	0.066
HSI	47.2	±8.3	45.2	48.4	±5.6	47.9	53.6	±7.5	53.0	52.4	±6.8	51.6	**0.032**[a]

[a]: One-Way ANOVA, Kruskal-Wallis test, post-hoc LSD test, HS: Hepatosteatosis, SD: Standard deviation, VAI: Visceral adiposity index, FLI: Fatty liver index, LAP: Lipid accumulation product index, HSI: Hepatosteatosis index

Table 2. Comparison of VAI, LBUI, FLU and HSI in HS(+) and HS(-) groups

	Hepatic USG						p
	HS(+)			HS(-)			
	Mean	SD	Median	Mean	SD	Median	
Age (years)	44	±16	45	42	±12	44	0.936
Height (cm)	156.2	±5.0	157.5	161.6	±10.0	160.0	0.205
Weight (kg)	94.1	±18.4	88.0	108.1	±18.0	111.5	**0.040**[a]
BMI (kg/m^2)	38.3	±7.1	35.7	41.0	±6.1	40.7	0.243[a]
WC (cm)	112.0	±13.1	110.0	121.5	±12.0	121.5	**0.039**[a]
Systolic BP (mmHg)	123.7	±9.1	120.0	123.4	±10.5	120.0	0.965
Diastolic BP (mmHg)	76.2	±7.4	80.0	77.6	±6.1	80.0	0.773
FBG (mg/dL)	97.7	±10.9	99.0	113.9	±36.6	104.0	0.163
TG (mg/dL)	145.5	±105.7	104.0	170.9	±122.7	150.0	0.173
HDL (mg/dL)	48.3	±13.8	47.0	46.9	±11.0	45.5	0.742[a]
LDL (mg/dL)	135.5	±23.7	134.5	129.2	±38.1	125.0	0.654[a]
Insulin	12.3	±10.6	6.7	15.0	±9.9	12.9	0.138
ALT (U/L)	16.2	±5.1	16.5	31.1	±23.2	23.0	**0.012**
AST (U/L)	20.0	±5.2	19.5	26.4	±15.5	21.5	0.261
GGT (U/L)	23.6	±7.0	23.0	30.1	±15.8	25.0	0.339
VAI	3.2	±3.5	2.0	3.2	±3.2	2.6	0.312
LAP	97.9	±93.3	52.0	121.6	±97.8	99.4	0.083
FLI	80.7	±21.0	88.0	92.3	±11.1	97.0	0.159
HSI	47.2	±8.3	45.2	52.4	±7.3	52.0	0.064[a]

[a]: Independent sample test, Mann-Whitney U test, SD: Standard deviation, BMI: Body mass index, VAI: Visceral adiposity index, FLI: Fatty liver index, LAP: Lipid accumulation product index, HSI: Hepatosteatosis index, ALT: Alanine transaminase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, TG: Triglyceride, FBG: Fasting blood glucose, HDL: High density lipoprotein

Table 3. Relationship between BMI and VAI, LAP, FLI and HSI

		BMI	VAI	LAP	FLI	HSI
BMI	r	1.000	0.071	0.374**	0.837**	0.917**
	p	-	0.531	**0.001**	**<0.001**	**<0.001**[a]
VAI	r	0.071	1.000	0.847**	0.414**	0.071
	p	0.531	-	<0.001	<0.001	0.534
LAP	r	0.374**	0.847**	1.000	0.700**	0.386**
	p	0.001	<0.001	.	<0.001	<0.001
FLI	r	0.837**	0.414**	0.700**	1.000	0.812**
	p	<0.001	<0.001	<0.001	-	<0.001
HSI	r	0.914**	0.071	0.386**	0.812**	1.000
	p	<0.001	0.534	<0.001	<0.001	-

[a]: Pearson correlation, Spearman correlation test, BMI: Body mass index, VAI: Visceral adiposity index, FLI: Fatty liver index, LAP: Lipid accumulation product index, HSI: Hepatosteatosis index

The disease is now referred to as "metabolic-associated fatty liver disease" because of its close association with metabolic dysfunction. Early diagnosis using simple tools is necessary to overcome these hepatic and cardiovascular morbidity and mortality risks (13,14).

The FLI, VAI, hepatosteatosis index, and LAP are mathematical models that use anthropometric data, lipid profile tests, and liver function tests to predict NAFLD. They demonstrated visceral adiposity, adipocyte dysfunction, insulin resistance, metabolic dysfunction, and cardiometabolic risk using simple regular patient data available in almost every patient file (8-11). These markers have been reported to be able to accurately diagnose hepatic steatosis in various studies using hepatic biopsy or hepatic USG data as references; however, they could not quantify the steatosis (15).

In our study, HSI correlated with liver USG for hepatosteatosis, but the other indices had no significant relationship. In different studies, different indexes were found to be more effective in predicting HS. In a study by Sheng et al. (16), HSI and LAP had the strongest relationship with HS, whereas Han and Lee (17) found that FLI was the best predictor of HS. Lee et al. (9) tested 5362 NAFLD patients for HSI and validated it as a HS predictor but suggested it to be used as a screening tool to predict the

patients to perform a hepatic USG. The patient population, number of subjects, and parameters used in the algorithm may have caused this difference.

90% of our study patients had USG-proven hepatostetaosis, and the majority of the HS was second degree. Obesity is well known to be related to fatty liver, and our results were in accordance with the literature (18). In our study, the HS(+) group had higher rates of DM, HT, other accompanying diseases, medications used for these diseases, and alcohol consumption within recommended limits when compared with the HS(-) group. Fatty liver disease is associated with cardiometabolic diseases (19).

NAFLD is associated with type 2 DM and insulin resistance. Type 2 DM causes an increased risk of hepatic morbidity (inflammation, fibrosis, cirrhosis, hepatocellular carcinoma) and mortality. At the same time, NAFLD increases the risk of type 2 DM (20). In a national study, it was shown that 32.8% of patients with NAFLD developed type 2 DM. In another study, 94.3% of the patients with diabetes were found to have NAFLD, and in this study population, 92.7% of the patients were diagnosed with obesity or overweight (21). The occurrence of obesity and NAFLD has been emphasized in several studies (22-24). In our study, all patients had obesity, and US-proven HS was more common in the DM group, but the NAFLD indexes did not support this finding. This might be due to the improvement of parameters used in NAFLD indexes because of the diet and exercise program the patients were on.

The severity of NAFLD is determined by a combination of factors, including obesity, insulin resistance, and lipotoxic lipids, along with genetic susceptibility (25). In a study by Sheng et al. (16), TyG index-related parameters, LAP, HSI, BMI, and WC appear to be good predictors of NAFLD. Kannangara et al. (26) showed that FLI and HSI positively correlated with US-proven HS in type 2 DM. In our study, BMI, type 2 DM, and HSI were also correlated with NAFLD.

In addition, alcohol consumption seems to affect hepatosteatosis even the amount is not at level of alcohol abuse and it does not have chronicity. Weight, WC, and ALT were also higher in the HS(+) group. HS is associated with obesity, particularly abdominal obesity (27) and ALT is a specific marker for hepatic inflammation and is more liver-specific (28). In our study, alcohol consumption did not affect the results, as very few patients had a very limited amount that could be ignored.

There was a positive correlation between BMI and LBUI, FLI, and HSI but not with VAI in our study. In the literature, NAFLD and VAI are usually related to obesity, but there are also studies showing the existence of NAFLD in lean subjects. In addition, although VAI is usually found to be related to cardiometabolic disease risk, there are studies that did not find this relationship in patients with obesity (29-31). Thus, there are different results about BMI and NAFLD/NAFLD indexes, as seen in our study. Still, it is a fact that 70-80% of people with NAFLD have obesity (27).

Study Limitations

USG can detect hepatosteatosis after 20% fat deposition, while 5% is the accepted cut-off. Although it was performed by the same senior radiologist, it is dependent on the operator and subjective. In addition, the NAFLD indexes are circumstantial calculations. The gold standard for detecting hepatosteatosis is liver biopsy.

Conclusion

Because NAFLD is a strong predictor of cardiometabolic morbidity and mortality, it is important to make a diagnosis before progression in people living with obesity, and simple non-invasive screening/diagnostic tools are needed for this purpose. VAI, LAP, FLI, and HSI are easily calculated scientific models that predicted NAFLD. Although we could only partially confirm this prediction, they could be used effectively after national validation studies that determine the cut-off values, and the prevention of NAFLD-related complications could be achieved with early diagnosis.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for this study from the Ethics Committee of University of Health Sciences Turkey, İstanbul Training and Research Hospital (05.03.2021/2764). All procedures performed in this study were in accordance with the 1964 Helsinki Declaration.

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Surgical and Medical Practices: F.A., I.İ., H.U.A., M.E.P., Concept: F.A., Design: F.A., Data Collection or Processing: F.A., I.İ., H.U.A., M.E.P., Analysis or Interpretation: F.A., I.İ., H.U.A., M.E.P., Literature Search: F.A., I.İ., H.U.A., M.E.P., Writing: F.A., I.İ., H.U.A., M.E.P.

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ORIGINAL RESEARCH

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Role of Low-dose Intramuscular Ketamine in Vascular Access in Pediatric Patients with Sedation Anesthesia in Magnetic Resonance Imaging

Pediyatrik Olguların Damaryolu Erişiminde Kullanılan Düşük Doz İntramusküler Ketaminin, Manyetik Rezonans Görüntülenmesinde Sedasyon Anestezisindeki Yeri

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Abstract

Objective: While there are few studies on the use of ketamine for sedation during magnetic resonance imaging (MRI) of pediatric patients, we aimed to investigate the effects of low-dose ketamine administered intramuscularly for vascular access on hemodynamics, sedation and recovery, and MRI quality for the first time.

Method: A total of 193 pediatric patients aged 3 months to 15 years who received sedation anesthesia for MRI were included in this study. Ninety-nine subjects in the group (Group K) administered ketamine 2.5 mg/kg and below intramuscularly and the propofol-control group (Group C), where 94 subjects were not administered intramuscular ketamine, were divided into two groups. The groups were compared in terms of demographic data, sedation and procedure times, anesthetic drug doses, Ramsay sedation score, hemodynamic parameters, recovery time, modified Aldrete recovery scores, MRI quality, and side effects.

Results: The mean values of first dose and additional dose propofol mg/kg in Group K were 0.56 (0.45/0.71) - 0 (0/0), respectively, whereas in Group C the values were 1.11 (0.87/1.33) - 0.14 (0/0.5), respectively. In Group K, the mean systolic arterial pressures, diastolic arterial pressures, and median values of mean arterial pressures during the procedure were found to be higher than those of Group C (p<0.001; =0.001; <0.001, respectively). While the jaw-thrust maneuver was performed in two

Öz

Amaç: Pediyatrik olguların, manyetik rezonans görüntüleme (MRG) işlemi esnasında sedasyon amaçlı ketamin kullanımına dair sayılı miktarda çalışma mevcutken, ilk kez çalışmamızda intramusküler yoldan damar yolu erişimi için uygulanılan düşük doz ketaminin hemodinamik, sedasyon ve derlenme ve MRG kalitesi üzerine olan etkilerini araştırmayı amaçladık.

Yöntem: Bu çalışmaya MRG işlemi için sedasyon anestezisi alan 3 ay-15 yaş arası toplam 193 pediyatrik hasta dahil edildi. Doksan dokuz kişi intramusküler ketamin 2,5 mg/kg ve altında uygulanılmış grup (Grup K) ve 94 kişi intramusküler ketamin uygulanılmayan propofol kontrol grubu (Grup C) olarak, iki grup halinde oluşturuldu. Gruplar, demografik veriler, sedasyon ve işlem süreleri, anestezik ilaç dozları, Ramsay sedasyon skoru, hemodinamik parametreler, derlenme süresi, modifiye Aldrete derlenme skorları, MRG kalitesi ve yan etkiler açısından karşılaştırıldı.

Bulgular: Grup K'de ilk doz ve ek doz propofol mg/kg ortalama değerleri sırasıyla 0,56 (0,45/0,71) -0 (0/0) iken, Grup C'de değerler sırasıyla 1,11 (0,87/1,33) - 0,14 (0/0,5) olarak bulundu. Grup K'de işlem sürecindeki sistolik arteriyal basınç, diastolik arteriyal basınç ve ortalama arteriyal basıncın medyan değerleri Grup C'nin değerlerinden daha yüksek bulundu (sırasıyla p<0,001; =0,001; <0,001). Grup K'de iki hastada çene itme-kaldırma manevrası uygulanılırken, Grup C'de bir hastada hava

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Abstract

patients in Group K, airway was required in one patient in Group C. The relationship between the groups in terms of MRI quality was found to be statistically significant (p<0.016).

Conclusion: It has been observed that low-dose intramuscular ketamine (2.5 mg/kg and less) used in vascular access provides a positive efficacy and safety profile with less sedative additional drugs, even in agitated children during sedation anesthesia during pediatric MRI, and better MRI quality is achieved.

Keywords: Intramuscular ketamine, magnetic resonance imaging, pediatrics, propofol, sedation

Öz

yolu aparatı ihtiyacı olmuştur. MRG kalitesi açısından gruplar arasındaki ilişkinin istatistiksel olarak anlamlı olduğu görüldü (p<0,016).

Sonuç: Damar yolu erişiminde kullanılan düşük doz intramusküler ketaminin (2,5 mg/kg ve altı), pediyatrik MRG esnasında sedasyon anestezisinde ajite çocuklarda dahi daha az sedatif ek ilaçla olumlu etkinlik ve güvenilirlik profili sağladığı, daha mükemmel MRG kalitesine ulaşıldığı gözlemlenilmiştir.

Anahtar kelimeler: İntramusküler ketamin, manyetik rezonans görüntüleme, pediyatri, propofol, sedasyon

Introduction

In pediatric cases, computed tomography and magnetic resonance imaging (MRI) have become more common; therefore, the provision of adequate sedation in such instances is important (1). MRI has become the imaging modality of choice for pediatric cases because it can provide non-invasive, multiplanar, and high-contrast imagingwith respect to blood flow, myelin maturation, hemoglobin breakdown products, and greater sensitivity. The disadvantages are that the imaging time tends to be longer (45-60 minutes) with image quality is affected by patient movements (2). Immobility and patient compliance are important factors in ensuring imaging quality; therefore, anesthesia and/or deep sedation are often necessary in pediatric MRI to minimize motion-related artifacts in almost all of the pediatric population, as in adult patients with claustrophobia, mental retardation, anxiety, and communication difficulties (3,4).

Ketamine not only results in deep sedation and analgesia, but the side effects, respiratory depression and cardiovascular, are minimal (5). It can be used either intramuscularly (im) or intravenously (v), with the profiles for both applications seen to be safe and efficacious; rates for respiratory side effects are also low (6). Numerous studies of ketamine use have reported a favorable safety profile with reduced airway complications. However, one of the most important disadvantages is the long recovery time (7). It can be administered both v and m and is widely used in situations where vascular access is limited (8). Nystagmus is common; eyes usually remain open. While the sympathomimetic pathway is frequently stimulated, tidal volume and functional residual capacity are retained because of relaxation in the bronchial smooth muscles (9).

Airway obstruction, laryngospasm, apnea, and hypoxia are the primary adverse events with respect to ketamine usage, with a reported overall rate of 3.9%. Of these, the rarest is laryngospasm, with a rate of 0.3% (10). With sedation/analgesia techniques, the patient's anxiety, restlessness, and pain can be reduced or completely eliminated. In addition, in initiatives that require immobility, such as pediatrics and non-cooperative adult patients, the success of the initiative by preventing movement is increased. Ketamine is a good analgesic. It is used in painful interventions. Minimal respiratory and cardiac depressant effects With ketamine, patient movement increase; therefore, movement it should be used with caution in undesirable interventions (11).

During diagnostic imaging tests, children require adequate sedation and appropriate doses of anesthetic agents for a successful examination to occur with minimal complications. The aim of this article was to examine the effect of low-dose m ketamine, which is used for vascular access, on sedation anesthesia in a group of pediatric patients who were accepted for MRI and compared with other sedative drugs. This study investigates low-dose (≤2.5 mg/kg) m ketamine, administered for vascular access during MRI in the pediatric population, with respect to its stability, safety, and efficacy on the assumption that it resulted in potentially fewer airway complications, sufficient immobility, and better quality MRI.

Materials and Methods

Approval for this study was obtained from the Local Ethics Committee of the University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (2018/48). The study included pediatric inpatients and outpatients aged 3 months to 15 years, ASA < IV, not allergic to any agent used in the study, and not presenting

a contraindication, who had been referred to the MRI unit for magnetic resonance diagnostic imaging under sedation for a total of four months. Patients aged 3 months and older than 15 years, who underwent mask, laryngeal mask, and/or endotracheal intubation under general anesthesia, who underwent imaging without anesthesia in the presence of their parents, and who experienced adverse events were excluded from the study. As an anesthesia application outside the operating room, oral or m sedative agents are used in the MRI unit in the pediatric patient group to provide routine vascular access. This study aimed to determine the perioperative effects, efficacy, and safety of these drugs. For this purpose, patients who received or did not receive m ketamine for vascular access before the imaging procedure were compared and evaluated. Two groups of 193 patients in total were created. The 99 patients in Group K received m ketamine (≤2.5 mg/kg), whereas the 94 subjects in Group C (as the propofol-control group) were not administered m ketamine.

The hemodynamic status and degree of sedation before, during, and after imaging were monitored by an anesthesiologist and an anesthesia technician. The presence of vascular access determined which of the two groups the patients were assigned to. Intramuscular ketamine of 2.5 mg/kg was administered to patients without vascular access, and when adequate sedation was achieved, cannula intervention was performed. In both groups, an extension line was placed in all vascular access cannulas so that the contrast agent used in MRI and additional doses of anesthetic drugs could be easily administered without creating a tactile stimulus. The drugs and the saline solution administered afterwards were administered as an v bolus. Monitoring devices for pulse oximetry, electrocardiography, non-invasive blood pressure measurement, and capnography were attached to the children before induction. Intravenous propofol was titrated and administered to both groups, where there was loss of consciousness after the use of midazolam at 0.02 mg/kg during induction, absence of eyelash reflex, and no response to a face mask. A further dose of propofol (0.25-0.5 mg/kg on average) was administered if the patient retained consciousness during imaging. A Ramsay sedation scale (RSS) level of 4 to 5 was maintained upon completion of imaging. When the imaging was completed, the child was brought to the recovery room. When they were within the pre-sedation values, at a modified Aldrete recovery score (MARS) of 10 points, i.e., when hemodynamic values were ±20% of their pre-sedation values, the child was discharged if fully conscious.

Patient demographic data, American Society of Anesthesiology (ASA) physical status, MRI area, time until induction, MRI times, total sedation time, sedative doses administered until unconsciousness, total and further doses of propofol, along with basal values, systolic arterial pressures (SAP), diastolic arterial pressures (DAP), mean arterial pressures (MAP), apex heart rate (HR), rates of respiration, end-tidal carbon dioxide ($EtCO_2$) measurements, and oxygen saturations (SpO_2) were reviewed and recorded. During the recovery period, 0^{th}, 15^{th}, 30^{th} minutes RSS values, 0^{th}, 15^{th}, and 2^{nd} hour MARS values and the period when the MARS was 10 points, developed side effects, and MRI quality were noted as per both of the forms for anesthesia and recovery follow-up. The groups were compared with respect to the examined parameters.

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, New York, United States) and PAST 3 (Hammer, Ø., Harper, D.A.T., Ryan, P.D. 2001). Paleontological statisticswere employed for variable analysis. The Shapiro-Wilk francia test was used to determine univariate data conformity to the normal distribution, and the Levene test was used to evaluate the homogeneity of variance. Multivariate data conformity to the normal distribution was evaluated using the Mardia test. with the Dornik and Hansen omnibus test and the Box-M test used in relation to variance homogeneity. In comparing two independent groups according to the quantitative variables, the Independent-Samples t-test and Bootstrap results were employed, as was the Mann-Whitney U test in conjunction with the Monte Carlo results. The combination of paired-samples t-test and Boostrap results were used for a comparison of two-repeat measurements of the dependent quantitative variables. The Wilcoxon signed rank test was used in conjunction with the Monte Carlo simulation results, while an examination of the interaction of repeated quantitative measurements of variables according to groups was undertaken with the general linear model repeated ANOVA test. The Pearson chi-square, Fisher's Exact, and Fisher-Freeman-Halton tests were tested with the Monte Carlo simulation technique when comparing the categorical variables with each other, and the Benjamini-Hochberg-corrected p-value results were used for column ratio comparisons. In the tables, the mean (standard deviation) and median (percentile 25/percentile 75) were used for the expression of the quantitative variables, as was n (%) for the categorization variables. A 95% confidence level was used for the analysis of the variables, and where the p-value was less than 0.05, this was

considered significant. Repeated analyses of variance are used to analyze variables showing normal distribution and variance homogeneity. To test this, the Mardia and Dornik and Hansen omnibus tests are used for normal distribution and the Box-m test is used for homogeneity of variance. In our study, we evaluated the multivariate normality test and Mardia and Dornik and Hansen omnibus tests to make repeated measurements and choose the right analysis from hypothesis tests. This test tests normality in terms of both kurtosis and skewness. There were cases where our parametric tests were not appropriate for analyzing the results of these analyses. Therefore, it was tested using non-parametric analyses.

Results

A comparison of Groups K and C was made with respect to both clinical and demographic data (Table 1).

Between the groups, SpO_2, HR, SAP, DAP, MAP, respiratory rate, and $EtCO_2$ were comparable hemodynamic parameters. In Group K, the mean SAP, DAP, and median values of MAP during the procedure were higher than those in Group C ($p<0.001$; $=0.001$; <0.001, respectively) (Table 2).

The relationship between the groups in terms of propofol used in the first dose (mg/kg) and that in the additional dose (mg/kg) was statistically significant ($p<0.001$; and $=0.005$, respectively) (Figure 1, 2). In a comparison between groups, the mean values of the first dose and additional dose of propofol (mg/kg) in Group K were 0.56 (0.45/0.71) - 0 (0/0), respectively, while in Group C, the values were 1.11 (0.87/1.33) - 0.14 (0/0.5), respectively (Table 1).

Baseline and mean values after sedation initiation, and the median measurements of the change calculations between the baseline and mean values in the RSS analyses of the groups were found to be significantly different ($p<0.001$; $=0.003$; <0.001, respectively). Accordingly, the median values of change in Group K from the beginning of sedation to the end showed a positive increase compared with those in Group C. The increase was found to be statistically significant (the median values of change were 2.0 and 2.8, respectively) (Figure 3).

In the 0^{th} minute, with respect to MARS values at awakening between the groups ($p<0.001$), it was seen that there were statistically significant differences. Group K, 0^{th} minute MARS values were found to be lower than Group C averages. MARS measurements at the 15^{th} and 120^{th} minutes showed no statistically significant differences ($p=0.066$; $=0.999$, respectively) (Figure 4). The time the MARS was 10 points between the groups was also statistically significantly different: in Group K, the time to MARS 10 points was found to be twice as long as that for Group C ($p<0.001$) (Table 1).

Airway intervention was performed in three patients. While the jaw-thrust maneuver was performed in two patients in Group K, an airway was required in one patient in Group C (Table 1).

A comparison of the groups with respect to the presence of nausea-vomiting showed that the relationship at both the 30^{th} and 60^{th} minutes was statistically significant, with a higher incidence of nausea and vomiting in Group K than in Group C ($p=0.010$; $=0.034$, respectively).

A statistically significant difference was also found in the relationship between the groups in terms of MRI quality ($p<0.016$) (Figure 5).

One of the 210 children who met the study criteria could not complete the MRI scan due to a power outage. In the other case, the patient was awakened due to excessive secretions and coughing, and 15 were excluded from the analysis because of parent support. In patients included in the study, 135 of the brain, 18 of the whole abdomen, 13 of the lumbar vertebrae, 12 of the pituitary gland, 10 of the whole spinal cord, 6 of the orbita, 6 of the extremities, 6 of the cervical, 4 of the thorax, 3 of the neck, 2 of the sacral, and 2 of the face MRI was applied.

Discussion

The use of MRI has increased in the pediatric patient group because it can be examined without exposure to radiation during medical diagnosis, disease staging, and follow-up. While older children and adolescents without neurological disabilities can go through this process using glasses and while watching movies without sedation, younger children, in particular those under 5 years of age, require pharmacological assistance, sedation, or general anesthesia (12).

The use of ketamine for sedation in pediatric patients is common because the incidence of complications, for example, cardiorespiratory depression, is low compared with the effects often observed following benzodiazepine or narcotic usage. It also provides sedation with effective analgesia during in- and out-of-operating room procedures. Although the administration route can be oral, rectal, or intranasal, the most effective and commonly used methods for the anesthesia of pediatric patients are v and m. Its effect begins 5 min following its use m with an effective duration of approximately 45 min (13).

Table 1. Comparison of the groups according to demographic and clinical variables

	Total (n=193)	Group C (n=94)	Group K (n=99)	p
	n (%)	n (%)	n (%)	
Gender (girl)	82 (42.5)	36 (38.3)	46 (46.5)	0.308[c]
Age (year)				0.254[c]
3-6 months	40 (20.7)	24 (25.5)	16 (16.2)	
6-12 months	24 (12.4)	10 (10.6)	14 (14.1)	
>1 year	129 (66.8)	60 (63.8)	69 (69.7)	
	Median (q1/q3)	Median (q1/q3)	Median (q1/q3)	
Height (cm)	75 (64/90)	73 (61/89)	77 (67/91)	0.143[u]
Weight (kg)	11 (8/15)	10.25 (7.5/16)	11.5 (9/15)	0.511[u]
Induction time (min)	9 (3/14)	3 (2/4)	14 (10/17)	**<0.001**[u]
MRI time (min)	16 (12/25)	15 (12/22)	20 (12/26)	0.130[u]
Sedation time (min)	26 (20/35)	20 (15/25)	35 (26/41)	**<0.001**[u]
Recovery time(10) (min)	8 (5/10)	5 (5/10)	10 (5/12)	**<0.001**[u]
First dose of midazolam (mg/kg)	0.02 (0.02/0.02)	0.02 (0.02/0.02)	0.02 (0.02/0.02)	0.943[u]
First dose of propofol (mg/kg)	0.83 (0.5/1.15)	1.11 (0.87/1.33)	0.56 (0.45/0.71)	**<0.001**[u]
Additional dose of propofol (mg/kg)	0.06 (0/0.2)	0.14 (0/0.5)	0 (0/0)	**0.005**[u]
Total dose of propofol (mg/kg)	0.93 (0.5/1.4)	1.25 (0.9/1.7)	0.59 (0.5/1)	**<0.001**[u]
	n (%)	n (%)	n (%)	
ASA				**<0.001 ff**
I	113 (58.5)	39 (41.5)	74 (74.7) **A**	
II	76 (39.4)	51 (54.3) B	25 (25.3)	
III	4 (2.1)	4 (4.3) B	0 (0)	
Movement				0.249 ff
No	153 (79.3)	69 (73.4)	84 (84.8)	
Minimal	30 (15.5)	18 (19.1)	12 (12.1)	
Moderate	6 (3.1)	4 (4.3)	2 (2)	
Intensity	4 (2.1)	3 (3.2)	1 (1)	
Airway intervention	3 (1.5)	1 (1.1)	2 (2)	0.999[f]
Increased secretion	4 (2.1)	0 (0)	4 (4)	0.122[f]
Atropin sulfate	14 (7.3)	6 (6.4)	8 (8.1)	0.784[c]
Metoklopramid hydrochloride	4 (2.1)	1 (1.1)	3 (3)	0.622[f]
Flumazenil	1 (0.5)	0 (0)	1 (1)	0.999[f]
Bradycardia	12 (6.2)	7 (7.4)	5 (5.1)	0.560[c]
Apnea (10 sn)	1 (0.5)	0 (0)	1 (1)	0.999[f]
SpO_2<90	3 (1.6)	2 (2.1)	1 (1)	0.613[f]
Agitation	3 (1.6)	0 (0)	3 (3)	0.247[f]
Nightmare	2 (1)	0 (0)	2 (2)	0.498[f]
Diplopia	12 (6.2)	0 (0)	12 (12.1)	**<0.001**[c]
Unsuccessful sedation	3 (1.6)	1 (1.1)	2 (2)	0.999[f]
Three or more additional doses	6 (3.1)	3 (3.2)	3 (3)	0.999[f]
MR sequence repetition	6 (3.1)	3 (3.2)	3 (3)	0.999[f]

t: Independent t-test (Bootstrap), Mann-Whitney U test (Monte Carlo), ff: Fisher-Freeman-Halton (Monte Carlo), f: Fisher's Exact test (Monte Carlo), [c]: Pearson chi-square test (Monte Carlo); post hoc test: Benjamini-Hochberg correlation, q1: 1st quartile, q3: quartile, SD: Standard deviation, MR: Magnetic resonance, MRI: Magnetic resonance imaging, American Society of Anesthesiology

Table 2. Comparison of the groups' hemodynamic parameters, including basal and mean values, and according to their variations

	Group C (n=94)	Group K (n=99)	p
	Median (q1/q3)	**Median (q1/q3)**	
SpO_2			
Bazal	99.0 (99.0/99.0)	99.0 (99.0/99.0)	0.775[u]
Mean	98.6 (98.0/99.0)	98.9 (98.3/99.0)	0.311[u]
Variation	-0.1 (-1.0/0.0)	0.0 (-0.7/0.0)	0.588[u]
p-value (Bazal vs. Mean)	**0.001[w]**	**<0.001[w]**	
Pulse			
Bazal	132.5 (118.0/151.0)	135.0 (125.0/146.0)	0.716[u]
Mean	117.2 (102.0/127.7)	116.0 (105.5/128.4)	0.558[u]
Variation	-17.6 (-23.7/-13.0)	-18.0 (-24.0/-10.6)	0.503[u]
p-value (Bazal vs. Mean)	**<0.001[w]**	**<0.001[w]**	
SAP			
Bazal	101.0 (94.0/111.0)	113.0 (100.0/124.0)	**<0.001[u]**
Mean	96.0 (90.0/103.0)	104.0 (95.0/112.0)	**<0.001[u]**
Variation	-5.0 (-9.0/-2.0)	-8.0 (-17.0/-0.5)	**0.039[u]**
p-value (Bazal vs. Mean)	**<0.001[w]**	**<0.001[w]**	
	Mean (SD)	**Mean (SD)**	
DAP			
Bazal	62.5 (11.3)	70.4 (11.7)	**<0.001[t]**
Mean	58.9 (7.9)	62.8 (7.3)	**0.001[t]**
Variation	-3.5 (7.2)	-7.6 (9.3)	**0.001[ra]**
p-value (Bazal vs. Mean)	**<0.001[e]**	**<0.001[e]**	
MAP			
Bazal	75.9 (10.7)	84.1 (11.5)	**<0.001[t]**
Mean	71.5 (8.0)	76.2 (7.9)	**<0.001[t]**
Variation	-4.4 (6.7)	-7.9 (8.8)	**0.002[a]**
p-value (Bazal vs. Mean)	**<0.001[e]**	**<0.001[e]**	
Respiratory rate			
Bazal	27.7 (7.8)	26.0 (6.9)	0.111[t]
Mean	26.1 (6.8)	24.7 (6.2)	0.138[t]
Variation	-1.7 (4.5)	-1.3 (4.4)	0.626[ra]
p-value (Bazal vs. Mean)	**0.001[e]**	**0.003[e]**	
$EtCO_2$			
Bazal	30.9 (2.8)	31.2 (3.0)	0.414[t]
Mean	32.1 (2.3)	32.2 (2.5)	0.697[t]
Variation	1.2 (1.6)	1.0 (1.7)	0.392[ra]
p-value (Bazal vs. Mean)	**<0.001[e]**	**<0.001[e]**	

[ra]General Linear Model Repeated ANOVA (Wilks' Lambda), [t]: Independent t-test (Bootstrap), Mann-Whitney U test (Monte Carlo), [w]: Wilcoxon signed ranks test (Monte Carlo), [e]: Paired t-test (Bootstrap), [f]: Fisher's Exact test (Monte Carlo), Pearson chi-square test (Monte Carlo), post hoc test: Benjamini-Hochberg correlation, q1: 1st quartile, q3: 3rd quartile, SD: Standard deviation, MAP: Mean arterial pressures, SAP: Systolic arterial pressures, DAP: Diastolic arterial pressures

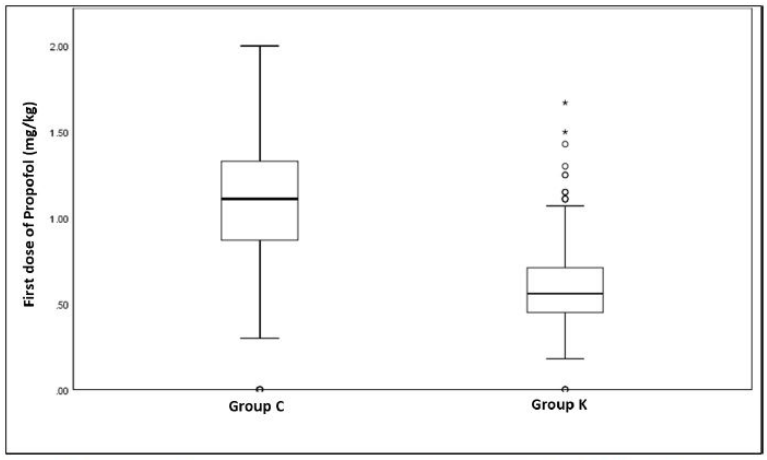

Figure 1. Comparision of first dose of propofol bolus between the groups. Propofol used in the first dose (mg/kg) was statistically significant (p<0.001). Group C (as the propofol-control group), Group K received im ketamine (≤2.5 mg/kg)

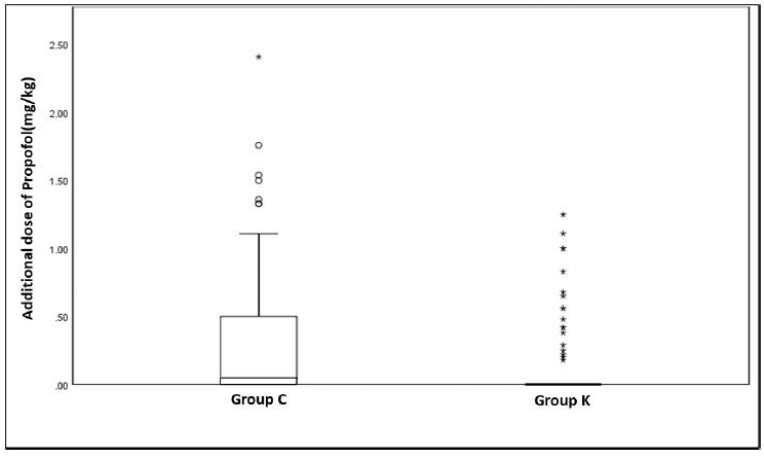

Figure 2. Comparision of additional dose of propofol bolus between the groups. The additional dose propofol (mg/kg) was statistically significant (p=0.005). Group C (as the propofol-control group), Group K received im ketamine (≤2.5 mg/kg)

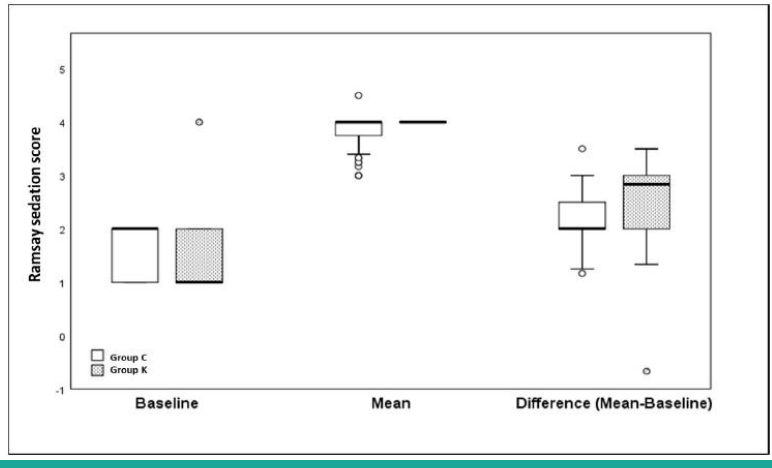

Figure 3. Comparison of the change calculations between the baseline and mean values in the Ramsay sedation scores between the groups. Group C (as the propofol-control group), Group K received im ketamine (≤2.5 mg/kg)

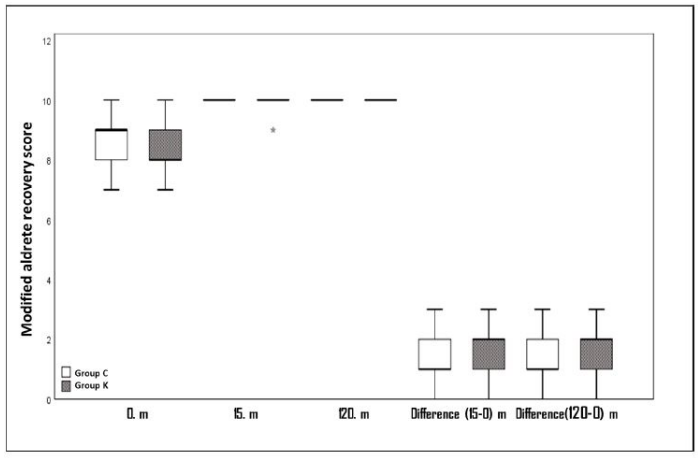

Figure 4. Illustrates the modified Aldrete recovery scores between the groups at each time. Group C (as the propofol-control group), Group K received im ketamine (≤2.5 mg/kg)

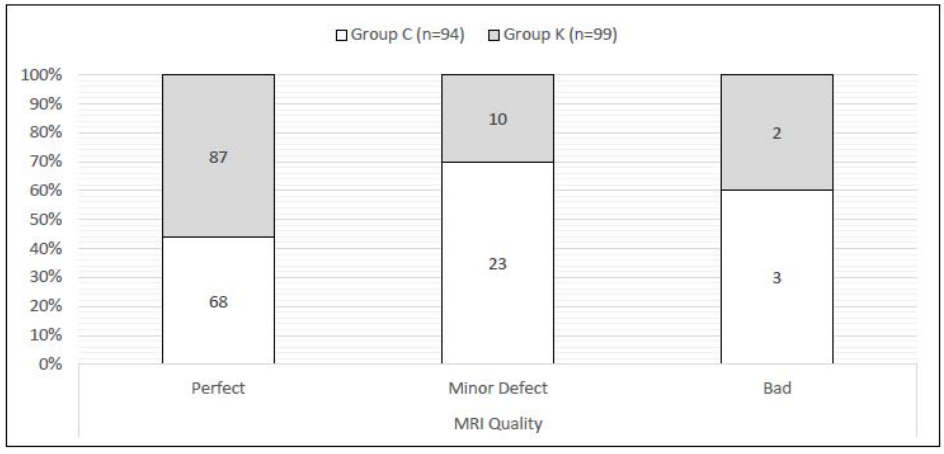

Figure 5. Bar chart of relationship between groups in terms of magnetic resonance imaging (MRI) quality. The scan quality was statistically comparable for the groups (p<0.016). Group C (as the propofol-control group), Group K, received im ketamine (≤2.5 mg/kg)

When ketamine is administered m for venous cannulation, it provides adequate analgesia with unique dissociative anesthesia, airway reflexes are usually preserved, and respiratory depression rarely occurs (14).

A comparison of the efficacy and quality of low-dose m ketamine (≤2.5 mg/kg), used for v access, with propofol in sedation anesthesia during pediatric MRI was undertaken in this study. According to the main findings, we observed that with m ketamine, without the need for additional doses of propofol, effective sedation, excellent immobility, and better MRI quality were achieved in more agitated children, based on RSS.

Eich et al. (15) reported that both bolus propofol requirement and total propofol consumption were lower in the propofol-ketamine group to which low-dose v ketamine was added, and recovery was faster. Tomatir et al. (16) showed that with small doses of ketamine (0.5 mg/kg), a scan in pediatric MRI could be completed successfully, with hemodynamic stability observed where both the induction and maintenance doses of propofol were lower (1.5 mg/kg, 75 mcg/kg/day). Sethi et al. (17) found that boluses of both propofol and ketamine (1 mg/kg each) administered during induction allowed sedation to be maintained with less propofol infusion (50 mcg/kg/min). As in the literature, it was found that the bolus doses of propofol used in induction in the ketamine group were half as low as those in the control group, and in the ketamine group, no additional propofol as a maintenance dose was required.

In the literature, it was seen that ketamine, which is used in different combinations in children for procedural sedation both in MRI and in the emergency department as well as

in laser applications, provides adequate sedation based on RSS (18-20). However, in a study that included intranasal ketamine use, it was reported that sedation failure was more common than intranasal dexmethotimidine (21). In our study, the depth of sedation was observed to be more consistent during the procedure in the ketamine group, and an increased level of sedation was found consistent with the effective level of m ketamine. Sedation failure, additional dose administration, and repeat MRI were observed in three patients in each group, with no difference observed. Although unsuccessful sedation was recorded in one patient with apnea in the control group, the procedure was stopped in 2 patients in the ketamine group because of excessive secretion and coughing.

In a study by Schmitz et al. (22) in which they compared two different propofol sedation regimens with and without ketamine in MRI, the MARS in the ketamine-propofol group gave evidence of faster normalization when compared to the propofol mono group recovery time [38 (22-65) - 54 (37-77) minutes], which was found to be significantly shorter. However, in a study comparing ketofol with a single agent, there is low evidence that recovery time is better (14). Shah et al. (23) showed that both mean total sedation and recovery times were shorter in the ketamine/propofol group than in the ketamine group. In our study, the mean total sedation and recovery times to MARS 10 were longer in the ketamine group than in the control group. MARS was determined as 10 points in both groups at the 15th minute measurements. We think that the efficacy of ketamine continues on average for 35 min of sedation, and that the lower first and total doses of propofol in the propofol group (1.1 mg/kg, 1.25 mg/kg, respectively) when compared with those used in other studies in the literature have an effect on recovery time.

Suryaprakash and Tham (24) observed that the effect of m ketamine on nausea-vomiting was correlated with age when used for pediatric procedural sedation in emergency contexts. In this same work, it was also seen that the patient was not predisposed to vomiting by the initial dose of ketamine (3 kg/mg or 4 kg/mg). Ketamine-sedation-associated vomiting was observed at a rate of 8.4% in pediatric patients, and there was a higher risk in children ≥8 years of age (24).

Akin et al.'s (25), which were used on auditory brainstem response test in pediatric cases, attributed the lower incidence of both nausea and vomiting in both groups (propofol and propofol-ketamin) to the fact that propofol has antiemetic properties by antagonizing dopamine D2 receptors, which was also similar to that in our study. In our study, we found that the 30th and 60th minute nausea-vomiting scores were higher in patients who were administered m ketamine.

In the study in which low-dose ketamine was added to propofol and compared solely with propofol, repetition of patient motion and single-sequence MRI were observed at a lower rate of 12.3% and 7%, respectively, in the ketamine group. As a result, they were found to provide equally suitable and safe imaging quality in both groups (15). Schmitz et al. (22) showed in their studies that long-term MRI was impaired more frequently due to patient movement in the ketamine-propofol group, and more sedative drugs were needed due to movement. We believe that the high rate of excellent MRI quality in the ketamine group observed in our study was due to effective and deep sedation despite low-dose ketamine usage (≤2.5 mg/kg).

Study Limitations

The limitations of our study are that it is a single-center study and data were collected from our own clinical experience.

In summary, during MRI, with respect to the m dose of ≤2.5 mg/kg we applied in pediatric cases, it was observed that ketamine maintains hemodynamic stability, has very few side effects, and achieves excellent MRI quality.

Conclusion

We believe that m ketamine, which we used to provide vascular access in pediatric patients, should be supported by further studies in terms of its effect on sedation and the recovery period, and that different dose ranges and agents should be evaluated in both MRI and other sedation procedures. The most appropriate doses that can provide immobility and their possible combinations with the most appropriate agents should be investigated in future studies.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Local Ethics Committee of the University of Health Sciences Turkey, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (2018/48).

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Surgical and Medical Practices: N.Y., Nu.Y., Concept: N.Y, A.D., Z.S., Design: N.Y., Nu.Y., A.S.Ş., Data Collection or Processing: N.Y., Nu.Y., K.A., Analysis or Interpretation: K.A.,

A.D., Z.S., Literature Search: N.Y., K.A., A.S.Ş., A.D., Z.S., Writing: N.Y., A.S.Ş.

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

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ORIGINAL RESEARCH

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Evaluation of the Efficacy of Neuronavigation-guided Scalp Block for Analgesia in Endoscopic Pituitary Surgery

Endoskopik Hipofiz Cerrahisinde Analjezi için Nöronavigasyon Kılavuzluğunda Skalp Bloğunun Etkinliğinin Değerlendirilmesi

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Abstract

Objective: Scalp block is used to manage pain caused by the skull pin during pituitary surgery. The neuronavigation device allows access to preoperative imaging in the perioperative period. The aim of this study was to determine the efficacy and feasibility of neuronavigation-guided scalp blocks.

Method: After ethics committee approval (decision no: 2023-130), patients over 18 years of age who underwent endoscopic pituitary adenoma surgery with scalp block were retrospectively reviewed. After the exclusion criteria, the patients who underwent scalp block were divided into two groups as neuronavigation or anatomical point-guided scalp block (neuronavigation and classic group). The groups were compared with respect to demographic and haemodynamic data, perioperative analgesic consumption, postoperative visual analogue scale (VAS) scores, and complications.

Results: The groups were similar in terms of demographics, haemodynamics, operative times, perioperative opioid use, postoperative VAS scores and analgesic use. Perioperative antihypertensive and postoperative rescue analgesic requirements were statistically similar in the neuronavigation and classics groups [1/4 and 6/9 (n/n); p=0.467 and p=0.537, respectively]. Postoperative rescue analgesic consumption at 24 hours was 87.50±30.62 mg in the neuronavigation group and 100.00±37.5 mg in the classic group (p=0.510). No patient had complications at any time.

Öz

Amaç: Skalp blok, hipofiz cerrahisi sırasında çivili başlığın neden olduğu ağrının yönetiminde kullanılmaktadır. Nöronavigasyon cihazı perioperatif dönemde preoperatif görüntülemeye erişim sağlamaktadır. Bu çalışmanın amacı nöronavigasyon kılavuzluğunda skalp bloklarının etkinliğini ve fizibilitesini belirlemektir.

Yöntem: Etik kurul onayından sonra (karar no: 2023-130), endoskopik hipofiz adenomu cerrahisinde skalp blok uygulanmış 18 yaş üstü hastalar retrospektif olarak incelendi. Dışlama kriterlerinden sonra, skalp bloğu uygulanmış hastalar nöronavigasyon veya anatomik nokta kılavuzluğunda skalp bloğu olarak iki gruba ayrıldı (nöronavigasyon ve klasik grup). Gruplar demografik ve hemodinamik veriler, perioperatif analjezik tüketimi, postoperatif görsel analog skala (VAS) skorları ve komplikasyonlar açısından karşılaştırıldı.

Bulgular: Gruplar demografik veriler, hemodinami, ameliyat süreleri, perioperatif opioid kullanımı, postoperatif VAS skorları ve analjezik kullanımı açısından benzerdi. Perioperatif antihipertansif ve postoperatif kurtarma analjezik gereksinimleri nöronavigasyon ve klasik grubunda benzerdi [sırasıyla 1/4 ve 6/9 (n/n); p=0,467 ve p=0,537]. Postoperatif 24. saat kurtarıcı analjezik tüketimi nöronavigasyon grubunda 87,50±30,62 mg iken Klasik grupta 100,00±37,5 mg'dir (p=0,510). Hiçbir hastada herhangi bir komplikasyon görülmedi.

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Abstract

Conclusion: In this study, the perioperative and postoperative efficacy was found to be similar for both methods. We believe that the use of neuronavigation in regional anaesthesia practice has the potential to increase efficacy and reduce the rate of adverse effects, and is therefore innovative and will find a place in existing anaesthesia methods.

Keywords: Neuronavigation, pituitary surgery, scalp block, skull pin

Öz

Sonuç: Bu çalışmada, perioperatif ve postoperatif etkinlik her iki yöntem için de benzer bulunmuştur. Rejyonel anestezi uygulamasında nöronavigasyon kullanımının etkinliği artırma ve yan etki oranını azaltma potansiyelinin yenilikçi olduğuna ve mevcut anestezi yöntemlerinde yer bulacağına inanıyoruz.

Anahtar kelimeler: Çivili başlık, hipofiz cerrahisi, nöronavigasyon, skalp blok

Introduction

Pituitary adenomas account for a large proportion of intracranial tumour surgery. Endonasal transsphenoidal pituitary surgery (EnTsPS) is used as an endoscopic approach to treat non-functioning pituitary macroadenomas with signs of mass effect and adenomas that continue to function despite medical treatment. As it involves many procedures, it requires careful perioperative anesthetic planning and management (1).

As the operative field in pituitary surgery is extremely limited, various anesthetic techniques, different pharmacological modalities and additional interventions are used to control intraoperative haemodynamic responses (2). Although haemodynamic monitoring is important to maintain cerebral perfusion and prevent the risk of haemorrhage, "controlled" hypotension may have side effects. Multimodal analgesia is effective in the management of postoperative pain and reduces the risk of postoperative complications such as respiratory depression, postoperative nausea and vomiting (3).

The use of skull pin to stabilise the head during cranial surgery produces strong sympathetic activation, resulting in a sudden increase in heart rate (HR) and arterial blood pressure and increased intracranial pressure. Scalp block has been associated with beneficial effects on haemodynamic responses in both primary and secondary outcomes and is used as part of multimodal analgesia (4).

Neuronavigation is an additional system that enhances the safety and comfort of cranial surgery. It allows all anatomical points to be identified using preoperative imaging and accessed in the perioperative period (5). In this study, we aimed to compare neuronavigation or anatomical point-guided scalp blocks.

Materials and Methods

After University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital's Ethics Committee approval (decision no: 2023-130, 22 March 2023), American Society of Anaesthesia (ASA) II-III patients aged 18-65 years who underwent EnTsPS and scalp block between 1 October 2021 and 1 April 2022 were retrospectively reviewed for prospectively designed follow-up data.

Patients were excluded if they weighed <50 kg or >100 kg, had a body mass index >30 kg/m^2, an entrance arterial pressure >140 systolic or >90 diastolic, underwent reoperation within 48 hours postoperatively or developed perioperative complications. Patients undergoing scalp block were divided into two groups (neuronavigation and classic group) and compared with respect to demographics, haemodynamics, analgesic requirements, postoperative visual analogue scale (VAS) scores and complications.

In routinely monitored patients, HR, non-invasive blood pressure and peripheral oxygen saturation (SpO_2) were recorded as baseline values. In our hospital, all patients undergoing surgery in EnTsPS receive 0.02 mg/kg intravenous midazolam in the preoperative unit after an eight-hour fast. Patients are started on a fluid infusion of 0.9% NaCl at a rate of 4-6 mL/kg/hour via a 20- or 22-gauge cannula on the dorsum of the hand. Induction is given with 0.5-1 mcg/kg IV fentanyl and 2 mg/kg IV bolus propofol.

Once the patient is ventilated with a face mask, 0.5 mg/kg IV rocuronium is added for muscle relaxation. Direct laryngoscopy and orotracheal intubation with an appropriate size 3-4 Macintosh blade is then performed 2-3 minutes later, followed by left radial artery catheterisation. Maintenance of anesthesia was initiated with 2% sevoflurane inhalation at 0.8-1.0 MAC and a remifentanil infusion of 0.05 mcg/kg/min. The total time from intubation to extubation of the patient is expressed as anesthesia time and the time from surgical incision to extubation is expressed as surgical time.

While the neuronavigation device is used to identify anatomical points in the neuronavigation group, the manual examination is used in the classic group (Figure 1).

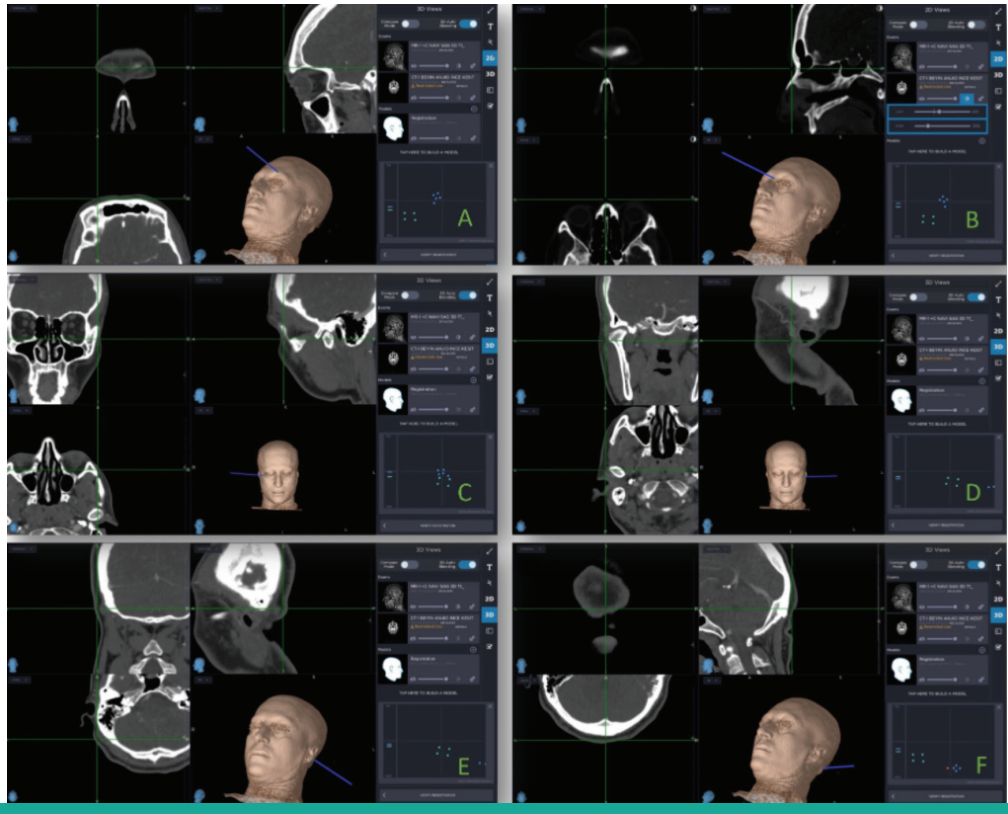

Figure 1. Determination of anatomical points using neuronavigation; (A) Supraorbital nerve (B) Supratrochlear nerve (C) Zygomaticotemporal nerve (D) Auriculotemporal nerve (E) Lesser occipital nerve (F) Greater occipital nerve

The anatomical points where the targeted nerves were applied and the total amounts of local anesthetic bilaterally are shown in Table 1. All patients routinely received 2 mcg/kg fentanyl and 0.5 mg/kg propofol prior to placement of the skull pin. Both groups underwent scalp block in a similar manner; 15 mL of 0.25% bupivacaine was administered after the skull pin in the neuronavigation group and before the skull pin in the classic group. In cases where the surgical team used neuronavigation, a scalp block was applied under neuronavigation guidance. Both block methods were applied by the anesthesiologist.

Before sterilising the surgical area, a sphenopalatine ganglion block is applied; after the cotton-tipped applicator touches the upper border of the middle turbinate, the cotton-tipped applicator is held for 5-10 minutes. This area is filled with a wet dressing to prevent passage from the nasopharynx to the oropharynx and hypopharynx. A nasal decongestant (oxymetazoline hydrochloride) is used to reduce secretions and povidone-iodine is used to sterilise the surgical site.

According to our routine remifentanil infusion algorithm in our hospital, the infusion is increased by 0.01 mcg/kg/min every 5 minutes if the MAP is >65 mmHg; if the MAP is <55 mmHg, the infusion is decreased by 0.01 mcg/kg/min every 3 minutes. The amount of remifentanil required by the patient after intubation, at the start of surgery and at the end of the first and second hour is recorded in mcg/kg/min. If the MAP is <55 mmHg, 5 mg of ephedrine is given as an intravenous bolus, and if the HR is <45 beats/minute, 0.5 mg of atropine is given intravenously. Diltiazem 0.05 mg/kg is given at regular intervals to patients who develop a perioperative need for antihypertensive treatment.

Before the end of surgery, all patients routinely receive 1 mg/kg tramadol citrate and 10 mg/kg paracetamol. Patients routinely receive 2 mg/kg sugammadex before extubation. During the postoperative period, patients are transferred to the post-anesthesia care unit. In the postoperative period, patients received 3x10 mg/kg paracetamol.

Patients' pain status was assessed using a VAS. Postoperative VAS scores were recorded at baseline, 4 hours, 12 hours and 24 hours. While patients with a VAS score of 0-3 do not receive additional analgesia, tramadol 1 mg/kg is routinely administered to patients with a VAS score greater than 3. Ondansetron 4 mg is routinely given for nausea and

Table 1. Nerves and anatomical localizations

Nerves	Anatomic localization	Volume applied (bilaterally)
Supraorbital nerve	Supraorbital notch-lateral supraorbital nerve foramen	1 mL
Supratrochlear nerve	Medial supraorbital nerve foramen-frontomaxillary suture	1 mL
Zygomaticotemporal nerve	Fronto-zygomatic suture	2 mL
Auriculotemporal nerve	Above the zygomatic arch and behind the temporal artery	3 mL
Lesser occipital nerve	SCM posterior junction of skull base	3 mL
Greater occipital nerve	Medial to the occipital artery, Just below the level of the external occipital protuberance	5 mL
3rd occipital nerve	None	None
Totally		**15 mL**

SCM: Sternocleidomastoid muscle

vomiting. The nurse, who was unaware of the patient's treatment during the data collection and recording phase, was enrolled in the study in a double-blind fashion.

The primary objective of this study was to identify anatomical points and tissues when applying the scalp block under neuronavigation guidance. The secondary objective was to assess whether the neuronavigation group had similar outcomes to the classic group in terms of medical management.

Statistical Analysis

In this study, statistical analyses were performed using the NCSS (Number Cruncher Statistical System) 2007 statistical software package (Utah, USA). In addition to descriptive statistical methods (mean ± standard deviation), the distribution of variables was examined using the Shapiro-Wilk normality test. Paired One-Way analysis of variance was used for time comparisons of normally distributed variables, Newman-Keuls multiple comparison test for subgroup comparisons, independent t-test for comparison of paired groups, and chi-squared test for comparison of qualitative data. Results were evaluated at a significance level of $p<0.05$.

Results

The groups were similar in terms of demographics, haemodynamics and operative times (Table 2). Anesthesia time was 235±13.82 minutes in the neuronavigation group and 233.7±10.36 minutes in the classic group (p=0.755). The surgical time was 195.42±16.16 minutes in the neuronavigation group and 200±13.14 minutes in the classic group (p=0.372). Baseline MAP values were 94.56±8.46 mmHg in the neuronavigation group and 89.87±8.76 mmHg in the classic group (p=0.138). After extubation, MAP values were 81.58±4.01 mmHg in the neuronavigation group and 81.17±2.42 mmHg in the classic group (p=0.708).

Perioperative and postoperative analgesic and antihypertensive requirements and postoperative pain scores were similar in the neuronavigation and classic groups (Table 3). Remifentanil consumption after intubation was 0.025±0.012 mcg/kg/min in the neuronavigation group and 0.026±0.015 mcg/kg/min in

Table 2. Demographics, haemodynamics and operative times

		Neuronavigation group (n=12)		Classic group (n=23)		p
Age		50.75±16.37		51.78±11.96		0.832
Gender	Male	6	50.00%	13	56.52%	0.713
	Female	6	50.00%	10	43.48%	
ASA classification (II/III)		9/3		16/7		0.735
BMI (kg/m²)		26.96±5.39		27.72±3.21		0.599
Anesthesia time (minute)		235.00±13.82		233.70±10.36		0.755
Surgical time (minute)		195.42±16.16		200.00±13.14		0.372
MAP (baseline) (mmHg)		94.56±8.46		89.87±8.76		0.138
MAP (after extubation) (mmHg)		81.58±4.01		81.17±2.42		0.708

ASA: American Society of Anaesthesia, BMI: Body mass index, MAP: Mean arterial pressure

Table 3. Perioperative and postoperative analgesic and antihypertensive requirements and postoperative pain score

		Neuronavigation group (n=12)		Classic group (n=23)		p
Remifentanyl consumption (mcg/kg/min)	After intubation	0.025±0.012		0.026±0.015		0.833
	Start of the surgery	0.063±0.007		0.056±0.016		0.090
	1st hour	0.063±0.013		0.053±0.014		0.071
	2 hours	0.042±0.009		0.050±0.015		0.055
Antihypertensive requirement (n)	(-)	11	91.67%	19	82.61%	0.467
	(+)	1	8.33%	4	17.39%	
Required rescue analgesic (24 hours) (n)	(-)	6	50.00%	14	60.87%	0.537
	(+)	6	50.00%	9	39.13%	
Rescue analgesic consumption (24 hours) (mg)		87.5±30.62		100±37.5		0.510
VAS	After extubation	3.00±0.60		2.87±0.55		0.523
	4 hours	2.83±0.58		2.70±0.56		0.499
	12 hours	2.67±0.49		2.96±0.47		0.100
	24 hours	2.67±0.49		2.70±0.47		0.866
	p	0.383		0.248		

VAS: Visual analogue scale

the classic group (p=0.833). Remifentanil consumption at the start of surgery was 0.063±0.007 mcg/kg/min in the neuronavigation group and 0.056±0.016 mcg/kg/min in the classic group (p=0.090). Remifentanil consumption during the first hour of surgery was 0.063±0.013 mcg/kg/min in the neuronavigation group and 0.053±0.014 mcg/kg/min in the classic group (p=0.071). Remifentanil consumption in the second hour of surgery was 0.042±0.009 mcg/kg/min in the neuronavigation group and 0.050±0.015 mcg/kg/min in the classic group (p=0.055).

Perioperative antihypertensive requirements were developed in one patient in the neuronavigation group and four patients in the classic group (p=0.467). In the postoperative period, six patients in the neuronavigation group and nine patients in the classic group required rescue analgesic (p=0.537). Rescue analgesic consumption was 87.50±30.62 in the neuronavigation group and 100.00±37.5 in the classic group (p=0.510).

No statistically significant difference was observed between the mean VAS scores of the neuronavigation and classic groups at baseline, 4 hours, 12 hours, and 24 hours (p>0.05). No statistically significant change was observed between the baseline, 4 hours, 12 hours, and 24 hours VAS scores of the neuronavigation group (p=0.383, p=0.248 respectively). No complications were observed in any patient during the peri- and post-operative period.

Discussion

As the use of nasal tampons after EnTsPS carries a risk of airway obstruction, early and predictable recovery of consciousness is essential. Postoperative extubation should not be performed before full recovery of reflexes, as postoperative application of positive pressure increases intracranial pressure and carries a risk of complications. For these reasons, complete analgesic control with multimodal analgesia becomes more important (6).

In pituitary surgery, a scalp block is used to avoid the additional stress of the skull pin on haemodynamic control (7). Reasons such as the need for multiple injections, individual variation and difficulty in visualisation reduce the chance of success (8). For scalp block application, the 6-point injection is the generally accepted approach. In addition, the innervation area of the 3rd occipital nerve can be included (9). In our cases, this innervation was not targeted because the head was placed in the horizontal plane.

In addition to analgesic control, scalp block results in a longer time to first request for rescue analgesic and fewer analgesics administered. The use of scalp block before or after incision or before or after surgery has been reported to make no difference to the incidence and severity of postoperative pain (10,11). The use of sphenopalatine block in addition to scalp block has been reported to contribute

to haemodynamic stability during craniotomy (12). In our study, the use of scalp block after craniotomy was found to be stable in the perioperative and postoperative periods and did not make a difference.

In cranial surgery, the neuronavigation device provides active access to preoperatively defined imaging, reducing the margin of error in the perioperative period by up to 2 mm (13). This access provides time and safety gains. Considering the limited space and variability of the EnTsPS, the importance of the device is even greater (14). As it is routinely used in these operations, it does not cause us any additional time problems to use it in areas that are difficult to access. The use of the scalp block does not change the accuracy of face recognition (15).

Several studies in the literature suggest the use of neuronavigation to detect variations (8). In imaging techniques, very small peripheral nerves can be imaged at thin section and high Tesla for targeted tissues (16). Using these images, potential variations can be identified and the appropriate injection site can be designed preoperatively. The ability of this device to use all imaging modalities together gives us a wide range of options for detecting relevant tissue. Computed tomography for bone, magnetic resonance imaging for soft tissue or angiography for vascular imaging are becoming increasingly important (17).

The use of neuronavigation is usually preferred in hard-to-reach and high-risk areas that cannot be distinguished macroscopically. There are studies showing its use in the treatment of trigeminal neuralgia as a contribution to deep access (18). No previous study has been conducted in relation to regional approaches to anesthesia. Our aim was to use this technique in anesthetic practice for scalp block. Our study, which we hope will contribute to the literature on its use in selected patient groups, is important and valuable in this regard.

Study Limitations

Our first limitation is that the scalp block may have been performed before the application of the skull pin in the classical group and after in the neuronavigation group. As we felt that it would be ethically inappropriate to target patients for scalp block after skull pin placement, patients received additional anesthesia and analgesia at this time. The retrospective design of this study, the small number of patients, and the lack of equal distribution between groups can be considered as secondary limitations. The fact that such devices are not yet widely used gives us the opportunity to use this device for a limited time before certain surgical procedures. This study is important because it is the first use of this method in regional anesthesia. Further prospective studies with larger case series are needed.

Conclusion

In this study, postoperative analgesic and perioperative haemodynamic data in both groups demonstrated the efficacy of scalp block in accordance with the literature. We believe that the use of neuronavigation and similar new developments in regional anesthesia practice have the potential to increase efficacy and reduce the rate of adverse effects by providing a predictable block with a lower local anesthetic dose. Today, detailed imaging of the peripheral nerves is available, and in the future, direct targeting of the peripheral nerve may be preferred to these reference point determinations in the neuronavigation group by demonstrating patient-specific variations. We believe that such modern imaging techniques and the use of neuronavigation can guide current anesthetic management in the future and take precedence when more is needed.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital's Ethics Committee approval (decision no: 2023-130, 22 March 2023).

Informed Consent: Patients give written consent for their images to be published without identifying information for research purposes.

Authorship Contributions

Concept: E.M., O.S., Y.K., B.T., F.G.Ö., Design: E.M., O.S., Y.K., B.T., F.G.Ö., Data Collection or Processing: E.M., O.S., Y.K., Ö.A., F.G.Ö., Analysis or Interpretation: E.M., O.S., Y.K., F.G.Ö., Drafting Manuscript: E.M., O.S., Y.K., F.G.Ö., Critical Revision of Manuscript: E.M., O.S., Ö.A., B.T., Final Approval and Accountability: E.M., O.S., Y.K., B.T., Ö.A., F.G.Ö., Technical or Material Support: E.M., O.S., Y.K., F.G.Ö., Supervision: E.M., O.S., Y.K., B.T., F.G.Ö., Writing: E.M., O.S., Y.K., B.T., Ö.A., F.G.Ö.

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ORIGINAL RESEARCH

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Evaluating Monocyte-to-high-density Lipoprotein Ratio Across Age and Gender in Healthy Individuals

Sağlıklı Bireylerde Monosit Yüksek Yoğunluklu Lipoprotein Oranının Yaş ve Cinsiyete Göre Değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate the monocyte-to-high-density lipoprotein (HDL) ratio (MHR) across age and gender among healthy individuals.

Method: In this single-center retrospective study, we analyzed patients who visited the Kayseri City Hospital Internal Medicine Clinic within a year, were free from chronic diseases, did not take any medications, and had C-reactive protein levels below 5 mg/L and erythrocyte sedimentation rates below 20 mm/h. Patients were categorized into four age groups: 20-39 years (Group 1), 40-59 years (Group 2), 60-79 years (Group 3), and ≥80 years (Group 4). HDL levels, complete blood count values, and demographic characteristics were recorded for all subjects. MHR was calculated by dividing the monocyte count by the HDL level.

Results: No significant differences were observed in HDL level, monocyte count, and MHR across age groups (p=0.46, p=0.26, and p=0.37, respectively). However, a significant difference was found in HDL level (53.52±12.44 vs. 43.25±10.96; p<0.001), monocyte count (0.53±0.16 vs. 0.60±0.18; p<0.001), and MHR (10.59±4.07 vs. 15.03±6.62; p<0.001) between gender groups.

Conclusion: MHR emerged as a biomarker of systemic inflammation, showing no significant variance across age groups among healthy individuals. Nonetheless, gender differences were evident in HDL level, monocyte count, and MHR, possibly attributable to the lower prevalence of cardiovascular diseases in females.

Keywords: HDL cholesterol, inflammation, MHR, monocyte

Öz

Amaç: Bu çalışmanın amacı sağlıklı bireylerde monosit/yüksek yoğunluklu lipoprotein (HDL) oranının (MHO) yaş ve cinsiyet açısından değerlendirilmesidir.

Yöntem: Tek merkezli retrospektif bu çalışmaya Kayseri Şehir Hastanesi İç hastalıkları Kliniği'ne 1 yıl içerisinde başvuran, herhangi bir kronik hastalığı bulunmayan, ilaç kullanımı olmayan ve C-reaktif protein değeri 5 mg/L'nin ve eritrosit sedimantasyon hızı 20 mm/h'nin altında olan 459 hasta dahil edildi. Hastalar 20-39 yaş (Grup 1), 40-59 yaş (Grup 2), 60-79 yaş (Grup 3) ve 80 yaş üzeri (Grup 4) olmak üzere dört gruba ayrıldı. Katılımcıların HDL seviyeleri, tam kan sayımları ve demografik verileri kaydedildi. MHO, monosit sayısının HDL düzeyine bölünmesiyle hesaplandı.

Bulgular: HDL, monosit sayısı ve MHO düzeyi karşılaştırıldığında gruplar arasında anlamlı fark yoktu (sırasıyla, p=0,46, p=0,26, p=0,37). HDL (53,52±12,44 ile 43,25±10,96; p<0,001), monosit sayısı (0,53±0,16 ile 0,60±0,18; p<0,001) ve MHO (10,59±4,07 ile 15,03±6,62; p<0,001) düzeyi bakımından iki cinsiyet grubu arasında istatistiksel olarak 2 grup arasında anlamlı fark tespit edildi.

Sonuç: MHO sistemik enflamasyonun bir biyobelirteci olup sağlıklı bireylerde yaş grupları arasında fark bulunmamıştır. Cinsiyet açısından ise HDL, monosit sayısı ve MHO düzeyleri farklılık göstermektedir. Bu durum kardiyovasküler hastalıkların kadın cinsiyette daha az görülmesi ile açıklanabilir.

Anahtar kelimeler: Enflamasyon, HDL kolesterol, MHO, monosit

Introduction

Many diseases have been associated with aging, primarily attributed to age-related physiological changes. Aging significantly impacts the heart and vascular system, contributing to heightened occurrences of atherosclerosis, hypertension, atrial fibrillation, myocardial infarction, and cerebrovascular events (1). While acute inflammation plays a crucial role in responding to infections and facilitating

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wound healing, it has become evident that chronic inflammation has deleterious effects on various systems, including the immune system. The rise in the population of aging cells and persistent low-grade inflammation with advancing age actively contribute to the development of age-related pathologies (2).

Monocytes/macrophages are the cell types that play a crucial role in releasing pro-inflammatory cytokines and participating in all stages of the inflammatory process (3). Monocytes constitute 3-8% of all leukocytes in peripheral blood and play a significant role in regulating inflammatory processes (4-7). Research has established a connection between monocytes/macrophages and conditions such as coronary artery disease, cerebrovascular events, and post-ischemic stroke injury, as these cells actively participate in the inflammatory processes associated with these health issues (8-10).

In old age, the prominence of low high-density lipoprotein (HDL) cholesterol, rather than low-density lipoprotein (LDL) cholesterol, continues to stand out as a robust risk predictor. HDL may directly impact the aging process. Conversely, aging can also exert influence on HDL concentration and function. The alteration in HDL cholesterol concentration holds significant clinical relevance. It is estimated that a 1% change in HDL cholesterol can modify the risk of myocardial infarction or mortality by 2-3 times in middle-aged individuals (11).

HDL cholesterol is recognized for diminishing the risk of atherosclerotic events through mechanisms such as reversing HDL transport, averting endothelial dysfunction, and exerting anti-apoptotic, anti-oxidant, anti-inflammatory, and anti-thrombotic effects. Furthermore, HDL assumes an anti-atherogenic role by regulating monocyte activation and precursor monocyte cell proliferation, impeding macrophage migration, preventing LDL oxidation, and safeguarding endothelial cells from inflammation and oxidative stress (12).

Recent years have revealed that MHR can serve as a novel marker for inflammation and oxidative stress. A recent review highlighted MHR as a prognostic marker in cardiovascular diseases (13,14). In this context, MHR can function as a readily assessable metric, indicating the presence and prognosis of inflammatory and inflammation-related disorders (15-17). However, there is no conclusive data on whether MHR exhibits significant changes in the healthy population. Our study aimed to assess MHR based on age and gender in a healthy population.

Materials and Methods

Patient Selection

In this retrospective study, we analyzed data from 459 patients without chronic diseases who visited the Internal Medicine Clinic at University of Health Sciences Turkey, Kayseri City Hospital within the past year and had C-reactive protein (CRP) values below 5 mg/dL and erythrocyte sedimentation rate under 20 mm/h. The study adhered to the principles of the Helsinki Declaration and the Patient Rights Act. All eligible patients provided written informed consent, and the study received approval from the Ethics Committee on Clinical Research of Erciyes University (approval #2019/504).

Clinical findings, demographic characteristics, and laboratory data were extracted from the hospital information management system and archives. Biochemical parameters, lipid panel, and peripheral complete blood count were analyzed for all patients. Exclusion criteria encompassed thyroid dysfunction, secondary hypertension, cardiovascular disease, acute and/or chronic infection, autoimmune disease, connective tissue disease, as well as a history of smoking, alcohol consumption, cancer, and the use of medications such as corticosteroids, non-steroidal anti-inflammatory agents, anti-lipid drugs, and immunosuppressive agents.

Patients were categorized into four age groups: 20-39 years (Group 1), 40-59 years (Group 2), 60-79 years (Group 3), and ≥80 years (Group 4). The distribution was as follows: 138 patients in Group 1, 141 patients in Group 2, 128 patients in Group 3, and 52 patients in Group 4. Recorded parameters included total cholesterol, triglyceride, HDL level, complete blood count, erythrocyte sedimentation rates and CRP levels. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from the total cholesterol value. MHR was determined by dividing the monocyte count (μL) by the HDL level (mg/dL).

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of data was assessed through the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are expressed as mean ± standard deviation, while categorical variables are presented as percentages and counts. Student's t-test was employed for binary comparisons of normally distributed data, and One-Way ANOVA was used for comparisons involving more than two groups. Kruskal-Wallis and Mann-Whitney U tests were utilized for data with skewed distribution. A p-value <0.05 was considered statistically significant.

Results

Overall, the analysis included data from 459 patients, with 205 women (44.7%) and 254 men (55.3%). Gender distribution did not show a significant difference across the groups. The mean age was 28.77±6.4 years in Group 1, 49.33±5.65 years in Group 2, 69.43±5.91 years in Group 3, and 86.19±4.69 years in Group 4.

In the study population, the mean HDL was 47.83±12.7, while the mean monocyte count was 0.57±0.17, and the mean MHR was 13.04±6.03. The mean MHR varied across the age groups, with values of 12.56±5.66 in Group 1, 13.55±6.24 in Group 2, 13.33±6.45 in Group 3, and 12.23±5.33 in Group 4. Regarding HDL levels, the mean was 48.33±13.36 in Group 1, 46.67±13.03 in Group 2, 48.93±13.04 in Group 3, and 46.98±8.48 in Group 4. Similarly, the mean monocyte count varied across groups, with values of 0.55±0.17 in Group 1, 0.57±0.16 in Group 2, 0.59±0.18 in Group 3, and 0.55±0.18 in Group 4. Table 1 presents the laboratory values in the patient groups. Significant differences were observed

Table 1. Demographic and clinical characteristics of participants

	Group 1 (n=138)	Group 2 (n=141)	Group 3 (n=128)	Group 4 (n=52)	p
Age	28.77±6.4	49.33±5.65	69.43±5.91	86.19±4.69	
Gender (female/male)	70/68	60/81	49/79	26/26	0.171[a]
Cholesterol (mg/dL)	169.29±35.64	194.18±37.68	210.57±42.62	187.07±35.69	**<0.001[b]**
LDL (mg/dL)	93.28±29.81	115.86±31.38	131.39±36.42	113.91±28.76	**<0.001[b]**
Triglyceride (mg/dL)	139.09±117.84	158.91±85.53	161.42±99.9	124.04±56.58	0.098[b]
HDL (mg/dL)	48.33±13.36	46.67±13.03	48.93±13.04	46.98±8.48	0.461[b]
WBC (10^3/μL)	7.55±1.7	7.22±1.84	8.29±±1.1	8.29±1.65	0.711[b]
Neutrophil (10^3/μL)	4.49±1.26	4.16±1.37	4.33±1.62	4.36±1.84	0.483[b]
Lymphocyte (10^3/μL)	2.26±0.68	2.31±0.59	2.1±0.83	1.61±0.61	**<0.001[b]**
Monocyte (10^3/μL)	0.55±0.17	0.57±0.16	0.59±0.18	0.55±0.18	0.261[b]
Hemoglobin (g/dL)	13.78±1.94	13.55±1.93	14.08±1.68	13.54±1.85	0.225[b]
Platelet (10^3/μL)	286.96±65.24	285.31±64.25	252.58±72.27	226.43±71.65	**<0.001[b]**
MPV (fL)	10.06±0.99	10.12±0.93	13.84±0.98	12.3±0.95	0.282[b]
MHR	12.56±5.66	13.55±6.24	13.33±6.45	12.23±5.33	0.379[b]
Non-HDL	119.31±34.41	143.24±35.70	159.69±40.26	139.39±34.57	**<0.001[b]**

[a]: Chi-square, [b]: One-Way ANOVA, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, MPV: Mean platelet volume, MHR: Monocyte to HDL ratio

Table 2. Significance levels between groups of clinical characteristics

	p-values*					
	Group 1 vs. Group 2	**Group 1 vs. Group 3**	**Group 1 vs. Group 4**	**Group 2 vs. Group 3**	**Group 2 vs. Group 4**	**Group 3 vs. Group 4**
Cholesterol (mg/dL)	**<0.001**	**<0.001**	**0.041**	**0.025**	**0.023**	**0.004**
LDL (mg/dL)	**<0.001**	**<0.001**	**0.002**	**0.008**	**0.002**	**0.015**
Triglyceride (mg/dL)	0.501	0.998	0.216	0.998	0.216	0.157
HDL (mg/dL)	0.693	0.981	0.914	0.464	0.999	0.788
WBC (10^3/μL)	0.988	0.878	0.932	0.744	0.841	0.934
Neutrophil (10^3/μL)	0.400	0.873	0.958	0,864	0.877	0.959
Lymphocyte (10^3/μL)	0.951	0.379	<0.001	0.188	**<0.001**	**<0.001**
Monocyte (10^3/μL)	0.922	0.309	0.990	0.676	0.864	0.379
Hemoglobin (g/dL)	0.823	0.667	0.885	0.236	0.976	0.384
Platelet (10^3/μL)	0,998	**0.002**	**<0.001**	**0.008**	**<0.001**	0.147
MPV (fL)	0.996	0.310	0.841	0.384	0.867	0.946
MHR	0.525	0.729	0.987	0.991	0.534	0.684
Non-HDL	**<0.001**	**<0.001**	**0.010**	**0.016**	**<0.001**	**0.012**

*: Post hoc analysis, Bonferroni correction. LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, MPV: Mean platelet volume, MHR: Monocyte to HDL ratio

in LDL cholesterol, lymphocyte, platelet, and non-HDL values across groups (p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001, respectively) (Table 1, 2).

When stratifying patients by gender, the mean age was 51.24±21.77 years among women and 54.3±19.67 years among men. No significant differences were observed in age distribution between women and men (p=0.171). The mean values for cholesterol, LDL, triglyceride, HDL, white blood cell, neutrophil, lymphocyte, monocyte, platelet, hemoglobin, MPV, MHR, and non-HDL were 195.06±41.49, 115.91±35.46, 139.97±83.22, 53.52±12.44, 8.1±8.79, 4.32±1.42, 2.18±0.7, 0.53±0.16, 13.24±1.67, 280.2±67.1, 12.29±1.38, 10.59±4.07, and 141.5±40.58 in women, respectively. In men, the corresponding values were 180.08±39.51, 106.66±34.07, 160.97±98.93, 43.25±10.96, 7.25±1.87, 4.38±1.57, 2.08±0.76, 0.60±0.18, 14.61±1.84, 251±73.8, 10.02±0.86, 15.03±6.62, and 135.32±37.78. Significant differences were observed in cholesterol, LDL, HDL, monocyte, hemoglobin, platelet, MHR, and non-HDL values across groups. (p=0.001, p=0.02, p=0.059, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001) (Table 3).

Discussion

In our study, variances were observed among cholesterol, LDL, lymphocyte, thrombocyte, and non-HDL groups. At the same time, when compared between genders, differences were detected in terms of cholesterol, LDL, HDL, monocyte, hemoglobin, platelet, MHR and non-HDL. HDL and non-HDL levels were significantly higher in females compared to males. Additionally, monocyte values were lower in females. There was no significant change in HDL levels with age, but non-HDL levels were observed to vary with age. Likewise, the MHR rate was found to be higher in males, with no observed change with age.

Age-related changes continue to be a focal point of interest in the research field, driven by the desire to extend healthy lifespan. Aging affects various cell types throughout the body, implying that all tissues may harbor aged cells. The impacts of aging have been demonstrated in numerous cell types, including macrophages and T-cells within the immune system (18-20). Structural stromal cells, such as fibroblasts, exhibit a high degree of aging with advancing age. These aged stromal cells lose the ability to undergo cell division and become resistant to apoptosis (21). The prolonged presence of chronic inflammation is a major contributor to the aging process. In our study, we evaluated MHR, employed as an inflammatory marker in research, based on age and gender in healthy individuals.

The study demonstrated that HDL can inhibit tissue factor expression in monocytes by preventing p38 activation and phosphoinositide 3-kinase (22). HDL exerts an anti-inflammatory effect by preventing pro-inflammatory and pro-oxidant effects on monocytes, as well as inhibiting the transport of vascular cholesterol, macrophage migration, and LDL oxidation in the vessel wall (23). It is believed that MHR can also serve as an inflammation marker, attributed to the pro-inflammatory effect of monocytes and the anti-inflammatory and antioxidant effects of HDL cholesterol (24).

Levels of all lipoproteins, including HDL, are significantly lower at birth compared to adolescence, and these levels increase during childhood. HDL concentrations in

Table 3. Comparison of clinical characteristics between genders

	Female (n=205)	Male (n=254)	p*
Cholesterol (mg/dL)	195.06±41.49	180.08±39.51	**0.001**
LDL (mg/dL)	115.91±35.46	106.66±34.07	**0.020**
Triglyceride (mg/dL)	139.97±83.22	160.97±98.93	0.059
HDL (mg/dL)	53.52±12.44	43.25±10.96	**<0.001**
WBC (10^3/μL)	8.1±8.79	7.25±1.87	0.277
Neutrophil (10^3/μL)	4.32±1.42	4.38±1.57	0.741
Lymphocyte (10^3/μL)	2.18±0.7	2.08±0.76	0.200
Monocyte (10^3/μL)	0.53±0.16	0.60±0.18	**<0.001**
Hemoglobin (g/dL)	13.24±1.67	14.61±1.84	**<0.001**
Platelet (10^3/μL)	280.2±67.1	251±73.8	**<0.001**
MPV (fL)	12.29±1.38	10.02±,86	0.191
MHR	10.59±4.07	15.03±6.62	**<0.001**
Non-HDL	141.5±40.58	135.32±37.78	**<0.001**

*: Student's t-test, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, MPV: Mean platelet volume, MHR: Monocyte to HDL ratio

men decrease during adolescence and early adulthood, remaining lower than in women thereafter (25). Previous studies have demonstrated that HDL cholesterol decreases in both men and women with advancing age during adulthood (26,27). In postmenopausal women, substantial reductions are observed in HDL cholesterol levels due to hormonal alterations. In our study, no significant difference was detected in HDL levels across groups, possibly because all included patients were healthy individuals. However, HDL values were found to be significantly higher in women than men, consistent with the existing literature (27). Consistent with the study by Ridefelt et al. (28), the estimated non-HDL value exhibited significant changes by age and between genders in our study.

Monocytes are influenced by numerous factors associated with atherosclerosis, including immunostimulant substances, growth factors, cytokines, oxidized lipids, platelet-derived activation products, and eicosanoid proteins (29). Circulating monocytes transition into a pro-coagulant phenotype by expressing tissue factor during inflammatory and pro-thrombotic states. Additionally, monocytes induce the secretion of pro-inflammatory cytokines, contributing to the pathogenesis of many inflammatory diseases (30). As individuals age, inflammation processes are heightened in many cell types that play a role in inflammation, such as monocytes and macrophages (31). In our study, we observed alterations in monocyte values with age, although they did not reach statistical significance. Additionally, we found that monocyte values were higher in the male gender.

Circulating levels of IL-6, CRP, TNF-α, IL-1ß, and other inflammatory cytokines are elevated in elderly individuals, thereby increasing the risk of all-cause mortality (32-34). In elderly individuals, lower levels of inflammatory cytokines in peripheral blood are associated with better health outcomes, longer lifespan, and reduced mortality risk (35). Inflammatory cytokines serve as indicators of chronic inflammation and are implicated in various disease processes, including diabetic complications (36). However, routine clinical use can result in high healthcare costs. Simple, readily available markers, such as MHR, are employed as inflammation markers in many studies. In our study, the aim was to investigate the use of MHR as an inflammation marker by stratifying it with age, but no significant difference was detected between age groups. We attribute this result to the inclusion of healthy adults in our study. MHR was found to be significantly higher among men compared to women. In a study conducted by Liu et al. (37), various inflammatory markers were compared based on age and gender. Similar to our study, no differences were found when compared by age, but significant variations were observed between genders. The observed higher prevalence of cardiovascular diseases caused by atherosclerosis in male patients is in line with these findings (38,39).

Study Limitations

The study's limitations include its retrospective, cross-sectional, and single-center design. To obtain more comprehensive results on this issue, a multicenter study involving different ethnicities is recommended. Additionally, a prospective study supported by cardiovascular imaging may offer a more accurate understanding of the link to atherosclerosis.

Conclusion

While the MHR can serve as a guide in atherosclerosis and various inflammatory conditions, it has been observed that its utility in evaluating inflammation status does not vary significantly with age. The gender differences in MHR can be attributed to the lower risk of cardiovascular events in the general population among females.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee on Clinical Research of Erciyes University (approval #2019/504).

Informed Consent: All eligible patients provided written informed consent.

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ORIGINAL RESEARCH

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Retrospective Analysis of Maternal and Perinatal Outcomes in Late Term Pregnancies

Geç Term Gebeliklerin Maternal ve Perinatal Sonuçlarının Retrospektif Analizi

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Abstract

Objective: The purpose of this study was to evaluate the maternal and perinatal outcomes of pregnancies beyond 40 weeks gestation.

Method: The study included 476 patients who gave birth between October 2016 and October 2017 at the Obstetrics and Gynecology Clinic of Prof. Dr. Cemil Taşcıoğlu City Hospital, University of Health Sciences Turkey. Of the patients included in the study, 342 had delivered between $40^{0/7}$ and $40^{6/7}$ gestational weeks, 115 between $41^{0/7}$ and $41^{6/7}$ gestational weeks, and 19 between $42^{0/7}$ and $42^{6/7}$ gestational weeks. Statistical analysis was conducted using the SPSS software, Windows version 24.0, and a p-value <0.05 was considered statistically significant.

Results: In our study, we found that maternal and perinatal outcomes, excluding cesarean deliveries, had a similar distribution across the weeks. The cesarean delivery rates for primiparous patients were significantly higher than those for multiparous patients between $40^{0/7}$ and $41^{0/7}$ weeks of gestation, but similar results were obtained at 42 weeks. There was no significant association between maternal age and maternal outcome. For pregnancies in women under 18 years of age, the need for a neonatal intensive care unit was significantly increased compared to other age groups. Primiparity and male fetus were associated with adverse maternal and perinatal outcomes.

Conclusion: There was no significant difference in adverse maternal and perinatal outcomes between $40^{0/7}$ and $42^{6/7}$ gestational weeks. However, the cesarean section rate was significantly increased at 40 weeks of gestation and in primiparous patients. In addition, primiparity

Öz

Amaç: Bu çalışmanın amacı 40 hafta ve üzeri gebeliklerin maternal ve perinatal sonuçlarını değerlendirmektir.

Yöntem: Sağlık Bilimleri Üniversitesi, Prof. Dr. Cemil Taşcıoğlu Şehir Hastanesi, Kadın Hastalıkları ve Doğum Kliniği'nde Ekim-2016 ile Ekim-2017 yılları arasında doğum yapan 476 hasta çalışmaya dahil edildi. Çalışmaya alınan hastaların 342'si $40^{0/7}$ ile $40^{6/7}$ gebelik haftası arasında, 115'i $41^{0/7}$ ile $41^{6/7}$ gebelik haftası arasında, 19'u $42^{0/7}$ ile $42^{6/7}$ gebelik haftası arasında doğumunu gerçekleştirmişti. İstatistiksel analizler için SPSS Windows version 24.0 paket programı kullanılmış ve p<0,05 istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmamızda sezaryen doğum hariç maternal ve perinatal sonuçlar haftalara göre dağılımını benzer bulduk. Primipar hastaların multipara göre sezaryen doğum oranları $40^{0/7}$'den $41^{0/7}$'ye kadar olan gestasyonel haftada anlamlı olarak daha yüksek bulundu, ama 42 haftada benzer sonuç elde edildi. Maternal yaş ile maternal sonuçlar arasında anlamlı bir bağlantı saptanmadı. On sekiz yaş altı gebeliklerde diğer yaş gruplarına göre yenidoğan yoğun bakım ünitesi ihtiyacı anlamlı olarak artmıştı. Primiparite ve erkek fetüs olumsuz maternal ve perinatal sonuçlarla birliktelik gösterdi.

Sonuç: $40^{0/7}$ ile $42^{6/7}$ gebelik haftaları arasında olumsuz maternal ve perinatal sonuçlarda belirgin fark bulunmamıştır. Ancak 40. gebelik haftasında ve primipar hastalarda sezaryen oranı anlamlı olarak artmıştır. Ek olarak, primiparitenin belirgin olumsuz maternal sonuçlarla birlikte gösterdiği ve ayrıca erkek yenidoğan cinsiyetinin hem olumsuz

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Abstract

was associated with significant adverse maternal outcomes, and male neonate gender was associated with both adverse maternal and adverse perinatal outcomes.

Keywords: Maternal-fetal relations, pregnancy complications, pregnant woman, prolonged pregnancy

Öz

maternal sonuçlarla hem de olumsuz perinatal sonuçlarla beraber olduğu saptanmıştır.

Anahtar kelimeler: Gebe kadın, gebelik komplikasyonları, maternal-fetal ilişkiler, uzamış gebelik

Introduction

Postterm pregnancies, considered to have exceeded the normal upper limit of gestational age, have been a subject of debate and discussion, ranging from nomenclature to definition, incidence, pathophysiology, monitoring, management, and mode of delivery preference. The American College of Obstetricians and Gynecologists (ACOG) has introduced a new classification in their definitions. According to ACOG, gestational ages are categorized as follows: Early term for pregnancies between $37^{0/7}$ and $38^{6/7}$ weeks of gestation from the first day of the last menstrual period (LMP), full term for pregnancies between $39^{0/7}$ and $40^{6/7}$ weeks of gestation, a late term for pregnancies between $41^{0/7}$ and $41^{6/7}$ weeks of gestation, and postterm for pregnancies beyond 42 weeks (1).

The most common risk factor for late term and postterm pregnancies is a history of postterm pregnancy (2). Many risk factors for post-term pregnancy, such as nulliparity, male fetus, and maternal obesity, are supported by observational studies. Although their exact physiological reasons are not known, some fetal diseases, such as anencephaly and placental sulfatase deficiency, are also associated with postterm pregnancy (1).

Many studies have shown that late term and postterm pregnancies are associated with increased perinatal morbidity and mortality. In postterm pregnancies, maternal risk, the risk of intrauterine death, perinatal asphyxia, shoulder dystocia, and neonatal mortality are increased (3). In pregnancies that go beyond term, the fetus continues to grow while the placenta-fetus ratio decreases. This situation can lead to impaired substrate transfer to the fetus and, ultimately result in fetal hypoxia. Observational studies that examine the relationship between an increase in gestational weeks and maternal and obstetric complications have also shown an increase in severe perineal tears, infections, postpartum bleeding, and cesarean deliveries in late term and postterm pregnancies (1,4). Hence, the management of patients between $40^{0/7}$ and $42^{6/7}$ weeks of gestation appears to be an essential problem for clinicians.

This study aimed to evaluate maternal and perinatal outcomes of pregnancies over 40 weeks of gestation.

Materials and Methods

Study Population

The study was conducted in the obstetrics and gynecology clinic of the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. Approval for the study was obtained from the Ethics Committee of the same institution under protocol number 786 on December 19, 2017. The patient files and records of 3907 patients who gave birth between October 2016 and October 2017 were obtained from the Hospital Information Management System and were retrospectively analyzed.

The gestational age of all patients was calculated using LMP and early ultrasound (US) data. Patients with undetermined gestational age, those with a history of cesarean section, pregnancies with non-cephalic presentation, multiple pregnancies, pregnancies with congenital fetal anomalies, placenta previa, placental abruption, and those diagnosed with severe preeclampsia were excluded from the study. The remaining 476 patients were included in the study, with 342 of them between $40^{0/7}$ and $40^{6/7}$ weeks, 115 between $41^{0/7}$ and $41^{6/7}$ weeks, and 19 were 42 weeks or beyond.

From the hospital data system and patient files, maternal age, number of parities, LMP, chronic diseases, US and non-stress test (NST) data, mode of delivery, maternal hemogram values at the time of hospitalization and hospital extirpation, indications for cesarean delivery, maternal blood transfusion requirements, maternal intensive care unit (ICU) needs, neonatal genders, neonatal 1^{st} and 5^{th} minute Apgar scores, meconium-stained amniotic fluid status, birth trauma, birth weight, NICU needs and stillbirth data were recorded.

Gestational Age Calculation

Gestational age calculation was done based on LMP and US measurements taken between the 6^{th} and 12^{th} weeks of pregnancy. If there was consistency between LMP and US

measurements, LMP was employed to calculate gestational age. In instances of inconsistency or when the patient's LMP information was unavailable, gestational age was determined based on US measurements taken between the 6th and 12th week.

Study Design

As per the protocol of the Department of Obstetrics and Gynecology at University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital, all pregnant women beyond 41 weeks of gestation are interned. Pregnant women between $40^{0/7}$ and $40^{6/7}$ gestational weeks are called for follow-up every 2 days and evaluated with NST and US.

Cesarean delivery, operative vaginal delivery, postpartum blood loss of more than 1000 cc, need for blood transfusion, patients with non-severe preeclampsia and maternal ICU requirement were defined as composite adverse maternal outcomes. The amount of blood loss was calculated by comparing the complete blood count of the patient upon admission to the hospital and after discharge and each 1 unit decrease in hemogram was calculated as 500 mL blood loss.

Meconium-stained amniotic fluid, 1st and 5th minute Apgar scores, birth trauma, birth weight, NICU requirement and stillbirth were specified as composite adverse perinatal outcomes. Those with a 1st minute Apgar score below 4 and a 5th minute Apgar score below 7 were grouped. According to birth weight, newborns were further grouped as below 2500 g and above 4000 g. The routine practice in our hospital does not involve the measurement of cord blood gas pH in all newborns; hence, this factor was not included in the study.

Statistical Analysis

The conformity of the data to normal distribution was tested with the Shapiro-Wilk test. The independent samples t-test was used to compare normally distributed characteristics between the two independent groups, while the Mann-Whitney U test was employed for non-normally distributed characteristics. Additionally, for comparing numerical data among more than two independent groups, One-Way Analysis of Variance and least significant difference post hoc tests were used for normally distributed features, and the Kruskal-Wallis test and All pairwise multiple comparison tests were employed for non-normally distributed characteristics. The relationship between categorical variables was analyzed using the chi-squared test. Descriptive statistics including mean ± standard deviation for numerical variables and counts with percentages for categorical variables were provided. Statistical analyses were performed using the SPSS software version 24.0 for Windows, and a significance level of $p<0.05$ was considered statistically significant.

Results

Patient Population

Out of the 3.907 patient files examined, 476 patients were included in the study, with 342 patients (71.8%) giving birth between $40^{0/7}$ and $40^{6/7}$ weeks of gestation, 115 patients (24%) between $41^{0/7}$ and $41^{6/7}$ weeks, and 19 patients (4%) between $42^{0/7}$ and $42^{6/7}$ weeks of gestation. The age of the patients included in the study ranged from 14 to 43 years, with a mean age of 26.78±5.44. Age ranged between 14 and 42 years for women between $40^{0/7}$ and $40^{6/7}$ gestational weeks with a mean of 26.84±5.46, between 18 and 39 years for women between $41^{0/7}$ and $41^{6/7}$ gestational weeks with a mean of 26.56±5.09, between 19 and 43 years for women between $42^{0/7}$ and $42^{6/7}$ gestational weeks with a mean of 27.11±7.13. There were 6 patients (1.2%) under 18 years old, 421 patients (88.4%) were between 18-34 years old, and 49 patients (10.2%) were older than 35 years. There was no significant difference observed among maternal age groups in terms of gestational weeks (Table 1).

Of 476 patients, 219 (46%) were nulliparous, 257 (54%) were multiples and the number of parities ranged between 1 and 8 with a mean of 2.03±1.2. According to gestational weeks, 150 (43.8%) were nulliparous and 192 (56.1%) were multiparous between $40^{0/7}$ and $40^{6/7}$ gestational weeks, 62 (53.9%) were nulliparous and 53 (46%) were multiparous between $41^{0/7}$ and $41^{6/7}$ gestational weeks, 7 (36.8%) were nulliparous and 12 (63.1%) were multiparous above 42 gestational weeks. There was no statistically significant relationship between parity status and gestational weeks (Table 1).

Out of the patients included in the study, 13 (2.7%) had gestational diabetes, 10 (2.1%) had gestational hypertension, 22 (4.6%) had thyroid disorders, 34 (7.1%) had other conditions such as hematological and orthopedic disorders, while 397 patients (83.4%) had no known medical conditions. Statistically similar results were obtained between medical history and gestational weeks (Table 1).

Maternal Outcomes

Statistical analysis revealed a statistically significant difference only in the group of patients who underwent a cesarean section when maternal outcomes were compared by gestational weeks ($p<0.05$) (Table 2). There was a higher

rate of cesarean section (19.2%) among the 66 patients who gave birth between $40^{0/7}$ and $40^{6/7}$ weeks of gestation when compared to other gestational weeks. When the cesarean section status was analyzed according to parity status, 43 (65.2%) primiparous patients between $40^{0/7}$ and $40^{6/7}$ gestational weeks, 38 (84.4%) patients between $41^{0/7}$ and $41^{6/7}$ gestational weeks, and 1 (20%) patient beyond 42 gestational weeks delivered by cesarean section, respectively. The cesarean section rates for primiparous patients were significantly higher compared to multiparous patients between $40^{0/7}$ to $40^{6/7}$ and $41^{0/7}$ to $41^{6/7}$ gestational weeks, but similar results were obtained for gestational weeks 42 and beyond (Table 3).

When examining the indications for cesarean section, 30 patients (6.3%) had fetal distress, 5 patients (1.1%) had maternal factors, 34 patients (7.1%) had arrested labor, 12 patients (2.5%) had cephalopelvic disproportion, 33 patients (6.9%) had macrosomic infants, and 2 patients (0.4%) had non-severe preeclampsia. No statistically significant difference was found between indications for cesarean section and gestational weeks (Table 4).

Maternal mortality, eclampsia, chorioamnionitis and endometritis were not observed in any of the patients Postpartum >1000 cc bleeding was observed in 83 patients (17.4%), and blood transfusions were administered to 24 patients (5%). One patient (0.8%) at 41 weeks of gestation

Table 1. Patient characteristics

	Gestational week								
	40 (n=342)		41 (n=115)		42 (n=19)		Total (n=476)		
	n	%	n	%	n	%	n	%	p
Maternal age range									0.414
<18	6	1.7	0	0	0	0	6	1.2	
18-34	299	87.4	106	92.1	16	84.2	421	88.4	
≥35	37	10.8	9	7.8	3	15.7	49	10.2	
Parity									0.124
Primiparous	150	43.8	62	53.9	7	36.8	219	46.0	
Multiparous	192	56.1	53	46.0	12	63.1	257	53.9	
Disease									0.377
Gestational DM	11	3.2	2	1.7	0	0	13	2.7	
Gestational HT	9	2.6	1	0.8	0	0	10	2.1	
Thyroid disease	14	4.0	8	6.9	0	0	22	4.6	
Other	28	81.8	6	5.2	0	0	34	7.1	
None	280	81.8	98	85.2	19	100	397	83.4	

DM: Diabetes mellitus, HT: Hypertension

Table 2. Evaluation of maternal outcomes according to gestational weeks

	Gestational week								
	40 (n=342)		41 (n=115)		42 (n=19)		Total (n=476)		
	n	%	n	%	n	%	n	%	p
Cesarean section	66	19.2	45	39.1	5	26.3	116	24.3	<0.001[a]
Operative vaginal delivery	2	0.5	1	0.8	0	0	3	0.6	0.888
Postpartum hemorrhage (>1000 cc)	53	15.4	28	24.3	2	10.5	83	17.4	0.069
Need for blood transfusion	15	4.3	8	6.9	1	5.2	24	5.0	0.552
Preeclampsia[b]	3	0.8	1	0.8	0	0	4	0.8	0.92
Maternal ICU admission	0	0	1	0.8	0	0	1	0.2	0.207

[a]: p-value <0.05 was considered statistically significant, [b]: Non-severe preeclampsia, ICU: Intensive care unit

required admission to the maternal ICU due to HELLP syndrome. In 4 patients (0.8%), non-severe preeclampsia was observed, while 3 patients (0.6%) had operative vaginal deliveries (Table 2).

In our study, no statistically notable difference was found between maternal age and adverse maternal outcomes. When we evaluated the relationship between parity status and maternal outcomes, we found that the composite adverse maternal outcome, operative vaginal delivery, postpartum bleeding >1000 cc and need for blood transfusion were statistically significantly higher in primiparous patients compared to multiparous patients ($p<0.05$). In the comparison between male and female fetuses, it was found to be statistically significant that male fetuses had a higher incidence of compound adverse maternal outcomes and cesarean section deliveries ($p<0.05$) (Table 5).

Perinatal Outcomes

Of all neonates, 246 (51.7%) were male and 230 (48.3%) were female, and there was no statistical relationship between gestational age at birth and neonatal sex. The mean birth weight of the newborn was 3498.76±437.04 g, and no statistically significant correlation was found between gestational weeks and birth weights (Table 6).

An analysis of 1-minute and 5-minute Apgar scores, the presence of meconium-stained amniotic fluid, birth trauma, and the necessity for NICU did not reveal any statistically significant differences concerning gestational weeks (Table 6). Since no stillbirths were observed among the patients included in the study, it could not be calculated whether there was a significant association with the weeks of gestation.

The analysis of the relationship between maternal age and perinatal outcomes revealed a statistically significant association only with the need for NICU admission ($p<0.05$). Particularly, in pregnancies involving individuals under the age of 18, the need for NICU admission was significantly higher compared to other age groups ($p<0.05$). In primiparous women, the incidence of birth weight less than 2500 g was found to be statistically significantly higher

Table 3. Cesarean section distribution based on parity status

	Caesarean section						
	No		Yes		Total		
	n	%	n	%	n	%	p
40 weeks of pregnancy							<0.001[a]
Primiparous	107	38.8	43	65.2	150	43.9	
Multiparous	169	61.2	23	34.8	192	56.1	
41 weeks of pregnancy							<0.001[a]
Primiparous	24	34.3	38	84.4	62	53.9	
Multiparous	46	65.7	7	15.6	53	46.1	
42 weeks of pregnancy							0.603
Primiparous	6	42.9	1	20.0	7	36.8	
Multiparous	8	57.1	4	80.0	12	63.2	

[a]: p-value <0.05 was considered statistically significant

Table 4. Indications for caesarean section

	Gestational week								
	40 (n=342)		41 (n=115)		42 (n=19)		Total (n=476)		
	n	%	n	%	n	%	n	%	p
Fetal distress	16	4.7	12	10.4	2	10.5	30	6.3	0.066
Maternal factors	5	1.5	0	0	0	0	5	1.1	0.138
Non-progressive labor	16	4.7	17	14.8	1	5.3	34	7.1	0.275
CPD	6	1.8	6	5.2	0	0	12	2.5	0.571
Macrosomia	21	6.1	10	2.9	2	10.5	33	6.9	0.537
Preeclampsia[b]	2	0.6	0	0	0	0	2	0.4	0.463

CPD: Cephalopelvic distortion, [b]: Non-severe preeclampsia

(p<0.05). Lastly, it was statistically significant that male neonates had a higher rate of composite adverse perinatal outcomes and birth weight (>4000 g) compared to female neonates (p<0.05) (Table 5).

Discussion

This study, conducted to assess the maternal and perinatal outcomes of pregnancies of 40 weeks and over, revealed that there were no significant differences among the gestational weeks of $40^{0/7}$-$40^{6/7}$, $41^{0/7}$-$41^{6/7}$, and $42^{0/7}$-$42^{6/7}$.

The characteristic features of the patients included in the study were parallel to those found in the literature. Some studies had excluded patients with any disease so as not to cause confounding results, while others included them. Considering the diverse perspectives, we have incorporated the notion that the presence of a maternal illness would not impact the outcomes in our assessment. As anticipated, no significant correlation was found between maternal illness and gestational age at birth. In order to assess the impact of maternal age on maternal-perinatal morbidity and mortality, three groups were examined (<18, 18-34, and ≥35 years), and maternal age factor had no significant effect except the need for NICU. In contrast, another study revealed an increased risk of adverse maternal and perinatal morbidity in pregnancies over 40 years of age, particularly in late-term and post-term pregnancies (5). Our research indicates a significant increase in the need for NICU in pregnancies of women below 18 years of age, so we believe that additional support should be provided for this group, given the number of patients involved. In a study conducted with a broader patient population, it has been reported that neonatal morbidity, including the need for NICU, significantly increased in adolescent pregnancies (6). In light of this, advancing the time of delivery to earlier weeks in the adolescent age group has been suggested as a potential positive contribution to maternal-perinatal morbidity and mortality.

Despite numerous studies suggesting an association between nulliparity and prolonged gestational weeks with

Table 5. Maternal and perinatal outcomes based on maternal age, parity status and neonatal gender

	Maternal age							Parity status					Neonatal gender				
	<18		18-34		≥35			Primipar		Multipar			Male		Female		
	(n=6)		(n=421)		(n=49)			(n=219)		(n=257)			(n=246)		(n=230)		
	n	%	n	%	n	%	p	n	%	n	%	p	n	%	n	%	p
Compound maternal adverse outcome	1	16.7	161	38.2	18	36.7	0.549	132	60.3	48	18.7	<0.001[a]	107	43.5	73	31.7	0.008[a]
Cesarean section	0	0.0	100	23.8	16	32.7	0.146	82	37.4	34	13.2	<0.001[a]	77	31.3	39	17.0	<0.001[a]
Operative vaginal delivery	0	0.0	2	0.5	1	2.0	*	1	0.5	2	0.8	*	1	0.4	2	0.9	0.612
Postpartum hemorrhage (>1000 cc)	1	16.7	78	18.5	4	8.2	0.194	65	29.7	18	7.0	<0.001[a]	46	18.7	37	16.1	0.453
Need for blood transfusion	1	16.7	23	5.5	0	0.0	0.108	19	8.7	5	1.9	0.001[a]	16	6.5	8	3.5	0.132
Preeclampsia[b]	0	0.0	3	0.7	1	2.0	*	3	1.4	1	0.4	*	2	0.8	2	0.9	0.946
Maternal ICU admission	0	0.0	0	0.0	1	2.0	*	0	0.0	1	0.4	*	0	0.0	1	0.4	0.483
Compound perinatal adverse outcome	4	66.7	182	43.2	20	40.8	0.482	95	43.4	111	43.2	0.967	120	48.8	86	37.4	0.012[a]
1-min Apgar score <4	0	0.0	3	0.7	0	0.0	*	1	0.5	2	0.8	*	3	1.2	0	0.0	0.249
5-min Apgar score <7	0	0.0	1	0.2	0	0.0	*	0	0.0	1	0.4	*	1	0.4	0	0.0	*
MAS	1	16.7	53	12.6	1	2.0	0.085	31	14.2	24	9.3	0.101	26	10.6	29	12.6	0.487
Birth trauma	0	0.0	36	8.6	7	14.3	0.307	16	7.3	27	10.5	0.225	23	9.3	20	8.7	0.804
Birth weight																	
<2500 g	0	0.0	4	1.0	0	0.0	*	4	1.8	0	0.0	0.044[a]	1	0.4	3	1.3	0.357
>4000 g	0	0.0	54	12.8	9	18.4	0.35	26	11.9	37	14.4	0.418	48	19.5	15	6.5	<0.001[a]
NICU admission	4	66.7	68	16.2	8	16.3	0.005[a]	44	20.1	36	14.0	0.077	41	16.7	39	17.0	0.933
Stillbirth	0	0.0	0	0.0	0	0.0	*	0	0.0	0	0.0	*	0	0.0	0	0.0	*

*: p-value not calculated, [a]: p-value <0.05 was considered statistically significant, [b]: Non-severe preeclampsia, ICU: Intensive care unit, MAS: Meconium aspiration syndrome, NICU: Neonatal intensive care unit

Table 6. Perinatal outcomes

	Gestation week								
	40 (n=342)		41 (n=115)		42 (n=19)		Total (n=476)		
	n	%	n	%	n	%	n	%	p[a]
Neonatal gender									0.772
Male	178	52.0	57	49.6	11	57.9	246	51.7	
Female	164	48.0	58	50.4	8	42.1	230	48.3	
1-min Apgar score <4	3	0.9	0	0	0	0	3	0.6	0.554
5-min Apgar score <7	1	0.3	0	0	0	0	1	0.2	0.822
Meconium-stained amniotic fluid	43	12.6	10	8.7	2	10.5	55	11.6	0.526
Birth trauma	30	8.8	12	10.4	1	5.3	43	9.0	0.729
Birth weight									
Mean ± SD	3484.18±440.03		3552.29±432.42		3437.16±402.09		3498.76±437.04		0.289[c]
<2500 g	4	1.2	0	0	0	0	4	0.8	0.454
>4000 g	42	12.3	19	16.5	2	10.5	63	13.2	0.478
NICU admission	51	14.9	26	22.6	3	15.8	80	16.8	0.16
Stillbirth	0	0.0	0	0.0	0	0	0	0.0	

[a]: The p-value was obtained from the Pearson chi-square (Exact test), SD: Standard deviation, [c]: The p-value was obtained from the ANOVA test, NICU: Neonatal intensive care unit

male fetuses, our study did not observe a notable difference. All pregnancies presenting to our clinic over $41^{0/7}$ weeks are designated for delivery, whereas pregnancies from $40^{0/7}$ to $40^{6/7}$ gestational weeks are optionally managed with inpatient care, which may have influenced the outcomes. In another study, it was reported that the risk of adverse pregnancy outcomes was higher in nulliparous pregnant women compared to multiparous women (5). In our study, compound adverse maternal outcomes, cesarean section rate and the need for blood transfusion were found to be significantly higher in nulliparous women despite the inability to calculate the p-value due to the low distribution of the number of patients in groups with operative vaginal delivery, non-severe preeclampsia and maternal ICU requirement. We observed a significantly increased rate of composite adverse maternal outcomes, cesarean delivery and macrosomia in pregnant women with male newborns compared to female newborns. Even though we did not find a significant difference between nulliparity and gestational weeks of male fetuses, we anticipate that our study, conducted between $40^{0/7}$ and $42^{0/7}$ gestational weeks, would align with the literature when compared with early term or full term pregnancies. According to widely accepted views, nulliparity and male fetus were associated with prolonged gestational age at delivery; thus, increased maternal morbidity was an expected outcome.

When reviewing the literature, we observed that the predominant opinion was that maternal and perinatal morbidity increased with advancing gestational age (7-9). It is widely accepted that when comparing gestational weeks between $40^{0/7}$ and $42^{6/7}$, there is a significantly lower perinatal mortality rate, especially in the 41^{st} week of pregnancy (2). According to our study, when analyzing gestational weeks between $40^{0/7}$ and $42^{6/7}$, perinatal outcomes were found to be similar, with only the cesarean section rate being significantly higher from $40^{0/7}$ to $40^{6/7}$ gestational weeks in maternal outcomes. Despite the lack of statistically significant perinatal mortality in the patient group under investigation, we endorse routine induction of labor at 41 weeks of gestation, aligning with the perspectives of most authors. This recommendation is based on the increased cesarean section rate at the 40^{th} week and the potential prevention of placental-related syndromes that may arise from prolonged pregnancies.

The timing of delivery between gestational weeks $40^{0/7}$ and $42^{6/7}$ has been a subject of debate. In a notable randomized controlled multicentric large study, it has been reported that elective induction of labor after the 39^{th} week in nulliparous women reduces the risk of primary cesarean delivery and hypertensive disorders without altering perinatal mortality and morbidity, in addition to less neonatal respiratory distress in the induction group (9). In response to this

study, the society of maternal-fetal medicine published a statement endorsing elective induction at 39 weeks for low-risk nulliparous women, a view further supported by the ACOG (10). These data should be interpreted with caution as elective induction at $39^{0/7}$ gestational weeks has been reported specifically for nulliparous women. In our study, the cesarean section rate was compared among gestational weeks, and additionally, the cesarean distribution between primiparous and multiparous patients was analyzed across gestational weeks. The cesarean rate at the 40^{th} week was found to be statistically higher in primiparous patients between gestational weeks $40^{0/7}$ and $41^{6/7}$ compared to other gestational weeks. Since we found no difference, except cesarean delivery, between maternal and perinatal morbidity, we tend towards elective induction based on parity status and gestational week.

Study Limitations

Our study has some limitations, one of which is the study's retrospective design. Our clinic had already initiated elective induction at $41^{0/7}$ weeks; consequently, we have a smaller number of patients in the group with pregnancies at 42 weeks and beyond. Additionally, it includes a small patient group that is similar demographically and socioeconomically.

Conclusion

In conclusion, there was no significant difference in adverse maternal and perinatal outcomes between $40^{0/7}$ and $42^{6/7}$ gestational weeks. However, the cesarean section rate was significantly increased at $40^{0/7}$ to $40^{6/7}$ gestational weeks and in primiparous patients. In addition, primiparity was associated with significant adverse maternal outcomes, and male neonatal sex was associated with both adverse maternal outcomes and adverse perinatal outcomes. The idea of determining the timing of delivery beyond 40 weeks based on parity status can be helpful for clinicians conducting future studies.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. Approval for the study was obtained from the Ethics Committee of the same institution under protocol number 786 on December 19, 2017.

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Concept: V.M., D.Y.Y.K., Y.Ö., Design: V.M., D.Y.Y.K., Y.Ö., Data Collection or Processing: D.Y.Y.K., M.İ.T., Analysis or Interpretation: M.İ.T., Y.K., Drafting Manuscript: D.Y.Y.K., Y.K., Y.Ö., Critical Revision of Manusciprt: V.M., Y.K., M.İ.T., Final Approval and Accountability: V.M., D.Y.Y.K., Y.K., M.İ.T., Y.Ö., Technical or Material Support: M.İ.T., Y.Ö., Supervision: M.İ.T., Y.Ö., Writing: V.M., D.Y.Y.K., Y.K., M.İ.T., Y.Ö.

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ORIGINAL RESEARCH

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Relation Between Patent Foramen Ovale and Cryptogenic Stroke: Single-center Echocardiographic Study

Patent Foramen Ovale ve Kriptojenik İnme Arasında İlişki: Tek Merkezli Ekokardiyografik Çalışma

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Abstract

Objective: The transcatheter closure of patent foramen ovale (PFO) has been proven effective in preventing cryptogenic stroke (CS), and it is necessary to determine the structure of PFO associated with CS. In this study, we sought to evaluate the characteristics of PFO by using transesophageal echocardiography (TEE) and contrast transesophageal echocardiography (c-TEE) to assess the characteristics of PFO associated with CS and seek out the high-risk factors for PFO for CS.

Method: A total of 52 test patients who suffered CS combined with PFO and 64 control patients diagnosed with PFO without stroke were enrolled. The structure of the PFO was observed by TEE and c-TEE. The differences in PFO structure between the test patients and controls were compared.

Results: The patients in the test group were older than the controls. The height and length of the PFO during Valsalva were found to be greater in the test group than in the control group. The occurrence rates of low-angle PFO (angle between inferior vena cava and PFO ≤10°) and atrial septal aneurysm (ASA) were higher in the test group than in the control group. Right-to-left shunt (RLS) ≥ grade II during Valsalva was significantly higher in the test group than in the control group. Regarding RLS ≤ grade II during Valsalva and all grades of RLS at rest, there was no difference between the two groups. Multivariate analysis showed that the length of the PFO during Valsalva, the presence of ASA, large (≥ grade II) RLS shunt during Valsalva and low-angle PFO were independent relevant factors for CS.

Conclusion: The length of the PFO tunnel, low-angle PFO, RLS III during Valsalva and the presence of ASA were associated with a greater risk for CS. TEE combined with c-TEE may be helpful in identifying PFO patients at great risk of CS and screening for transcatheter closure of PFO.

Keywords: Cryptogenic stroke, echocardiography, patent formane ovale

Öz

Amaç: Patent foramen ovalenin (PFO) transkateter kapatılması kriptojenik inmeli (Kİ) hastalarda sıklıkla gerçekleştirilir, ancak inme ile ilişkili PFO'nun ekokardiyografik belirleyicileri bilinmemektedir. Bu çalışmada, Kİ ile ilişkili PFO'nun özelliklerini değerlendirmek ve Kİ için PFO için yüksek risk faktörlerini araştırmak üzere transözofageal ekokardiyografi (TEE) ve kontrast transözofageal ekokardiyografi (c-TEE) kullanarak PFO'nun özelliklerini değerlendirmeyi amaçladık.

Yöntem: PFO ile birlikte CS geçiren toplam 52 test hastası ve inme olmadan PFO tanısı alan 64 kontrol hastası kaydedildi. PFO'nun yapısı TEE ve c-TEE ile gözlemlendi. Test hastaları ve kontroller arasındaki PFO yapısındaki farklılıklar karşılaştırıldı.

Bulgular: Kİ geçiren hastalar kontrol grubundaki hastalardan daha yaşlıydı. Valsalva manevrası sırasında PFO'nun hem yüksekliği hem de uzunluğu Kİ grubunda kontrol grubuna göre daha fazlaydı. Düşük açılı PFO (alt vena kava ile PFO arasındaki açı ≤10°) ve atriyal septal anevrizma (ASA) görülme sıklığı Kİ grubunda kontrol grubuna göre daha yüksekti. Valsalva manevrası sırasında sağdan sola şant (RLS) ≥ derece II, Kİ grubunda kontrol grubuna göre anlamlı olarak daha yüksekti. İstirahatte RLS dereceleri açısından iki grup arasında anlamlı fark yoktu. Çok değişkenli analiz sonucunda Valsalva sırasında PFO uzunluğunun ≥10 mm olması, düşük açılı PFO, ASA varlığı ve Valsalva sırasında ≥ derece II HBS'nin Kİ'nin bağımsız öngördürücüleri olduğu belirlendi.

Sonuç: Çalışmamız TEE ve c-TEE ile belirlenen PFO'nun yapısal özelliklerinin Kİ açısından yüksek riskli hastaların belirlenmesine yardımcı olabileceğini düşündürmektedir.

Anahtar kelimeler: Ekokardiyografi, kriptojenik inme, patent foramen ovale

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Introduction

The prevalence of patent foramen ovale (PFO) in the general population is approximately 25% (1). The connection of PFO with various conditions such as cryptogenic stroke (CS) and migraine has been demonstrated (2-7). The effectiveness of transcatheter closure of PFO in preventing CS has been demonstrated, but there is limited data on the comprehensive evaluation of PFO morphology associated with the development of CS. Therefore, it is necessary to determine the structure of PFO associated with CS (8-10). Transesophageal echocardiography (TEE) allows detailed visualization of the foramen ovale area. In this study, we sought to evaluate the characteristics of PFO by using TEE and contrast transesophageal echocardiography (c-TEE) to assess the characteristics of PFO associated with CS and seek out the high-risk factors for PFO for CS.

Materials and Methods

We retrospectively recorded 116 patients diagnosed with PFO using TEE and c-TEE in the echocardiography laboratory from May 2016 to December 2023. The occurrence of cerebral infarction in patients with CS has been demonstrated using magnetic resonance imaging. CS was diagnosed by a neurologist based on the exclusion of all other identifiable causes of stroke such as large artery atherosclerosis, cardioembolism, small vessel disease, or arterial dissection after clinical examinations including brain and carotid imaging, electrocardiography, and echocardiography.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (1964) and the study protocol was approved by Local Ethics Committee (İstanbul Atlas University Non-Invasive Research Ethics Committee: 08.01.2024, No: 01/14).

TEE

After undergoing routine transthoracic echocardiography, all patients underwent biplane TEE with saline contrast injection. The presence of PFO was confirmed by the passage of microbubbles from the right atrium to the left atrium within the three cardiac cycles following opacification of the right atrium using intravenous agitated saline contrast injection. The anatomical and functional characteristics of PFO, including PFO height, tunnel length, presence of atrial septal aneurysm (ASA), hypermobile interatrial septum, presence of prominent Eustachian valve or Chiari's network, grade of right-to-left (RL) shunt at rest and during the Valsalva maneuver, and the angle between the inferior vena cava (IVC) and PFO, were assessed by independent cardiologists who were unaware of the patient's CS status. The height of the PFO was measured as the maximum separation between the septum primum and septum secundum in the end-systolic frame, and a height greater than 2 mm was classified as indicative of a large-sized PFO (11). The length of PFO tunnel was determined by measuring the maximum overlap between the septum primum and septum secundum, and a length greater than 10 mm was designated as indicative of a long-tunnel PFO (12). ASA was characterized by a septal excursion of greater than 10 mm from the midline into the right or left atrium, or a total excursion of more than 15 mm between the right and left atrium (2). Additionally, we defined a hypermobile interatrial septum as a moving and floppy septum with a septal excursion exceeding 5 mm in every heartbeat. The grade of RL shunt was assessed at rest and during Valsalva maneuver using agitated saline contrast. The maximum number of microbubbles that appeared in the left atrium was counted in a single frame, and the large (≥ grade II) RLS shunt was defined as >20 microbubbles (2,9). We measured the angle between the IVC and the PFO flap on an imaging plane that displayed the IVC and interatrial septum. An angle of the PFO from the IVC less than 10 degrees was defined as indicative of a low-angle PFO.

Statistical Analysis

The data are expressed as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Differences between the two groups were analyzed using the t-test and Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables. Univariate and multivariate logistic regression analyses were conducted to identify independent factors associated with CS. All p-values were 2 sided, and a $p<0.05$ was considered statistically significant. All statistical assessments were carried out using the Statistical package for Social Sciences (SPSS for Windows, version 23.0. IBM Corp. Armonk, NY, USA) software.

Results

A total of 52 test patients who suffered CS combined with PFO and 64 control patients diagnosed with PFO without stroke were enrolled. The mean age of all patients was 41±17 years. The comparison of patient characteristics between those with CS and those without CS is presented in Table 1.

Patients with CS were older than those without CS (48±15 vs. 40±18, p=0.01). The prevalence of hypertension (36% vs. 14%, p=0.02) and smoking (38% vs. 17%, p=0.03) was higher in patients with CS compared to those without CS.

Comparisons of the echocardiographic characteristics of PFO between the two groups are shown in Table 2. The height (2.4±1.7 vs. 1.6±1.1, p<0.01) and length (9.3±4.5 vs. 8.1±4.3, p=0.03) of the PFO during Valsalva were found to be greater in the test group than in the control group. The occurrence rates of low-angle PFO (angle between IVC and PFO ≤10°) (27% vs. 8%, p<0.01) and ASA (39% vs. 11%, p<0.01) were higher in the test group than in the control group. The large (≥ grade II) RLS shunt during Valsalva was significantly higher in the test group than in the control group (25% vs. 8%, p<0.01). Regarding RLS ≤ grade II during Valsalva and all grades of RLS at rest, there was no difference between the two groups. Multivariate analysis showed that the length of the PFO during Valsalva [odds ratio (OR)= 3.27, p=0.03], the presence of ASA (OR= 4.96, p=0.02) large (≥ grade II) RLS shunt during Valsalva (OR= 3.63, p=0.02) and low-angle PFO (OR= 5.80, p=0.01) were independent relevant factors for CS.

Table 1. Patient characteristics

	CS group (n=52)	Control group (n=64)	p-value
Age, years	48±15	40±18	0.01
Woman	28 (54)	30 (47)	>0.05
Hypertension	19 (36)	9 (14)	0.02
Diabetes mellitus	3 (5)	2 (3)	>0.05
Smoking	20 (38)	11 (17)	0.03

Data are presented as mean ± standard deviation or number (%) of patients. CS: Cryptogenic stroke, chi-square test, t-test and Mann-Whitney U tests were used, as apropiate

Discussion

A PFO is a highly prevalent finding in cryptogenic ischaemic stroke, particularly in young adults. A common challenge in clinical practice is to distinguish between incidental and pathogenic PFO. Some clinical features and tools such as the risk of paradoxical embolism score may help determining the probability of a stroke-related PFO. Nonetheless, the best therapeutic option to reduce stroke recurrence after a CS with PFO has been a matter of debate for a long time.

The current study assessed the anatomical and functional characteristics of PFO in patients with CS and those without CS. Long-tunnel PFO, the presence of hypermobile interatrial septum, the large RL shunt during Valsalva maneuver, and low-angle PFO were identified as independent factors associated with CS.

A hypermobile interatrial septum, characterized by a floppy septum with movement of the free edge in every

Table 2. Echocardiographic characteristics of PFO

	CS group (n=52)	Control group CS (n=64)	p-value
Length of PFO, mm	9.3±4.5	8.1±4.3	0.03
Height of PFO, mm	2.4±1.7	1.6±1.1	<0.01
Long-tunnel PFO (>10 mm)	28 (54)	18 (28)	<0.01
Large-size PFO (>2 mm)	11 (21)	4 (6)	<0.01
Hypermobile interatrial septum	38 (73)	9 (14)	<0.01
Atrial septal aneurysm (ASA)	20 (39)	7 (11)	<0.01
Angle between IVC and PFO, degrees	27±18	36±17	<0.01
Low-angle PFO (<10°)	14 (27)	5 (8)	<0.01
≥ Grade II RLS	13 (25)	5 (8)	<0.01

Data are presented as mean ± standard deviation or number (%) of patients. CS: Cryptogenic stroke, PFO: Patent foramen ovale, RLS: Right-to-left, chi-square test, t-test and Mann-Whitney U tests were used, as apropiate

Table 3. Independent predictors of cryptogenic stroke according to the multivariate regression analyses in the study population

	Odds ratio (95% CI)	p-value
Long-tunnel PFO (>10 mm)	3.27 (1.11-10.6)	0.03
Atrial septal aneurysm (ASA)	4.96 (1.82-13.5)	0.02
Low-angle PFO (<10°)	5.80 (1.38-29.7)	0.01
Moderate to large (≥ grade II) RLS shunt during valsalva maneuver	3.63 (1.23-11.3)	0.02

PFO: Patent foramen ovale, RLS Right-to-left, CI: Confidence interval. Logistic regression analyses stepwise forward was used

heartbeat, can frequently result in the enlargement of the PFO orifice, thereby increasing the potential for thrombus passage (2). In our study, we found that the presence of hypermobile interatrial septum was associated with CS. Our findings indicate that the presence of a hypermobile interatrial septum and ASA should be meticulously assessed using TEE. The mechanism of CS may be connected to the angle between the IVC and PFO. Our study presents fresh evidence indicating a correlation between CS and a low angle between the IVC and PFO. This low angle may selectively guide blood flow from the IVC toward the interatrial septum and the orifice of the PFO.

Consistent with the prior investigation (12,13), our study demonstrates an association between CS and a PFO with an extended tunnel length. The extended tunnel length of PFO could potentially serve as a location for thrombus formation due to turbulent and stagnant blood flow, as indicated in previous research (12).

New randomized trials have provided evidence supporting the effectiveness of transcatheter closure in reducing the occurrence of strokes when compared to traditional medical therapy (8-10). The length of the PFO tunnel, low-angle PFO, large (≥ grade II) RLS shunt during Valsalva and the presence of ASA were associated with a greater risk for CS. TEE combined with c-TEE may be helpful in identifying PFO patients at great risk of CS and screening for transcatheter closure of PFO.

Study Limitations

Our study contains some limitations. In our study, CS was diagnosed by a neurologist based on the exclusion of all other identifiable causes of stroke such as large artery atherosclerosis, cardioembolism, small vessel disease, or arterial dissection after clinical examinations including brain and carotid imaging, electrocardiography, and echocardiography. Apart from these basic investigations, a detailed thrombophilia panel could not be checked in every patient. Additionally, asymptomatic paroxysmal atrial fibrillation attacks could not be examined in detail in every patient. Another limitation is that brain MRI findings and localizations were not recorded in CS patients.

Conclusion

A higher risk for CS was linked to the length of the PFO tunnel, low-angle PFO, substantial (≥ grade II) RLS shunt during Valsalva, and the presence of ASA. When screening for transcatheter closure of PFO and dentifying PFO patients at high risk of CS, TEE in conjunction with c-TEE may be useful.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki (1964) and the study protocol was approved by Local Ethics Committee (İstanbul Atlas University Non-Invasive Research Ethics Committee: 08.01.2024, No: 01/14).

Informed Consent: Not necessary for this manuscript.

Authorship Contributions

Concept: Z.D., G.B., Design: Z.D., Data Collection or Processing: Z.D., G.B., Analysis or Interpretation: G.B., Literature Search: Z.D., Writing: Z.D., G.B.

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ORIGINAL RESEARCH

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Surgical Problems and Results in Horseshoe Kidney

Atnalı Böbrekte Cerrahi Sorunlar ve Sonuçlar

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Abstract

Objective: We aimed to evaluate the clinical features, accompanying surgical problems, and renal development outcomes during nephrological follow-up in patients with horseshoe kidney (HSK).

Method: We retrospectively reviewed the medical records of 24 patients with HSK who underwent surgery in our pediatric surgery clinic between 2015 and 2023.

Results: Sixteen of the patients were boys and eight were girls. The mean age was 77.3 (1.5-192) months. The mean follow-up period was 48 (12-120) months. HSK was found incidentally in 10 patients and diagnosed prenatally in seven patients. Eleven children had bladder dysfunction and six patients were diagnosed with spina bifida. Thirteen of the patients were found to have frequent urinary tract infections. Anderson-Hynes pyeloplasty for ureteropelvic junction stenosis, ureteroneocystostomy for vesicourethral reflux (VUR) and ureterovesical stricture, vesicourethral injection sting for VUR, upper pole heminephrectomy for nonfunctioning dual system, Holmium laser-guided lithotripsy and unilateral nephrectomy, isthmusectomy and contralateral kidney nephron-sparing surgery were required due to bilateral Wilms tumor. During the postoperative follow-up, three patients continued to have urinary tract infections, five developed renal scarring, three developed proteinuria and four developed hypertension. A total of three patients, including two patients operated for Wilms tumor, had elevated cystatin-C levels and developed chronic kidney disease (CKD).

Conclusion: Patients with HSK should be followed up for urologic abnormalities that may require surgery and postoperative urinary tract infection and scar formation in the kidneys. In our study, it was demonstrated that surgical intervention alone cannot prevent CKD.

Keywords: Child, horseshoe kidney, retrospective study

Öz

Amaç: Atnalı böbrek (ANB) tanılı hastaların klinik özelliklerini, eşlik eden cerrahi sorunlarını ve nefrolojik takipte böbrek gelişim sonuçlarını değerlendirmeyi amaçladık.

Yöntem: 2015-2023 yılları arasında pediyatrik cerrahi kliniğimizde, ANB tanısı olup cerrahi endikasyon konularak ameliyat edilen 24 hastanın tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Hastaların 16'sı erkek, sekizi kızdı. Yaş ortalamaları 77,3 (1,5-192) ay olarak hesaplandı. Ortalama takip süresi 48 (12-120) aydı. ANB 10 hastada tesadüfen bulunurken, yedi hastada prenatal olarak teşhis edildi. 11 çocukta mesane disfonksiyonu ve altı hastada spina bifida tanısı vardı. Hastaların 13'ünün sık üriner sistem enfeksiyonu geçirdiği tespit edildi. Hastalara üreteropelvik bileşke darlığı tanısıyla Anderson-Hynes piyeloplastisi, vezikoüretral reflü (VUR) ve üreterovezikal darlık tanılarıyla üreteroneosistostomi, VUR nedeniyle vezikoüretral enjeksiyon sting, nonfonksiyone çift sistem tanısıyla üst kutup heminefrektomi, taş saptanması üzerine holmium lazer eşliğinde litotripsi ve bilateral Wilms tümörü saptanarak tek taraflı nefrektomi, isthmusektomi ve karşı taraf böbrek nefron koruyucu cerrahi şeklinde cerrahi müdahale gerekti. Ameliyat sonrası takip sürecinde, üç hastanın idrar yolu enfeksiyonu geçirmeye devam ettiği, beşinde böbrekte skar oluştuğu, üçünde proteinüri ve dördünde hipertansiyon geliştiği görüldü. Wilms tümörü nedeniyle ameliyat edilen iki hasta ile beraber toplamda üç hastada sistatin-C değerlerinin yükseldiği ve kronik böbrek hastalığı (KBH) geliştiği saptandı.

Sonuç: ANB tanılı hastalar tetkik edilirken cerrahi gerektirebilecek ürolojik anormallikler ve ameliyat sonrasında özellikle üriner sistem enfeksiyonu geçirme ve böbreklerde skar oluşumu açısından takip edilmelidir. Çalışmamızda, cerrahi olarak müdahale edilse de tek başına cerrahi işlemin KBH'sini engelleyemeyeceği ortaya konuldu.

Anahtar kelimeler: Atnalı böbrek, çocuk, retrospektif çalışma

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Introduction

Horseshoe kidney (HSK), the most common congenital fusion anomaly of the urinary system, occurs in approximately one in 400 individuals (1). It is twice as prevalent in males (2). In 20% of cases, HSK is located within the pelvis, while the remainder are at the normal anatomical site (3). In over 90% of cases, the two kidney masses join at the lower poles by a parenchymal or fibrous band. In rare instances, the bridge connects the upper poles, forming an inverse HSK. Some kidneys may develop as nonfunctional or dysplastic (4).

These anatomical abnormalities predispose to drainage issues in the collecting system, urinary stasis, infection, and stone formation. While 30-90% of patients with HSK are asymptomatic, nearly one-third to half have additional urological or systemic abnormalities (5). Accompanying surgical pathologies, primarily causing obstructive hydronephrosis, may include ureteropelvic junction obstruction (UPJO), vesicoureteral reflux (VUR), ureterovesical junction obstruction (UVJO), duplex systems, malignancy, and stones.

Literature data lack long-term outcome information for patients with HSK. This study aims to assess the clinical features, surgical problems leading to obstructive hydronephrosis, and nephrological follow-up outcomes regarding kidney development in patients with HSK.

Materials and Methods

Between 2015 and 2023, at our pediatric surgery clinic, we retrospectively reviewed the medical records of 24 patients with HSK who were examined for this condition and subsequently underwent surgery. Demographic, clinical, laboratory, and radiological data were recorded. We assessed age, gender, clinical presentation, surgical pathology, frequency of urinary tract infections (UTIs), blood pressure (BP), serum creatinine (SCr), cystatin-C, urea, glomerular filtration rate (GFR), and urine protein (UP) levels, as well as the status at the latest follow-up.

The diagnosis of HSK was made using urinary ultrasonography and confirmed with radionuclide scanning scintigraphy. Kidney scars (KS) and renal cortical functions were determined using 99mTc-dimercaptosuccinic acid (DMSA) scintigraphy. KS was defined as a defect in contrast material uptake in the normal renal contour in subsequent DMSA scintigraphy (Figure 1). All patients underwent US and DMSA. A widespread decrease in radionuclide uptake indicated a congenital KS, while focused peripheral defects in DMSA scans were identified as acquired KS. All patients underwent bladder and urethral cystography to detect VUR, UPJO, UVJO, stones, or related urinary system abnormalities. VUR was graded from I to V according to the International Reflux Study Committee and decisions for injection or ureteroneocystostomy were made. Estimated GFR (eGFR) was calculated using the new Schwartz formula [eGFR (mL/min/1.73 m²) = 0.413 x height (cm) / SCr (mg/dL)]. Chronic kidney disease (CKD) was defined as a GFR of <90 mL/min/1.73 m². Patients were followed clinically and radiologically every three to six months with urine analysis, UP, SCr, BP measurements, and serial ultrasonography. Those with frequent UTIs underwent DMSA after six months.

Hypertension was defined as systolic and/or diastolic BP above the 95th percentile for age, gender, and height. BP data were recorded as the average of three consecutive measurements taken with a mercury sphygmomanometer after five minutes of rest. A UP to creatinine ratio >0.2 in the first morning urine sample was considered significant. The presence of significant bacteriuria (>105 cfu/mL) in the urinary culture determined the presence of a UTI.

The study was ethically approved by the relevant Institutional Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital under the reference number 228-10.01.2021. As our study had a retrospective design, informed consent was not required from the patients.

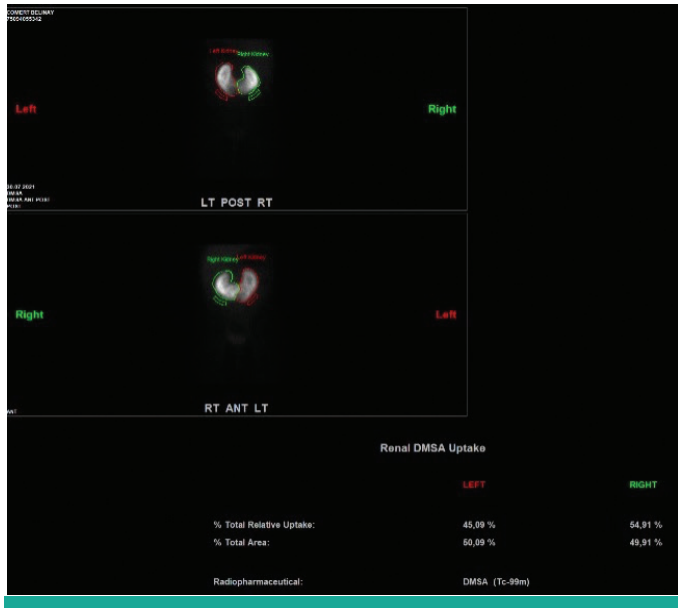

Figure 1. DMSA image
DMSA: Dimercaptosuccinic acid

Statistical Analysis

In this study, we employed a range of statistical techniques to analyze patient data. This involved using descriptive statistics to determine frequencies and characteristics specific to each variable. For continuous variables, we calculated the mean and standard deviation, or median and interquartile range, as appropriate for summarizing the data. We also evaluated the distribution of these continuous variables with the Shapiro-Wilk and Kolmogorov-Smirnov tests to check for normality. In cases where the continuous data did not exhibit a normal distribution, we opted for non-parametric methods over the standard t-test, which is better suited for normally distributed continuous variables. For the analysis of categorical variables, the chi-square test was primarily used, along with Fisher's Exact test in specific situations. All data processing and analysis tasks were carried out using SPSS Statistics software, Version 26.0 (IBM Corp., Armonk, NY, USA), with a p-value of less than 0.05 considered to indicate statistical significance.

Results

Of the patients, 16 were male (66.6%), and eight were female (33.3%). The average age was 77.3 months (ranging from 1.5 to 192 months). The mean follow-up period was 48 months (ranging from 12 to 120 months). HSK was incidentally discovered in 10 patients (41.6%) and prenatally diagnosed in seven patients (29.1%). In patients undergoing surgery for urinary system anomalies, diagnoses included VUR in 7 patients, UPJO in 8, duplex systems in 2, UVJO in 2, urinary stones in 3, and bilateral Wilms tumors in 2. Bladder dysfunction was noted in 11 children (45.8%), and six patients (25%) were diagnosed with spina bifida. It was found that 13 patients (54.1%) had frequent urinary system infections.

Surgical interventions were required for various conditions: Anderson-Hynes pyeloplasty for UPJO (n=8), ureteroneocystostomy for VUR and UVJO (7 patients), vesicoureteral injection-sting for VUR (n=3), upper pole heminephrectomy for nonfunctional duplicated systems (n=2), holmium laser lithotripsy for stones (n=3), and unilateral nephrectomy, isthmusectomy, and contralateral kidney nephron-sparing surgery for bilateral Wilms tumors (n=2) (Table 1).

During the postoperative follow-up of the surgically treated patients, it was observed that three patients (12.5%) continued to experience UTIs, five (20.8%) developed KS, three (12.5%) had proteinuria, and four (16.6%) developed hypertension. Including two patients who underwent surgery for Wilms tumors, a total of three patients (12.5%) developed CKD (Table 2).

The analysis of age at diagnosis revealed an average of 76.6 months (range: 1.5-187 months) for males and 79.2 months (range: 2-192 months) for females, with no significant difference between genders (p>0.05). Regarding the type of diagnosis, incidental findings were observed in 43.8% of males and 37.5% of females, while antenatal diagnoses accounted for 31.2% and 25%, respectively. Other included flank pain (6.25% in males and 12.5% in females), enuresis (12.5% for both genders), and hematuria (6.25% in males and 12.5% in females) (p>0.05). Bladder dysfunction was identified in 43.8% of males and 50% of females, VUR in

Table 1. Demographic and clinical characteristics

Age at diagnosis	**77.3 (1.5-192)**
	n (%)
Gender	
Male	16 (66.6)
Female	8(33.3)
Type of diagnosis	
Incidental	10 (41.6)
Antenatal diagnosis	7 (29.1)
Flank pain	2 (8.3)
Enuresis	3 (12.5)
Hematuria	2 (8.3)
Bladder dysfunction	11 (45.8)
Urinary tract abnormality	
VUR	7 (29.1)
UPJO	8 (33.3)
UVJO	2 (8.3)
Duplex system	2 (8.3)
Stone	3 (12.5)
Wilms tumor	2 (8.3)
Systemic abnormality	
Spinal deformity	6 (25)

VUR: Vesicoureteral reflux, UPJO: Ureteropelvic junction obstruction, UVJO: Uretterovesical junction obstruction

Table 2. Nephrological problems of patients with HSK who were operated on

Outcome	**n (%)**
Surgery	24 (100)
UTI	3 (12.5)
Renal scarring	5 (20.8)
Proteinuria	3 (12.5)
Hypertension	4 (16.6)
CKD	3 (12.5)

UTI: Urinary tract infection, CKD: Chronic kidney disease

Table 3. Comparisons in terms of gender

	Male (n=16)	Female (n=8)	p-value
Age at diagnosis (month)*	76.6 (1.5-187)	79.2 (2-192)	>0.05*
Type of diagnosis			>0.05[&]
Incidental	7 (43.8%)	3 (37.5%)	
Antenatal diagnosis	5 (31.2%)	2 (25%)	
Flank pain	1 (6.25%)	1 (12.5%)	
Enuresis	2 (12.5%)	1 (12.5%)	
Hematuria	1 (6.25%)	1 (12.5%)	
Bladder dysfunction	7 (43.8%)	4 (50%)	>0.05[&]
VUR	5 (31.2%)	2 (25%)	>0.05[&]
UPJO	5 (31.2%)	3 (37.5%)	>0.05[&]
UVJO	1 (6.25%)	1 (12.5%)	>0.05[&]
Duplex system	1 (6.25%)	1 (12.5%)	>0.05[&]
Stone	2 (12.5%)	1 (12.5%)	>0.05[&]
Wilms tumor	1 (6.25%)	1 (12.5%)	>0.05[&]
Spinal deformity	4 (25%)	2 (25%)	>0.05[&]

VUR: Vesicoureteral reflux, UPJO: Ureteropelvic junction obstruction, UVJO: Uretterovesical junction obstruction, *: Median (min-max) Mann-Whitney U test. [&]: Chi-square test

31.2% of males and 25% of females, UPJO in 31.2% of males and 37.5% of females, UVJO in 6.25% of males and 12.5% of females, and duplex systems in 6.25% of males and 12.5% of females. The presence of stones was noted in 12.5% of both males and females, while Wilms tumor was found in 6.25% of males and 12.5% of females. Spinal deformity was reported in 25% of both genders. Across all these categories, no significant gender differences were observed (p>0.05) (Table 3).

Discussion

In most cases, fusion occurs at the lower poles. This fusion is twice as common in males. It is often associated with a narrow pelvis, as typically seen in trisomy 18. Most fused kidneys are positioned lower than normal. HSKs can sometimes be associated with UPJO and may present with UTIs, abdominal masses, and hematuria in children. One alternative treatment is transperitoneal laparoscopic pyeloplasty, which allows for better exploration of the pyelocalyceal system and detection of anatomical anomalies like crossing vessels, more commonly found in HSKs (1-4). In our study, similar to the literature, we found that the condition was more common in male patients. Additionally, in most cases of HSK, the fusion involves the lower poles. In all 24 of our patients, the fusion was observed at the lower poles.

Consistent with existing literature, 30-90% of patients with HSK are asymptomatic. In our patient population, 41.6% were incidentally identified, often diagnosed during imaging procedures (5). Due to its anatomy and embryogenesis, HSK is prone to various complications (6). Variable arterial and venous blood supply, the presence of a midline isthmus, and abnormal positioning of the ureters contribute to the incidence of complications (7). Symptoms typically arise from urological abnormalities such as hydronephrosis, infection, or urolithiasis. Common presentations include abdominal pain, flank pain, nausea, vomiting, UTIs, hematuria, and decreased urine output. Pain that intensifies with hyperextension of the spine is a suspicious symptom (8). In our study, similar to what is reported in the literature, we observed pathologies like VUR, UPJO, UVJO, duplex systems, urinary stones, and tumors in patients undergoing surgery for urinary system anomalies. Additionally, some patients were diagnosed with bladder dysfunction and spina bifida.

In HSK, the most common urinary pathology observed is UPJO, present in approximately 35% of cases and can be bilateral (9). Similarly, in our study, 33.3% of the children were diagnosed with UPJO and underwent surgical intervention. UPJO is likely due to delayed pelvic discharge associated with the high placement of ureters to the renal pelvis. The intersection of the ureter over the isthmus may also

contribute to the obstruction (10). The diagnosis is typically made using intravenous pyelography (IVP), which shows a typical appearance of a dilated pelvis and an adynamic narrow transition zone between the pelvis and ureter. It can also be frequently detected with renal scintigraphy (11,12). In our cases, we primarily used ultrasonography and mercaptoacetyltriglycine (Mag-3) scintigraphy, and in doubtful cases, IVP was additionally employed for diagnosis. Among surgical techniques, options include open pyeloplasty or ureterocalicostomy, while more recent laparoscopic techniques feature dismembered pyeloplasty. This technique involves the removal of the narrowed section of the ureteropelvic junction and reconstruction of the renal pelvis and ureter by creating an anastomosis with the upper part of the renal pelvis (13). In the past, division of the isthmus was routinely recommended post-pyeloplasty to improve drainage. However, it is rarely performed today due to increased risks of complications like bleeding and renal infarction. In our study, all patients requiring surgical intervention had unilateral conditions and underwent open Anderson-Hynes pyeloplasty. There were no interventions on the isthmus, and no recurrences were observed in the follow-up period.

Patients with HSK are prone to infections due to a direct correlation with VUR, stasis, and stone formation (14). One-third of these patients experience frequent urinary infections, which are considered a significant cause of patient morbidity. Literature suggests that approximately half of the patients with HSK exhibit VUR, and it should be a primary consideration in patients with recurrent UTIs, proteinuria, and unexplained renal failure. In our study, in contrast to the literature, VUR was identified in 29.1% (7 patients) and surgical intervention was performed. However, this lower incidence compared to the literature might be due to the inclusion of only patients who underwent surgery in our study, while those managed conservatively were not considered.

In HSKs, the anatomical placement of calyces can hinder drainage, leading to stasis and stone formation (15). The treatment procedure is the same as for a normal kidney. In our study, 12.5% of the patients were found to have stones, for which holmium laser lithotripsy was performed. HSK is associated with various benign and malignant tumors (16). The most common associated cancer is renal cell carcinoma, accounting for 45% of these tumors. Transitional cell cancers constitute 20% of the tumors, and it has been reported that there is a three to four-fold increased risk in HSKs (17-19). This risk is thought to be partly related to chronic infection, stones, and obstruction in the affected kidney. Carcinoid and Wilms tumors also show an increased incidence in HSKs. Similarly, in our study, 8.3% of the patients were diagnosed with Wilms tumor and underwent surgical intervention.

Study Limitations

There are limited studies on the long-term outcomes of patients with HSK. It is believed that patients who are asymptomatic and managed conservatively generally have an excellent prognosis without the need for any treatment. In contrast, the patients included in our study required surgical intervention. These patients were monitored post-surgery, particularly for CKD progression. They were observed for indicators of CKD progression such as proteinuria, hypertension, SCr, cystatin-C levels, GFR results, and the development of KS. In the postoperative follow-up period, it was noted that three patients (12.5%) continued to experience UTIs, KS developed in five patients (20.8%), proteinuria was observed in three (12.5%), and hypertension developed in four (16.6%). Including two patients who underwent surgery for Wilms tumors, a total of three patients (12.5%) developed CKD.

This study has some limitations. First, the sample size is relatively small and represents the experience of a single center. Second, the follow-up period may be considered short.

Conclusions

Patients diagnosed with HSK often have accompanying urinary anomalies. Therefore, during examination, it is crucial to evaluate for urological pathologies that may require surgical intervention. Even after surgical procedures, close monitoring is essential, particularly for urinary system infections and the development of KS. In our study, when assessing surgical issues and outcomes in HSK, we found, in line with the literature, that surgical intervention alone cannot prevent the progression of CKD.

Ethics

Ethics Committee Approval: The study was ethically approved by the relevant Institutional Ethics Committee of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital under the reference number 228-10.01.2021.

Informed Consent: As our study had a retrospective design, informed consent was not required from the patients.

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CASE REPORT

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A Case Diagnosed with Chronic Granulomatous Disease Presenting with Dactylitis

Daktilit ile Prezente Olan Kronik Granülomatöz Hastalık Tanısı Konulan Bir Olgu

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Abstract

Chronic granulomatous disease is a rare primary immunodeficiency seen in 1/70,000-1/200,000 births. It is a monogenetic disease caused by defects in the nicotinamideadenine-dinucleotide-phosphate oxidase enzyme complex. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase produces reactive compounds necessary for the lysis of phagocytized microorganisms. Defects in the NADPH oxidase enzyme complex predispose to granuloma formation and the development of life-threatening recurrent bacterial and fungal infections. Infections usually occur with involvement of the lungs, lymph nodes, liver, bone and skin. Rarely, it may present with dactylitis. A case of chronic granulomatous disease presenting with dactylitis in the third finger of the left hand and abscess on the wrist. The patient who didn't respond to empirical antibiotic treatment was referred to our hospital. *Serratia marcescens* was detected in the drained abscess. After the detection of *Serratia marcescens,* which we see rarely as a causative agent, in the wound culture, the detection of granulomatous inflammation in the biopsy and the NBT test: 0%; the patient was diagnosed with chronic granulomatous disease. Significant regression was observed in the lesion after ceftriaxone and gentamicin treatment given for 14 days. Recurrent and/or unusually severe infections, particularly abscesses and infections commonly caused by CGD-associated pathogens, should suggest chronic granulomatous disease. Early screening of potentially affected children; early diagnosis as well as timely antimicrobial therapy followed by adequate antimicrobial prophylaxis will prevent infectious relapses and sequelae.

Keywords: Chronic granulomatous disease, CYBB, dactylitis, *Serratia marcescens*

Öz

Kronik granülomatöz hastalık 1/70.000-1/200.000 doğumda görülen nadir bir primer immün yetmezliktir. Nikotinamidadenin-dinükleotit-fosfat oksidaz enzim kompleksindeki kusurların neden olduğu monogenetik bir hastalıktır. Nikotinamid adenin dinükleotid fosfat (NADPH) oksidaz, fagosite edilmiş mikroorganizmaların parçalanması için gerekli reaktif bileşikleri üretir. NADPH oksidaz enzim kompleksindeki kusurlar, granülom oluşumuna ve yaşamı tehdit eden tekrarlayan bakteriyel ve mantar enfeksiyonlarının gelişmesine zemin hazırlar. Enfeksiyonlar genellikle akciğer, lenf bezleri, karaciğer, kemik ve deri tutulumu ile ortaya çıkar. Nadiren daktilite de neden olabilir. Sol el üçüncü parmağında daktilit ve el bileğinde apse ile başvuran kronik granülomatöz hastalık olgusunu sunuyoruz. Ampirik tedaviye yanıt alınamaması üzerine tarafımıza sevk edildi. Boşaltılan apsede *Serratia marcescens* saptandı. Yara kültüründe etken olarak nadiren gördüğümüz *Serratia marcescens*'in saptanması, biyopside granülomatöz enflamasyon saptanması ve NBT testinin %0 olarak saptanması üzerine hastaya kronik granülomatöz hastalık tanısı kondu. On dört gün süreyle verilen seftriakson gentamisin tedavisi sonrasında lezyonda belirgin gerileme gözlendi. Tekrarlayan ve/veya alışılmadık derecede şiddetli enfeksiyonlar, özellikle apseler ve genellikle CGD ile ilişkili patojenlerin neden olduğu enfeksiyonlar, kronik granülomatöz hastalığı düşündürmelidir. Potansiyel olarak etkilenen çocukların erken taranması; erken tanı ve zamanında antimikrobiyal tedavi ve ardından yeterli antimikrobiyal profilaksi, enfeksiyöz relapsları ve sekelleri önleyecektir.

Anahtar kelimeler: CYBB, daktilit, kronik granülomatöz hastalığı, *Serratia marcescens*

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Introduction

Chronic granulomatous disease is a rare primary immunodeficiency seen in 1/70,000-1/200,000 births. It is a monogenetic disease caused by defects in the nicotinamide-adeninedinucleotide-phosphate (NADPH) oxidase enzyme complex. NADPH oxidase produces reactive compounds necessary for the lysis of phagocytized microorganisms. Defects in the NADPH oxidase enzyme complex predispose to granuloma formation and the development of life-threatening recurrent bacterial and fungal infections. Infections usually occur with involvement of the lungs, lymph nodes, liver, bone and skin. Rarely, it may present with dactylitis (1,2). Here we present a case of chronic granulomatous disease presenting with dactylitis in the third finger of the left hand and abscess on the wrist.

Case Report

Three-year-old 10-month-old male patient had a lesion that started as dactylitis on the middle finger of the left hand three months ago and gradually became an infected ulcerated wound. He was referred to us after there was no response to the treatment given. He has a history of frequent upper respiratory tract and lower respiratory tract infections, hospitalization with a diagnosis of sepsis in the neonatal period and infected lesion on the edge of the nose 4 months ago.

Our case was born as the third child of a 27-year-old mother and a 32-year-old father. There is no consanguinity between his parents. He was born at term as 3330 gr.

On physical examination, there was an infected and ulcerated lesion extending from the proximal phalanx to the distal phalanx of the left third finger. Contracture developed in his left hand middle finger (Figure A, B). In the oropharynx examination, there were caries in the anterior upper teeth. He has a left axillary lymphadenomegaly around 1 cm. His chest and cardiac auscultation was normal. He has not organomegaly. Fever was 36 degrees, heart rate was 90/min, respiratory rate was 20/min, blood pressure was 85/55 mmHg. Oxygen saturation was measured at 96% in room air. Body weight: 16 kg (25-50p), height: 96 cm (3-10 p).

Complete blood count; leukocyte count: 9850/mm^3, hemoglobin: 9.5 g/dL, platelet count: 436000/mm^3 neutrophil: 2750/mm^3, lymphocyte: 5690/mm^3, C-reactive protein: 25 mg/L, procalcitonin was 0,02 ng/mL. Biochemical parameters were normal. A 31.5 mm lesion which is located under the skin in the area extending from the proximal phalanx to the distal phalanx of the left hand 3rd finger and 17x20x6 mm wrist abscess was detected in magnetic resonance imaging. *Serratia marcescens* was detected in the drained abscess. Quantiferon was negative. No pathogenic microorganisms were detected in the fungal culture, mycobacterial culture and blood culture. In the biopsy material was taken from the lesion on the finger, granulomatous inflammation was detected. *Serratia marcescens* was detected in tissue culture. IgG: 1348 mg/dL (640-2010), IgM: 194 mg/dL (52-297), IgA:198 mg/dL (44-241), total IgE: 212 mg/dL, anti-HBs positive. In flow cytometry analysis of lymphocyte subgroups: CD 45:99%,

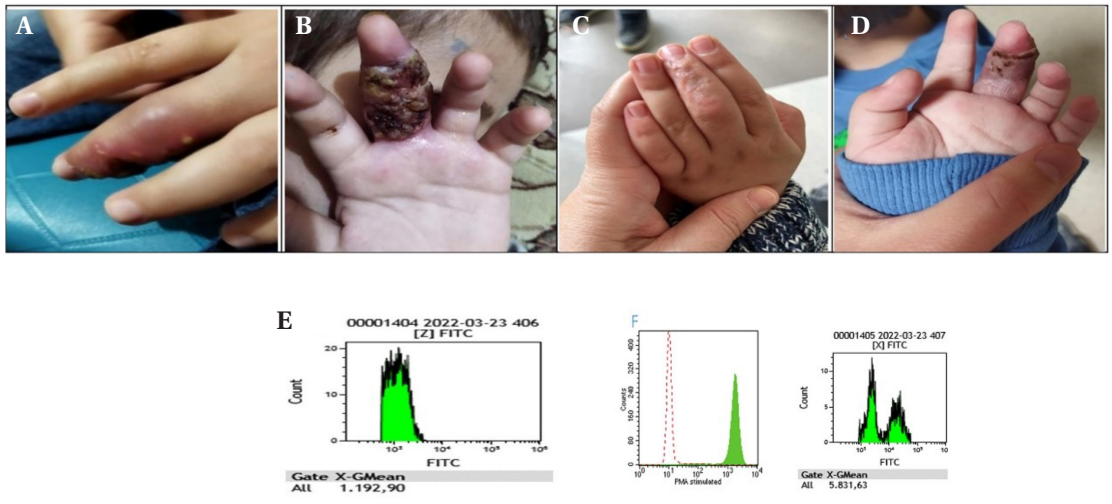

Figure. A, B) An infected and ulcerated lesion extending from the proximal phalanx to the distal phalanx of the left third finger, **C, D)** Patient's finger after treatment, **E)** Histogram image remained on the left in the patient's dihydrorhodamine test, **F)** Histogram images were detected in the dihydrorhodamine test of our patient's mother, one normal and one affected

CD 19: 22 (11-31), CD3: 66% (55-79), CD4: 35% (28-51), CD8: 30% (16-42), CD 16-56 9% (5-28), HLA DR 21.6 (18-38), NBT: 0% in the dihydrorhodamine test, the fluorescent effect we see in healthy people did not occur. While the histogram image remained on the left, two separate histogram images were detected in the dihydrorhodamine test of our patient's mother; one normal and one affected (Figure E, F). With these data, it was thought that there may be a *CYBB* gene mutation with X-linked inheritance and accordingly Gp91 phox deficiency. As a result of the genetic test sent from our patient a hemizygous mutation *CYBB* gene was detected (c.868C>T (p.aRG290*).

After the detection of *Serratia marcescens*, which we see rarely as a causative agent, in the wound culture, the detection of granulomatous inflammation in the biopsy and the NBT test: 0%; the patient was diagnosed with chronic granulomatous disease.

Significant regression was observed in the lesion after ceftriaxone gentamicin treatment given for 14 days (Figure C, D). We started trimethoprim-sulfamethoxazole and itraconazole prophylaxis. Physiotherapy was started for finger contracture. Permission was obtained from the parents of the case to use the pictures and present the case.

Discussion

More than 50 percent of pathogenic variants that cause CGD are X-linked the disease therefore primarily affects men, as in our patient. However, in cultures where consanguineous marriage is common, autosomal recessive forms of CGD are more common than X-linked forms (3). Although autosomal recessive forms of CGD are more common in our country due to the frequent occurrence of consanguineous marriage, X-linked CGD form was seen in our patient. The mother was found to be a CGD carrier.

Patients with CGD often have growth retardation. In a series of 94 patients, approximately 75 percent of the patients had low height and weight values at the time of diagnosis (2). Although our patient's weight was in the normal percentile, his height value was below the 10th percentile.

CGD can occur at any time from infancy to late adulthood. However, most patients are diagnosed before the age of five. Consistent with the literature, our patient was first diagnosed when he was 3 years and 10 months old (2-7). X-linked CGD tends to start earlier and be more severe than p47phox deficiency, which is the most common autosomal recessive form (8). Infections usually occur in organs exposed to the external environment such as the lungs, gastrointestinal tract and skin, as well as in the lymph nodes that drain these areas. In addition to infection and granuloma formation in patients with CGD, autoimmune diseases; including systemic lupus erythematosus, antiphospholipid antibody syndrome, autoimmune thrombocytopenia, rheumatoid arthritis, IgA nephropathy, sarcoidosis and Celiac disease, can also be seen rarely (about 10%) (9-11). Our patient also had an abscess on the left wrist and dactylitis, which is rarely seen in CGD, and an enlargement was detected in the left axillary lymph node that drains this region.

Most commonly, patients with CGD typically present with infections due to catalase-positive organisms. Catalase is an enzyme that can inactivate hydrogen peroxide produced by some bacteria and fungi. It is believed that patients with CGD can use hydrogen peroxide produced by catalase-negative microbes to generate reactive oxidants and, as a result, bypass the intrinsic CGD defect (12).

The most common pathogens detected in 268 patients followed in a single center over a 40 year period were *Aspergillus species, S. aureus, Burkholderia (Pseudomonas) cepacia complex, Serratia marcescens, Nocardia* (13). In another series of 27 patients followed in a different center in North America from 1985 to 2013, it was found that the most common severe infections, in order of frequency, were due to *S. aureus, Serratia, Klebsiella Aspergillus,* and *Burkholderia* (14). In our case, *Serratia marcescens*, which is among the most common organisms CGD, was detected in wound culture. Overall, *Serratia* spp. has low virulence and is considered an opportunistic pathogen (12). In infants with CGD, *Serratia marcescens* infections often present as bone and soft tissue infections, whereas in older children and adults with CGD, they present as abscesses and large, poorly healing ulcerated skin infections. Osteomyelitis is rare (15,16).

Patients with CGD are prone to make granuloma formation. These may affect the lumen organs, but they are more common especially in the gastrointestinal and genitourinary tracts (17). Other tissues and organs, such as the retina, liver, lungs, and bone, may also be affected, to a lesser extent by granuloma (18). In our patient, granulomatous inflammation was detected in the lesion on the finger with atypical presentations. The causes of granuloma formation in CGD are unknown.

However, CGD cells normally disrupt chemotactic and inflammatory signals and fail to lyse apoptotic cells normally, which can lead to persistent and excessive

inflammation (19). Up to 20 percent of cells with normal respiratory burst activity are sufficient to prevent serious bacterial and fungal infections. Therefore, most female carriers of X-linked gp91 phox CGD variants can generate adequate immune responses against infections (19-22). In a large series of X-linked carriers, those with <20% DHR+ cells had severe infectious complications, while all carriers had increased rates of inflammatory and autoimmune complications, regardless of the percentage of DHR+ cells (23).

Although the mother of our patient had a history of frequent upper respiratory tract infections, there was no history of serious infection, autoimmune or chronic disease detected so far.

It is very important to identify the complicated infectious agent in the treatment of infections in CGD. Early and aggressive treatment is essential to prevent the spread of infection.

Infections that do not respond to treatment within 24 to 48 hours, additional diagnostic procedures should be used to identify the microorganism (24). Unfortunately, the starting of effective treatment was delayed in our patient, and therefore a contracture developed in his finger.

Cotrimoxazole is the antimicrobial of choice for bacterial prophylaxis in CGD, because of its broad spectrum and activity against *Nocardia* spp. It also reaches a good concentration in polymorphonuclear cells and does not affect the intestinal anaerobic microbiota (25). It is the most common cause of fungal infection in *Aspergillus* spp. CGD, but has been less frequently identified in different pathogens. Itraconazole has traditionally been the azole of choice for prophylaxis. It was observed that invasive fungal disease had seen less frequently in patients who received prophylaxis compared to those who did not (26).

We started trimethoprim-sulfamethoxazole and itraconazole prophylaxis for our patient whose intravenous treatment was completed in the hospital. No serious infection was observed in our patient after discharge.

Conclusion

Recurrent and/or unusually severe infections, particularly abscesses and infections commonly caused by CGD-associated pathogens, should suggest chronic granulomatous disease. Early screening of potentially affected children; early diagnosis as well as timely antimicrobial therapy followed by adequate antimicrobial prophylaxis will prevent infectious relapses and sequelae.

Ethics

Informed Consent: Permission was obtained from the parents of the case to use the pictures and present the case.

Authorship Contributions

Concept: S.U., I.T., Ç.A., Design: S.U., I.T., Ç.A., Data Collection or Processing: S.U., G.K., M.H.Ç., Analysis or Interpretation: S.U., Ç.A., S.N., Drafting Manuscript: S.U., I.T., S.N., G.K., Critical Revision of Manuscript: Ç.A., M.H.Ç., Final Approval and Accountability: S.U., S.N., I.T., Ç.A., G.K., M.H.Ç., Writing: S.U., S.N., I.T., Ç.A., G.K., M.H.Ç., Technical or Material Support: S.U., Supervision: S.U.

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CASE REPORT

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An Extremely Rare Cause of Rhabdomyolysis: Emery Dreifuss Syndrome

Rabdomyolizin Çok Nadir Nedeni: Emery Dreyfuss Sendromu

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Abstract

Intense physical activity, medications and trauma are common causes of rhabdomyolysis. However, etiologic factor of rhabdomyolysis can not be determined in a remarkable proportion of the cases. Here, we present a rare case of muscular dystrophy related rhabdomyolysis.

Keywords: Emery Dreifuss syndrome, muscular dystrophy, rhadbomyolysis

Öz

Ağır fiziksel aktivite, ilaçlar ve travma rabdomyolizin sık görülen nedenleridir. Yine de olguların dikkate değer bir kısmında rabdomyolizin nedeni ortaya konamamaktadır. Bu olgu raporunda, muküler distrofi ilişkili rabdomyolizin nadir bir nedenini sunmaktayız.

Anahtar kelimeler: Emery Dreifuss sendromu, musküler distrofi, rabdomyoliz

Introduction

Rhabdomyolysis is characterized by the lysis of skeletal muscle cells and release of intracelular content, including creatine kinase (CK), glutamic oxalacetic transaminase, lactate dehydrogenase, aldolase, the haeme pigment myoglobin, electrolytes such as potassium and phosphates to extracelular fluid (1). The symptoms at admittance are fatigue, fever, tachycardia, nausea, vomiting, dark urine and myalgia. The manifestations of rhabdomyolysis may range from mild electrolyte imbalances to life-threatening acute kidney injury.

Although the etiology of rabdomyolysis is so diverse, muscle necrosis is common pathogenetic mechanism of traumatic and non-traumatic rhabdomyolysis (2). Injuries, heavy exercise, severe dehydration, medications (antipsychotics, colchicine, antidepresants, anticonvulsants, statins), substance abuse (alcohol, eroin, cocaine), ischemia, and viral infections are common causes of rhabdomyolysis.

On the other hand, congenital muscle disorders, lipid and purine metabolism disorders and glycolytic enyzme deficiencies are rare reasons of the situation (3). Acquired causes of muscular dystrophies are immobility, malnutrition and malignancy-related cachexia that is caused by imbalance of synthesis and degradation of myocytes. Additionally there are genetical causes of dystrophies. Both forms of the muscular dystrophies clasically presented with progressive muscle weakness and degeneration.

Emery dreifuss (EMD) syndrome is a X-linked genetical muscle dystrophy (4). The mutations on *FHL1* ve *LMNA* genes are frequently observed in patients with EMD. Skeletal muscle and myocardium are sites of involvement. Manifestations of the syndrome are arythmias, heart

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conduction disorders, palpitation, bradycardia, syncope, heart failure and sudden death. The age at the onset of the symptoms may change from childhood to early adulthood.

Our aim is to present a case of EMD muscular dystrophy patient that admitted with rhabdomyolysis.

Case Report

A 32-year old male had a history of myalgia for 3 days before admitting to emergency department of our medical center. His past medical history, including excessive exercise or medication, was eventless. He had the same clinical situation in the last few months, after an upper airway tract infection. His physical appearance was pale, and has no additional abnormal finding on cardiovascular and neuromotor examination.

Laboratory examination revealed out elevated creatinine kinase (CK: 7000 U/L) and acute kidney failure. On admission, creatinine levels were 3.9 mg/dL and hyperphosphatemia (P: 5.4 mg/dL). Furthermore, liver function tests including alanine transaminase (240 IU/L) and aspartate transaminase (300 IU/L) were higher.

The patient underwent to radiographic studies to exclude renal parenchymal and postrenal abnormalities. Ultrasonographic studies showed no signs of abnormality, except renal parenchymal disease. Fluid resuscitation was initiated and patient was recommended to stay at rest. He required no session of hemodialysis, and acute renal injury was resolved with fluid resuscitation. On the 3rd day of hospitalization, his symptoms were recovered, and laboratory abnormalities turned to normal range.

Because there was no apparent cause of rhabdomyolysis, rare cause of the disorder, such genetic mutations were studied. After consultation with the department of medical genetics, a number of mutations which are associated with rhabdomyolysis were analyzed. Genetical analysis indicated muscular dystrophy of EMD syndrome. He was discharged with the recommendation of regular nephrology outpatient service visits. On his follow-up at the 3rd month of discharge from the hospital, laboratory parameters of the patient were normal, and he had no complaint.

Discussion

The early complications of rhabdomyolysis are compartmant syndrome, hypovolemia, electrolyte disorders, acidosis, hepatic dysfunctions (5). In the advanced stages, patients may experience acute kidney failure or disseminated intravascular coagulation. Although patients may have no apparent symptom, a number of patients may experience life-threatening situation associated with myoglobinuria, extremely elevated CK levels and acute kidney failure,

Classical triad of EMD is muscle contractures, especially elbows and Achilles tendons, muscle weakness and cardiomyopathy (6). In contrast to other muscular distrophies, contractures are early findings. Muscle weakness is commonly observed in the proximal of upper extremities and in the distal of lower extremities after the development of contractures. Patients with EMD usually have moderately increased CK levels which is considered as an evidence of chronic rhabdomyolysis (7). Patients with EMD are under increased risk of cardiomyopathy and first degree heart block.

MM subtype of CK which starts to rise within the 12 hours of muscle injury and generally peaks at 72 hours, is the most sensitive indicator of rhabdomyolysis (5). The CK concentration is proportional to muscle damage, and CK higher than 5 times the upper limit of normal indicates mild rhabdomyolysis.

Another marker of rhabdomyolysis, myoglobin, binds to globulin, and rapidly cleared by kidneys. However, subsequent to muscle damage, myoglobulin levels may exceed protein binding and renal clearance capacity. Serum levels of myoglobin usually resolves in the first 24 hour of injury. Early resolution and false negativity in the presence of high urine nitrite concentration or decreased GFR are the drawbacks of myoglobinuria in the diagnosis of rhabdomyolysis (5).

Muscle biopsy is not a routine diagnostic procedure. However, in patients with suspicion of muscular dystrophy, such as repetitive rhabdomyolysis or co-existing muscle contracture or weakness, within the 3rd month ofresolution of rhabdomyolysis may show fragmentation and necrosis of muscle fibers without the presence of inflmmatory cells strongly suggests muscular dystrophy (8).

Therapeutic options are mainly palliative. First and foremost, preventive strategies such as avoidance of nephrotoxic agents are the mainstay of the therapy. Similarly, volume replacement is also essential to reverse the situation. Effective fluid resucitation that resolves volume loss and stimulates urine output should be initiated. Osmotic diuretics like mannitol acts increasing renal blood flow and preventing the obstruction of myoglobin casts (2). Furthermore, urine alkalinization is

also beneficial to excrete intraceluler contents. Dialysis is required for patients with progressive decline in kidney functions, resistant hyperkalemia, hypervolemia, acidosis or ureamic encephalopathy. On contrary, plasmapheresis has no benefit to resolve the metabolic complications (9).

In conclusion, EMD should be considered in patients presented with rhabdomyolysis that has no apperant risk factor and lasting muscle and cardiac symptoms that can be confirmed by muscle biopsy. After the diagnosis of EMD, routine cardiac screening has crucial importance to establish the development of cardiomyopathy and arrythmias in the long-term.

Ethics

Informed Consent: Written consent was received from the patient.

Authorship Contributions

Concept: H.L., Y.Ç., N.G., E.I.Ş., Design: H.L., Y.Ç., N.G., E.I.Ş., Data Collection or Processing: H.L., Y.Çe., A.M., N.G., Analysis or Interpretation: Y.Ç, E.I.Ş., A.M., A.Ç., Drafting Manuscript: H.L., N.G., A.Ç., A.M., Critical Revision of Manuscript: Y.Ç., E.I.Ş., Y.Çe., Technical or Material Support: Y.Ç., Y.Çe., Supervision: E.I.Ş., H.L., N.G., A.Ç., Final Approval and Accountability: N.G., H.L., A.M., Writing: N.G., H.L., A.M.

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

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CASE REPORT

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A Rare Diagnosis in A Pediatric Case Without Metabolic Alkalosis; Bartter Syndrome

Metabolik Alkaloz Olmayan Pediyatrik Olguda Nadir Bir Tanı; Bartter Sendromu

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Abstract

Inherited salt-wasting tubulopathies include antenatal Bartter syndrome (BS), classical (tip 3) BS, and Gitelman syndrome. BS is an autosomal recessive inherited syndrome associated with impaired sodium and chloride reabsorption in the renal tubule. In classical BS cases with mutations in *CLCNKB* gene, dehydration episodes are observed within the first year of life. Polyuria, polydipsia, and dehydration are common symptoms in BS. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the cases. In this article, we presented a case of type 3 BS without metabolic alkalosis. In the presence of failure to thrive, polyuria, and low sodium, potassium, and chloride, even in the absence of metabolic alkalosis, type 3 BS should be considered in the differential diagnosis.

Keywords: Bartter syndrome, hypokalemia, metabolic alkalosis

Öz

Tuz kaybettiren herediter tübülopatiler arasında antenatal Bartter sendromu (BS), klasik (tip 3) BS ve Gitelman sendromu yer alır. BS, renal tübülde sodyum ve klorürün geri emiliminde bozukluk ile ilişkili otozomal resesif kalıtsal bir sendromdur. *CLCNKB* geninde mutasyon bulunan klasik BS olgularında yaşamın ilk yılında dehidrasyon atakları görülür. BS'de poliüri, polidipsi ve dehidrasyon sık görülen semptomlardır. Olguların hemen hepsinde hipokalemi, hipokloremi ve metabolik alkaloz görülür. Bu yazıda metabolik alkalozu olmayan tip 3 BS olgusunu sunduk. Gelişme geriliği, poliüri ve düşük sodyum, potasyum ve klorür varlığında, metabolik alkaloz olmasa bile tip 3 BS ayırıcı tanıda düşünülmelidir.

Anahtar kelimeler: Bartter sendromu, hipokalemi, metabolik alkaloz

Introduction

Hypokalemic salt-losing tubulopathies are those in which salt-wasting occurs proximal to the potassium-secreting segments of the distal nephron, resulting is excessive potassium excretion. Inherited salt-wasting tubulopathies include antenatal Bartter syndrome (BS), classical (tip 3) BS, and Gitelman syndrome. BS with autosomal recessive inheritance associated with impaired sodium and chloride reabsorption in the renal tubule. It leads to excessive salt and water loss. It causes hyperaldosteronism secondary to Renin-Angiotensin-Aldosterone system activation due to volume loss.

In classical BS cases with mutations in *CLCNKB* gene, dehydration episodes are observed within the first year of life. Polyuria, polydipsia, and dehydration are common symptoms in BS. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the cases (1).

In this article, we presented a case of type 3 BS without metabolic alkalosis.

Case Report

A child at three years and six months age has been admitted to a pediatric outpatient clinic due to nausea and vomiting which accompanied with moderate dehydration. It was

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learned that she ate salt, drank a lot of water, and urinated a lot.

Her perinatal history was unremarkable. There was no polyhydramnios in prenatal history. She was a term baby and her birth weight was 3.2 kg. Her parents were non-consanguineous. There was a sibling death history. Our patient has been hospitalized because of dehydration before.

As the medical history has been elaborated we have learnt that she has been admitted to the pediatric outpatient clinic with the complaint of poor weight gain at 18 months age. Slightly low potassium, sodium, and chloride levels have been detected at that time. Her weight and height were below the 3 percentile. A *CFTR* gene analysis was requested due to the findings of an elevated chloride level (50 mmol/L) in her sweat test, indicating the possibility of cystic fibrosis. Further testing was needed to confirm the diagnosis (Between 30-59 mmol/L = Cystic fibrosis is possible, and additional testing is required) (2). The hypercaloric enteral formula and pancreatin (Creon®) have been started. Pancreatin was discontinued because *CFTR* gene analysis was not compatible with cystic fibrosis.

At our hospital admission; the physical examination revealed the weight 10.1 kg (below 3rd percentile, SDS: -3.9), and the height 91 cm (below 3rd percentile, SDS:-3). She had a dry tongue and dry lips. Arterial blood pressure was 90/50 mmHg. Hypokalemia, hypochloremia, hyponatremia, hypomagnesemia, hypophosphatemia, and hypocalcemia were found in laboratory tests. Nevertheless, serum creatinine level was within the usual range. The patient's urine output rate was 10 mL/kg/h (high). Urinary density was 1005. Urine electrolyte measurement showed the urinary potassium level of 35 mmol/L (high). There were proteinuria, hyperuricosuria, hypercalciuria, hypermagnesuria, and a decrease in tubular reabsorption of phosphorus (TRP). The first laboratory findings of the patient on admission are shown in Table 1.

Parathyroid hormone was 137 pg/mL (high), and 25OHD was 3.8 ng/mL (low). As a result, the patient was diagnosed with nutritional 25OHD deficiency. 25OHD deficiency affected TRP by causing phosphaturia.

Reabsorption of protein, uric acid, sodium and potassium occurs from the proximal tubules. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the BS cases. Despite the absence of metabolic alkalosis, the suspected diagnosis was BS due to low sodium, potassium, chloride, and hypercalciuria. Additionally,

Table 1. Laboratory findings (at admission)

		Standard range
Sodium (meq/L)	126	135-145
Potassium (meq/L)	1.59	3.5-5.5
Chloride (meq/L)	83	96-106
Phosphorus (mg/dL)	1.5	3.5-5.5
Magnesium (mg/dL)	1.64	1.8-3.5
Calcium (mg/dL)	8.4	9-11
Albumin (g/dL)	4	3.5-5.5
Urea (mg/dL)	16	7-20
Creatinine (mg/dL)	0.32	0.3-0.6
Uric acid (mg/dL)	2.21	7-8
pH	7.45	7.35-7.45
pCO_2 (mmHg)	32	35-45
HCO_3 (meq/L)	24.7	21-24
Uric acid/creatinine in spot urine (mg/mg)	2.2	<1.5
Calcium/creatinine in spot urine (mg/mg)	0.6	<0.2
TRP (%)	80	>90
Urinary calcium excretion (mg/kg/day)	16	<4
Proteinuria (mg/m²/hr)	31	<4
Magnesium excretion (mg/1.73 m²/day)	100	<30

TRP: Tubular reabsorption of phosphorus

the genetic test result corroborated our diagnosis [whole exome sequencing revealed a homozygous pathogenic mutation in c.371C>T(p.Pro124Leu) *CLCNKB* gene], and she was diagnosed BS type 3.

Cholecalciferol (Devit-3®) 2000 IU/kg, oral potassium chloride (4 mmol/kg per day), indomethacin enteric-coated tablets (0.5 mg/kg per day), and oral magnesium supplement (50 mg/kg per day) treatments were started to the patient. The dosage of indomethacin was increased to 2 mg/kg per day as the treatment continued. Urine output decreased from 10 mL/kg/h to 7 mL/kg/h. Electrolyte disturbance was corrected.

At the time of this writing, she has been 6 years old, 108 cm tall (3rd percentile, SDS:-1.8), and weighed 18.5 kg (15th percentile, SDS:-1).

Discussion

Tubulopathy should be kept in mind in cases of failure to thrive, polyuria, dehydration, and electrolyte imbalance. In the atypical presentation, genetic testing can provide the diagnosis (3,4).

Polyuria, polydipsia, and dehydration are common symptoms in BS. Hypokalemia, hypochloremia, and metabolic alkalosis are observed in almost all of the cases (3). Our patient did not have metabolic alkalosis, clinically, BS was considered possible due to the presence of hypomagnesemia, hypokalemia, hypochloremia, hyponatremia, and hypercalciuria, and genetic testing confirmed the diagnosis.

To our knowledge, this is the first case of type 3 BS in terms of the absence of metabolic alkalosis. Cases with the diagnosis of type 1 and 2 BS without metabolic alkalosis have been described very rarely in the literature (5,6). One of these cases in the literature is a 5-month-old male patient with a history of preterm birth and polyhydramnios. He had hypercalcemia, elevated PTH, hypercalciuria, and nephrocalcinosis. Sodium and potassium levels were within the usual range, and metabolic alkalosis was absent. However, the diagnosis of type 1 BS was made by genetic testing.

Another case in the literature is a 7-year-old female patient with mild hypercalcemia, hypophosphatemia, hypercalciuria, hyperphosphaturia, elevated parathyroid hormone levels, serum creatinine levels within the standard range, and absence of hypokalemic alkalosis, diagnosed with BS type 2 based on the presence of homozygous pathogenic variation in *KCNJ1* gene (7).

The clinical spectrum of type 3 BS is very wide, from classical BS to antenatal BS, to Gitelman syndrome. Sometimes its presentation could seem like antenatal BS or Gitelman syndrome. There should be a history of polyhydramnios and preterm birth in antenatal BS (7). Our patient neither has polyhydramnios nor preterm delivery. Gitelman syndrome is characterized by hypokalemia, metabolic alkalosis, hypomagnesemia, and hypocalciuria. Symptoms of Gitelman syndrome usually begin during adolescence (7,8). Our patient was in early childhood and had hypercalciuria.

Urinary calcium excretion in patients with type 3 BS is often within the usual range, yet reports of hyper- or hypocalciuria have been reported (7). The major site of active regulation of magnesium excretion is the loop of Henle. Hypomagnesemia often can be observed in type 3 BS (8).

Conclusion

We present atypical type 3 BS without metabolic alkalosis. In the presence of failure to thrive, polyuria, and low sodium, potassium, and chloride, even in the absence of metabolic alkalosis, type 3 BS should be considered in the differential diagnosis.

Ethics

Informed Consent: The consent form from the family of the case is obtained.

Authorship Contributions

Concept: D.T., S.T., R.Y.Ç., Design: D.T., S.T., R.Y.Ç., Data Collection or Processing: D.T., S.T., Analysis or Interpretation: D.T., S.T., Drafting Manuscript: D.T., S.T., Critical Revision of Manuscript: S.T., R.Y.Ç., Final Approval and Accountability: S.T., R.Y.Ç., Writing: D.T., S.T., R.Y.Ç.

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CASE REPORT

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A Rare Case of Pediatric Pelvic Ectopic Kidney Injury Management

Nadir Bir Pediyatrik Pelvik Ektopik Böbrek Yaralanması

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Abstract

Renal injury occurs in 10-20% of all abdominal blunt traumas and 3-4% of penetrating traumas in the pediatric population. A 6-year-old girl who had blunt abdominal trauma as a result of a motor vehicle accident was evaluated in the emergency department of our hospital. She complained of a severe left flank and abdominal pain. Defensiveness was detected in the left quadrants of the abdomen and costovertebral angle tenderness was detected in the left. Abdominal computed tomography revealed a left pelvic ectopic kidney with a grade three laceration. The patient was admitted to our urology department, and conservative follow-up was decided after hemodynamic stability was achieved. During the follow-ups, clinical manifestations, vital signs, and laboratory values remained stable, the patient was discharged. In conclusion, based on this experience, we believe that the management of child pelvic ectopic kidney injury can be similar to that of orthotopic kidneys in accordance with the classification of the injury.

Keywords: Acute kidney injury, conservative treatment, ectopic pelvic kidney

Öz

Pediyatrik popülasyonda ise tüm abdominal künt travmaların %10-20'sinde ve penetran travmaların %3-4'ünde renal yaralanma meydana gelmektedir. Motorlu araç kazası sonucu künt batın travması geçiren 6 yaşındaki kız çocuğu hastanemiz acil servisinde değerlendirildi. Şiddetli sol yan ve karın ağrısı şikayeti vardı. Karın sol kadranlarda defans ve yine solda kostovertebral açı hassasiyeti saptandı. Abdomen bilgisayarlı tomografisi neticesinde sol pelvik ektopik böbrek ve bu böbrekte grade üç laserasyon saptandı. Hasta üroloji servisimize yatırıldı ve hemodinamik stabilite sağlandıktan sonra konservatif izleme karar verildi. Takiplerinde kliniği, vital bulguları ve laboratuvar değerleri stabil seyreden hasta taburcu edildi. Sonuç olarak bu deneyimden yola çıkarak çocuk pelvik ektopik böbrek yaralanması tedavi yönetiminin, yaralanmanın sınıflamasına uygun olarak ortotopik böbrekler ile benzer şekilde yapılabileceği düşüncesindeyiz.

Anahtar kelimeler: Akut böbrek hasarı, ektopik pelvik böbrek, konservatif tedavi

Introduction

Renal injury occurs in 10-20% of all abdominal blunt traumas and 3-4% of penetrating traumas in the pediatric population (1). It has been reported that the incidence of pelvic ectopic kidney varies between 1/500 and 1/1200. While pelvic ectopic kidneys are often associated with anomalies such as hydronephrosis and vesicoureteral reflux, they are typically asymptomatic (2).

After blunt abdominal trauma, the probability of urinary tract injury in children is higher than in adults due to various anatomical differences such as weaker abdominal muscles, relatively lower location of the kidneys in the abdomen, and less perirenal adipose tissue (3). The lack of protective anatomical structures in the pelvic kidneys causes them to be more prone to injury in blunt trauma (4).

Over the past few decades, there has been a major shift in the management of renal trauma in children, with the primary focus being on conservative follow-up instead of surgical intervention (5).

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A lack of adequate data exists in the literature regarding the management of pelvic ectopic kidney injuries. In this case report, we aimed to present ectopic pelvic left kidney injury after blunt abdominal trauma.

Case Report

A 6-year-old female presented to the emergency department following a motor vehicle collision, suffering from blunt abdominal trauma. She complained of a severe left flank and abdominal pain. Vital signs were notable for hypotension with a blood pressure of 83/58 mmHg, tachycardia with a heart rate of 108 beats per minute, a respiratory rate of 18 breaths per minute, and an oxygen saturation of 96%. She had no previous history of chronic disease.

Defensiveness was detected in the left quadrants of the abdomen and costovertebral angle tenderness was detected in the left. Macroscopic hematuria was not detected in the patient with a Foley catheter. Laboratory tests revealed hemoglobin 12 g/dL, hematocrit 36%, urea 12 mg/dL and creatinine 0.5 mg/dL.

In the radiological evaluation, chest radiography was unremarkable. Abdominal computed tomography (CT) revealed a left pelvic ectopic kidney with a grade three laceration (Figure 1).

The patient was admitted to our urology department, and conservative follow-up was decided after hemodynamic stability was achieved. Typical conservative follow-up procedures include supportive care, bed rest, periodic monitoring of vital signs and laboratory tests, and close monitoring of the patient's condition using imaging techniques. During the follow-ups, the patient's clinical manifestations, vital signs, and laboratory values remained stable. After a significant improvement was detected on the control ultrasonography and abdominal CT performed on the seventh day, the patient was discharged. Informed consent was obtained from the relatives.

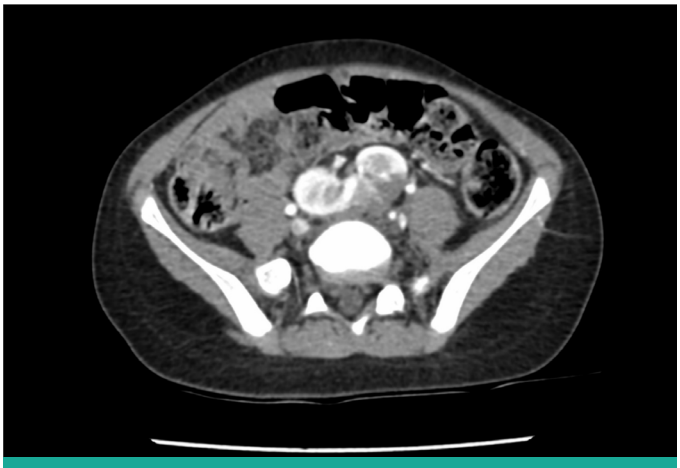

Figure 1. Image of abdominal computed tomography revealed a left pelvic ectopic kidney with a grade three laceration

Discussion

Six-eight weeks of fetal development kidney formation begins. Pathologies in this process may lead to ectopic kidney development (6). The ectopic kidney is classified as an abdominal, lumbar, or pelvic kidney according to its location in the abdominal cavity. On the other hand, it is rare in the thoracic cavity (7).

Kidney traumas are more risky in children due to their anatomical structure compared to adults. Children's kidneys are less protected because they have larger kidneys relative to their body size, the kidneys are located lower in the abdomen, there is less peri-renal adipose tissue around them, and the abdominal wall muscles are weaker.

Children are more likely to have renal parenchymal laceration, bleeding, and urinary leakage than adults. Because the renal capsule and gerota fascia are weaker (4). The incidence of renal injury after blunt abdominal trauma is approximately 10% (4). As abnormal kidneys, including those located ectopically, are generally located in a less protected location in the retroperitoneal space, they may be more vulnerable to injury (8). According to a meta-analysis, ectopic kidneys account for 7% of all abnormal kidney injuries. In most cases of ectopic kidneys, patients are asymptomatic and are diagnosed incidentally. The diagnosis is usually made on the evaluation of infection, pain, kidney stone, or trauma, as in our patient (9). In blunt abdominal trauma, peritoneal lavage, focused assessment with sonography in trauma examination, and CT can be performed for diagnostic purposes after patient history and physical examination. Abdominal CT good recognition tool for the diagnosis of organ injury and the detection of incidental findings after blunt abdominal trauma (10). Because clinical manifestations may not be a reliable indicator of the severity of visceral organ injury, notably in children, CT should not be delayed to avoid a delay in the diagnosis of kidney injury (11). Thus, we also quickly performed an abdominal CT on our pediatric patient and found a grade 3 laceration in the left pelvic ectopic kidney.

Pelvic kidney injuries can be treated just like normal kidney injuries. Low-grade renal injuries and selected Grade IV, and Grade V renal trauma can be managed with conservative follow-up (12). Hence, we followed a 6-year-old girl with a Grade III laceration and an ectopic kidney in the left pelvis with conservative follow-up in accordance with our standard procedure for orthotopic kidney injuries. In the follow-up examination, the patient's hemodynamics were stable, and no surgical intervention was required.

In conclusion, based on this experience, we believe that the management of pelvic ectopic kidney injury can be similar to that of orthotopic kidneys in accordance with the classification of the injury.

Ethics

Informed Consent: Informed consent was obtained from the relatives.

Authorship Contributions

Surgical and Medical Practices: E.Y., K.Ö., Concept: E.Y., Design: E.Y., Data Collection or Processing: E.Y., K.Ö., Analysis or Interpretation: E.Y., K.Ö., Literature Search: E.Y., K.Ö., Writing: E.Y.

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

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