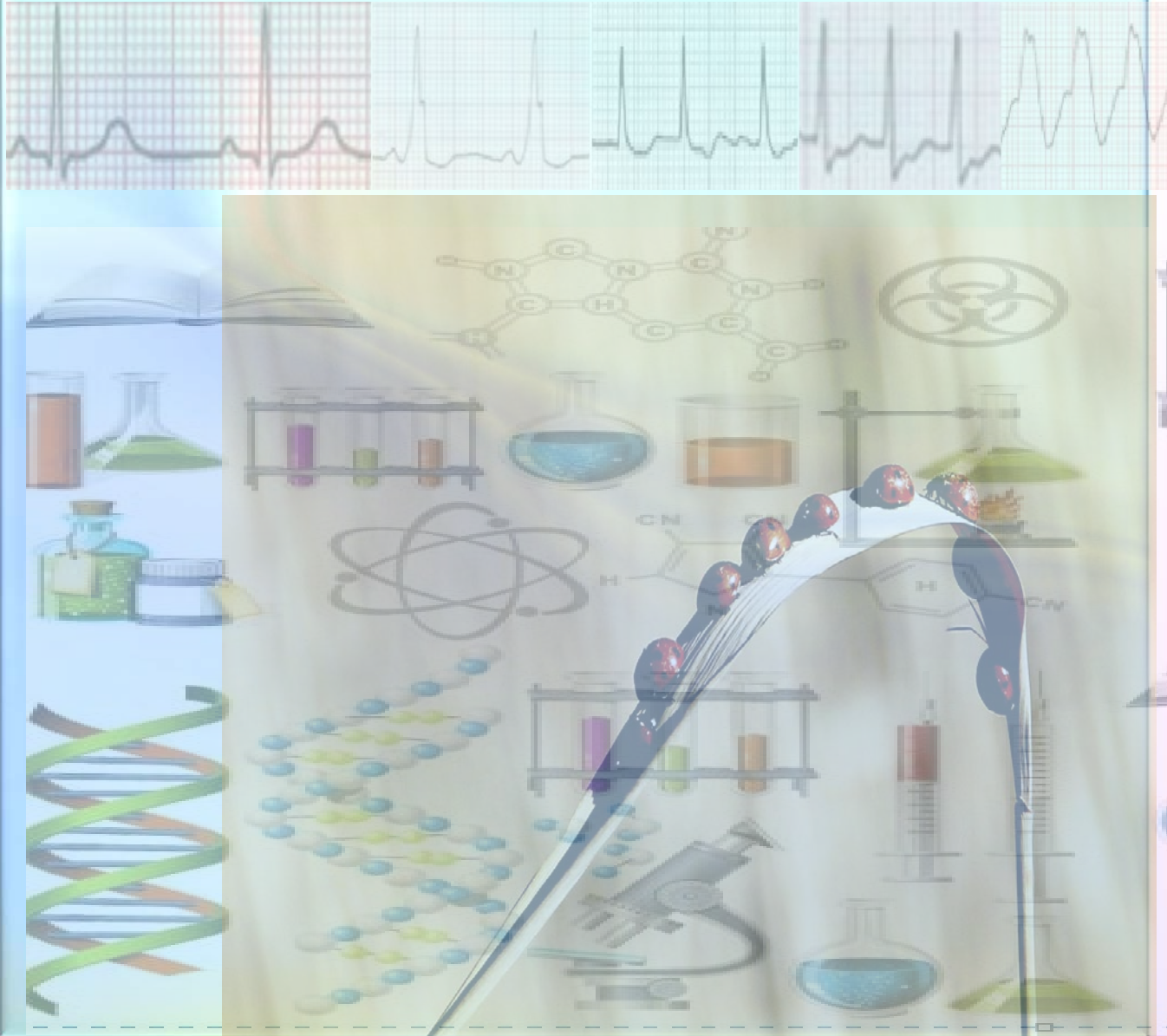


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It consists of Introduction, Material and method, Results, Discussion and Conclusion sections.

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Books; 1. Wagner G. S. Marriott's Practical electrocardiography, Tenth ed. Lippincott Williams Publisher, 2000: 124-129

Web article: Abood S. Quality improvement initiative in nursing homes: The ANA acts in an advisory role. *Am J Nurs* [serial on the Internet] 2002 [cited 12 Aug 2002]. Available from: www.nursingworld.org/AJN/2002/june/wawatch.htm

Website; Cancer-pain.org [homepage on the Internet]. New York: Association of Cancer Online Resources [updated 16 May 2002; cited 9 July 2002]. Available from: www.cancer-pain.org

Thesis; Gezer R: Morphological Characteristics and Individual Differences of Rugae Palatines. Master Thesis, Şanlıurfa: Harran University Institute of Health Sciences, 2016.

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*Letter to The Editor***Combined acupuncture for the treatment of pregnancy nausea and vomiting****Kıymet İclal Ayaydın Yılmaz** Gynecology and Obstetrics, Giresun University Faculty of Medicine, Gynecology and Pediatrics
Training and Research Hospital. Giresun/TURKIYE

We read with great interest Şahin et al.'s case report on nausea and vomiting in pregnancy (morning sickness), titled "Nausea, vomiting in pregnancy and acupuncture", published in your journal (1). The case report of a 31-year-old pregnant woman who presented at 14 weeks of gestation with refractory to medical treatment: severe nausea, sometimes vomiting, and aversion to odors, especially food, provides interesting information. It has been reported that nausea and vomiting decreased 2 days after the session in the patient in whom body and ear acupuncture was applied. It has been stated that the ongoing feeling of nausea can be relieved by putting pressure on the bands attached to the ears.

There are examples of the case presentation presented by the authors with different designs in the literature. However, some points where this case report made a difference caught our attention. It is observed that most of the acupuncture studies for pregnancy nausea and vomiting focus on the P6 point (2). In this presentation, ST36 and REN12 points are used in addition to P6 in order to balance the energy circulating in the stomach canal in body acupuncture. Similarly, sterile permanent seeds were placed at 3 different points in ear acupuncture, and an effective treatment response was obtained by applying pressure in the presence of recurrent symptoms.

Nausea and vomiting (morning sickness) during pregnancy is one of the most common symptoms during pregnancy and may rarely continue throughout the pregnancy. These ongoing complaints may turn into a severe form called "hyperemesis gravidarum" (3). In this patient group, an early-onset treatment may prevent the development of serious complications and increase the quality of life of the pregnant woman. According to the results of the network meta-analysis of randomized controlled trials evaluating the treatment modalities of pregnancy nausea and vomiting by Sridharan K et al.: It was reported that acupuncture was effective against placebo in the primary outcome expressed as the nausea score, but the power of evidence was low (4). However, it is noteworthy that only the P6 point is preferred in the acupuncture studies evaluated in the meta-analysis. On the other hand, according to network meta-analysis results of randomized controlled trials evaluating the treatment modalities of hyperemesis gravidarum by Sridharan K et al.: Acupuncture, acupressure, and methylprednisolone were observed with better therapeutic benefits than other interventions for treating hyperemesis grvidaum (5). Combined body and ear acupuncture applied by the authors and the use of additional focal points may provide more successful results in the prevention of pregnancy nausea and vomiting in the early period. In this regard, the power of evidence for this treatment modality with a low side-effect profile will increase with randomized controlled studies of appropriate design.

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Original Article

The Mediterranean Diet Effects on in-Stent Restenosis

Akdeniz Diyetinin Stent Restenozu Üzerine Etkileri

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Highlights

• It has recently become the focus of clinical studies that feeding a Mediterranean diet may help prevent cardiovascular events and atherosclerosis.

• Restenosis rates are lower in stented patients who score high on the Mediterranean diet.

Abstract

Background: There is evidence that Mediterranean diet nutrition can help prevent cardiovascular events and atherosclerosis, but researchs are limited. Despite advances in interventional techniques, medical treatments, and lower cardiovascular disease (CVD) mortality, increasing percutaneous coronary interventions have made in-stent restenosis (ISR) an important problem in interventional cardiology. This study aims to assess the relationship between in-stent restenosis and the Mediterranean diet score.

Material and Method: The diet quality of 100 patients with ISR and 100 patients without ISR was determined and compared using a scoring method (5, 6, 9, and 10 points) using the 'Mediterranean Diet Compliance Scale'.

Results : Patients with ISR had lower Mediterranean diet scores (odds ratio [OR]: 0.572, 95% confidence interval [CI]: (0.480-0.681), p<0.001). The ISR and Mediterranean diet score had a significant negative correlation (p<0.001, r = -0.679).

Conclusion: In our study, we found that patients who scored high on the Mediterranean diet had a lower risk of ISR, and there was also a negative correlation between the Mediterranean diet and ISR. It is the first study to look at the effects of the Mediterranean diet on patients with a previous percutaneous coronary intervention. This study, examining the relationship between the Mediterranean diet and ISR, may aid in understanding the pathophysiology of ISR.

Keywords: In-stent restenosis; Mediterranean diet score; Coronary artery disease

ÖZ

Amaç: Akdeniz diyeti ile beslenmesinin kardiyovasküler olayları ve aterosklerozu önlemeye yardımcı olabileceğine dair kanıtlar vardır, ancak araştırmalar sınırlıdır. Girişimsel tekniklerdeki ilerlemelere, tıbbi tedavilere ve düşük kardiyovasküler hastalık (KVH) mortalitesine rağmen, artan perkütan koroner girişimler stent içi restenozu (SİR) girişimsel kardiyolojide önemli bir sorun haline getirmiştir. Bu çalışma, stent içi restenoz ile Akdeniz diyeti skoru arasındaki ilişkiyi değerlendirmeyi amaçlamaktadır.

Materiyal ve Metod: SİR'u olan 100 hastanın ve SİR'u olmayan 100 hastanın diyet kalitesi belirlendi ve 'Akdeniz Diyet Uyum Ölçeği' kullanılarak bir skorlama yöntemi (5, 6, 9 ve 10 puan) ile karşılaştırıldı.

Bulgular: SİR'u olan hastalarda Akdeniz diyeti puanları daha düşüktü (olasılık oranı [OR]: 0,572, %95 güven aralığı [CI]: (0,480-0,681), p<0,001). SİR ve Akdeniz diyeti puanı arasında anlamlı bir negatif korelasyon vardı (p<0.001, r = -0.679).

Sonuç: Çalışmamızda, Akdeniz diyetinden yüksek puan alan hastaların SİR riskinin daha düşük olduğunu ve ayrıca Akdeniz diyeti ile SİR arasında negatif bir korelasyon olduğunu bulduk. Daha önce perkütan koroner girişim geçirmiş hastalarda Akdeniz diyetinin etkilerini inceleyen ilk çalışmadır. Akdeniz diyeti ile SİR'u arasındaki ilişkiyi inceleyen bu çalışma, SİR'nin patofizyolojisinin anlaşılmasına yardımcı olabilir.

Anahtar Kelimeler: Stent içi restenoz; Akdeniz diyeti puanı; Koroner arter hastalığı

Introduction

Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality in developed countries, imposing a significant economic burden on the healthcare system and society(1-3). Cardiovascular risk has been shown to be influenced by lifestyle and dietary habits(4-6). Evidence supports that certain individual nutrients and foods provide cardiovascular benefits(7, 8). Examining general dietary patterns, on the other hand, may provide a more powerful tool for assessing dietary habits by assessing the synergistic and cumulative effects of specific nutrients on cardiovascular health(7).

The Mediterranean diet is a dietary pattern that is becoming increasingly popular owing to its health benefits, such as CVD prevention(9). Typical Mediterranean dietary habits and styles include a high consumption of fruits, vegetables, monounsaturated fats, fish, whole wheat, legumes, and nuts, as well as a low consumption of red meat(10). In primary prevention, the Mediterranean diet has been shown to be effective in lowering the cardiovascular risk (11). In this context, the PREDIMED study found that the Mediterranean diet had a higher long-term benefit for CVD than a low-fat diet(11). Another study that compared the Mediterranean diet to another low-fat diet found that it reduced plaque load in the carotid arteries and was more effective in secondary prevention(7). A Mediterranean-style diet has the potential to be anti-inflammatory, antioxidant, and cytoprotective(8, 12, 13).

Despite advances in interventional techniques and medical treatments, as well as lower CVD mortality, increasing percutaneous coronary interventions have made in-stent restenosis (ISR) an important problem in interventional cardiology(14, 15). Although ISR is linked to a variety of inflammatory markers(14, 16), no studies have investigated a possible association between the Mediterranean diet and ISR.

This study aims to assess the relationship between ISR and the Mediterranean diet score.

Materials and Methods

Study design

200 patients with stable or unstable angina pectoris underwent coronary drug-eluting stent implantation and were divided into the restenosis group and non-restenosis group.

Patient population

The clinical protocol was approved by the institutional Medical Ethics Committee no:364, and the study was conducted according to the ethical guidelines outlined in the Declaration of Helsinki. All patients were informed about the study, and their written consent forms were obtained.

A total of 200 patients with the chronic coronary syndrome who underwent coronary stent implantation after coronary angiography at Süleyman Demirel University of Research and Application Hospital were included in this study. The patients were divided into 2 groups according to the results of coronary angiography: the restenosis group (>50% diameter stenosis, n=100) and the non-restenosis group (<50% diameter stenosis, n=100). Patients were excluded from analysis if they had clinical evidence of cancer, chronic inflammatory disease, or any active infectious disease and those who did not want to do the diet questionnaire. All laboratory data were obtained from venous blood samples up to 6 hours before stent implantation. Total WBC, neutrophil, lymphocyte, and monocyte counts were calculated using an automated blood cell counter (ADVIA 2120i Hematology System, Siemens Healthcare Diagnostics, Deerfield, Illinois). NLR was calculated as the preprocedural ratio of neutrophils to lymphocytes, which were obtained from the same blood samples. CRP levels were measured by an immunonephelometric method (Roche Diagnostics GmbH, Marburg, Germany). Coronary interventions were performed according to current practice guidelines and recorded in digital storage for quantitative analysis. The degree of coronary stenosis was visually estimated by experienced interventional cardiologists. A luminal narrowing >50% in a major subepicardial vessel (left anterior descending, left circumflex, or right coronary artery) was defined as significant stenosis. Each patient received aspirin plus clopidogrel (loading dose 300 or 600 mg) before or during coronary intervention. Unfractionated heparin 100 U/kg was administered at the beginning of the procedure to keep the activated clotting time >200 seconds. The access site for percutaneous coronary intervention (PCI) was at the physician's preference (femoral or radial). Usage of glycoprotein IIb/IIIa inhibitors and predilatation or post-dilatation after stent implantation of the lesion was at the operator's discretion. Successful PCI was defined as a <20% decrease in diameter stenosis and residual stenosis <50% in diameter with final Thrombolysis In Myocardial Infarction grade 3 flow without any major complication. After stent placement, clopidogrel was used for one year, and aspirin was used indefinitely. During routine clinical follow-up, coronary angiography was performed secondarily in patients with stable or unstable angina pectoris. Control coronary angiograms were recorded with the Judkins technique and interpreted by two independent cardiologists who were blinded to patients' data. Stent

restenosis was accepted as narrowing >50% in an otherwise normal diameter, including 5 mm proximal and distal to the stent edge, according to results of control coronary angiographies. Intra- and interobserver variabilities of stent restenosis analysis were minimal in a representative subset of 50 patients. Interpretations of the two investigators on the presence or absence of ISR were agreed in 98% (49 of 50) and 98% (49 of 50), respectively. One investigator assessed intraobserver variability. The two readings were concordant for the presence or absence of ISR in 90% (45 of 50) and 96% (48 of 50), respectively. Patients with chronic total occlusions, bifurcation lesion stenting, and stenting longer than 60 mm were excluded from the study. Patients diagnosed with diabetes mellitus at the time of admission were excluded from the study.

The use of oral antidiabetic drugs or the use of insulin was accepted as diabetes criteria. Glucose levels at the time of admission were recorded.

Questionnaire of Mediterranean diet adherence

Questionnaire on Mediterranean diet adherence” is a questionnaire validated in Turkish (17). In the questionnaire of Mediterranean diet adherence, 14 questions were asked by the researcher (Table 1) (18). Colored visual images belonging to foods were used to assess the portion sizes consumed by individuals (19). We assessed the individual consumption of vegetables, fruits, legumes, nuts, whole grains, fermented dairy products, fish and monounsaturated fats, average alcohol, and red meat according to the scoring method of (≤ 5 , 6-9 or ≥ 10 points) (18). Individuals with higher points were considered to be fed more consistently with the Mediterranean diet(20).

Table 1. Validated 14-item Questionnaire of Mediterranean diet adherence.

Questions	Criteria for 1 point
1. Do you use olive oil as main culinary fat?	Yes
2. How much olive oil do you consume in a given day (including oil used for frying, salads, out-of-house meals, etc.)?	≥ 4 tbsp
3. How many vegetable servings do you consume per day? (1 serving : 200 g [consider side dishes as half a serving])	≥ 2 (≥ 1 portion raw or as a salad)
4. How many fruit units (including natural fruit juices) do you consume per day?	≥ 3
5. How many servings of red meat, hamburger, or meat products (ham, sausage, etc.) do you consume per day? (1 serving: 100–150 g)	< 1
6. How many servings of butter, margarine, or cream do you consume per day? (1 serving: 12 g)	< 1
7. How many sweet or carbonated beverages do you drink per day?	< 1
8. How much wine do you drink per week?	≥ 7 glasses
9. How many servings of legumes do you consume per week? (1 serving : 150 g)	≥ 3
10. How many servings of fish or shellfish do you consume per week? (1 serving 100–150 g of fish or 4–5 units or 200 g of shellfish)	≥ 3
11. How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits, or custard?	< 3
12. How many servings of nuts (including peanuts) do you consume per week? (1 serving 30 g)	≥ 3
13. Do you preferentially consume chicken, turkey, or rabbit meat instead of veal, pork, hamburger, or sausage?	Yes
14. How many times per week do you consume vegetables, pasta, rice, or other dishes seasoned with sofrito (sauce made with tomato and onion, leek, or garlic and simmered with olive oil)?	≥ 2

Statistics analysis

All statistical analyses were performed using SPSS for Windows version 19.0 (SPSS, Chicago, IL). The number of each group was adjusted to 100 patients. We calculated the minimum number of individuals that should be sampled with 90% power and 0.05 Type-I error as at least 44 (R 3.0.1. open source program). The primary effect variable was calculated as ± 0.18 . For the descriptive statistics of the data, mean, standard deviation, rate, and frequency values were used. The Kolmogorov–Smirnov test was used to evaluate whether the distribution of continuous variables was normal. For the analysis of parametric data, Student's t-test was used. For the analysis of nonparametric data, the Mann–Whitney U test was used. The Pearson's χ^2 test was used to compare the categorical variables between groups. Pearson correlation analysis was used to assess the correlation between the number of ISR and the Mediterranean diet score. Statistical significance was defined as $p < 0.05$.

Results

The basic parameters of both groups are shown in Table 2. Diabetes, smoking, Hs CRP, stent length, and Mediterranean diet score were observed to be statistically different between the two groups. Parameters that were considered to be risk factors for ISR were evaluated with logistic regression analysis. We included Diabetes Mellitus, Smoking, Hs-CRP, and Mediterranean diet score in these risk factors. Each risk factor was evaluated by univariate analysis to investigate its interaction with ISR. We evaluated all the parameters in which we observed interaction with multivariate analysis. Multivariate logistic regression analysis showed that patients with ISR had lower Mediterranean diet scores (odds ratio [OR]: 0.572, 95% confidence interval [CI]: (0.480-0.681), $p < 0.001$) (Table 3). The significant negative correlation between the ISR and the Mediterranean diet score is shown in Figure 1 ($p < 0.001$, $r = -0.679$).

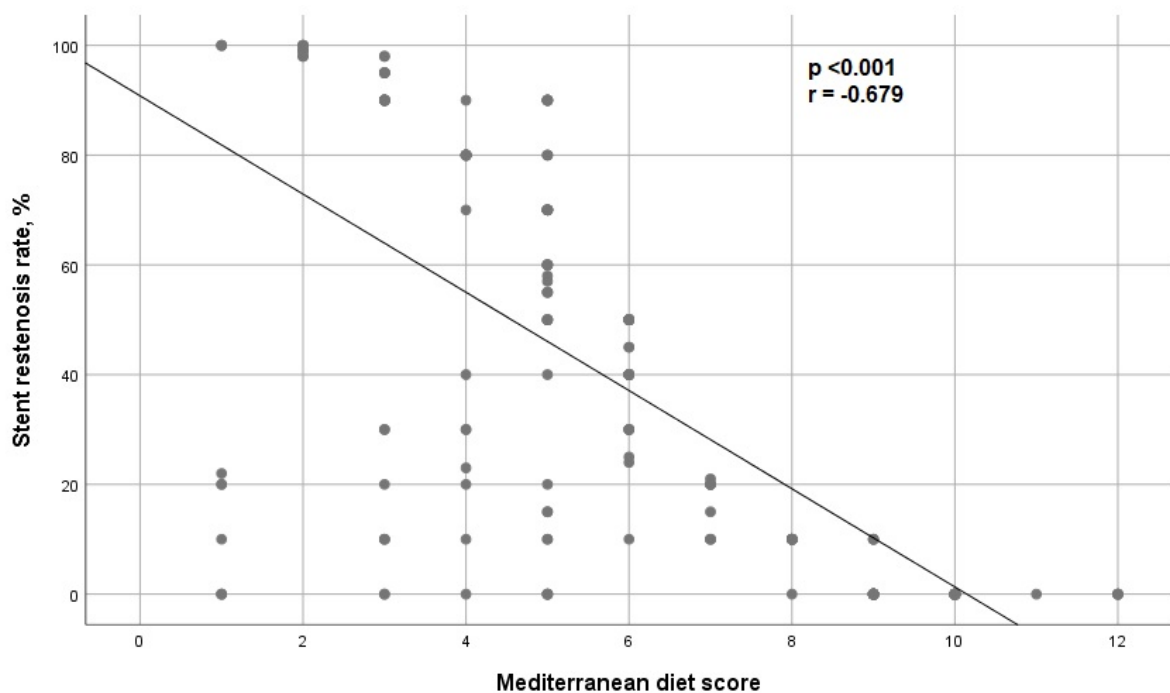


Figure 1: Correlation between Mediterranean diet score and stent restenosis

Table 2. Baseline characteristics, laboratory findings, procedural characteristics and Mediterranean diet score of the study groups (n=100).

Parameters	Patients without stent restenosis	Patients with stent restenosis	P value
Age, years	64.5 ± 12.2	67.1 ± 10.1	0.097
BMI, kg/m ²	28.1 ± 5.8	28.2 ± 4.9	0.915
Female, n (%)	38 (38.0)	32 (32.0)	0.374
Diabetes Mellitus, n (%)	30 (30.0)	46 (46.0)	0.020
Hypertension, n (%)	46 (46.0)	55 (55.0)	0.203
Dyslipidemia, n (%)	27 (27.0)	32 (32.0)	0.438
Family history, n (%)	23 (23.0)	26 (26.0)	0.622
Smoking, n (%)	38 (38.0)	55 (55.0)	0.016
Glucose, mg/dl	119.4 ± 50.7	128.2 ± 57.6	0.257
Creatinine, mg/dl	1.04 ± 0.45	1.05 ± 0.37	0.913
Uric Acid, mg/dl	6.1 ± 2.9	6.4 ± 3.5	0.770
WBC, 10 ³ /mm ³	8.1 ± 4.3	8.4 ± 3.5	0.975
Hemoglobin, g/dL	13.9 ± 1.9	13.8 ± 2.2	0.752
Platelete, 10 ³ /mm ³	235 ± 62	247 ± 71	0.212
Total cholesterol, mg/dL	193.5 ± 49.3	188.9 ± 54.9	0.524
Triglyceride, mg/dL	118.6 ± 81.8	130.7 ± 129.6	0.447
LDL-cholesterol, mg/dL	126.3 ± 40.9	120.2 ± 45.9	0.337
HDL-cholesterol, mg/dL	45.0 ± 11.2	45.1 ± 11.0	0.945
Hs-CRP, mg/L	5.79 ± 3.1	10.6 ± 8.1	< 0.001
LVEF, %	49.2 ± 9.7	50.1 ± 9.1	0.526
Time between 2 procedures, month	18 ± 5.7	19 ± 7.3	0.421
Stent length, mm	31.75 ± 11.1	37.4 ± 16.7	0.006
Stent diameter, mm	2.74 ± 0.41	2.68 ± 0.35	0.213
Mediterranean diet score	7.43 ± 2.87	4.32 ± 1.38	< 0.001

Abbreviations:Data are given as mean ± SD, number (n). BMI, Body mass index; HDL, high density lipoprotein; Hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricle ejection fraction; WBC, white blood cells.

Table 3. Multivariate logistic regression analysis to predict the ISR.

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Diabetes Mellitus	1.988 (1.112-3.554)	0.020	1.036 (0.267-4.015)	0.541
Smoking	1.194 (1.134-3.506)	0.016	2.687 (0.704-10.257)	0.148
Hs-CRP	1.108 (1.052-1.068)	< 0.001	1.076 (1.019-1.136)	0.007
Stent length	1.033 (1.009-1.052)	0.007	1.033 (1.002-1.064)	0.035
Mediterranean diet score	0.562 (0.477-0.663)	< 0.001	0.572 (0.480-0.681)	< 0.001

Abbreviations: CI, confidence interval; Hs-CRP, high-sensitivity C-reactive protein; OR, Odds ratio.

Discussion

In our study, we found that patients who scored high on the Mediterranean diet had a lower risk of ISR, and there was also a negative correlation between the Mediterranean diet and ISR. It is the first study to look at the effects of the Mediterranean diet on patients with a previous percutaneous coronary intervention.

Numerous studies in recent years have revealed a link between nutrition and cardiovascular disease(10, 21, 22). The Mediterranean diet is widely regarded as one of the healthiest to prevent cardiovascular disease and metabolic syndrome (23). People in the Mediterranean region consume moderate amounts of ethanol, low meat and meat products, and eat a substantial amount of vegetables, fruits, fish, nuts, whole wheat, and legumes(24, 25). The Mediterranean diet's primary source of fat is olive oil, and major constituents of the Mediterranean diet have been shown to have potential cardiovascular protective such as antioxidant and anti-inflammatory effects(26). Several clinical trials have been conducted to determine the effect of the Mediterranean diet on markers of atherosclerosis progression, mainly in primary prevention. In a randomized controlled trial involving over a thousand patients, Torres et al. demonstrated that the Mediterranean diet reduced plaque load in the carotid arteries and improved secondary prevention(7). Similar findings were also found in the PREDIMED study(27). The Mediterranean diet significantly reduced the incidence of the composite endpoints of cardiovascular death, stroke, and myocardial infarction, according to the same study(28). The biological mechanisms by which the Mediterranean diet protects against CVD remain unknown. The Mediterranean diet's high concentration of bioactive phytochemicals with antioxidant and anti-inflammatory properties explains why its consumption lowers circulating inflammatory biomarkers associated with atherogenesis(29).

The invention of the coronary stent in 1987 transformed the field of interventional cardiology by lowering the incidence of restenosis following balloon angioplasty(30). Compared to percutaneous transluminal coronary angioplasty alone, coronary stents significantly reduced the angiographic and clinical restenosis rate. This notable advancement resulted in a significant reduction in the frequency of major adverse cardiac events following percutaneous coronary interventions, owing primarily to a decrease in target vessel revascularization(31). Furthermore, intracoronary stents improve procedure success rates while also increasing procedure safety by reducing the need for emergency coronary artery bypass graft surgery. Consequently, stents are widely used in the "real world" of clinical coronary interventional practice(32).

However, coronary stent implantation is indeed associated with the complication of in-stent restenosis (ISR)(33, 34). ISR remains common and a challenge for interventional cardiologists. Whatever percutaneous approach is used to treat the in-stent restenotic lesion, including balloon angioplasty, stenting, rotational atherectomy, or laser angioplasty, 30-80% of patients will develop restenosis within the stent, stent margins, or both. Therefore, knowledge about the evolution of ISR is critical for effective prevention and safe intervention strategies. Among the factors that may cause ISR are vessel diameter, lesion length, bare metal stent use, and patient-related factors such as diabetes (especially insulin requirement)(32). However, the underlying causal mechanisms remain unclear. Nonetheless, the common intersection of many possible reasons points to inflammation as the most significant risk factor for restenosis(26, 35, 36).

Our findings show that the Mediterranean diet can reduce the risk of ISR through unknown mechanisms, including increased insulin sensitivity and other effects such as anti-inflammatory and antioxidant content.

Study limitations

Some limitations of our study include a cross-sectional design, a small sample size, and no MACE follow-up data. In addition, the diabetic status of the patients could not be evaluated clearly. This is one of the limitations of our study. In addition, we could not analyze ISR subgroups such as acute, subacute, and chronic due to missing data. To validate our findings, multicenter prospective longitudinal studies with larger sample sizes should be used.

Conclusion

This study may help us understand the relationship between the Mediterranean diet and ISR and may lead to new research. The Mediterranean diet, in addition to current medical treatments, is likely to play a protective role in the treatment of coronary artery disease. Our country is primarily agricultural, with the Mediterranean climate dominating roughly one-fifth of the land area. Furthermore, while the Mediterranean diet is "sustainable," it is a fundamental nutrition model for current and future generations thanks to this feature. The spread of the Mediterranean diet as a health policy may benefit the country's economy and public health. A multidisciplinary approach with a specialized team, rather than medical treatment options alone, may be more effective in preventing and treating the disease. In light of these data, it is clear that maintaining a Mediterranean diet throughout life can reduce the risk of coronary artery disease.

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Original Article

The Relationship of Inclination and Anteversion Angles in The Femur with Other Osteometric Parameters

Femurda İnklinasyon ve Anteversiyon Açılarının Diğer Osteometrik Parametreler İle İlişkisi

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Abstract

Background: The aim of this study is to demonstrate the morphometry of the femur, the component of the bony framework of the hip and knee joint, as a basis for clinically successful and accurate analysis.**Materials and Methods:** The study included 65 dry femur bones and parameters determined; the femur length (FL), length of the bicondylar femur (LBF), diameter of the caput femoris (DCF), anteroposterior diameter of the corpus femoris (APDCF), transverse diameter of the corpus femoris (TDCF), circumference of the corpus femoris (CCF), inclination angle (IA), anteversion angle (AA), circumference of the caput femoris (CACF), femoral neck width (FNW), anterior femoral neck length (AFNL), femoral neck axis length (FNAL), intertrochanteric distance (ID), femoral body length (FBL), femoral body width (FBW), bicondylar distance (BD), width of the condylus lateralis (WCL), width of the condylus medialis (WCM), height of the fossa intercondylaris (HFI), width of the fossa intercondylaris (WFI) and fossa intercondylaris shape index (FISI) were measured. **Results:** Mean±SD values of the determined parameters; FL; 42.2±2.7, LBF; 72.7±6.3, DCF; 74.5±6.1, APDCF; 44±4.1, TDCF; 27±2.3, CCF; 30.8±3, IA; 8.6±0.6, AA; 43.6±4.8, CACF; 16.5±4.4, FNW; 13.2±1.8, AFNL; 27.4±8.5, FNAL; 32.8±4.2, ID; 94.7±8.4, FBL; 73.4±8.8, FBW; 32.5±2.4, BD; 8.9±0.8, WCL; 32.6±4.4, WCM; 35.2±4.3, HFI; 16.7±4.1, WFI; 10.1±3 and FISI was calculated 0.6±0.2. **Conclusion:** The analysis of the parameters will add clinical depth to many surgical approaches such as more accurate analysis of femoral anomalies and fractures, strain and tendinopathies occurring in soft tissues. **Keywords:** Femur, morphometry, inclination angle, anteversion angle, index.

ÖZ

Amaç: Bu çalışmanın amacı kalça ve diz eklemine temel bileşeni olan femur morfometrisini, klinik bilimlere temel veri niteliği sağlamasına zemin teşkil etme açısından ortaya koymaktır. **Gereç ve Yöntem:** Çalışmaya 65 adet kuru femur kemiği dahil edildi. Femur üzerinden belirlenen parametreler; femur uzunluğu (FU), bicondiler femur uzunluğu (BFU), caput femoris çapı (FBÇAP), corpus femoris anterior-posterior çap (CFAPÇ), corpus femoris transvers çap (CFTÇ), corpus femoris çevre (CFÇ), inklinasyon açısı (İA), anteversiyon açısı (AA), caput femoris çevresi (FBÇEV), collum femoris genişliği (CFG), collum femoris ön uzunluğu (CFÖÜ), collum femoris eksen uzunluğu (CFEU), intertrochanterik mesafe (İTM), corpus femoris uzunluğu (CFU), corpus femoris genişliği (CFEG), bicondiler mesafe (İEM), condylus lateralis genişliği (CLG), condylus medialis genişliği (CMG), fossa intercondylaris genişliği (FİY), fossa intercondylaris genişliği (FİG) ve fossa intercondylaris şekil indeksi (Fİİ) olarak ölçülmüştür. **Bulgular:** Belirlenen parametrelerin ort ± ss değerleri; FU; 42.2±2.7, BFU; 72.7±6.3, FBÇAP; 74.5±6.1, CFAPÇ; 44±4.1, CFTÇ; 27±2.3, CFÇ; 30.8±3, İA; 8.6±0.6, AA; 43.6±4.8, FBÇEV; 16.5±4.4, CFG; 13.2±1.8, CFÖÜ; 27.4±8.5, CFEU; 32.8±4.2, İTM; 94.7±8.4, CFU; 73.4±8.8, CFEG; 32.5±2.4, İEM; 8.9±0.8, CLG; 32.6±4.4, CMG; 35.2±4.3, FİY; 16.7±4.1, ve FİG ; 10.1±3 olarak bulunmuştur. Ayrıca Fİİ; 0.6±0.2 olarak hesaplanmıştır. **Sonuç:** Analiz sonuçlarının femur anomalileri ve kırıkların daha doğru analiz edilmesinde, strain ve tendinopatiler gibi birçok cerrahi yaklaşıma klinik açıdan derinlik katacağı düşünülmektedir. **Anahtar Kelimeler:** Femur, morfometri, inklinasyon açısı, anteversiyon açısı, indeks.

Highlights

- In clinically, anthropometric measurements are significant.
- At this point, it's essential to do clinical and anatomical research.

Introduction

The femur, the longest and strongest bone of the body, has two end parts called extremitas proximalis and extremitas distalis and a body called corpus femoris. The femur begins the ossification process after the clavicle and ossifies from five centers: corpus, caput, trochanter major, trochanter minor and extremitas distalis (1).

The upper end of the femur where the structures called caput femoris, collum femoris, trochanter major and trochanter minor are located is called the proximal femur. This is followed by the corpus femoris, which is almost cylindrical. The lower end, called extremitas distalis, is wider than the upper end and has tuberos structures called condylus medialis and condylus lateralis on the sides (2,3). The femur, together with the tibia and patella, forms the knee joint, the largest joint in the body. It makes the tibiofemoral joint with the tibia and the patellofemoral joint with the patella in the quadriceps tendon. The knee joint, which is surrounded by a fibrous capsule, provides mobility and carries body weight (3,4). The femur forms the hip joint, which connects the body to the lower extremity with the os coxae and can move in three axes and perform circulation (5). The femoral inclination angle (FA) occurs between the long axis of the collum femoris and the corpus femoris (6). It averages 126 degrees and varies during the growth process, in different geographical areas, in different periods and in different populations at a wide range of ages (7). This angle changes throughout early development and decreases with age and is lower in women than in men because the pelvic structure is wider (8). The clinical condition in which the IA increases is called coxa valga and the condition in which it decreases is called coxa vara. IA enables the caput femoris to adapt to the acetabulum and the body weight to be distributed evenly, thus ensuring coordinated movements in the hip. It has also been an important determinant in hip prosthesis designs (6). In the literature, it is also referred to as the collodiaphyseal angle or the neck-shaft angle (7). The femoral anteversion angle (AA) is defined as the inclination of the femoral neck axis on a plane projected perpendicular to the shaft axis with reference to the knee axis, or as an angulation with an opening between the femoral neck axis proximally and the axis passing through the femoral condyles distally (7). The anteversion angle is 30 degrees after birth and is expected to decrease to 15 degrees by adulthood. If this angle is greater than 20 degrees, it not only affects hip rotation, but also causes a decrease in hip external rotator and extensor muscle strength control (9). Anteversion, antetorsion, or anterotation to the clinical condition in which the anteversion angle increases anteriorly; The clinical condition in which it increases posteriorly is called retroversion, retrotorsion or retrorotation, and the absence of any angulation is called the neutral version (7). The femoral anteversion angle (AA) is defined as the inclination of the femoral neck axis on a plane projected perpendicular to the shaft axis with reference to the knee axis, or an angulation between the femoral neck axis proximally and the axis passing through the femoral condyles distally, with the opening facing forward (7). The anteversion angle is 30 degrees after birth and is expected to decrease to 15 degrees until adulthood. When this angle exceeds 20 degrees, it affects hip rotation and causes a decrease in hip external rotator and extensor muscle strength control (9). The clinical condition in which the anteversion angle increases anteriorly is called anteversion, antetorsion or anterotation; the clinical condition in which it increases posteriorly is called retroversion, retrotorsion or retrorotation, and the absence of any angulation is called neutral version (7). The femur is directly or indirectly involved in many clinical cases due to its morphologic features and position. Some problems that occur especially at the proximal end of the bone, which participates in the formation of the hip joint proximally and the knee joint distally, not only cause diseases related to the hip joint, but also cause rotational changes in other bones of the lower extremity, which may lead to abnormal conditions such as knee joint diseases and gait disturbance (2,3). In this study, the morphometric parameters, anteversion and retroversion angles of dry femur bones, which are clinically important, were measured. It is thought that the results of the analysis of the parameters determined in the study may be useful as a database for future anthropometric studies and may be useful in hip and knee prosthesis designs and in the correct analysis of hip and knee anomalies and fractures.

Materials and Methods

The study was initiated with the permission of Clinical Research Ethics Committee with decision number 2022/54. In the present study, sixty-five (65) dry bone femurs of unknown age, sex and identity were measured in the anatomy laboratory. Partially broken, fragmented or damaged parts of the dry bones were not measured. A digital caliper (Baker 0-150 mm) with a sensitivity of 0.01 millimeter was used for the measurements on the femur and the values found were recorded as mm.

Measured Parameters (Figure 1):

• The femur length (FL)	• Intertrochanteric distance (ID)
• Length of the bicondylar femur (LBF)	• The femoral body length (FBL)
• Diameter of the caput femoris (DCF)	• The femoral body width (FBW)
• Anterioposterior diameter of the corpus femoris (APDCF)	• Bicondylar distance (BD)
• Transverse diameter of the corpus femoris (TDCF)	• Width of the condylus lateralis (WCL)
• Circumference of the corpus femoris (CCF)	• Width of the condylus medialis (WCM)
• Inclination angle (IA)	• Height of the fossa intercondylaris (HFI)
• Anteversion angle (AA)	• Width of the fossa intercondylaris (WFI)
• Circumference of the caput femoris (CACF)	• Fossa intercondylaris shape index (FISI).
• The femoral neck width (FNW)	• The anterior femoral neck length (AFNL)
• The femoral neck axis length (FNAL)	



Figure 1. Variables representation; A: AA (anteversion angle), B: FBL (femoral body length), C: FL (femur length), D: IA (inclination angle), E: FNW (femoral neck width), F: DCF (diameter of the caput femoris), G: FNAL (femoral neck axis length), H: HFI (height of the fossa intercondylaris), I: WFI (width of the fossa intercondylaris), J: WCM (width of the condylus medialis), K: WCL (width of the condylus lateralis), L: BD (bicondylar distance).

Statistical Analysis

Statistical analyses were performed using Minitab® 21.2 (64-bit) package program. The compatibility of the variables with normal distribution was tested with Anderson Darling test. Mean and standard deviation values were calculated for normally distributed variables and minimum, maximum and median values were calculated for non-normally distributed variables. The relationship between the variables was analyzed by Pearson correlation test. For directional discrimination of bones, Two Simple T Test was used for normally distributed variables and Mann-Withney U test was used for non-normally distributed variables.

Results

According to Anderson-Darling analysis, FL, APDCF, TDCF, IA, AA, CACF, FNW, AFNL, FNAL, ID, FBL, FBW, BD, WCM, WFI, FISI variables were not normally distributed, whereas LBF, DCF, CCF, WCL and HFI variables were normally distributed. The minimum (min), maximum (max), median and p value according to the Mann-Whitney U test results of the variables that did not show normal distribution are shown in **Table 1**.

The mean, standard deviation (Sd) and p-value of two simple t-test results of LBF, DCF, CCF, WCL and HFI variables are shown in the table. According to two simple t test results, no significant difference was found for the right and left bones (**Table 2**).

The Pearson correlation result table showing the relationship between IA and AA variables of the right femur and other variables is given below. According to the table, no correlation was found between the IA angle and other variables. According to the Pearson correlation test result, a moderate positive correlation was found between the AA variable and the FNW variable (**Table 3**). The Pearson correlation result table showing the relationship between IA and AA variables of the left femur and other variables is given below (**Table 4**). According to the table, no correlation was found between IA and other variables. There was a moderate positive correlation between the AA and HFI (**Table 4**).

Table 1. Variables that do not show normal distribution: direction, number of bones, minimum, maximum, median and p value*

Variables	Minimum		Maximum		Median		P
	R (39)	L (26)	R (39)	L (26)	R (39)	L (26)	
Direction (n)							
FL	35.3	36.3	48.4	46.9	42.3	42.2	0.32
APDCF	33.9	33.7	53.0	50.1	44.6	43.3	0.05 ^a
TDCF	23.5	23.3	32.9	32.0	27.3	26.7	0.28
IA	7.6	7.6	10.2	9.7	8.7	8.6	0.54
AA	35	36	53	52	41.8	46.5	0.001 ^a
CCF	7	8	25	22	18.2	14.2	0.001 ^a
FNW	8.3	11.5	16.3	16	13.1	13.5	0.45
AFNL	16.4	21.7	36	44.7	22.4	34.1	0.001 ^a
FNAL	24.6	26.4	41.2	40.6	32.7	32.8	0.99
ID	76.7	82.4	109.5	121.5	92.7	97.7	0.001 ^a
FBL	48.1	43.1	91.1	88.3	74.2	72.3	0.10
FBW	28.7	27.3	40.8	36.1	32.6	32.4	0.12
BD	7.8	7.8	13.1	10.0	9.1	8.6	0.008 ^a
WCM	27.2	29.8	45.8	45.3	34.1	37.0	0.002 ^a
WFI	6.1	5.5	16.1	16.8	10.2	10.0	0.56
FISI	0.4	0.3	1.0	1.7	0.6	0.6	0.57

Abbreviations: (*): FL: Femur length, APDCF: Anteroposterior diameter of the corpus femoris, TDCF: Transverse diameter of the corpus femoris, IA: Inclination angle, AA: Anteversion angle, CCF: Circumference of the corpus femoris, FNW: Femoral neck width, AFNL: Anterior femoral neck length, FNAL: Femoral neck axis length, ID: Intertrochanteric distance, FBL: Femoral body length, FBW: Femoral body width, BD: Bicondylar distance, WCM: Width of the condylus medialis, WFI: Width of the fossa intercondylaris, FISI: Fossa intercondylaris shape index, R: Right, L: Left, n: Number of bones, (°): A significant difference was found as a result of the t-test.

Table 2. Direction, number of bones, mean, standard deviation (Mean±Sd) and p value of two simple t test result of normally distributed variables*

Variables	Mean±Sd		p
	R (39)	L (26)	
LBF	72.3±6.7	73.4±3.8	0.43
DCF	74.5±6.5	74.5±3.7	0.97
CACF	30.9±2.7	31.7±2.6	0.21
WCL	32.0±3.8	33.5±3.9	0.14
HFI	17.0±3.9	16.3±3.8	0.45

Abbreviations: (*): LBF: Length of the bicondylar femur (LBF), DCF: Diameter of the caput femoris, CACF: Circumference of the caput femoris, WCL: Width of the condylus lateralis, HFI: Height of the fossa intercondylaris (HFI), R: Right, L: Left, n: Number of bones.

Table 3. Pearson correlation test result for the right femur bone*

	FL	LBF	DCF	APDCF	TDCF	CCF	IA	AA	CACF	FNW	AFNL
LBF	0.55										
DCF	0.57	0.94									
APDCF	0.23	0.16	0.14								
TDCF	0.44	0.40	0.40	0.10							
CCF	0.35	0.25	0.26	0.15	0.71						
IA	0.07	-0.19	-0.19	-0.01	-0.26	-0.08					
AA	0.16	0.26	0.19	0.05	0.33	0.27	0.08				
CACF	0.14	0.22	0.24	-0.06	0.13	-0.03	-0.08	0.07			
FNW	0.40	0.34	0.33	0.26	0.36	0.58	0.20	0.57	-0.14		
AFNL	0.25	0.03	0.02	0.02	0.27	0.50	0.10	0.20	-0.45	0.50	
FNAL	0.55	0.37	0.39	0.28	0.29	0.38	-0.21	0.07	-0.16	0.42	0.26
ID	0.44	0.32	0.28	0.37	0.30	0.36	0.21	0.06	-0.004	0.26	0.10
FBL	0.27	0.15	0.17	0.56	0.25	0.21	0.06	0.12	0.30	0.23	-0.09
FBW	0.56	0.24	0.27	0.27	0.34	0.21	0.07	0.29	0.16	0.33	0.23
BD	0.25	0.32	0.37	0.21	0.14	0.18	-0.14	-0.24	0.19	-0.01	-0.12
WCL	0.36	0.48	0.51	-0.04	0.16	0.10	0.03	0.07	0.13	0.21	0.02
WCM	0.31	0.46	0.45	0.06	0.17	0.12	0.06	0.10	0.10	0.24	0.06

HFI	0.40	0.36	0.39	0.05	0.17	-0.03	-0.26	0.03	-0.04	0.13	-0.003
WFI	0.30	0.22	0.25	-0.01	0.10	-0.12	-0.008	-0.14	0.20	-0.08	-0.08
FISI	-0.04	-0.08	-0.09	-0.05	-0.04	-0.10	0.24	-0.18	0.28	-0.19	-0.08
	FNAL	ID	FBL	FBW	BD	WCL	WCM	HFI	WFI		
LBF											
DCF											
APDCF											
TDCF											
CCF											
IA											
AA											
CACF											
FNW											
AFNL											
FNAL											
ID	0.17										
FBL	0.22	0.41									
FBW	0.30	0.38	0.51								
BD	0.39	0.44	0.20	-0.06							
WCL	0.24	-0.03	0.02	0.10	0.12						
WCM	0.21	0.01	0.02	0.11	0.05	0.90					
HFI	0.34	0.25	0.24	0.32	0.13	-0.01	-0.08				
WFI	0.14	0.17	0.35	0.33	0.14	-0.24	-0.31	0.57			
FISI	-0.16	-0.06	0.16	0.11	-0.01	-0.27	-0.26	-0.35	0.55		

Abbreviations: (*): FL: Femur length, APDCF: Anteroposterior diameter of the corpus femoris, TDCF: Transverse diameter of the corpus femoris, IA: Inclination angle, AA: Anteversion angle, CCF: Circumference of the corpus femoris, FNW: Femoral neck width, AFNL: Anterior femoral neck length, FNAL: Femoral neck axis length, ID: Intertrochanteric distance, FBL: Femoral body length, FBW: Femoral body width, BD: Bicondylar distance, WCM: Width of the condylus medialis, WFI: Width of the fossa intercondylaris, FISI: Fossa intercondylaris shape index, LBF: Length of the bicondylar femur, DCF: Diameter of the caput femoris, CACF: Circumference of the caput femoris, WCL: Width of the condylus lateralis, HFI: Height of the fossa intercondylaris.

Table 4. Pearson correlation test result for the left femur*

	FL	LBF	DCF	APDCF	TDCF	CCF	IA	AA	CACF	FNW	AFNL
LBF	0.53										
DCF	0.55	0.91									
APDCF	0.55	0.41	0.40								
TDCF	0.05	0.07	0.13	0.27							
CCF	0.31	0.28	0.38	0.47	0.64						
IA	0.01	0.02	0.03	0.10	0.40	0.01					
AA	0.35	0.26	0.10	0.45	0.11	0.09	0.09				
CACF	0.28	0.20	0.16	0.09	0.06	0.12	0.32	0.15			
FNW	0.64	0.44	0.38	0.91	0.29	0.42	0.04	0.39	0.21		
AFNL	0.33	0.34	0.28	0.45	0.17	0.15	0.002	0.32	0.34	0.50	
FNAL	0.55	0.33	0.28	0.83	0.11	0.37	0.02	0.38	0.14	0.87	0.58
ID	0.77	0.45	0.44	0.54	0.17	0.29	0.14	0.30	0.26	0.63	0.14
FBL	0.57	0.41	0.41	0.87	0.11	0.34	0.04	0.42	0.02	0.83	0.56
FBW	0.87	0.43	0.44	0.57	0.19	0.21	0.24	0.40	0.28	0.61	0.45
BD	0.33	0.39	0.35	0.60	0.65	0.58	0.26	0.25	0.29	0.76	0.22
WCL	0.46	0.47	0.60	0.42	0.17	0.14	0.27	0.22	0.03	0.36	0.46
WCM	0.43	0.32	0.48	0.36	0.11	0.19	0.16	0.03	0.05	0.36	0.43
HFI	0.65	0.43	0.32	0.52	0.08	0.41	0.08	0.52	0.07	0.52	0.12
WFI	0.23	0.10	0.06	0.23	0.19	0.20	0.19	0.17	0.12	0.27	0.14
FISI	0.46	0.30	0.25	0.19	0.23	0.07	0.10	0.22	0.07	0.17	0.22
	FNAL	ID	FBL	FBW	BD	WCL	WCM	HFI	WFI		
LBF											
DCF											
APDCF											
TDCF											

CCF											
IA											
AA											
CACF											
FNW											
AFNL											
FNAL											
ID	0.42										
FBL	0.73	0.42									
FBW	0.58	0.67	0.57								
BD	0.60	0.42	0.53	0.30							
WCL	0.44	0.40	0.35	0.55	0.12						
WCM	0.47	0.28	0.35	0.43	0.12	0.82					
HFI	0.58	0.48	0.45	0.60	0.32	0.25	0.20				
WFI	0.17	0.38	0.05	0.23	0.23	0.008	0.18	0.27			
FISI	0.34	0.05	0.33	0.42	0.03	0.19	0.36	0.57	0.51		

Abbreviations: (*): FL: Femur length, APDCF: Anteroposterior diameter of the corpus femoris, TDCF: Transverse diameter of the corpus femoris, IA: Inclination angle, AA: Anteversion angle, CCF: Circumference of the corpus femoris, FNW: Femoral neck width, AFNL: Anterior femoral neck length, FNAL: Femoral neck axis length, ID: Intertrochanteric distance, FBL: Femoral body length, FBW: Femoral body width, BD: Bicondylar distance, WCM: Width of the condylus medialis, WFI: Width of the fossa intercondylaris, FISI: Fossa intercondylaris shape index, LBF: Length of the bicondylar femur, DCF: Diameter of the caput femoris, CACF: Circumference of the caput femoris, WCL: Width of the condylus lateralis; HFI: Height of the fossa intercondylaris.

Discussion

In our study, there was no significant difference between the right and left femur on the normally distributed variables, a significant difference was found between right and left bones in APDCF, AA, CCF, AFNL, ID, BD, WCM parameters. In addition, a moderate positive correlation was found between AA angle and FNW variable on the right side, while a moderate positive correlation was found between AA and HFI variables on the left side.

There are two important aspects that affect hip joint movements and therefore hip joint space width. The inclination angle (collodiaphyseal angle) is the measure of the medial inclination of the proximal femur and acts as a lever especially for the abductor muscle group. In the anteversion angle (declination angle), the hip external rotator and extensor muscles are of great importance. Therefore, it is of great importance to evaluate the parameters of the femur, especially IA and AA.

In a study, those with and without hip fracture were compared and it was found that the mean values of IA and femoral neck width were higher in patients with hip fractures. They also stated that FNAL and FBW values were lower in those with hip fractures (10).

In another study investigating the IA value, 171 (83 right, 88 left) dry femurs were analyzed and AFNL was measured as 28.4 mm and IA was 126.7°, and the strong positive correlation between these two values ($r=0.773$, $p<0.001$) can be used in the determination of IA during the prosthesis design phase in the surgical treatment of hip fractures (11).

When the literature was examined, no significant difference was found in the comparison of the right-left side in a study in which IA and femoral parameters were evaluated. In the same study, a significant negative correlation was found between the anterior and axial length of the femoral neck and IA ($r=-0.255$, $p=0.005$; $r=-0.190$, $p=0.038$). In addition, a strong positive correlation was observed between other proximal femur parameters except IA (6).

In our study, a moderate positive correlation was found between AA and FNW on the right side, and a moderate positive correlation between AA and HFI on the left side. In addition to these data, no correlation was found between IA and other variables on the left and right sides.

As a result of the inability to identify the dry femur bones that we used to make measurements in our study, the gender and age were not known, which limited our study. Due to this limitation, the accuracy rate of the measurement results in the estimation of age and gender could not be determined. In addition, the fact that the measurement results, which did not show a statistically significant difference between the right and left sides in our study, are not known how they are distributed according to age and gender limits their use, especially in the clinical field. We think that a study that includes femoral shape variations and the distribution of IA and AA values according to gender and age may yield more meaningful results.

Study Limitation

The study was severely constrained by the lack of information regarding the age, gender, and living circumstances of the individuals whose bones were included in the study.

Conclusion

This study is a cross-sectional study and although it does not reflect the entire population of Turkey, it gives general information in the context of the Bolu example. The literature review and the data obtained show that among long bones, sex determination from the femur gives the highest accuracy rates. The morphometric data obtained from the femur by various methods can be a reference for the studies planned for the problems encountered in the fields of anthropology, radiology, physiotherapy-rehabilitation and in the clinic. In addition, it has the potential to be a guiding resource for a better understanding of the radiological anatomy of the femur, for femoral fractures and conditions affecting the knee and leg, as well as for various operations such as knee joint prosthesis surgery and surgical interventions such as grafting. In the field of forensic medicine, these data provide data on the average dimensions of the femur. Moreover, knowing the anatomical localization of important arteries, veins and nerves associated with the sub-anatomical structures included and measured in femur-based topography will help prevent possible complications. We hope that the data obtained in our study will form a database for many clinical and basic science studies on femur morphology and morphometry. In addition, we think that it will be a source of inspiration for future studies on this subject.

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Original Article**Evaluation of morphological changes on the proximal part of the ulna from the 13th century to the contemporary***13. yüzyıldan günümüze proksimal ulnadaki morfolojik değişikliklerin değerlendirilmesi*Nilgün TUNCEL ÇİNİ^{1*}, İlknur ARI²¹ Department of Anatomy, Bilecik Şeyh Edebali University, Faculty of Medicine, Bilecik, Türkiye² Department of Anatomy, Bursa Uludağ University, Faculty of Medicine, Bursa, Türkiye***Corresponding author:**Asst. Prof. Dr. Nilgün TUNCEL
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10.5281/zenodo.8042847**Highlights**

- Due to external factors such as lifestyle, nutrition and climate changes, bones may show morphological differences between individuals.
- In particular, functionally changing muscle strength due to different lifestyles causes anatomical changes on the bones.

Abstract**Background:** The aim of the study is to evaluate the proximal part of the ulna bone of the present and 13th century Byzantine period using the attachment points of the muscles and to evaluate the morphological changes.**Materials and Methods:** A total of 81 ulnae, 29 of which belong to the contemporary and unknown gender, and 52 from the thirteenth-century late Byzantine period are included in the study. The parameters were measured in millimeter on the photos with the ImageJ software. For the statistical analysis, SPSS 22.0 (IBM) software was used (p<0.005).**Results:** The descriptive values of the variables were given as mean±standard deviation and minimum-maximum values. According to the results of the statistical analysis, there is no difference in the right and left sides. Except for the angle between the the most prominent anterior point of the olecranon (MAPO) - the most posterior point of the olecranon (MPPO) - the point of the maximum anterior angulation (MAA) parameter, the rest of the parameters were higher in the Byzantine period ulnae.**Conclusions:** In this study, we showed the period differences on the proximal part of the ulna especially the olecranon because of the using the extensor muscle of the forearm and the stabilizer muscle of the elbow. We believe that the data obtained will functional perspective help different disciplines, especially anthropologists and anatomists.**Keywords:** Ulna, Byzantine, contemporary, proximal, morphometry**ÖZ****Amaç** Çalışmanın amacı, günümüz ve 13. yüzyıl Bizans dönemine ait ulna kemiğinin proksimal kısmının kasların bağlantı noktaları kullanılarak değerlendirilmesi ve morfolojik değişimlerinin incelenmesidir. **Gereç ve Yöntem:** Cinsiyeti bilinmeyen 29 tanesi günümüze ait ve 52'si 13. yüzyıl geç Bizans dönemine ait olmak üzere toplam 81 ulna çalışmaya dâhil edilmiştir. Parametreler, ImageJ yazılımı ile fotoğraflar üzerinde milimetre cinsinden ölçülmüştür. İstatistiksel analiz için SPSS 22.0 (IBM) programı kullanılmıştır (p<0.005). **Bulgular:** Değişkenlerin tanımlayıcı istatistikleri ortalama±standart sapma ve minimum-maksimum değerler olarak verilmiştir. İstatistiksel analiz sonuçlarına göre sağ ve sol tarafta fark bulunmamıştır. Olecranon en belirgin ön çıkıntısı (MAPO) - olecranon arka çıkıntısı (MPPO) - maksimum ön açılanma noktası (MAA) arasındaki açı değeri dışında diğer parametreler Bizans dönemi ulnae'de daha yüksek değerlere sahip olarak belirlenmiştir. **Sonuç:** Bu çalışmada, ön kolun ekstansör ve dirseğin stabilizatör kasının kullanılması nedeniyle ulna proksimal kısmında özellikle olecranon üzerindeki periyod farklılıklarını gösterdik. Elde edilen verilerin başta antropolog ve anatomistler olmak üzere farklı disiplinlere fonksiyonel açıdan yardımcı olacağına inanıyoruz.**Anahtar kelimeler:** Ulna, Bizans, günümüz, proksimal, morfometri

Introduction

The morphological diversity of an anatomical structure is determined by the specific requirements of the human body from the anthropometric or functional perspectives (1). All tissues undergo morphological changes as a result of phylogenetic and ontogenetic factors in accordance with function (2). After human adaptation to bipedalism, the load lifted from the upper extremities has also allowed the development of fine motor skills (3). The realization of these skills at the motor function level occurs due to the coordination of different joints and muscles in spatial patterns (4). Anthropometric analyzes are performed to evaluate certain indices necessary to describe morphometric variability in humans. Human bones are very important in physical anthropological studies, forensic science studies and surgical planning (5). The ulna is one of the forearm bones located on the medial side in the anatomical position. It is accepted that the strongest and thickest part of the bone is the proximal part. It plays a significant role in the formation of the elbow joint and wrist joint and its anatomical geometry is of great concern (6). The triceps brachii is the only muscle on the back of the arm and acts as the strongest extensor of the forearm. The muscle, which begins as three heads (long, lateral, and medial heads) on the scapula and humerus, ends distally on the olecranon located on the head of the ulna (7). Another muscle of the back of the elbow is the anconeus. It begins from the lateral condyle of the humerus and inserts into the olecranon and the proximal part of the dorsum of the ulna (8). While the triceps brachii muscles act as an extensor, the anconeus provides stabilization of the elbow and abduction during the pronation and supination movements of the ulna (9). From a different perspective, forensic identification is among the important issues that forensic sciences and anthropologists deal with. Here, biological characteristics such as age, gender, ethnicity and etc. gain more importance (10). Periodic changes detected on the bones can also be used for identification, especially on the age factor.

The aim of the study is to evaluate the proximal part of the ulna bone of the present and 13th century Byzantine period using the attachment points of the muscles and to evaluate the morphological changes in the bone, especially the effects of the triceps brachii muscle, with morphometry by making a period comparison. In this way, we aimed to determine possible lifestyles and, therefore, possible functional changes on bones of the past centuries. As far as we know, there is no other study similar to the one we looked at from a different perspective.

Material and Methods

A total of 81 ulnae in the Department of Anatomy, Bursa Uludag University, Faculty of Medicine, 29 (12 left, 17 right) of which belong to the contemporary and unknown gender, and 52 (20 left, 32 right) from the 13th late Byzantine period and thought to be all soldiers were included in the study. Skeletal remains were excavated in the amphitheater located in the Bursa/Iznik Saraybahce district by Prof. Dr. Metin Ozbek, an instructor of the Department of Anthropology at Hacettepe University, in 1984 (13). When determining the parameters to be measured certain landmarks were chosen; the most prominent anterior point of the olecranon (MAPO), the most posterior point of the olecranon (MPPO), the point of the maximum anterior angulation (MAA) (**Figure 1**). The following parameters were respectively (**Figure 2**) (11,12):

P1) The distance between the most prominent anterior point of the olecranon (MAPO) and the distal point of the ulnar styloid process

P2) The distance between the most posterior point of the olecranon (MPPO) and the distal point of the ulnar styloid process

P3) The distance between the point of the maximum anterior angulation (MAA) and the distal point of the ulnar styloid process

P4) The vertical distance between the MPPO and the MAA

P5) The angle between the MAPO-MPPO-MAA

P6) The angle between the posterior border of the ulna line using the MAA and the linear distance between MPPO- MAA. The bones which have deformities or fractures were excluded from the study.

The photographs of the bones were taken with the Nikon D5000 camera with the standard position using the ruler on one side to provide calibration. The parameters were measured in millimeter on the

photos with the ImageJ software. For the statistical analysis, SPSS 22.0 (IBM) software was used ($p < 0.005$). Shapiro Wilk test was used to show the normality distributions of the variables. To evaluate the period differences Students' T-test and the Mann Whitney-U test were used. Using Spearman's correlation test, the correlation between the parameters was determined for the contemporary and Byzantine periods separately. The angle between the MAPO-MPPO-MAA (P5) was non parametric for both contemporary and 13th century. The distance between the MAA and the distal point of the ulnar styloid process (P3) was not normally distributed in the 13th century bones.

Results

According to the results of the statistical analysis, there was no difference in the right and left sides, so the data were examined without considering the side difference (Table 1). The descriptive values of the variables were given as mean \pm standard deviation and minimum-maximum values in Table 2. According to the Shapiro-Wilk test, P3 and P5 were non-parametric parameters. When we examined the results, except for the angle between the MAPO-MPPO-MAA parameter, the rest of the parameters were higher in the Byzantine period ulnae. The angle between the MAPO-MPPO-MAA just had a high mean value in the contemporary. When we examine the results to reveal the period difference we saw that the distance between the MPPO and the distal point of the ulnar styloid process (P2), the distance between the MAA and the distal point of the ulnar styloid process (P3), and the angle between the MAPO-MPPO-MAA (P5) were shown differences (Table 1). When the correlation values for contemporary and Byzantine period bones were examined separately, the P1 and the P2 parameters were correlated with each other. For the contemporary R-value was 0.972 and for the Byzantine period bones, it was 0.982. The correlation between the P1 and P3 were $R = 0.862$ and $R = 0.811$, for the P2 and P3 R values were $R = 0.869$ and $R = 0.819$ respectively. It was seen that the angle between the MAPO-MPPO-MAA (P5) and the angle between the posterior border of the ulna-line passing through the MAA and MPPO-MAA (P6) had a low and negative correlation with each other in contemporary ($R = -0.502$) but this relationship was not seen in the Byzantine period. In the same way, it was seen that between the P1-P4 (the vertical distance between the MAA and the MAPO), and P2-P4 there were low correlations ($R = 0.448$ and $R = 0.418$, respectively) but in contemporary, there were not any correlation.

Table 1. Descriptive values of the variables according to the side in millimeter ($p < 0.005$)

Parameter	Contemporary			Byzantine		
	R	L	p value	R	L	p value
1	233.07 \pm 15.75	232.51 \pm 17.25	0.928	249.26 \pm 19.42	251.10 \pm 17.88	0.735
2	225.95 \pm 15.81	226.35 \pm 15.73	0.951	244.52 \pm 18.17	246.23 \pm 17.29	0.986
3	186.21 \pm 13.32	188.86 \pm 19.04	0.663	200.89 \pm 13.74	204.26 \pm 20.20	0.481
4	47.89 \pm 8.40	43.47 \pm 6.67	0.141	49.72 \pm 11.14	47.50 \pm 9.44	0.465
5	115.70 \pm 5.58	119.74 \pm 8.05	0.121	112.38 \pm 7.74	114.77 \pm 7.00	0.531
6	7.34 \pm 2.77	7.07 \pm 3.03	0.859	8.45 \pm 3.52	8.09 \pm 3.34	0.714

Table 2. Descriptive values of the variables in millimeter ($p < 0.005$)

Parameter	Contemporary		Byzantine		p value
	Mean \pm S.D.	Min. - Max.	Mean \pm S.D.	Min. - Max.	
1	232.84 \pm 16.08	188.72 - 278.75	249.98 \pm 19.52	188.72 - 278.75	0.146
2	226.13 \pm 15.49	205.71 - 281.20	245.19 \pm 17.68	205.71 - 281.20	0.001
3	187.31 \pm 15.67	168.72 - 275.42	202.22 \pm 16.46	168.72 - 275.42	0.001
4	46.07 \pm 7.92	29.30 - 72.70	48.85 \pm 10.47	29.30 - 72.70	0.218
5	117.37° \pm 6.88°	87.37° - 135.63°	113.31° \pm 7.48°	87.37° - 135.63°	0.023
6	7.23° \pm 2.83°	1.01° - 19.88°	8.31° \pm 3.42°	1.01° - 19.98°	0.151

Abbreviations: S. D.; Standart deviation, Min.; Minimum, Max.; Maximum

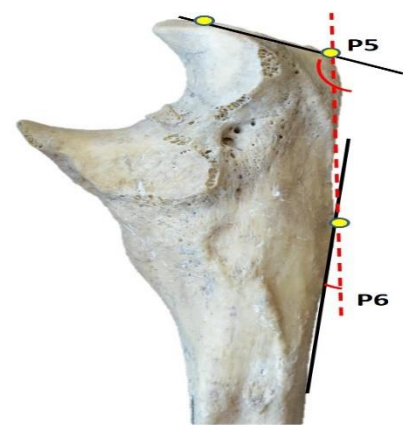
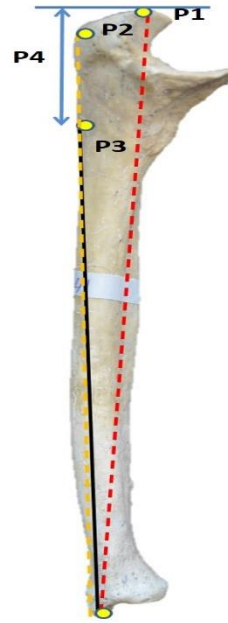


Figure 1. The definitons of the landmarks

Figure 2. Measured parameters on the ulna

Aberrivations: MAPO; the most prominent anterior point of the olecranon, MPPO; the most posterior point of the olecranon, MAA; the point of the maximum anterior angulation

Discussion

In this study, we showed the period differences on the proximal part of the ulna, especially the olecranon. It is aimed to determine the biological profiles of individuals belonging to the Byzantine period, as well as to reveal the changes that have occurred as a result of the intervening centuries from an anatomical perspective.

Muscles, which reveal the function of an organism, are anatomical structures that can be used in the examination of morphological changes that occur or may occur in the human body structure. Muscle attachment marks in bones can provide complementary information about both individual differences and individuals in ancient times. This information can shed light on the function of skeletal elements so the size of soft tissues, and life habits (14). External factors such as climate change, nutrition, population growth, emerging diseases and mutations that may occur in genes or epigenetic factors can cause morphological differences between periods (15).

In the study, it was observed that P1, P2 and P3 parameters showed a period difference and these values were higher in Byzantine bones. Interestingly, the vertical distance between the MAA and the MAPO did not show the period difference. In the morphometric study we conducted using the whole ulna before, we reached the data that all values were higher in Byzantine bones. In the study where we measured the vertical distance between the horizontal plane passing over MAPO and the styloid process, we measured the ulna length as 25.68 cm on the right, 25.56 cm on the left, and 23.35 cm on the right and 22.91 cm on the left in Byzantine bones (16). In this study, the directly measured distance between MAPO and the styloid was found to be a mean of 249.98 mm in Byzantine bones and 232.84 mm in contemporary bones. The results of our study using different parameters in the same bones support this information.

On the other side, while the P5 had a difference, the P6 had not. P5 has a narrower angle in Byzantine bones, but it is seen to have a wider angle in contemporary. This result made us think that the MAA point was more anterior in Byzantine bones, that is, the back of the bone had a flatter structure. Considering that the bones belonging to the Byzantine period are thought to belong to the soldiers and the people living in this period were engaged in agriculture, it is not surprising to see the effect of muscles in the bones of these individuals. When we look at this situation from a different perspective,

it may be possible that the MPO is positioned higher and this may cause the P5 to be narrower angled in the Byzantine bones.

Correlation analyses showed that while there was a low correlation between P4 (the vertical distance from the MAPO-MAA) and P1 and P2 in Byzantine bones, there was no such relationship in contemporary bones. On the contrary, while there was no correlation between the angular parameters between P5 and P6 in Byzantine bones, a negative correlation was determined in contemporary bones. It is reported that the individuals belonging to the Byzantine period bones were soldiers and were engaged in jobs that required intense manpower, such as farming (13). Depending on the dominant function of the biceps brachii muscle, the presence of stronger flexion movement and straightening of the back are expected for us. Similarly, due to the expected dominant extension due to the triceps brachii muscle, the MAPO point may be located higher. It is possible that the anconeus, which is the stabilizer muscle of the region, establishes the balance. Today, due to the deterioration of this balance, the fact that there are changes between the angles can be accepted as an indicator of the change.

It is possible to say that the bones of the Byzantine period, belonging to the late 13th century, have shortened in the 800-year period between the present day. In the literature, there is information that human height varies according to race and even countries regarding ancient populations (17). Considering that there are many factors related to height, it is not appropriate to say that the neck has shortened over the period.

The parameters selected for the study are the basic and also functional anatomical points due to the muscles attached to the region in the proximal part of the ulna. In the literature, there are studies on plate design for proximal part of the ulna, especially olecranon fractures (18,19). In this study, we evaluated the ulna anatomy from a different perspective by showing an anthropometric approach. We have shown the effect of the changes in lifestyle with the changing centuries on the proximal part of the ulna. Again, from the point of view of forensic sciences, we think that data can be used from different angles by different disciplines. We believe that the data obtained will functionally help different disciplines, especially anthropologists and anatomists.

Study Limitations

Limitations of this study are the low number of bones and the unknown gender. This study, which has been examined from a functional point of view, will bring different perspectives in case of higher number of bones and especially gender determination.

Conclusions

Many factors such as lifestyle, diet and climate differences affect the bones morphologically. In this study, we showed the effect of the period difference on the proximal part of the ulna using bones from the Byzantine period and contemporary's bones. It is expected that the bone anatomy of this group, which is more engaged in agriculture and has a different diet than today, is different from people of contemporary.

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Original Article

Histopathological Evaluation of The Protective Effects of Resveratrol Against Gastrointestinal Tissue Damage Induced by Cisplatin in Rats

Sıçanlarda Sisplatin Tarafından İndüklenen Gastrointestinal Doku Hasarına Karşı Resveratrolün Koruyucu Etkilerinin Histopatolojik Olarak Değerlendirilmesi

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Highlights

• Cisplatin renders the metabolically active intestinal mucosa highly susceptible to cytotoxic effects.

• The resveratrol application demonstrates a dose-dependent protective effect against intestinal damage caused by cisplatin.

Abstract

Background: The purpose of this study was to investigate the effects of differing doses of resveratrol (RES) against cisplatin (CP)-induced gastrointestinal injury in small intestinal tissue using histopathological and immunohistochemical methods.

Materials and Methods: Forty-eight healthy male Wistar albino rats aged 12-16 weeks were divided into eight groups, control RES-30, RES-60, RES-90, CP, CP+RES30, CP+RES60, and CP+RES90. Small intestine tissues were collected at the end of the experimental period and subjected to routine Hematoxylin & Eosin (H&E) and Periodic Acid Schiff (PAS) staining. Tumor necrosis factor alpha (TNF- α) and interleukin 1 beta (IL-1 β) were evaluated from immunohistochemically stained tissues. DNA fragmentation was evaluated using the TUNEL technique.

Results: Based on the histopathological findings, vacuolization and shedding were observed in the small intestine surface epithelium with notable fusion and shortening in the villus structure in the CP group. Significant decreases were observed in the CP+RES30, CP+RES60, and particularly CP+RES90 groups compared to the CP group in terms of apical surface epithelial degeneration, villous fusion, and inflammatory cell infiltration. The apoptotic index (AI) and TNF- α immunoreactivities were significantly higher in the CP group ($p < 0.05$). AI and TNF- α immune intensity were significantly lower in the treatment groups ($p < 0.05$). It has been determined that among the treatment groups, particularly the CP+RES30 group showed the lowest damage score values and immunoreactivity of TNF- α with AI. **Conclusions:** CP caused severe histological tissue injury, intestinal apoptosis, and proinflammatory cytokine release, while RES administered before CP treatment exhibited a dose-dependent protective effect (particularly at RES30 mg/kg) against CP-induced intestinal injury.

Key Words: Cisplatin, Resveratrol, Histopathology, Small Intestine, Apoptosis

ÖZ Amaç: Çalışmamızda, Resveratrolün (RES) farklı dozlarının sıçanlarda Sisplatinin (CP) indüklediği gastrointestinal hasara karşı olan etkisini ince bağırsak dokusunda histopatolojik ve immunohistokimyasal yöntemler ile araştırmayı amaçladık. **Gereç ve yöntem:** Çalışmada, 12-16 haftalık sağlıklı 48 adet Wistar Albino cinsi erişkin erkek sıçanlar kullanıldı ve kontrol, RES-30, RES-60, RES-90, CP, CP+RES30, CP+RES60 ve CP+RES90 olmak üzere 8 gruba ayrıldı. Deneysel sürenin sonunda ince bağırsak dokuları Hematoksilin & Eosin (H&E) ile Periyodik Asit Schiff (PAS) boyamasına tabi tutuldu. Tümör nekroz faktörü alfa (TNF- α) ve interleukin 1 beta (IL-1 β) immünhistokimyasal olarak boyanmış dokularda, DNA fragmentasyonu ise TUNEL tekniği kullanılarak değerlendirildi. **Bulgular:** Çalışma bulgularına göre CP grubunun incelenmesinde, ince bağırsak yüzey epitelyumunda ciddi oranda vakualizasyon ve dökülme ile birlikte villus yapılarında kısalma ve füzyon dikkati çekmiştir. Tedavi gruplarının değerlendirilmesinde ise, CP grubuna kıyasla sırası ile CP+RES30, CP+RES60 ve CP+RES90 gruplarında apikal yüzey epitelyal dejenerasyonunun, villar füzyon oluşumunun ve inflamatuvar hücre infiltrasyonunun anlamlı ölçüde azaldığı görülmüştür. Apoptotik indeks (AI) ile TNF- α immünreaktiflikleri, CP grubuna kıyasla kontrol grubunda önemli ölçüde yüksekti ($p < 0,05$). AI ve TNF- α immün yoğunluğu, CP+RES30, CP+RES60 ve CP+RES90 gruplarında, CP grubuna kıyasla önemli ölçüde daha düşüktü ($p < 0,05$). Tedavi grupları arasında özellikle CP+RES30 grubunun hasar skoru değerlerinin ve AI ile TNF- α immünreaktifliklerinin CP grubuna kıyasla en aza indiği belirlenmiştir. **Sonuç:** CP'nin şiddetli histolojik doku hasarına, bağırsak apoptozuna ve proinflamatuvar sitokin salınımına neden olduğu, ancak CP tedavisinden önce uygulanan RES'in, CP'nin neden olduğu bağırsak hasarına karşı doza bağımlı (özellikle RES30 mg/kg) koruyucu etki gösterdiği belirlenmiştir.

Anahtar Kelimeler: Sisplatin, Resveratrol, Histopatoloji, İnce bağırsak, Apoptozis

Introduction

Cisplatin (MF-Cl₂H₆N₂Pt, CP) cis-diamminedichloroplatinum II is one of the most potent DNA-modifying chemotherapeutic agents and plays an important role in the treatment of human solid tumors. CP cytotoxicity is associated with its capacity to cause inter- and intrastrand cross-linking, to interfere with the DNA repair mechanism, to cause DNA damage, to inhibit DNA replication mechanisms and/or transcription, and thus to induce apoptosis in cancer cells (1).

CP remains the main antiproliferative drug among the various therapeutic protocols, and is widely employed, with cure rates exceeding 90%, in the treatment of cancers of the bladder, head and neck, esophagus, testis, and ovaries, and in small cell lung cancers (2). Despite its many side-effects, including renal dysfunction, hepatotoxicity, neurotoxicity, myelosuppression, spermiotoxicity, and ototoxicity (3), CP is also the principal drug used in the therapeutic protocol for advanced gastrointestinal cancers (4). In terms of CP's known toxicity profile, the principal dose-limiting side-effect is nephrotoxicity. However, gastrointestinal symptoms present as a lifelong dominant clinical problem (1). The rapidly proliferating cells of the gastrointestinal epithelium mean that the gut is particularly vulnerable to the cytotoxic effects of CP. Chemotherapeutic agents, including CP, are capable of inducing wide morphological alterations (such as delayed gastric motility, diarrhea, and mucositis) that have a significant impact on adherence to treatment (3).

Extracts obtained from plant materials have historically been employed in the treatment of various diseases. RES is an endogenous agent found in various foodstuffs including grape, blueberry, and peanut. Chemically, it is known as trans-3,4,5-trihydroxystilbene, or more commonly as RES. It is a member of the stilbene family (synthetic aromatic hydrocarbon) and possesses geometric stereoisomers in cis and trans conformations (5). Research into the biological activities of RES has increased in recent years and has emphasized its antioxidant, anti-inflammatory, antiapoptotic, antiplatelet, antiatherogenic, and anticancer properties. RES is a polyphenolic phytoalexin present in grape, red wine, chocolate, Japanese knotweed root, peanut, mulberry, carnelian cherry, and Vaccinium plants such as blueberry (7).

Due to the risks associated with traditional cancer treatment methods, the use of this compound is particularly important in cancer patients (8). However, only a limited number of publications have examined the effect of RES in reducing the tumor burden in such patients. Moreover, no studies have investigated the dose-dependent effect of RES on CP-related gastrointestinal toxicity. Since CP is also absorbed by passive diffusion throughout the gastrointestinal system, the purpose of this study was to investigate the effects of differing doses of RES against CP-induced gastrointestinal damage in rats using histopathological, histomorphometric, and immunohistochemical methods.

Material and Method

Experimental Study Plan

This experimental study commenced following receipt of approval from the Harran University animal experiments local ethical committee (HAYDEK) (study protocol license no. 2022/006/20). The male Wistar albino rats used in the research were obtained from the Harran University Surgical Application and Research Center. Throughout the experiment, all rats were housed at a room temperature of $22 \pm 2^\circ\text{C}$, in $50\% \pm 10$ humidity, and in a 12-h light:dark cycle. All rats were allowed ad libitum access to standard rat chow and tap water. All animals received humane care in line with the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health.

Establishment of the Experimental Animal Groups

The number of animals to be employed in the study was determined on the basis of the 3R3 principle and in consideration of avoidance of unnecessary animal use. Forty-eight healthy male Wistar albino rats aged 12-16 weeks and weighing 350-400 g were divided into eight groups. Control group, (C; n=6); Not subjected to any procedure. Resveratrol 30 mg group, (RES-30; n=6); RES 30 mg/kg per day (9) was dissolved in dimethyl sulfoxide (DMSO) and administered by the intragastric route for eight days. Resveratrol 60 mg group, (RES-60; n=6); RES 60 mg/kg per day administered by the intragastric route for eight days. Resveratrol 90 mg group, (RES-90; n=6); RES 90 mg/kg per day administered by the intragastric route for eight days. Cisplatin group, (CP; n=6); No procedure was performed for the first five of the eight day experimental period days. On the fifth day, a single dose of CP 16 mg/kg (10) was administered via the intraperitoneal (i.p.) route. Cisplatin+Resveratrol 30 mg group, (CP+RES30; n=6); RES 30 mg/kg per day was administered via the intragastric route for five days. On the fifth day, a single dose of CP 16 mg/kg was administered i.p., and RES 30 mg/kg per day was administered via the intragastric route for the following three days.

Cisplatin+Resveratrol 60 mg group, (CP+RES60; n=6); RES 60 mg/kg per day was administered via the intragastric route for five days. On the fifth day, a single dose of CP 16 mg/kg was administered i.p., and RES 60 mg/kg per day was administered via the intragastric route for the following three days. Cisplatin+Resveratrol 90 mg group, (CP+RES90; n=6); RES 90 mg/kg per day was administered via the intragastric route for five days. On the fifth day, a single dose of CP 16 mg/kg was administered i.p., and RES 90 mg/kg per day was administered via the intragastric route for the following three days.

Histological Methods

Tissue Preparation Procedures for Morphometric Measurements

At the end of the experimental period (day 8), all rats were sacrificed by exsanguination under deep anesthesia. A midline incision was first made, after which the small intestine was carefully and quickly severed and removed. Feces within the tissues were removed, and the specimens were fixed in 10% formalin solution. Following fixation, tissues collected for histological examinations were passed through 70%, 90%, 96%, and 100% alcohol series. After being rendered transparent with xylene, the tissues were embedded in paraffin blocks. Next, sections 5 μ m in thickness were taken from the paraffin blocks using a fully automated microtome (Histo-Line ARM 3700, Pantigliate MI, Italy) and placed onto slides, before being stained with hematoxylin eosin (H&E) and PAS in order to reveal the general morphological characteristics of the small intestine tissues. All the histological layers of each tissue were subjected to separate histological examination under a light microscope at X40, X100, X200, and X400 magnifications. General gastrointestinal damage was scored semi-quantitatively based on specific criteria of apical surface epithelial degeneration, villar fusion, hemorrhage, and inflammatory cell infiltration (0: none; 1: mild; 2: moderate, and 3: severe), and a mean histopathological score was calculated for each experimental group (11). All tissue analyses were performed under a light microscope (Olympus BX 51; Olympus Optical Co. Ltd., Tokyo, Japan) on cellSens imaging software (Olympus Life Science Solution, Germany).

Immunohistochemical Methods

The Terminal Deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling (TUNEL) technique was used to evaluate apoptosis in the intestinal tissue. Cells exhibiting DNA fragmentation were identified using this technique. Cells with homogeneous staining and no necrotic areas, showing brown-stained nuclei and TUNEL positivity, were defined as apoptotic cells. The In Situ Cell Death Detection Kit (Roche, Mannheim, Germany) was used following the manufacturer's protocol for the TUNEL technique. The stained sections were examined under a light microscope (Olympus BX 51; Olympus Optical Co. Ltd., Tokyo, Japan) at 400X magnification, and a total of 100 cells were counted in 5 different areas to calculate the apoptotic index (AI) (AI = number of TUNEL-positive cells / total number of cells x 100) (12).

Paraffin-embedded blocks were sectioned into 5 μ m thickness and then deparaffinized. Following that, the sections were washed with a PBS buffer solution for 5 minutes. Subsequently, the sections underwent antigen retrieval by boiling in citrate buffer at a pH of 6.0. To block endogenous peroxidase activity, the sections washed in PBS were treated with a 3% H₂O₂ solution. The specimens were then incubated with TNF- α (Santa Cruz Biotechnology Inc., cat no. sc-52746) and IL-1 β (Santa Cruz Biotechnology Inc., cat no. sc-52012) antibodies, diluted to a 1:100 ratio, at a temperature of +4°C. The subsequent steps were carried out using secondary antibody kits (Thermo Scientific, MA, USA, cat no. TP-060-HL) following the manufacturer's instructions. For visualization, a 3,3'-Diaminobenzidine (DAB) chromogen kit was utilized (Sigma-Aldrich St. Louis, USA, cat no. D3939). The specimens were counterstained with Mayer's hematoxylin, covered and observed under a light microscope. Microphotographs were captured. For immunohistochemical analyses, three random areas were selected in each section. TNF- α and IL-1 β positivity were identified by the presence of a brown color, and numerical evaluations were conducted. Scores were assigned based on the percentage frequency of TNF- α and IL-1 β expression in the examined area: no expression (0), mild (1), moderate (2), strong (3), and very strong (4) expression. The percentage of positive cells was scored as follows: <5% positive expression (0), 6%-15% (1), 16%-50% (2), 51%-80% (3), and >80% (4) (13).

Statistical Analysis

All statistical analyses were performed using the SPSS 26.0 V software (Statistical Package for the Social Sciences, version 26.0, SSPS Inc., Chicago, IL, USA). All data were presented as standard deviation (SD) (\pm) mean. Kruskal Wallis analysis of variance was used to compare differences between group parameters. Dual comparisons between groups exhibiting significant values were evaluated with a Mann-Whitney U-test- with corrected Bonferroni test. Statistical significance was accepted for all tests at p<0.05.

Results

Histopathological Findings

All histopathological examinations of small intestinal tissues were conducted using sections stained with H&E and PAS. Examinations performed under light microscopy revealed preservation of the integrity of the lamina propria and epithelium in the small intestinal tissue mucosal layer, a normal histological structure in the brush border, enterocytes, and goblet cells, and preserved crypt/villus organization in tissues from the C, RES-30, and RES-60 groups. However, apical surface epithelium degeneration and fusion in villus structures were observed in the RES-90 compared to the control group (**Figure 1,2**).

CP group tissues exhibited severe vacuolization and shedding in the small intestine surface epithelium, together with shortening and fusion in villus structures. In addition to degeneration, the epithelium and lamina propria could not be distinguished, the villi lost their finger-like structure, and microvillus structures were impaired. Moreover, goblet cells lost their oval nucleus structure, and widespread inflammatory cell infiltration was observed in the mucosa, together with intense cystic formations (**Figure 1,2**). In terms of parameter analyses, gastrointestinal damage scores were significantly higher in the CP group than in the control group ($p < 0.05$) (**Table, 1**).

Evaluation of the treatment groups showed significant decreases in apical surface epithelial degeneration, villous fusion, and inflammatory cell infiltration in the CP+RES30, CP+RES60, and CP+RES90 groups compared to the CP group ($p < 0.05$) (**Table, 1**). Degeneration in epithelial cells and microvilli decreased, while villous structures were preserved. Although the treatment groups' histological findings were similar to one another, the damage score in the CP+RES30 group in particular decreased significantly compared to the CP group ($p < 0.05$) (**Table 1**).

Table 1. The histological damage scores on the basis of analysis parameters and Immunohistochemical scores of the experimental groups

	Parameters						
	AI	TNF- α	IL-1 β	DASE	VF	ICI	H
C	4.570 \pm 1.027	0.333 \pm 0.516	0.167 \pm 0.408	0.500 \pm 0.548	0.167 \pm 0.408	0.167 \pm 0.408	0.000 \pm 0.000
RES30	5.342 \pm 1.194	0.500 \pm 0.548	0.333 \pm 0.516	0.667 \pm 0.516	0.333 \pm 0.516	0.333 \pm 0.516	0.000 \pm 0.000
RES60	6.123 \pm 1.006 ^a	0.667 \pm 0.816	0.167 \pm 0.408	0.833 \pm 0.753	0.833 \pm 0.408 ^a	0.500 \pm 0.548	0.167 \pm 0.408
RES90	8.232 \pm 0.852 ^a	0.833 \pm 0.408	0.500 \pm 0.548	1.167 \pm 0.408 ^a	1.333 \pm 0.516 ^a	0.667 \pm 0.516	0.333 \pm 0.516
CP	58.250 \pm 10.153 ^a	2.500 \pm 0.548 ^a	1.167 \pm 0.408 ^a	2.667 \pm 0.516 ^a	2.833 \pm 0.408 ^a	1.667 \pm 0.516 ^a	0.500 \pm 0.548
CP+RES30	26.442 \pm 3.700 ^{ab}	0.833 \pm 0.408 ^b	0.500 \pm 0.837	1.333 \pm 0.516 ^{ab}	1.167 \pm 0.408 ^{ab}	0.667 \pm 0.516 ^b	0.167 \pm 0.408
CP+RES60	32.263 \pm 4.897 ^{ab}	1.000 \pm 0.632 ^{ab}	0.500 \pm 0.548	1.667 \pm 0.516 ^{ab}	1.500 \pm 0.548 ^{ab}	0.833 \pm 0.408 ^{ab}	0.333 \pm 0.516
CP+RES90	38.130 \pm 5.239 ^{abc}	1.500 \pm 0.548 ^{abc}	0.667 \pm 0.516	1.833 \pm 0.408 ^{ab}	1.667 \pm 0.516 ^{ab}	0.833 \pm 0.408 ^{ab}	0.333 \pm 0.516

Abbreviations:The data represent means \pm standard deviation; n = 6 for each group. RES; Resveratrol, CP; Cisplatin, AI; Apoptotic Index, TNF- α ; Tumor Necrosis Factor-alpha, IL-1 β ; Interleukin-1 beta, DASE; Degeneration of the apical surface epithelium, VF; villar fusion, H; hemorrhage, ICI; inflammatory cell infiltration.*; C group values compared to all groups, ($p < 0.05$);^b; CP group values compared to the treatment groups (CP+RES30, CP+RES60, and CP+RES90), ($p < 0.05$);^c; CP+RES30 group values compared to the CP+RES60 and CP+RES90 groups, ($p < 0.05$).

Immunohistochemical Findings

Based on findings evaluated using the TUNEL technique, AI values in the CP group were significantly higher than those in the control group ($p < 0.05$). AI values decreased in the CP+RES30, CP+RES60, and CP+RES90 groups compared with the CP group ($p < 0.05$). No significant difference was observed between the AI values in the CP+RES30 and CP+RES60 groups ($p > 0.05$), but AI values in the CP+RES90 group were significantly higher than those in the CP+RES30 group ($p < 0.05$) (**Table 1, Figure 3**).

Analysis of TNF- α and IL-1 β scores used to determine proinflammatory cytokine levels showed that TNF- α values in the CP group were significantly higher than those in the control group ($p < 0.05$). In terms of the treatment groups, TNF- α values in the CP+RES30, CP+RES60, and CP+RES90 groups were significantly lower than those in the CP group ($p < 0.05$). While no significant difference was observed in TNF- α values between the CP+RES30 and CP+RES60 groups ($p > 0.05$), they were significantly higher in the CP+RES90 group compared to the CP+RES30 group ($p < 0.05$) (**Table 1, Figure 4**). No significant difference in IL-1 β score findings was determined between the groups ($p > 0.05$) (**Table 1, Figure 5**).

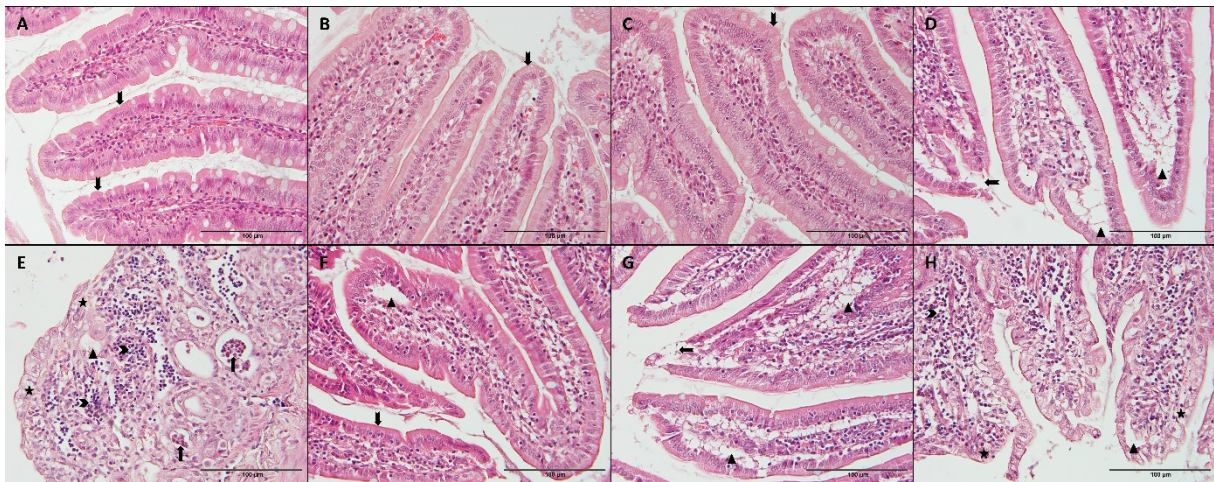


Figure 1. Light microscopic micrographs of rat small intestine sections stained with hematoxylin and eosin from control group (A), RES-30 (B), RES-60 (C), RES-90 (D), CP (E), CP+RES30 (F), CP+RES60 (G), and CP+RES90 (H). Normal villus structure with surface enterocytes and goblet cells (down notched arrow), vacuolization (triangle), shedding of surface enterocytes (left notched arrow), villar fusion accompanied by epithelial degeneration (asteriks), inflammatory cell infiltration (chevrons), cystic structures (up arrow), RES; Resveratrol, CP; Cisplatin, (Hematoxylin and eosin staining, X400).

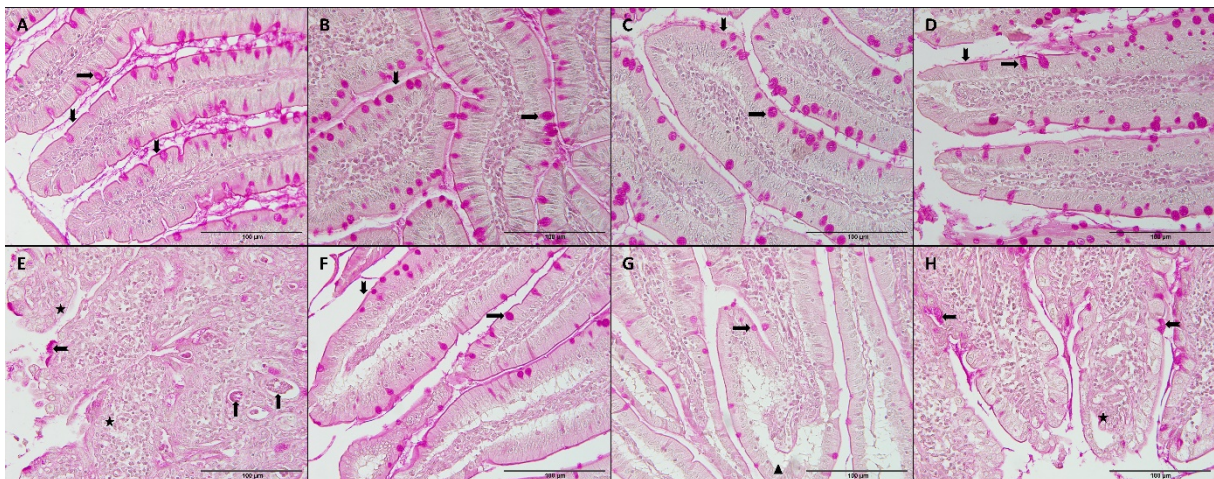


Figure 2. Light microscopic micrographs of rat small intestine sections stained with PAS from control group (A), RES-30 (B), RES-60 (C), RES-90 (D), CP (E), CP+RES30 (F), CP+RES60 (G), and CP+RES90 (H). Normal villus structure with surface enterocytes (down notched arrow), normal goblet cells (right arrow), goblet cells lost their oval nucleus structure (left notched arrow), vacuolization (triangle), villar fusion accompanied by epithelial degeneration (asteriks), RES; Resveratrol, CP; Cisplatin, PAS; Periodic Acid Schiff, (PAS staining, X400).

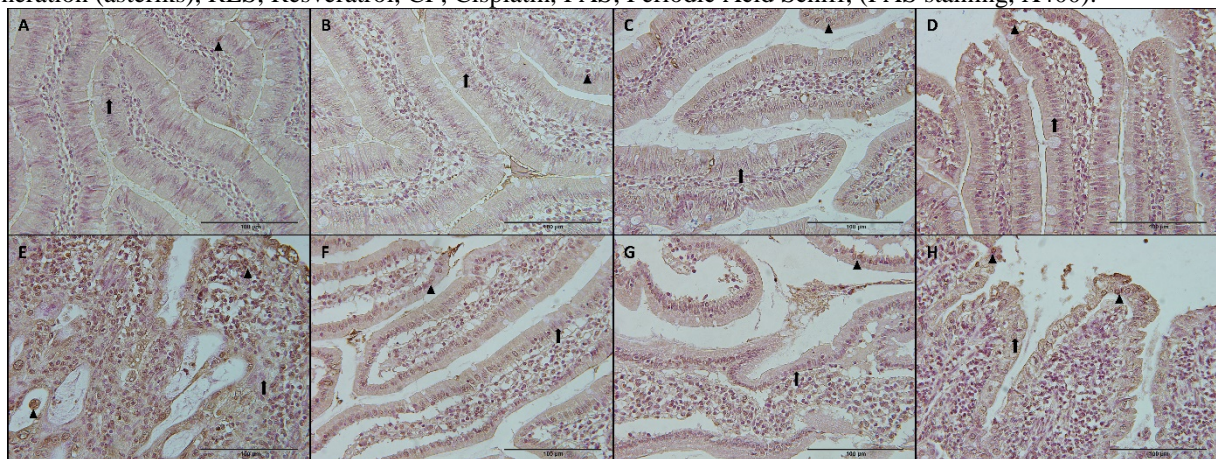


Figure 3. TUNEL-stained rat small intestine micrographs from control group (A), RES-30 (B), RES-60 (C), RES-90 (D), CP (E), CP+RES30 (F), CP+RES60 (G), and CP+RES90 (H). Normal (up arrow) and TUNEL (+) (triangle) nucleus, RES; Resveratrol, CP; Cisplatin, TUNEL; The Terminal Deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling, (TUNEL, X400).

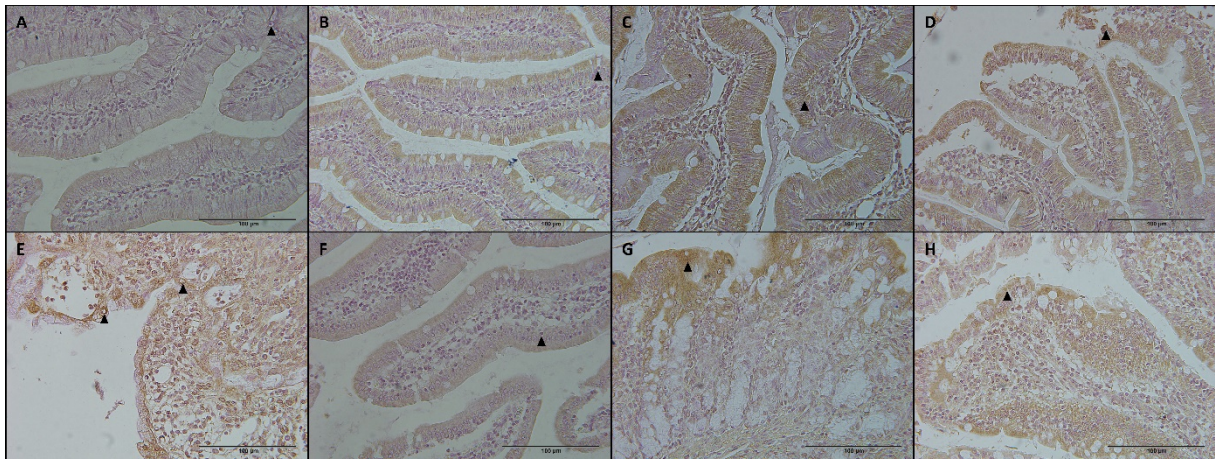


Figure 4. TNF- α -stained rat small intestine micrographs from control group (A), RES-30 (B), RES-60 (C), RES-90 (D), CP (E), CP+RES30 (F), CP+RES60 (G), and CP+RES90 (H). TNF- α (+) cell (triangle), RES; Resveratrol, CP; Cisplatin, TNF- α ; Tumor Necrosis Factor-alpha, (TNF- α , X400).

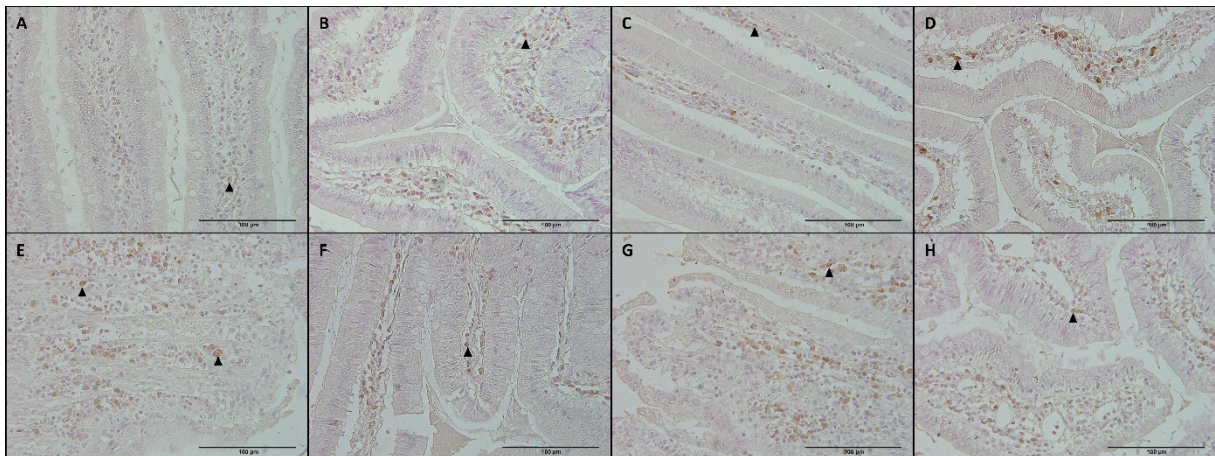


Figure 5. IL-1 β -stained rat small intestine micrographs from control group (A), RES-30 (B), RES-60 (C), RES-90 (D), CP (E), CP+RES30 (F), CP+RES60 (G), and CP+RES90 (H). IL-1 β (+) cell (triangle), RES; Resveratrol, CP; Cisplatin, IL-1 β ; Interleukin-1 beta, (IL-1 β , X400).

Discussion

CP, one of the most effective DNA-modifying chemotherapeutic agents, is a heavy metal complex exhibiting synergistic effects with various antitumor drugs and with no cross-resistance (14). However, in addition to its therapeutic benefits, CP and its metabolites can cause side-effects including nephrotoxicity, hepatotoxicity, and long-term gastrointestinal damage as a result of severe damage to the intestinal mucosa (15). Almost all patients can experience marked gastrointestinal side-effects due to CP-related intestinal dysfunction, generally consisting of varying degrees of nausea, diarrhea, mucositis, and delayed gastric motility (16,17). Although the clinical limitations of CP due to the side-effects described above have encouraged researchers to produce several CP analogues, the majority of platinum compounds exhibited no significant advantage over CP. For that reason, CP continues to be employed as a first-line drug in the treatment of several types of cancer, including those of the testis, prostate, ovary, cervix, bladder, and lung (16,18).

Due to its anatomical position, physiological characteristics, wide surface area, and high cell cycle, the small intestine is particularly susceptible to the adverse effects of chemotherapeutic agents such as CP. In addition, similarly to the majority of antineoplastic agents, CP is not target-specific, meaning that it affects all

proliferating cells and cause side-effects generally observed during cancer treatment (19). The brush border membrane, which covers the epithelial cells of the small intestine and performs various digestive and transport tasks, constitutes a highly differentiated cell membrane. The structural integrity of the intestinal mucosa, which is organized into crypts and villi in order to increase nutrient absorption and surface area, relies on the crypt cell production rate and the crypt/villus ratio. The gastrointestinal toxicity caused by CP is characterized by villus degeneration and desquamation, decreased villus height and density, crypt loss in structural terms, apoptosis and necrosis in intestinal epithelial cells, and glandular dilatation (20).

CP has the potential to stimulate widespread morphological variations in the intestinal mucosa. Studies showing that CP therapy lowers the total surface area of villi and microvilli, thus reducing intestinal motility, and causes changes in the intestine's digestive and metabolic functions have appeared in the literature. CP applied at low doses has been shown to cause villous atrophy but not to affect the crypt depth, thus reducing the villus/crypt ratio by approximately half. However, reports in the literature concerning high doses have shown that CP causes mucosal glandular distortion, inflammatory cell infiltration into the mucosal and submucosal layers, crypt ablation and abscess formation, villous degeneration, and decreased villous height (21,22). Zhang et al. (2022) also reported that CP injection caused a series of pathological changes leading to atrophy of the small intestine villi, crypt cell necrosis, epithelial cell shedding, and impairment of the submucosa and muscular layer (23).

In the present study of CP-induced gastrointestinal damage, and in agreement with previous research in the literature, severe vacuolization and shedding were observed in the small intestinal surface epithelium together with fusion and shortening in villous structures in the CP group. In addition to degeneration, the epithelium and lamina propria could not be distinguished in the mucosal layer, the villi lost their finger-like structure, and the structures of the microvilli were compromised. The goblet cells also lost their oval nucleus structures, and widespread inflammatory cell infiltration in the mucosa and intense cystic structures were detected. In a study investigating CP-related intestinal toxicity, Jin et al. (2022) reported breaks in villous structures as well as increased erythrocytes and inflammatory cells, decreased goblet cells, and degeneration in their CP group (24). Consistent with the literature, Yilmaz et al. (2022) also reported vacuolization in duodenal sections in the CP group, in addition to widespread necrotic epithelial cells, loss of microvillus structures, mucosal ulceration due to epithelial cell loss, and widespread inflammation in the lamina propria (25).

Patients being treated for cancer undergo a number of different therapeutic regimens, including the administration of cancer chemotherapy drugs, radiation, surgery, and immunotherapy. Treatment using chemotherapy agents is associated with a very high side-effect rate, ranging from milder effects such as nausea, vomiting, hair loss, and bone marrow suppression, to more serious manifestations including neuropathy, liver failure, and hepatotoxicity. Herbal extracts have historically been employed in the treatment of various human diseases. RES is an endogenous agent found in foodstuffs such as grape, blueberry, and peanut (26). Studies of the biological activities of RES have shown that it exhibits antioxidant, anti-inflammatory, antiapoptotic, anticancer, antiatherogenic, and cardioprotective properties (9). In their clinical study, Nguyen et al. (2009) reported the potential effects of RES on colorectal and prostate cancer in particular, and stated that the preoperative administration of RES exhibited beneficial effects in patients with colorectal cancer (27). Patel et al. (2010) showed that the administration of RES once daily for eight days prior to colon resection in 20 patients aged 46-83 reduced cell proliferation in tumor tissue (28).

Some studies in the literature have reported that treatment with RES reduces tissue damage associated with villous atrophy and shedding in the jejunum, produces an increase in villous length, and significantly improves intestinal cell morphology (29,30). Dong et al. (2013) reported preservation of the lamina propria despite partial villous damage, and significantly lower intestinal damage scores, following 50 mg/kg RES administration in the damaged intestinal wall with loss of villous structure and severe necrosis (31). Another study of severe mucosal damage ranging from villous loss with leukocyte infiltration and necrosis to mucosal infarction reported that 15 mg/kg application of RES prevented damage occurring in the crypts, but that villous loss could not be reduced with the use of RES (32). In another study, morphological changes such as a necrotic epithelium in intestinal tissue, mucosa ulceration, and widespread inflammatory cell infiltration in the mucosa and submucosa decreased after RES treatment (10 mg/kg) and that the mucosal architecture was preserved (33). In agreement with the previous literature, the results of the present study show that apical surface epithelial degeneration, villar fusion, and inflammatory cell infiltration decreased significantly in the CP+RES30, CP+RES60, and CP+RES90 groups compared to the CP group. Shedding and degeneration of epithelial cells and their microvilli also decreased, while villous structures were preserved. Although the histological findings of the treatment groups were similar to one another, damage score values decreased significantly, especially in the CP+RES30 group, compared to the CP group.

Studies have reported that due to the natural high sensitivity of the rapidly proliferating intestinal epithelium, the use of the chemotherapeutic agent CP and other radiotherapeutic approaches renders the metabolically active intestinal mucosa highly susceptible to cytotoxic effects and may cause an increase in intestinal apoptosis (34). Bodiga et al. (2012) developed an acute intestinal injury model in rats through the intraperitoneal injection of the broad spectrum antitumor drug CP at a dose of 2.61 mg bodyweight. Those authors determined that CP caused apoptosis in the villus and crypt and that the rapidly proliferating crypt region was more sensitive to CP, with higher rates of apoptosis (35). In their study of CP-induced intestinal injury, Hu et al. (2021) showed that exposure to 20 mg/kg CP caused an increase in the numbers of TUNEL-positive intestinal cells (17). Another study reported significantly fewer apoptotic cells in mice treated with RES (29). AI findings evaluated using the TUNEL method in the present study were significantly higher in the CP group. AI values in the treatment groups decreased significantly compared to the CP group. While no significant difference in AI values was observed between the CP+RES30 and CP+RES60 groups, these were significantly higher in the CP+RES90 group than in the CP+RES30 group. These results suggest that dosages of 30 and 60 mg/kg RES may be sufficient in terms of antiapoptotic efficacy, while a dosage of 90 mg/kg may be excessive and capable of reducing the antiapoptotic effects of RES.

Tumor necrosis factor-alpha (TNF- α) is a proinflammatory cytokine (signaling molecule) produced by the immune system. It plays an important role in inflammation and apoptosis signaling. TNF- α is also an important step in the initiation of an inflammatory response (36). Interleukin-1 beta (IL-1 β), another proinflammatory cytokine, is a protein molecule released in conditions such as inflammation and tissue damage (37). In the present study, TNF- α values in the CP group were significantly higher than those in the control group. However, TNF- α values in the treatment groups were significantly lower compared to those in the CP group. No significant difference was observed between the CP+RES30 and CP+RES60 treatment groups, but TNF- α levels in the CP+RES90 group were significantly higher than those in the CP+RES30 group. Some studies investigating CP-induced intestinal damage have reported findings consistent with our own results, with exposure to CP significantly increasing TNF- α levels in mice (17,38). The anti-inflammatory effect of RES derives from its ability to inhibit the synthesis and release of inflammatory mediators (39). Parlar and Arslan (2019) examined the effects of RES on TNF- α following ischemic injury and reported that RES administration at 15 mg/kg once daily for five days prior to surgery significantly lowered increased TNF- α activity (40). Another study reported that RES reduced TNF- α values that had risen as a result of intestinal injury (30). These studies support our findings regarding the anti-inflammatory effects of RES. However, no significant variation was found between the experimental groups in terms of score findings for IL-1 β that we used to determine proinflammatory cytokine levels. In their investigation of intestinal injury resulting from CP, Hu et al. (2021) reported, in contrast to the present study, that exposure to CP significantly increased IL-1 β levels in mice (17). Nardini et al. similarly detected mucosal damage, inflammation, and rising IL-1 β levels in mice receiving CP treatment (41). Another study of the protective and anti-inflammatory effects of RES also found that RES significantly reduced increased IL-1 β activity (40).

Study Limitations

Our research findings should be supported by different parameters and analysis methods. Different studies are needed for dose evaluation.

Conclusion

In conclusion, CP was observed to render the metabolically active intestinal mucosa highly susceptible to cytotoxic effects, resulting in severe histological tissue damage, intestinal apoptosis, and an increase in proinflammatory cytokines. The administration of RES, a potent antioxidant, prior to CP treatment in rats was found to exhibit a protective effect against CP-induced intestinal damage, apoptotic cell death, and proinflammatory cytokines, particularly at dosages of 30 and 60 mg/kg. We also think that our results will serve as a useful reference in determining suitable dose intervals for future RES studies.

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Ethical Approval: Permission was obtained from Harran University animal experiments local ethical committee (HAYDEK) (study protocol license no. 2022/006/20).

Author Contributions: Concept: HH, ST Literature Review: HH Design: HH, ST Data acquisition: HH, ST Analysis and interpretation: HH, ST Writing manuscript: HH Critical revision of manuscript: HH

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Original Article**Comparison the efficacy of intravenous and topical tramadol on postoperative pain control after septoplasty***Septoplasti sonrası postoperatif ağrı kontrolünde intravenöz ve topikal tramadol etkinliğinin karşılaştırılması***Ahmet Kaya^{1*}**, **Burhanettin Usta²**¹University of Health Science, Mehmet Akif İnan Training and Search Hospital, Department of Anesthesiology and Reanimation Şanlıurfa, Türkiye²Department of Anesthesiology and Reanimation, Nile University, Nizamiye Teaching Hospital, Nigeria***Corresponding author:**

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Comparison the efficacy of intravenous and topical tramadol on postoperative pain control after septoplasty. IJCMBBS 2023;3(2):105-110 doi.org/ 10.5281/zenodo.8072162

Highlights

- Nasal packings used in septoplasty surgeries cause increased pain associated with the surgery.

- Tramadol infiltrating nasal tampons reduces the need for additional analgesics in the postoperative period, similar to the effectiveness of intravenous tramadol.

Abstract**Background:**Tramadol hydrochloride is an analgesic drug used in the treatment of moderate or severe postoperative pain. The local anaesthetic effects of tramadol were demonstrated in previous studies. The aim of this study was to compare the postoperative analgesic efficacy of intravenous tramadol with the local application of tramadol by injection into merocel in patients undergoing septoplasty.**Materials and Methods**A prospective, randomized, controlled study included ASA I-II, 18-65 aged, 60 patients who underwent elective septoplasty. The patients were divided into two groups. Group 1 (i.v) received 1mg.kg⁻¹ tramadol i.v. and Group 2 (Merocel®) 100 mg tramadol injected to the Merocel® nasal packs. Postoperative pain scores, nausea, vomiting and rescue analgesic drug were recorded at the first, second, fourth, sixth, twelfth and twenty fourth postoperative hours.**Results**

No significant differences were found between two groups for demographic data. There were no statistically significant differences between two groups on VAS scores, nausea-vomiting and needing rescue drug.

Conclusion

With its local effects, topical tramadol application to nasal packs seems to be a comfortable approach for pain control in patients undergoing septoplasty.

Key words: Pain, Septoplasty, Topical, Tramadol**ÖZET****Amaç:**Tramadol Hidroklorid orta ve ciddi postoperatif ağrı tedavisinde kullanılan bir analjezik ilaçtır. Tramadolün lokal anestezi etkileri önceki çalışmalarda gösterilmişti. Bu çalışmadaki amacımız, septoplasti olan hastalarda, intravenöz tramadol ile Merocel® içine enjekte edilen tramadolün lokal kullanımını arasında postoperatif analjezik etkinliğini araştırmaktır.**Gereç ve Yöntem:**Prospektif, randomize kontrollü çalışma, septoplasti olacak ASA I-II, 18-65 yaş 60 hasta içerdi. Hastalar iki gruba ayrıldı. Grup 1 (iv) e 1mg.kg⁻¹ tramadol i.v. yapılırken Grup 2 (Merocel®) 100 mg tramadol Merocel® nazal tampon içine enjekte edildi. Postoperatif ağrı skorları, bulantı, kusma ve ek analjezik ilaç ihtiyacı 1., 2., 4., 6., 12. ve 24. saatlerde kaydedildi.**Bulgular:**İki grubun demografik bulguları arasında anlamlı fark bulunamadı. İki grubun VAS skorları, bulantı-kusma ve ek analjezik ilaç ihtiyaçları arasında istatistiksel olarak anlamlı fark bulunamadı (p>0.05).**Sonuç:**Tramadolün lokal etkilerinin varlığıyla septoplasti olan hastalarda nazal tampon uygulanması, konforlu bir ağrı kontrolü sağladı.**Anahtar kelimeler:** Ağrı, Septoplasti, Topikal, Tramadol

Introduction

Postoperative pain is an acute form of pain that begins with surgical trauma and ends with tissue healing. Stress response to surgery plays an important role in postoperative pain. As a result of untreated postoperative pain, an increase in the amount of catabolic hormones such as cortisol, adrenocorticotrophic hormone (ACTH), glucagon, aldosterone and catecholamines; The amount of anabolic hormones such as insulin and testosterone decreases, resulting in negative effects on the respiratory, circulatory, gastrointestinal, renal and autonomic nervous systems. Postoperative pain control is becoming increasingly important because of the undesirable and healing-delaying effects of pain (1,2).

In the treatment of postoperative pain, analgesic agents can be administered systemically or regionally, and the most commonly preferred method is parenteral administration. One of the analgesic agents used in the treatment of postoperative pain is opioids. Opioids are the leading analgesic drugs used in the treatment of moderate and severe postoperative pain in patients with cancer pain and many acute pain syndromes (3,4). One of the most preferred opioids -tramadol hydrochloride- it is a centrally effective synthetic analgesic (5). Tramadol, which is in the weak opioid group in the analgesic classification, has both opioid and nonopioid action mechanisms. In addition to its weak μ -opioid receptor agonist effect, it inhibits the presynaptic reuptake of noradrenaline (NA) and serotonin (5-HT). In addition to these effects, tramadol also stimulates the release of 5-HT (6). Thus, the additive effect obtained by potentiating the endogenous analgesia system with both the opioid agonist mechanism and its monoaminergic effect has a significant effect on antinociception, and less side effects have been the reason for the widespread use of tramadol in the treatment of moderate-severe cancer and non-cancer acute and chronic pain (7).

In our study, we aimed to show the efficacy of tramadol and saline mixture absorbed into merocel buffer for postoperative pain control after septoplasty operation, by comparing it with intravenously used tramadol.

Materials and Methods

Patient Group

Sixty patients with American Society of Anaesthesiology (ASA) evaluations core I-II between the ages of 18-65 who were planned for septoplasty operation were included in the study, whose approval was obtained by the Ethics Evaluation Commission of Fatih University at the meeting numbered 6 on 23/09/2010. The study was planned prospectively. Written informed consent was obtained from all patients who participated in the study, after giving detailed explanations about the study.

Patient Exclusion Criteria

Patients with known allergic reactions to study drugs, morbidly obese (BMI>35), patients with sleep-apnea syndrome, patients with renal, hepatic, cardiovascular or neuromuscular disease, atrioventricular conduction disorder, bleeding disorders, and patients with opioid or analgesic abuse was excluded.

The patients were randomly divided into two groups:

Group 1: intravenous tramadol group; 30 minutes before the end of the surgery, 1 mg.kg⁻¹ tramadol hydrochloride iv was administered to the patients. (8-10)

Group 2: Merocel infiltration topical tramadol group; After the post-surgical packing was placed, 50 mg tramadol hydrochloride 4 cc saline mixture (5 cc fluid in total) was injected into merocel® for both noses.

Procedure

All patients were taken to the operating room and electrocardiogram (ECG), noninvasive blood pressure, oxygen saturation (SpO₂) monitoring; Vascular access was established with a pink branule in the left hand, and fluid infusion was started, taking into account body weights and fluid deficit. Induction of anesthesia with 2.5 mg.kg⁻¹ propofol, 0.6 mg.kg⁻¹ rocuronium and 1 μ g.kg⁻¹ fentanyl

was applied to all patients with a tube size 8.0-8.5 for men and 7.0-7.5 for women. After intubation, 6% desflurane anesthesia was administered. Mean arterial pressure (MAP), heart rate (HR), SpO₂ and end-tidal carbon dioxide (ETCO₂) values were recorded before induction of anesthesia, after intubation, every 10 minutes during the operation, before and after extubation.

If tachycardia developed 20% above preoperative values during anesthesia, it was considered as insufficient anesthesia and iv bolus 1 µg.kg⁻¹ fentanyl was administered. If hypotension below 60 mmHg and heart rate values below 20% of preoperative values occurred, iv 5 mg ephedrine for hypotension and iv 0.5 mg atropine for bradycardia were administered.

Desflurane maintenance was discontinued when the surgery was over. 30 minutes before the end of surgery, 1mg.kg⁻¹ tramadol hydrochloride was administered to Group 1 (intravenous) patients. Group 2 (merocel® infiltration) patients were injected with 50 mg tramadol hydrochloride 4 cc saline mixture (5 cc fluid in total) into merocel® for both noses after post-surgical packing was placed. When necessary, neuromuscular blockade was reversed with neostigmine and atropine, and the patients were extubated. The time to 9-10 Aldrete Scale Score was recorded, and after reaching this score, the patient was removed from the operating room. The pain of the patients was evaluated with the Visual Analogue Scale (VAS)(11).

Patients were followed up for 24 hours in terms of postoperative side effects such as nausea, vomiting and tremor (none/available), pain and additional analgesia need. Patients with pain (VAS 3 and above) were given 0.5 mg.kg⁻¹ tramadol hydrochloride iv, and patients with nausea and vomiting were given ondansetron 4 mg iv.

Statistical analysis

13 of SPSS (Statistical Package for Social Sciences) for Windows package program was used in the analysis of statistical data. Student-t test in the analysis of continuous variables with normal distribution by testing the suitability of the data for normal distribution; Mann Whitney U test was used in the analysis of continuous variables that did not show normal distribution. Chi-square test was used in the analysis of discrete variables. Results were expressed as mean±standard deviation (mean±SD), median (min-max), n (number of patients), and percent (%). According to the results of the analysis, cases where the p value was <0.05 were considered statistically significant.

Results

Demographic Data

Our study was performed on a total of 60 cases, 20 female and 40 male, ranging in age from 18 to 65. No statistical difference was observed between the age, weight, height, and gender (p:0.584) and ASA scores (p:0.519) of the 1 and 2 groups (**Table 1**).

Table 1: Demographic Data of Patients

Variabales	Group 1 (n:30)	Group 2 (n:30)	p value
Age (years)	29±5	29±6	0.668
Weight (kg)	79±14	81±14	0.551
Height (cm)	174±9	175±8	0.629
Gender Male (n,%)	19 (63)	21 (70)	0.584
ASA			
I (n,%)	23 (77)	25 (83)	0.519
II (n,%)	7 (23)	5 (17)	
Anesthesia Duration (min)	58 (49-65)	63 (54-71)	0.473
Surgery Time (min)	50 (44-60)	55 (45-61)	0.687
Time to Aldrate 9-10 (min)	9 (5-10)	8 (6-10)	0.858
Total Desflurane Consumption (ml)	35 (30-40)	35 (30-40)	0.886
Total Tramadol Consumption (mg)	78 (69-93)	100 (100-100)	0

Abberivations: ASA: American Society of Anaesthesiology

Pre-induction, post-intubation, 5th minute, 10th minute, 20th minute, 30th minute, 40th minute, 50th minute, 60th minute, 70th minute, 80th minute, 90th minute, pre-extubation and after extubation,

there was no statistically significant difference between mean arterial pressure and heart rate values measured ($p>0.05$).

Postoperative VAS Scores

There was no statistically significant difference between the postoperative, postoperative 1st hour, postoperative 2nd hour, postoperative 4th hour, postoperative 6th hour VAS scores of the groups ($p>0.05$) (**Table 2**). No pain was observed in any of the patients at the postoperative 12th hour and postoperative 24th hour, and the VAS scores were evaluated as 0.

Table 2: Postoperative VAS Scores

	Group 1 (n:30)	Group 2 (n:30)	p value
Basal VAS	1 (1-2)	1 (1-2)	0.289
1st hour VAS	2 (1-2)	2 (1-2)	0.543
2nd hour VAS	1 (1-2)	1 (1-2)	0.559
4th hour VAS	1 (0-1)	1 (0-1)	0.657
6th hour VAS	1 (0-1)	0 (0-1)	0.608

Postoperative, postoperative 1st hour, postoperative 2nd hour, postoperative 4th hour, postoperative 6th hour nausea and vomiting complaints of the groups were questioned and no statistically significant difference was found between them ($p>0.05$). Nausea and vomiting were not observed in any of the patients at the postoperative 12th hour and the postoperative 24th hour.

Postoperative Shivering Evaluation

There was an equal number of tremors in the postoperative and postoperative 1st hour in the groups, and there was no statistically significant difference between them ($p:1,00$) (**Table 3**). No shivering was observed in any of the patients at the postoperative 2nd hour, postoperative 4th hour, postoperative 6th hour, postoperative 12th hour and postoperative 24th hour.

Table 3: Postoperative Shivering Evaluation

		Group1 (n:30)	Group2 (n:30)	Total (n:60)	
1st hour Tremor (n,%)	None	24 (80)	24 (80)	48 (80)	p:1.00
	Available	6 (20)	6 (80)	12 (80)	

Evaluation of Postoperative Additional Analgesic Need

Comparing the need for additional analgesia in the first 24 hours postoperatively in the groups, it is seen that 2 patients in Group 1 and 7 patients in Group 2 received additional medication in a total of 9 patients (**Table 4**). No statistical difference was observed between the 1 and 2 groups in terms of additional analgesia need ($p:0.071$) (**Table 4**).

Table 4: Evaluation of Postoperative Additional Analgesic Need

		Group 1 (n:30)	Group 2 (n:30)	Total (n:60)	
Postoperative Additional Analgesic Need (n,%)	None	28 (93)	23 (77)	51 (85)	p:0.071
	Available	2 (7)	7 (23)	9 (15)	

Discussion

Septoplasty is one of the most common surgical procedures in the practice of otolaryngology. Two important problems encountered after septoplasty are pain and bleeding (12). After Septoplasty operations, dry merocel®, which is among the tampons used to prevent bleeding and possible hematoma, is inflated with saline after it is placed into the nose. Most of the studies on merocel and pain in the past aimed to prevent the pain that will occur when the tampon is removed (13, 14).

The ideal agent should be short-acting, safe, inexpensive, and easy to administer to deal with pain or discomfort during nasal packing removal. Many previous reports were about injection methods into

nasal packings. Local anesthetics such as lignocaine, prilocaine, prilocaine plus meperidine, levobupivacaine were used in nasal packing (15-18). In these studies, it was stated that the local anesthetics mentioned in the early period, alone or in combination, reduced the level of pain and anxiety compared to the control group.

In recent studies; Tramadol hydrochloride, which is a frequently used opioid providing effective analgesia and mild sedation, stands out in this regard. In the retrospective study of Tulaci et al. (18); Prilocaine, tramadol 1 mg/kg combined with prilocaine, and tramadol 2 mg/kg combined with prilocaine in merocel nasal packings were compared in terms of pain, sedation, and anxiety related to this removal procedure before removal of the nasal packing using normal saline solution, which is the control group. The combined infiltration of prilocaine and tramadol 1 mg/kg into the nasal packing was found to be effective in reducing the pain and anxiety of the patients during the removal of the nasal packing.

Şimsek et al. (19) conducted the most recent study on this subject, and in their retrospective study, patients were divided into three groups according to the application of lidocaine, tramadol and 0.9% NaCl on merocel nasal packings. In the postoperative period, VAS scores, side effects, and additional analgesic requirements were recorded for 24 hours, starting from the PACU (post-anesthesia care unit). They stated that tramadol infiltrated into nasal packings reduces the need for additional analgesics in the postoperative period, increases patient satisfaction, decreases the length of hospital stay, and as a result, reduces the secondary infection rate. In our study, tramadol was compared with iv as infiltration and although no significant differences could be detected between the two groups, the iv of the infiltrated tramadol group was compared. It was found that the effect was equivalent to the group that was administered.

In many previous postoperative studies, it was reported that tramadol caused less respiratory depression and less sedation compared to strong opioids (20). In our study, the frequently used Aldrate recovery score was used to evaluate the recovery process of patients in the postoperative period, and the time it took for patients to reach 9-10 points in this assessment was measured. While we expected the recovery time to be longer in the group that received intravenous tramadol because of its involvement in the systemic circulation and its possible sedative feature, the average time to reach Aldrate recovery score of 9-10 in Group 1 was 9 minutes, while in Group 2 this time was determined to be 8 minutes on average. No statistical difference was found between them.

Another parameter examined in the study was tremor in the postoperative period. Only tremors were detected in the groups after the operation and at the postoperative 1st hour, and there was no statistically significant difference between the groups. It was attributed to the coldness of the operating room and the infused fluid.

Limitation

Analgesia was provided with tramadol administered to the patients. While the average amount of tramadol in Group 1 was 79 mg, this amount was 100 mg in Group 2. There was no statistically significant difference between the groups. As a result of insufficient data on the absorption of tramadol in merocel®, the difficulty in determining the drug dose used in this group was the limitation of our study, with the routine use of 100 mg tramadol for each patient in Group 2 in this parameter.

Conclusion

In conclusion, it was shown in our study that peripheral nerves were blocked by the nasal route and that nociception was prevented, providing a comfortable postoperative analgesia, as well as its effectiveness and side-effect profile being indistinguishable from intravenous administration. Thus, we think that tramadol can be used topically in the septoplasty operation, avoiding possible side effects, since there is no need for systemic administration and additional analgesia.

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Original Article

Effect of Intermittent Online Training on Adult Cardiopulmonary Resuscitation Management in
A Tertiary Care SettingÜçüncü Basamak Bir Acil Serviste Çevrim İçi Ve Tekrarlı Eğitimlerin Erişkin Kardiyopulmoner Resüsitasyon
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Highlights

- Correct drug administration rates increased after training.

- There was a significant increase in the use of capnography after training.

Abstract

Background: Cardiac arrest is one of the clinical conditions with the highest mortality rate in the emergency department. The purpose of this study was to assess the impact of education on the quality of cardiopulmonary resuscitation(CPR) performed on patients with out-of-hospital and in-hospital cardiac arrest, as well as to analyze other factors influencing Return of Spontaneous Circulation(ROSC).**Materials and Methods:** This study was conducted in the Gulhane Training and Research Hospital's Emergency Department. Cardiopulmonary arrest patients' data were collected using the "Resuscitation Follow-up Form". Descriptive data, including adult arrest case characteristics and CPR protocols, were acquired. ROSC and CPR management parameters were compared in cases that received CPR before and after training.**Results:** A total of 95 patients were included in the study. The mean age of the patients was 69,16±14,606. The 64,2%(n=61) of patients were cardiac arrest patients who were intervened before education and 35,7%(n=34) were after education. The ROSC rate in arrest patients before training was 36,1%, and 38,2% after training. When comparing the pre-training and post-training groups in terms of ROSC, it was seen that the ROSC rates increased after the training. While the rate of EtCO₂ use was 3,3%(n=2) in pre-training cases, this rate was 97,1%(n=33) in post-training cases. EtCO₂ usage rate increased significantly with education(p=0.001). **Conclusions:** It was observed that EtCO₂ usage and correct drug administration increased after the training. It was determined that repetitive trainings improved CPR management in arrest cases.**Keywords:** Cardiopulmonary resuscitation, education, return of spontaneous circulation

ÖZ

Amaç: Kardiyak arrest, acil servislerde görülen mortalitesi yüksek klinik olayların başında gelir. Bu çalışmanın amacı, eğitimin hastane dışı ve hastane içi kardiyak arrest hastalarında uygulanan kardiyopulmoner resüsitasyonun (KPR) kalitesi üzerindeki etkisini değerlendirmek ve Spontan Dolaşımın Geri Dönüşü (ROSC) üzerine etkisini incelemektir. **Gereç ve Yöntem:** Bu çalışma Gülhane Eğitim ve Araştırma Hastanesi Acil Servisinde yapıldı. Kardiyopulmoner arrest hastalarının verileri "Resüsitasyon Takip Formu" kullanılarak toplandı. Erişkin arrest vakalarının demografik verileri CPR parametreleri toplanarak tanımlayıcı veriler elde edildi. Eğitim öncesi ve sonrası ROSC ve CPR yönetimi parametreleri karşılaştırıldı. **Bulgular:** Çalışmaya toplam 95 hasta dahil edildi. Hastaların yaş ortalaması 69,16±14,606 idi. Hastaların %64,2'si (n=61) eğitim öncesi, %35,7'si (n=34) eğitim sonrası müdahale edilen kardiyak arrest hastalarıydı. Arrest hastalarda eğitim öncesi ROSC oranı %36,1 iken, eğitim sonrası %38,2 idi. Eğitim öncesi ve eğitim sonrası gruplar ROSC açısından karşılaştırıldığında, eğitim sonrasında ROSC oranlarının arttığı görüldü. EtCO₂ kullanım oranı eğitim öncesi olgularda %3,3 (n=2) iken, eğitim sonrası olgularda bu oran %97,1 (n=33) oldu. EtCO₂ kullanım oranı eğitimle anlamlı olarak arttı (p=0.001).**Sonuçlar:** Eğitim sonrası EtCO₂ kullanımı ve doğru ilaç uygulamasının arttığı görüldü. Tekrarlı eğitimlerin arrest vakalarda CPR yönetimini iyileştirdiği saptandı.**Anahtar Kelimeler:** Kardiyopulmoner resüsitasyon, eğitim, spontan dolaşımın geri dönüşü

Introduction

The absence of signs of breathing and circulation resulting from the sudden and unexpected cessation of the heart's pumping function is defined as cardiopulmonary arrest (CPA), and the resulting death is defined as sudden cardiac death (1). The main clinical findings seen in CPA patients can be considered impaired consciousness, respiratory arrest, and pulselessness (2, 3). CPA is one of the clinical conditions with the highest mortality rate in the emergency department (4). The non-traumatic cardiac arrest rate of the CPA patients admitted to the ED was 80-90%, and the traumatic arrest rate was reported as 12-13% (5). According to the place of occurrence, CPA can be classified into two main groups, in and out of the hospital. Cardiopulmonary resuscitation (CPR) is a whole of basic and advanced life support applications applied to patients inside or outside the hospital in cases with CPA development. The most critical factors for the Return of Spontaneous Circulation (ROSC) in patients are the early diagnosis of cardiac arrest, early CPR, and rapid defibrillation (6). After that, appropriate post-resuscitation care increases the patient's neurological survival and ensures that one can return to their social life by discharge. For this purpose, periodic guidelines are being published (7).

One of the most important issues highlighted in current CPR guidelines is the uninterrupted application of chain of life rings in CPA cases. Adult life chain steps in resuscitation can be summarized as I. Calling for help, ii. Starting cardiac massage, iii. Applying electrical therapy, iv. Transporting to the appropriate center in the early period, v. Providing care in optimal intensive care conditions (7). According to the current guidelines, the training must be repeated frequently. However, time, space, and instructor constraints are essential issues for training in this field to be given optimally to different groups of medical personnel (such as physicians, nurses, emergency medical technicians (EMT), paramedics, etc.). Another issue area is the inability to perform adequate training. The recent COVID-19 pandemic has also not allowed face-to-face training in terms of contact isolation and emphasized the importance of online training (8).

The emergency physician and nurse provide the first response to CPA in the emergency department. CPR training aims to diagnose the patient early, recognize arrest rhythms early, and gain the skills to apply the basic and advanced life support steps quickly and accurately. Studies have revealed that online training can be helpful and improve CPR quality (9). This study's primary outcome: This study investigates the effect of an online and targeted repetitive education systems on CPR quality in the tertiary emergency department. Secondary outcomes: to investigate whether online training contributes to the standardization of teamwork and personnel practices in the CPR process and other factors that affect the return of spontaneous circulation.

Materials and Methods

The study is designed as a prospective observational study in the emergency department of a tertiary university hospital. The local Ethics Committee approved our study (March 25, 2021, approval number 2021/123).

The patients' demographic data (age and gender) and their comorbidities (diabetes mellitus, hypertension, chronic renal failure, chronic obstructive pulmonary disease, malignancy, asthma) were first questioned, and the cases were gathered with the Utstein style data form and descriptive observational data were obtained (10). All adult patients who underwent CPR in the emergency department were included. The study did not include patients with incomplete data, patients under 18, patients with traumatic cardiac arrest, and pregnant patients.

According to the place of emergence, cardiac arrest is classified as in-hospital and out-of-hospital, and the time to intervene is recorded if there are witnesses. In cases of CPA with out-of-hospital cardiac arrest (OHCA), EMS team formations, time to arrive at the scene, the first rhythm seen in the patient, the first medical intervention and airway clearance (airway/LMA/intubation), whether defibrillation or cardioversion was performed according to the rhythm observed on the monitor, the medications administered were recorded.

For the in-hospital cardiac arrests (IHCA), the location of the arrest (Trauma room/emergency room/CT/MR/elevator), initial rhythm observed on the monitor during CPR, the time of intubation, and whether etCO₂ monitoring was performed were recorded. Defibrillation, cardioversion, pacemaker, and mechanical chest compression device use status were also recorded. Peripheral vascular access, central catheter, and intraosseous catheter placement have been questioned. Medications (epinephrine, calcium, sodium bicarbonate, insulin, amiodarone, magnesium) and IV fluids administered during CPR were recorded. Spontaneous circulation was expected to continue for 20 minutes to exclude cases of recurrent arrest in patients with a pulse after CPR (11). Patients who were provided with ROSC were followed up for their further prognosis.

Blood gas analysis results, routine biochemistry values (blood glucose, renal function tests, sodium, potassium, CRP (C- Reactive Protein), cardiac markers, INR, D-dimer), and complete blood count (CBC)

parameters were recorded in routine blood tests taken from patients. No supplementary biochemical procedures were explicitly performed for the study.

Two online pieces of training were planned for the study, and the data gathered during the study were divided into two groups: pre-training and training. An emergency service resuscitation follow-up form was created with all the parameters listed above, and the same form was used in pre- and post-education evaluations. Changes in practice in resuscitation management after training in the parameters examined were evaluated. Statistical analysis of the data obtained and the effect of online and targeted repetitive training on CPR quality were investigated. Secondly, it was investigated whether the training contributed to the standardization of the personnel practices through teamwork during the CPR process. These trainings aim to highlight the algorithms taken from the current guidelines for CPR. The first training was given online on April 12, 2021, via zoom to nurses and emergency physicians actively involved in CPR. The trainings given were recorded. On May 28, 2021, emergency physicians and nurses who participated in the first training via zoom were given second online training. In these trainings, the information highlighted in the current guidelines is emphasized. The training content is prepared according to the AHA 2020 guideline.

Statistics analysis

In the power analysis, it was calculated that a total of 55 patients would be sufficient when the current ROSC rate is taken as 32%, the expected ROSC rate as 50%, the alpha value as 0.005%, and the power as 80% (5, 12). Due to possible data deficiencies, it was decided to take 95 patients into the study. The continuous data were given as frequency, percentage, mean, and standard deviations. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. If it revealed a normal distribution, the comparison was conducted by Student's t-test; if it did not reveal a normal distribution, it was carried out with a Mann-Whitney U test. Chi-Square test was used to compare the two groups for categorical variables. The significance was evaluated at a $p < 0.05$ level. The data was analyzed using the IBM SPSS 22.0 statistical package program.

Results

A total of 95 patients were included in the study, and 69.5% (n=66) of the patients were male, and 30.5% (n=29) were female. The mean age of the patients was 69.16 ± 14.6 . Demographic data of the patients included in the study are summarized in **table 1**.

Table-1. Demographic data

Parameter	Mean \pm Standard Deviation or n (%)
Age	69.16 \pm 14.6
Gender	
Female	29 (%30.5)
Male	66 (%69.5)
Comorbidities	
None	16 (%16.8)
DM	24 (%25.3)
HT	37 (%38.9)
CRF	10 (%10.5)
COPD	7 (%7.3)
Malignancy	16 (%16.8)
CAD	8 (%8.4)
Asthma	1(%1.1)
Pacemaker	
With the Pacemaker	6 (%6.3)
Prognosis	
ROSC in the Emergency Department	32 (%33.6)
Exitus in the Emergency Department	63 (%66.3)
Total	n=95 (%100)

Abberivations: DM: Diabetes Mellitus, HT: Hypertension, CAD: Coroner Arter Disease CRF: Chronic Renal Failure, COPD: Chronic Obstructive Pulmonary Disease

Out-of-hospital arrest patients accounted for 52.6% (n=50) of the total patients. Among these, 12% (n=6) had been arrested in the ambulance. The initial arrest rhythm in patients with Out-of-hospital CPA was 92% (n=45) as asystole. The findings of out-of-hospital arrest patients are summarized in **table 2**.

Table-2. Demographic data of pre-hospital arrest patients.

Arrest Location	
Pre-Hospital	50 (%100)
-Ambulance	6 (%12)
-Out of Hospital	44 (%88)
Arrest Time	
08.00 – 18.00	27 (%54)
18.00 – 24.00	17 (%34)
24.00 – 08.00	6 (%12)
Arrest Type	
Nontraumatic	48 (%96)
Traumatic (fall)	2 (%4)
Witnessing the arrest	
Witnessed	22(%44)
Not witnessed	28(%56)
Witness Intervention	
No intervention	37 (%74)
CPR performed	2 (%4)
CPR and respiratory support	11 (%22)
First Arrest Rhythm	
Asystole	46 (%92)
VT	0 (%0)
VF	1 (%2)
PEA	3 (%6)
First 112 intervention	
CPR performed	48 (%96)
CPR not performed	2 (%4)
Airway management of 112 team	
Airway	29 (%58)
LMA	14 (%28)
Intubation	7 (%14)
Surgery	0 (%0)
Defibrillation by 112 team	
Scoop	1 (%2)
Cardioversion by 112 team	
Cardioversion performed (Pad)	1 (%2)
Pre-Hospital Vascular Access	
Peripheral Vascular Access	43 (%86)
No Vascular Access	7 (%14)
Total patients	n=50

Abbreviations: 112: Emergency Call Center of Turkey, 112 Team Formation: Doctor, Nurse, Paramedic, Emergency Medical Technician, VT: Ventricular Tachycardia, VF: Ventricular Fibrillation, PEA: Pulseless Electrical Activity, CPR: Cardiopulmonary Resuscitation, LMA: Laryngeal Mask

A total of 45 patients were included in the study, 91.1% of whom had been arrested in the emergency room. The first arrest rhythm evaluated in 86.6% (n=39) is asystole. The first evaluation data of in-hospital cardiac arrest patients is given in **table 3**. 64.2% (n=61) of the patients included in the study were pre-training arrest patients, and 35.7% (n=34) were post-training patients. In these patients, post-training ROSC incidence was 38.2% (n=13) and observed to increase. However, this difference was not statistically significant. etCO₂ usage rate is 3.3% (n=2) in pre-training cases, compared to 97.1% (n=33) in post-training cases. etCO₂ usage rate increased significantly with training (p 0.001). etCO₂ was used in patients both to evaluate the accuracy of the location of the intubation tube and to evaluate the quality of CPR. Comparison data on cardiac arrest applied before and after training of patients are summarized in **table 4**.

Once the vascular access is provided during CPR, the epinephrine should be initiated to be administered 1 mg every 3 to 5 minutes. In our study, it was observed that there was an improvement in the correct epinephrine

timing after the training. While epinephrine administration time was correct in 20 (32.7%) of 57 cases pre-training, it was correct in 18 (52.9%) of 34 cases post-training. CPR management is carried out only by physicians. However, after the training of the nurses, the deficiencies during drug administration were eliminated. After the epinephrine administration to all patients in the post-training term, their extremities were positioned, and 10 cc saline was administered as a flush.

Table-3. In-hospital arrest patients.

Arrest Location	
Emergency Department observation units	41 (%91.1)
Ultrasound room	1 (%2.2)
Computed Tomography	2 (%4.4)
Elevator	1 (%2.2)
Arrest Time	
08:00 - 18:00	27(%60)
18:00 - 24:00	12(%26.6)
24:00 - 08:00	6(%13.3)
First Arrest Rhythm	
Asystole	39(%86.6)
VT	0
VF	3(%6.6)
PEA	3(%6.6)
Total Patients	n=45

Abberivations: VT: Ventricular Tachycardia, VF: Ventricular Fibrillation, PEA: Pulseless Electrical Activity

Table-4. Comparison of pre-training and post-training practices on patients with CPR in the emergency department.

	Pre-training (n=61)	Post-training (n=34)	p
ROSC/Total CPA	22/61 (36.1%)	13/45 (38.2%)	0.829
etCO₂	2 (3.3%)	33 (97.1%)	0.001
Defibrillation	17 (27.9%)	6 (17.6%)	0.324
Exitus in the Emergency Department	41 (67.2%)	22 (64.7%)	0.824

Abberivations: ROSC: Return of Spontaneous Circulation, EtCO₂: End Tidal Carbon Dioxide

Table-5. Comparison of pre-training and post-training medications administered during CPR.

	Pre-Training (n=61)	Post-Training (n=34)	p
Atropine	8 (13.1%)	1 (2.9%)	0.149
NaHCO₃	26 (42.6%)	15 (44.1%)	0.100
Ca	18 (29.5%)	12 (35.2%)	0.725
Mg	0 (0%)	2 (5.8%)	0.560
Amiodarone	8 (13.1%)	6 (17.6%)	0.559
Insulin	8 (13.1%)	8 (23.5%)	0.310
Norepinephrine	5 (8.1%)	2 (5.8%)	1.000
Normal saline solution	61 (100%)	34 (100%)	N/A (not applicable)
Dextrose (5% Dx, 500 cc)	7 (11.4%)	7 (20.5%)	0.05

Medication administrations for pre-training arrest patients covering 64.2% (n=61) of the patients included in the study, were compared with post-training arrest patients covering 35.7% (n=34). The administered medications are presented in **table 5**. Although routine atropine application is not included in the up-to-date guidelines in CPR application, it was observed that it was applied to 8 patients from 61 patients before training. The number of patients administered atropine was seen in 1 out of 34 patients after the training, and unnecessary application of atropine was largely prevented. However, this value is not statistically significant and is p=0.149. Another medication evaluated during CPR is amiodarone. Amiodarone was administered to a total of 14 patients before and after training. Pre-training amiodarone administration was 13.1% (n=8), compared to 17.6% (n=6) post-training. The training increased the rate, but there was no statistically significant difference (p=0.559). Before the training, amiodaron was given in saline in a few patients, while

after the training, it was administered to all patients as an intravenous push. When CPR medication administrations were evaluated, it was observed that no Mg was administered to any patients before training. As a result of rhythm analyses performed during CPR, the monitor rhythm was evaluated as torsades de pointes, and Mg was added to the treatment in 2 patients.

Discussion

Enabling ROSC in CPA patients, instead of CA development, varies according to whether the arrest is witnessed, the first intervention, the time it takes to reach the hospital, other diseases of the patient, and the medications they use. In our study, we evaluated that targeted, recurrent, online CPR training improved the management quality of arrest cases and achieved clinically positive results. 69.5% of the patients included in the study were male, and 30.5% were female. Berdowski et al. stated that the rate of the male was higher in cases brought as arrests (13). In the studies conducted by Bertoia et al. and Adabag et al., they found that the rate of the male was 2-3 times higher than females in non-hospital arrest cases. These studies stated that estrogen has a protective effect on the cardiovascular system during the premenopausal period (14, 15). In our study's data, as in the studies of Berdowski et al., Bertoia et al., and Adabag et al., it was observed that the male gender was more common in arrest cases admitted to the hospital. These data were found to be similar to the literature. The mean age of the patients who underwent CPR in the study was 69.1 ± 14.6 . In the study of Van Gijn MS et al., the mean age of cardiac arrest patients was found to be between 60-75 years, which was evaluated in line with our study (16). 16.8% of the patients in our study did not have any comorbidities. When the comorbidities of the patients participating in the study are evaluated, the most common is HT, followed by DM, malignancy, CRF, and CAD. In a study by Isenschmid et al., when the comorbidities of 321 patients with cardiac arrest were examined, CAD and diabetes mellitus were observed most frequently, and CRF and malignancy were observed less frequently (17). In a series of cardiac arrest studies conducted by Geçmen et al. in a tertiary center, HT and DM were most common in patients, followed by CRF, CHF, CAD, and COPD (18). In our study, the rate of comorbid disease is high in arrest cases, similar to the literature. It has been evaluated that the differences between comorbidities are because the studies are conducted in different populations and different geographical regions.

In our study, 92% asystole and 6% PEA were observed as the first arrest rhythm in OHCA patients. According to Bayes et al.'s study, the basic rhythm was VF, and pulseless VT is approximately 25-35% of out-of-hospital sudden cardiac arrests. In comparison, PEA was observed in approximately 25% of the patients. Bradyarrhythmia and asystole are reported as less common (19). In a study on sudden cardiac death by Katrictis et al., it was reported that the incidence of VF or pulseless VT as the first arrest rhythm in OHCA decreased below 30% (20). PEA and asystole are more common in OHCA (20). According to the study of Myerburg et al., the incidence of PEA as the first arrest rhythm in OHCA was found to be 19-23% (21). We think that the reason for the higher incidence of asystole in our study may have changed from a shockable rhythm or PEA to asystole because of the recognition of out-of-hospital arrest, the delay in the intervention due to lack of training in the witnessed arrest, the time to reach emergency call center team, and the delayed access to the AED.

Although 74% of OHCA patients were witnessed, CPR was not initiated, and chest compressions are recommended in the case of CPA regardless of the sociocultural level (22). Neumar et al.'s study suggest that chest compression significantly increases the survival rate (23). For this reason, we think that CPR training should be given to citizens other than healthcare workers. In OHCA patients brought by EMS teams, it was observed that airway was applied in 58% of patients, and LMA was applied in 28%. In a study published in 2018 comparing patients with endotracheal intubation (ETI) and balloon mask (BVM) in 2040 OHCA patients, no statistically significant difference was found between ETI and BVM in terms of 28-day neurologic survival (24). Since the average time to reach the hospital is 12-20 minutes, we think it aims not to waste time with ETI by prioritizing chest compressions by EMS teams.

Studies have shown that blood pressure changes during the day in healthy individuals, and the incidence of myocardial infarction increases in the morning is associated with increased catecholamine levels in addition to increased blood pressure and increased platelet aggregation in the morning (25). Increasing blood pressure with the circadian rhythm leads to the deterioration of atherosclerotic plaque stability in the coronary arteries and myocardial infarction, with the increase in cardiac sympathetic activation triggered by the catecholamine level (26). Increased sympathetic stimulation in the morning due to circadian rhythm increases the risk of MI

and the incidence of arrest associated with it (27). In our study, per these data, it was observed that the most common arrest development time of the patients was between 08:00 am and 6:00 p.m.

In 9% of the patients who developed IHCA included in the study, arrest developed in areas out of treatment service. These are the patients who are followed up in the emergency department and planned for transport due to the need for imaging and further examination. 3 of these 4 patients in whom CPR application was started outside the emergency department were provided with ROSC. We think that monitoring these patients during transport, early recognition of the arrest rhythm and the experience of the healthcare personnel accompanying the patient increase this rate. In our study, patients with in-hospital arrest were divided into two groups: pre-training and post-training, and it was observed that the ROSC rate increased by 38.2% after training. Although the ROSC rate increased after the training, this difference was not statistically significant ($p=0.829$). When the studies of Toubasi et al. and Nil Kaan et al. were examined, it was found that the quality of CPR increased after the basic life support-defibrillation course given interactively (28, 29). However, these studies were carried out on manikins, and ROSC was not evaluated in the study. In our study, the post-training mortality rate was 64.7%, which decreased but was not statistically significant. We think that the referral of patient groups with high comorbidity through the prehospital emergency medicine system caused the reduced ROSC rate.

In the study, the use of capnography was evaluated in evaluating $etCO_2$ before and after the training. Post-training $etCO_2$ use increased significantly ($p=0.001$). $etCO_2$; reflects alveolar CO_2 pressure, production, and cardiac output in the general (30). In a series of three cases reported in 1977, Schoonees first suggested that $etCO_2$ monitoring with a capnography may be an early indicator of ineffective cardiopulmonary resuscitation, emphasizing the need for further studies on this issue (31). The $etCO_2$ measured during CPR reflects the cardiac output generated during chest compressions. It has been reported that $etCO_2$ cannot be used alone for the decision to terminate CPR, but if the 20-min $etCO_2$ value is <10 mmHg, the probability of developing ROSC is low (32). The usage of capnography was analyzed before and after training in our study as an application used during CPR and the frequency of use. Although the usage of capnography, which is considered a quality indicator, rose after schooling, there was no influence on ROSC.

In patients undergoing CPR, administration of 1 mg epinephrine is recommended as soon as vascular access is established and repeated every 3-5 min until ROSC is achieved (33). The amount of epinephrine used in the Wang et al. study was 8.1 ± 7.1 mg (34). In the study of Tezcan Keleş et al., who evaluated IHCA cases, the amount of epinephrine administered was found to be 7.63 ± 3.1 mg (35). When we grouped our patients as pre-training and post-training, the average amount of adrenaline before the training was 9.24 mg, and the amount of epinephrine after the training was 7.91 mg. The amount of epinephrine administered in the study was compatible with the literature.

In our study, another medication administered during CPR and whose frequency of administration was evaluated before and after training is amiodarone. Amiodarone is a membrane-stabilizing medication. It is used in refractory VF and VT (33). In our study, it was administered to 14.7% of the patients. This rate was 13.1% in the pre-training group and 17.6% in the post-training group. In the study of Laina et al. investigating the effects of amiodarone use on survival and neurological recovery in patients with CPA, it has been found that amiodarone increases survival but does not have a significant benefit in the neurological recovery (36).

Study limitations

There were certain limitations to this study. First, the single-center study was identified as a research limitation. Another limitation is the lack of training for the EMS staff that respond to OHCA patients. Evaluation of the training provided was done using the emergency department resuscitation follow-up form, however no individual standardized test was performed after the training.

Conclusions

It was evaluated that although repeated training did not statistically reflect the success of ROSC, it increased the quality of management of arrest cases, and clinically positive results were obtained. After the training, end-tidal carbon dioxide monitoring, which shows the quality of cpr, increased. The rate of correct use of epinephrine and amiodaron was found to be increased. To improve the quality of CPR and increase the success of ROSC, it was evaluated that it is necessary to provide repetitive training to the healthcare teams who intervene in prehospital cardiac arrest, which is one of the essential elements of the survival chain.

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Author Contributions: Concept: ZS, TO Literature Review: ZS, AYA, TO Design: ZS, TO Data acquisition: AYA, ZS, TO Analysis and interpretation: TO, ZS Writing manuscript: ZS, TO Critical revision of manuscript: AYA, TO

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Original Article

Comparison of The Effects of Erector Spina Plane Block and Transversus Abdominis Plane Block Methods on Postoperative Analgesia in Elective Caesarian Section with Ultrasonography Account
*Elektif Sezaryen Operasyonlarında Ultrasonografi Eşliğinde Erektör Spina Düzlem Bloğu Ve Transversus Abdominis Düzlem Bloğu Yöntemlerinin Postoperatif Analjezi Üzerine Etkilerinin Karşılaştırılması*Melike ABAN YILMAZ¹, Mehmet Kenan EROL^{2*}¹Gülhane Training and Research Hospital, Ankara, Türkiye²Department of Anaesthesiology and Reanimation, Harran University, Faculty of Medicine, Sanliurfa, Türkiye***Corresponding author:**

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Received: 13/07/2023**Accepted:** 30/07/2023**Cite as:** ABAN YILMAZ. M. and et al. Comparison of The Effects of Erector Spina Plane Block and Transversus Abdominis Plane Block Methods on Postoperative Analgesia in Elective Caesarian Section with Ultrasonography Account. IJCMBMS 2023;3(2):120-9 doi.org/10.5281/zenodo.8180178**Highlights**

- ESP block found more effective regarding VAS scores, tramadol consumption, and patient satisfaction for elective cesarean section.

Abstract**Background:** The study aimed to compare the efficacy of erector spina plane (ESP) block and transversus abdominis plane (TAP) block in postoperative analgesia in cesarean section operations.**Materials and Methods:** The study included a total of 90 pregnant women scheduled for elective cesarean section under spinal anesthesia between February 2021 and February 2022. Following the completion of the operation, the patients were randomly assigned to three groups: TAP, ESP, and a control group using a closed envelope technique. Demographic data, postoperative Visual Analog Scale (VAS) scores at 0, 2, 4, 8, 12, and 24 hours, time of first analgesic administration in the patient control analgesia (PCA), the total amount of tramadol consumed, complications, surgeon, and patient satisfaction were recorded.**Results:** The time of first analgesic administration was statistically significantly lower in the TAP group than in the ESP group ($p<0.01$). Postoperative tramadol consumption at 0, 2, 4 and 8 hours was statistically significantly lower in the ESP group than in other groups ($p<0.01$). At 24 hours, the total amount of tramadol consumed was statistically significantly lower in the ESP group than in other groups ($p<0.01$). Patient satisfaction was higher in the ESP group compared to the TAP and control groups ($p<0.01$).**Conclusion:** The study found that ESP and TAP block groups consumed less tramadol postoperatively and had lower VAS scores than the control group in cesarean section operations. We found that the ESP block was more effective regarding VAS scores, tramadol consumption, and patient satisfaction.**Keywords:** Cesarean section operation, postoperative analgesia, patient-controlled analgesia, transversus abdominis plane block, erector spina plane block**ÖZ****Amaç** Çalışmanın amacı, erektör spina düzlem (ESP) bloğu ile transversus abdominis düzlem (TAP) bloğunun elektif sezaryen operasyonlarında postoperatif analjezi üzerine etkinliğini ve hasta memnuniyetine etkilerini karşılaştırmaktır.**Gereç ve Yöntem:** Çalışmaya, 15/02/2021-15/02/2022 tarihleri arasında elektif şartlarda spinal anestezi altında sezaryen operasyonu olacak toplam 90 gebe dahil edildi. Çalışma prospektif, randomize, çift kör karşılaştırmalı olarak yapıldı. Operasyon bitiminde hastalar kapalı zarf tekniği ile TAP, ESP ve kontrol grubu olarak rastgele 3 gruba ayrıldı. Demografik veriler, postoperatif 0., 2., 4., 8., 12., 24. saatlerde Vizüel Analog Skala (VAS) skorları, HKA'de ilk analjezik uygulama zamanı, toplam tüketilen tramadol miktarı, komplikasyonlar, cerrah ve hasta memnuniyeti kaydedildi.**Bulgular:** Hastaların demografik verilerinde, vital bulgularının takiplerinde istatistiksel anlamlı fark izlenmedi. HKA'de ilk analjezik uygulama zamanı TAP grubunda ESP grubuna göre istatistiksel olarak anlamlı düşük saptandı ($p<0,01$). Postoperatif tramadol tüketimi 0,2,4 ve 8. saatlerde ESP grubunda diğer gruplara kıyasla istatistiksel olarak anlamlı düşük saptandı ($p<0,01$). 24 saatte toplam tüketilen tramadol miktarı karşılaştırıldığında ESP grubunda diğer gruplara kıyasla istatistiksel olarak anlamlı düşük değerler izlendi ($p<0,01$). Hasta memnuniyeti ESP grubunda TAP ve kontrol grubuna göre daha yüksek bulundu ($p<0,01$).**Sonuç:** Bu çalışmanın sonucunda sezaryen operasyonlarında hem ESP hem de TAP blok gruplarının kontrol grubuna kıyasla postoperatif daha az tramadol tükettiğini ve VAS skorlarının daha düşük olduğunu saptadık. Özellikle ESP bloğunun VAS skorları, tramadol tüketimi ve hasta memnuniyeti açısından daha etkili olduğunu tespit ettik. ESP bloğunun, sezaryen sonrası ağrı yönetiminde diğer analjezi yöntemlerine iyi bir alternatif olacağı kanaatindeyiz.**Anahtar Kelimeler:** Sezaryen operasyonu, postoperatif analjezi, hasta kontrollü analjezi, transversus abdominis düzlem bloğu, erektör spina düzlem bloğu

Introduction

Effective pain management after cesarean section provides early recovery and mobilization of the mother, prevents the undesirable effects of pain, and ensures the earlier establishment of mother-baby bonding (1). Inadequate postoperative pain control may lead to delayed recovery, decreased function, and life quality, persistent postoperative pain, and increased risk of complications and postpartum depression (2).

Multidisciplinary approach of anesthesiology and obstetrics clinics is very important for pain control after cesarean section. Many new peripheral and regional block techniques have been described to avoid the side effects of opioids administered systemically or neuraxially. With the widespread use of ultrasonography, the complication risk of these techniques has decreased, and the success rate has increased (3).

Pain after cesarean section is of somatic and visceral origin. Most of the pain is of somatic origin. Somatic pain control can be achieved with regional block techniques. A Transversus abdominis plane (TAP) block is a commonly used technique in cesarean section operations due to its proven efficacy (4). The TAP block targets the transversus abdominis plane, which is an anatomical space situated between the internal oblique and transversus abdominis muscles, located superficially to the transversus abdominis muscle. This space contains the thoracolumbar nerves between the T10 and L1 vertebrae. By administering a local anesthetic agent between the internal oblique and transversus abdominis muscles, sensory blockade of the entire abdominal wall can be achieved (5). The erector spina plane (ESP) block is a paraspinal fascial plane block in which the needle is inserted between the erector spina muscle and the thoracic transverse processes, and a local anesthetic is administered that blocks the dorsal and ventral branches of the thoracic and abdominal spinal nerves (7). ESP block, first described by Mauricio Forrero et al. in 2016, is a new block with increasing popularity in postoperative pain management (6). Although it was first applied in treating thoracic neuropathic pain, many studies showing its efficacy in different surgeries have been published. ESP block provides both somatic and visceral analgesia (7-8). In this study, it was planned to compare the effectiveness of USG-guided TAP and ESP blocks on postoperative pain and to evaluate patient and surgeon satisfaction after the end of the surgical procedure in patients undergoing cesarean section under spinal anesthesia.

MATERIAL AND METHODS

The study was planned as single-center, prospective, double-blind, and randomized. Ethics committee approval of Harran University Faculty of Medicine Ethics Committee dated 15/02/2021 and numbered 2021.04/17 was obtained. Between 15/02/2021 and 15/02/2022, a total of 90 pregnant women aged 18-45 years, ASA II, who would undergo cesarean section under spinal anesthesia under elective conditions, were included. All patients were informed about the study and their written and verbal consents were obtained.

In the operation room, a vascular line was inserted with a 20G cannula, 0.9% NaCl infusion was started, and monitoring was performed. Patients were placed in the right or left lateral decubitus position to perform the intervention. After asepsis with an alcohol-based povidone-iodine solution, the skin was covered with a sterile drape. A 25 G pencil-tipped spinal needle was inserted into the spinal space at the T10-L1 interval, determined as the Tuffier line. After CSF flow was observed, 2 ml (10 mg) 0.5% hyperbaric bupivacaine was administered into the subarachnoid space, and the patient was placed in a supine position. The operating table was tilted 15 degrees to the left until the baby came out. The level of sensory block was determined by a 'pin-prick' test, and the operation was allowed when it reached the T4-6 level. Demographic data, vital signs (heart rate, non-invasive blood pressure measurement, oxygen saturation) of the patients were recorded at the beginning of surgery at 0. min. At the end of the surgery, the patients were randomly divided into 3 groups using the closed envelope technique:

Group T: Patients who will undergo TAP block.

Group E: Patients who will undergo ESP block.

Group K: Control group patients who will not be blocked and will only be subjected to patient control analgesia (PCA)

The responsible investigator performed all blocks applied to the patients. Ultrasound devices and linear probes were used for the blocks. Both blocks were performed bilaterally, and 40 ml of the local anesthetic mixture, 20 ml of 0.25% bupivacaine, and 0.5% lidocaine were injected on each side. Patients to undergo ESP block were placed in the right or left lateral decubitus position. Under USG guidance, the vertebrae were counted, and the T9 vertebra level was marked. After the necessary asepsis conditions were met, the linear USG probe was placed longitudinally lateral to the spinous process of the T9 vertebra. With a 22 G, 50 mm, insulated facet-type needle, 1 mL of the prepared local anesthetic solution was administered, and the location of the needle tip was checked. Then, the entire solution was injected into the area by aspiration at frequent intervals. Local anesthetic distribution was monitored by USG. The same procedure was performed on the other side. Patients who were to undergo a TAP block were placed in a supine position, and after the necessary asepsis conditions

were met, the linear USG probe was placed on the iliac crest perpendicular to the mid-axillary line. A 22 G, 100 mm, insulated facet-type needle was inserted with 1 mL of local anesthetic to confirm the needle location. The entire solution was then injected into the field by aspiration at frequent intervals. Local anesthetic distribution was monitored by USG. The same procedure was performed on the other side. At the end of the operation, all patients were administered tramadol 5mg/ml concentration in a volume of 100 mL, 20 mg bolus, without background dosage, 30 minutes locked time, and a 4-hour limit of 150 mg with a patient-controlled analgesia device. The VAS score was recorded by asking the severity of the pain by the nurse. In addition, at postoperative hours 0, 2, 4, 8, 12, and 24, the VAS scores of the patients, the amount of tramadol consumption and demand, blood pressure, heart rate and saturation values, nausea and vomiting, and other complaints were recorded by a nurse who did not know which group the patients were in. Patient and surgeon satisfaction were asked at the end of the 24th postoperative hour, and scores were recorded.

Statistical Method

In this study, the NCSS (Number Cruncher Statistical System) 2007 program was used for statistical analysis. Data were evaluated by various descriptive statistical methods. The conformity of the quantitative data to the normal distribution was examined using the Shapiro-Wilk test and graphical analysis. ANOVA and Bonferroni-adjusted pairwise comparisons were used to compare normally distributed quantitative variables among multiple groups. Kruskal-Wallis test and Dunn-Bonferroni test were used for quantitative variables that did not fit normally. Repeated measures ANOVA and Bonferroni-adjusted pairwise comparisons were used for intra-group comparisons of normally distributed quantitative variables. In intra-group comparisons of quantitative variables that did not fit the normal distribution, Friedman test and Wilcoxon signed-ranks test and Bonferroni corrected pairwise comparisons were performed. Fisher-Freeman-Halton exact test was used to compare qualitative data. Pearson correlation was used in the evaluation of the patient-surgery satisfaction relationship according to the groups. p<0.05 was accepted as statistical significance level and results with p-value less than 0.05 were considered statistically significant.

RESULTS

Ninety out of 97 patients who had elective cesarean section were included in this study, which was carried out in the operating room of Harran University Medical Faculty Hospital between 15/02/2021 and 15/02/2022, and 7 patients were excluded. All pregnant women participating in the study were at term.

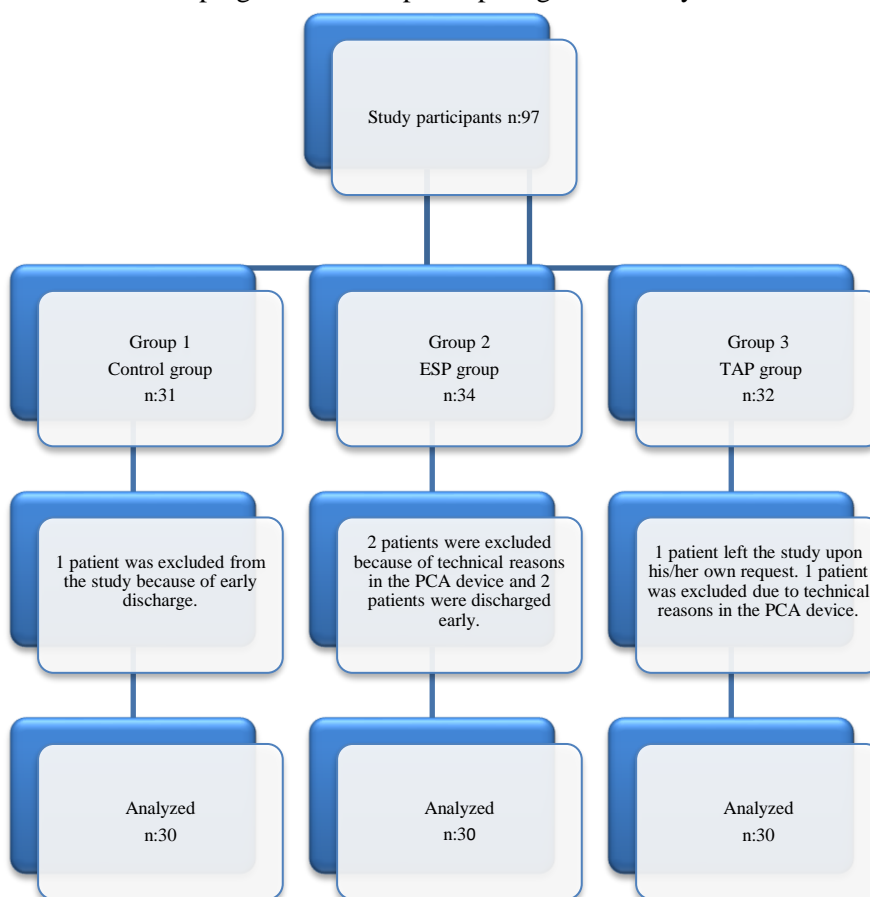


Figure-1: Flowchart

A statistically significant difference was found in the time taken for the first bolus dose between the groups (p=0.001; p<0.01). Pairwise comparisons revealed that the time elapsed in the K group was significantly lower than both the E and T groups (p=0.001; p=0.001; p<0.01).

Age, weight, height, comorbidities, number of previous cesarean sections, and duration of surgery were not statistically significantly different between the groups (p>0.05). The groups had no statistically significant difference in postoperative heart rate measurements.

In addition, when the study findings were analyzed, it was determined that there was no statistically significant difference in systolic blood pressure measurements between the groups. The groups had no statistically significant difference in diastolic blood pressure measurements.

Table-1: Evaluation of Demographic Data by Groups

		Group E	Group K	Group T	
Age	<i>Mean±Sd</i>	31.5±5.01	32.73±4.64	31.13±5.94	^a 0.465
	<i>Median (Min-Max)</i>	31 (22-41)	33 (25-44)	31 (20-41)	
Weight (kg)	<i>Mean±Sd</i>	77.07±12.81	81±10.20	77.57±12.40	^a 0.380
	<i>Median (Min-Max)</i>	75.5 (55-108)	79.5 (64-105)	74.5 (60-109)	
Height (cm)	<i>Mean±Sd</i>	160.23±4.38	162.07±3.58	162.43±4.87	^a 0.112
	<i>Median (Min-Max)</i>	160 (150-168)	162 (155-168)	163 (151-170)	
BMI	<i>Mean±Sd</i>	74.09±12.81	79.80±10.20	79.82±12.39	^a 0.380
	<i>Median (Min-Max)</i>	75.5 (58-95)	79.5 (64-100)	75.5 (60-109)	
Comorbidity	<i>Median (Min-Max)</i>	24 (%80.0)	21 (%70.0)	22 (%73.3)	^b 0.753
	Yes	6 (%20.0)	9 (%30.0)	8 (%26.7)	
	Asthma	0 (0)	1 (%11.1)	3 (%37.5)	^b 0.257
	Diabetes	3 (%50.0)	2 (%22.2)	1 (%12.5)	^b 0.360
	Hypertension	1 (%16.7)	2 (%22.2)	0 (0)	^b 0.446
	Cigarette	4 (%66.7)	2 (%22.2)	3 (%37.5)	^b 0.275
	Hyperthyroidism	0 (0)	1 (%11.1)	2 (%25.0)	^b 0.589
	Hypothyroidism	0 (0)	1 (%11.1)	0 (0)	^b 1.000
	Psoriasis	0 (0)	1 (%11.1)	0 (0)	^b 1.000
	Glaucoma	0 (0)	1 (%11.1)	0 (0)	^b 1.000
	Gastritis	0 (0)	0 (0)	1 (%12.5)	^b 0.609
Number of previous cesarean sections	<i>Mean±Ss</i>	3.67±1.52	3.42±1.53	3.19±1.36	^a 0.508
	<i>Median (Min-Max)</i>	4 (1-6)	4 (1-6)	4 (1-6)	
Surgical time (min)	<i>Mean±Sd</i>	50.3±12.56	47.7±11.19	50.47±11.07	^a 0.588
	<i>Median (Min-Max)</i>	47.5 (33-100)	45 (30-70)	50 (30-82)	

Abbreviations:^aOneway ANOVA Test,^bFisher Freeman Halton Tes, ^{*}p<0.01, BMI: Body mass index (BMI),Group E: Group Erector Spina Plane,Group K: Group Control,Group T: Group Transversus Abdominis Plane

Table-2: Evaluation of Postoperative VAS Scores by Groups

Postoperative VAS		Group E	Group K	Group T	
Hour 0	<i>Mean±Sd</i>	0.20±0.55	2.13±2.66	0.77±1.14	^d 0.002**
	<i>Median (Min-Max)</i>	0 (0-2)	0.5 (0-8)	0 (0-4)	
Hour 2	<i>Mean±Sd</i>	0.67±1.09	4.90±1.73	1.93±1.86	^d 0.001**
	<i>Median (Min-Max)</i>	0 (0-4)	4 (3-10)	2 (0-8)	
Hour 4	<i>Mean±Sd</i>	1.93±1.89	4.80±1.00	4.10±1.95	^a 0.001**
	<i>Median (Min-Max)</i>	2 (0-6)	5 (3-7)	4 (0-8)	
Hour 8	<i>Mean±Sd</i>	3.37±1.75	4.73±1.39	4.83±1.12	^a 0.001**
	<i>Median (Min-Max)</i>	4 (0-6)	5 (2-7)	5 (3-7)	
Hour 12	<i>Mean±Sd</i>	3.67±1.63	3.70±1.51	3.43±1.19	^a 0.742
	<i>Median (Min-Max)</i>	4 (0-8)	4 (0-6)	4 (0-6)	
Hour 24	<i>Mean±Sd</i>	2.93±1.78	3.47±1.63	2.77±1.25	^a 0.203
	<i>Median (Min-Max)</i>	4 (0-6)	3.5 (0-6)	3 (0-5)	

Abbreviations:^aOneway ANOVA Test,^dKruskal Wallis Test, ^{*}p<0.05, ^{**}p<0.01, VAS: Visual Analog Scale,Group E: Group Erector Spina Plane,Group K: Group Control, Group T: Group Transversus Abdominis Plane

According to the groups, there was a statistically significant difference between the patients' postoperative 0. and 2. hour VAS scores. As a result of the pairwise comparisons made to determine the difference, the postoperative 0. hour VAS scores of the patients in the K group (Group Control) were statistically significantly higher than those in the Group E (Group Erector Spina Plane) and T groups (Group Transversus Abdominis Plane) ($p=0.001$; $p<0.01$). Postoperative 2nd-hour VAS scores were significantly higher than those in the E and T groups ($p=0.001$; $p=0.001$; $p<0.01$).

There was a statistically significant difference between the patients' 4th and 8th-hour postoperative VAS scores according to the groups ($p=0.001$; $p<0.01$). As a result of pairwise comparisons made to determine the difference, the postoperative 4th-hour VAS scores of the patients in the E group were statistically significantly lower than those in the K and T groups ($p=0.001$; $p=0.001$; $p<0.01$). The postoperative 8th-hour VAS scores of the E group were statistically significantly lower than those of the K and T groups ($p=0.004$; $p=0.001$; $p<0.01$).

There was no statistically significant difference in the patients' postoperative 12th and 24th-hour VAS scores according to the groups ($p>0.05$).

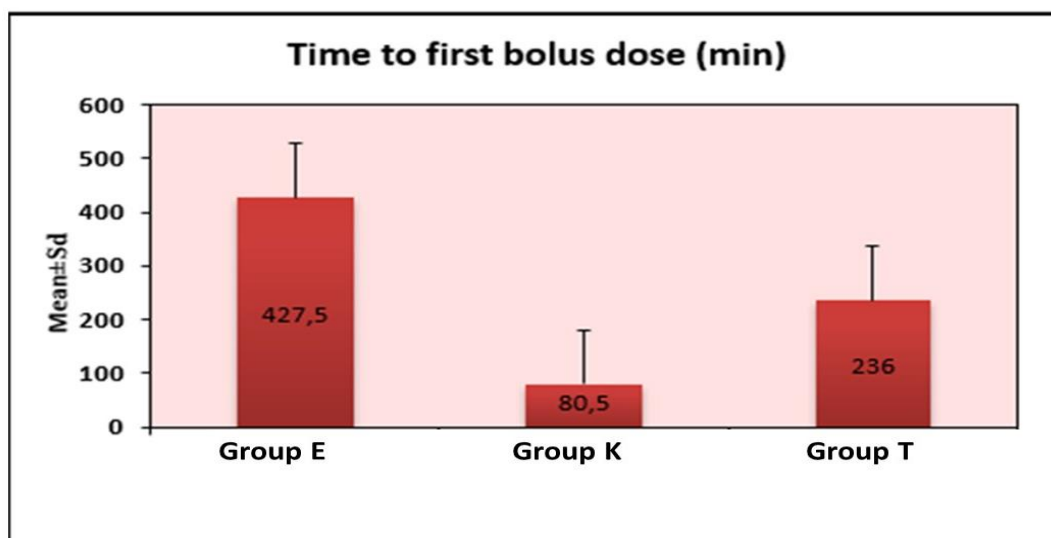


Figure-2: Distribution of the time taken for the first bolus dose by groups.

A statistically significant difference was found between the time taken for the first bolus dose according to the groups ($p=0.001$; $p<0.01$). As a result of the pairwise comparisons made to determine the source of the difference, the time elapsed in the K group was found to be statistically significantly lower than those in the E and T groups ($p=0.001$; $p=0.001$; $p<0.01$).

Table-3: Evaluation of Postoperative Tramadol Consumption by Groups

Postoperative Opioid		Group E	Group K	Group T	P
Hour 0 dose (mg)	Median (Min-Max)	0 (0-0)	0 (0-20)	20 (20-20)	^d 0.001**
Hour 2 dose (mg)	Median (Min-Max)	0 (0-20)	20 (0-40)	0 (0-40)	^d 0.001**
Hour 4 dose (mg)	Median (Min-Max)	0 (0-40)	20 (0-40)	20 (0-40)	^d 0.001**
Hour 8 dose (mg)	Median (Min-Max)	20 (0-40)	20 (0-40)	20 (20-40)	^d 0.001**
Hour 12 dose (mg)	Median (Min-Max)	20 (0-40)	20 (0-20)	20 (0-40)	^d 0.024*
Hour 24 dose (mg)	Median (Min-Max)	20 (0-40)	20 (0-20)	0 (0-40)	^d 0.080

*Abbreviations: Post hoc test (Tamhane),^dKruskal Wallis Test, ** $p<0.01$, Group E: Group Erector Spina Plane, Group K: Group Control, Group T: Group Transversus Abdominis Plane*

When the data in Table 3 were analyzed, it was determined that there was a statistically significant difference between the 0th and 2nd hour tramadol consumptions of the subjects according to the groups ($p=0.001$; $p<0.01$). As a result of the pairwise comparisons made to determine the source of the difference, it was determined that the 0th and 2nd hour tramadol consumption of the subjects in the K group was significantly higher than the subjects in the E and T groups ($p=0.001$; $p=0.001$; $p<0.01$).

It was determined that there was a statistically significant difference between the 4th hour tramadol consumption of the cases according to the groups ($p=0.001$; $p<0.01$). As a result of the pairwise comparisons made to determine the source of the difference, it was determined that the 4th hour tramadol consumption of

the subjects in the E group was significantly lower than the subjects in the K and T groups ($p=0.001$; $p=0.002$; $p<0.01$).

It was determined that there was a statistically significant difference between the 8th hour tramadol consumption of the subjects according to the groups ($p=0.001$; $p<0.01$). As a result of the pairwise comparisons made to determine the source of the difference, the 8th hour tramadol consumption of the subjects in the T group was found to be significantly higher than the subjects in the E and K groups ($p=0.001$; $p=0.013$; $p<0.05$).

It was determined that there was a statistically significant difference between the 12th hour tramadol consumption of the cases according to the groups ($p=0.024$; $p<0.05$). As a result of the pairwise comparisons made to determine the source of the difference, it was determined that the 12th hour tramadol consumption of the subjects in the E group was significantly higher than the subjects in the K group ($p=0.019$; $p<0.05$). In addition, it was determined that the 24th hour tramadol consumption of the patients did not show a statistically significant difference according to the groups ($p>0.05$).

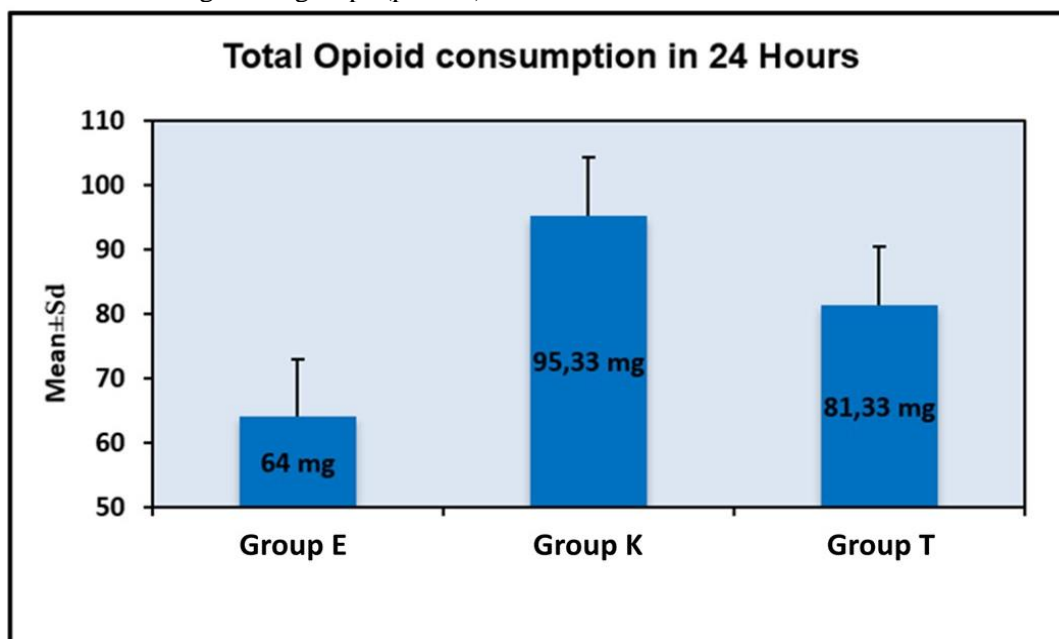


Figure-3: Distribution of total tramadol consumed in 24 hours by groups

When Figure 3 was examined, it was determined that there was a statistically significant difference between the total amount of tramadol taken by the patients in the postoperative 24 hours according to the groups ($p=0.001$; $p<0.01$). As a result of the pairwise comparisons made to determine the source of the difference, it was determined that the total amount of tramadol taken by the E group patients in 24 hours was significantly lower than the K and T groups ($p=0.001$; $p=0.012$; $p<0.05$).

Intraoperative and postoperative side effects were not statistically significantly different between the groups ($p>0.05$). A statistically significant difference was found in the time taken for the first bolus dose between the groups ($p=0.001$; $p<0.01$). Pairwise comparisons revealed that the time elapsed in the K group was significantly lower than both the E and T groups ($p=0.001$; $p=0.001$; $p<0.01$).

Table-4: Evaluation of Intraoperative and Postoperative Side Effects by Groups

		Group E	Group K	Group T	P
Intraoperative side effects	No	16 (53.3)	20 (66.7)	19 (63.3)	^b 0.631
	Yes	14 (46.7)	10 (33.3)	11 (36.7)	
	Nausea	2 (14.3)	1 (10.0)	0 (0)	^b 0.622
	Hypotension	12 (85.7)	10 (100)	11 (100)	^b 0.335
	Bradycardia	1 (7.1)	0 (0)	0 (0)	^b 1.000
Postoperative side effects	Drowsiness	2 (66.7)	2 (100)	3 (75.0)	^b 1.000
	Nausea and vomiting	0 (0)	0 (0)	1 (25.0)	
	Dizziness	1 (33.3)	0 (0)	0 (0)	

Abbreviations: ^bFisher Freeman Halton Test, ^{**} $p<0.01$, VAS: Visual Analog Scale, Group E: Group Erector Spina Plane, Group K: Group Control, Group T: Group Transversus Abdominis Plane

Table-5: Evaluation of Patient and Surgeon Satisfaction by Groups

		Group E	Group K	Group T	P
Patient satisfaction	Mean±Sd	4.23±0.73	1.87±0.94	3.57±0.77	^a 0.001**
	Median (Min-Max)	4 (3-5)	2 (1-4)	4 (2-5)	
Surgeon satisfaction	Mean±Sd	4.27±0.74	1.80±0.81	3.57±0.82	^a 0.001**
	Median (Min-Max)	4 (3-5)	2 (1-3)	4 (2-5)	
Patient-Surgery Satisfaction relationship					
	r	0.905	0.923	0.729	
	p	0.001**	0.001**	0.001**	

Abbreviations:^aOneway ANOVA Test, r: Pearson Correlation Coefficient, **p<0.01, Group E: Group Erector Spina Plane, Group K: Group Control, Group T: Group Transversus Abdominis Plane

DISCUSSION

Multimodal analgesia is one of the most effective and up-to-date approaches to treating postoperative pain. This approach, which involves the combined administration of opioid or non-opioid analgesics with regional methods, reduces opioid consumption and reduces the systemic side effects related to opioids, reduces costs by shortening the length of hospital stay with early recovery (9-12). The results of this study showed that the time to first analgesic administration was statistically significantly lower in the TAP group than in the ESP group. In addition, it was determined that the consumption of tramadol at the postoperative 0,2,4, 8 and 24 hours was statistically significantly lower in the ESP group compared to the other groups. In addition, it was determined that patient satisfaction was higher in the ESP group than in the TAP and control groups. While the TAP block provides sensory blockade of the entire abdominal wall, the ESP block provides both somatic and visceral analgesia by blocking both the dorsal and ventral branches of the thoracic and abdominal spinal nerves. This mechanism explains the effectiveness of the ESP block over TAP.

IV tramadol can be used effectively in combination with non-opioid drugs (13). In many studies comparing tramadol and morphine administered with PCA devices, it was found that both drugs provided adequate analgesia, but the rate of nausea, vomiting, sedation, and respiratory depression was higher in patients treated with morphine (14-16). Illett et al. reported that short-term tramadol use after a cesarean section is very effective and safe in terms of analgesia and is compatible with breastfeeding (17). In another study conducted on 120 pregnant women, continuous opioid infusion and PCA and opioid administration were compared, and lower incidence of nausea and vomiting, greater patient satisfaction, and more effective pain control were observed in the group using PCA devices (18). In our study, we applied tramadol to our patients with PCA devices for the first 24 hours. While none of our patients had respiratory depression and sedation, nausea-vomiting rates were similar to the tramadol groups of these studies.

Using LA combinations in regional anesthesia reduces the toxicity risks that may occur due to using these drugs alone in higher dosages (19-20). TAP block was first described by Rafi in 2001 as a local anesthetic injection into the anatomical area determined as the Petit triangle and then developed by Hebbard et al. in 2007 by applying USG-guided (21-22). It has been reported that the USG-guided block is more reliable and effective than the anatomical marking technique, reducing the risk of complications.

Many studies are investigating the efficacy of TAP block for postoperative pain control after cesarean section in the literature. Some of these studies were performed with general anesthesia (23-24) and most of them compared the effectiveness of TAP block in cesarean section operations performed with spinal anesthesia (25-26). In these studies, with both anesthesia techniques, TAP block has been shown to be highly effective in postoperative analgesia

In another study (25) with 60 patients who underwent cesarean section under spinal anesthesia, the analgesic efficacy of TAP block after cesarean section was evaluated, 15 ml of 0.5% ropivacaine was administered to the TAP block group, and 15 ml 0.9% saline was applied to the control group and the salvage analgesia time was found to be 593 minutes. In our study, unlike this, the first tramadol requirement was 236 minutes on average in the TAP block group. We think that this difference is because the local anesthetic agent used is different.

The ESP block, described in 2016 by Mauricio Forrero et al. (6), is a new block in postoperative pain management that is growing in popularity. Although it was first applied in treating thoracic neuropathic pain, many studies have been published showing its effectiveness in different surgeries. The number of studies showing the effectiveness of ESP block after cesarean section operation is very limited.

In a study conducted by Malavat et al. (27) comparing TAP block and ESP block in 60 patients undergoing elective cesarean section under spinal anesthesia, it was found that ESP block provided longer analgesia

compared to TAP block. The mean time to first rescue analgesia was 43.53 hours for ESP block and 12.07 hours for TAP block. Furthermore, the total analgesic requirement was significantly lower in the ESP group compared to the TAP group. In the study, both groups received a bilateral administration of 0.2% ropivacaine at a dose of 0.2 ml/kg as a local anesthetic. Additionally, 15 mg of intravenous diclofenac was administered as an analgesic. In a study conducted by Boules et al. (28) on 60 patients who delivered elective cesarean section under spinal anesthesia, the effect of TAP and ESP blocks on postoperative pain was investigated. In this study, 20 mL of 0.25% bupivacaine was used as a local anesthetic solution. Median tramadol consumption in the first 24 hours was significantly higher in the TAP group than in the ESP group (125 mg [100 - 150] and 100 mg [75 - 100]).

In a meta-analysis, Wang et al. (29) examined studies on local anesthetic techniques for postoperative pain control after cesarean section. A total of 5039 patients were included in 68 studies, and pain control and analgesia consumption were investigated in these patients who underwent six local anesthesia techniques, including TAP block, ilioinguinal and iliohypogastric nerve block, quadratus lumborum blocks, transversalis fascia plan block, ESP block, and wound infiltration. It has been shown that fascial blocks and wound infiltration techniques reduce opioid consumption within the first 24-48 hours. In particular, the most effective method of TAP block has been found. However, since there are numerical differences between the methods in the study and there are differences in local anesthetic doses, we think that this study provides insufficient data, especially in terms of ESP block. A study of 60 patients who underwent abdominal hysterectomy showed that total opioid consumption in the first 24 hours was significantly higher in the control group than in the group with ESP block (30). A similar ten-disease case report published by Altınpulluk et al. (31) revealed that ESP block is effective in postoperative analgesia in patients undergoing abdominal hysterectomy.

One of the biggest advantages of ESP block is that the risk of complications is low because the injection site is quite far from the pleura, neural structures, and major vascular structures (32) (33). The first complication reported after ESP block is pneumothorax (34). In a case report published by Selvi et al. (35), a 29-year-old patient reported unexpected motor weakness as a side effect of an epirector spina plane block after a cesarean section. The incidence of TAP block complications is also considered to be low. Complications such as visceral organ injuries, intraperitoneal injection, and transient femoral nerve palsy have been reported in several publications (36-37).

Nausea and vomiting are common side effects of opioid agents and significantly reduce patient comfort. A published meta-analysis found that the rate of nausea and vomiting in 1018 patients who underwent ESP block for postoperative analgesia in breast and thoracic surgery was significantly reduced in the ESP block group (38). On the other hand, in a study conducted by Aksu et al. (39) comparing ESP block and control groups, no significant difference was found in terms of postoperative nausea and vomiting. In a study comparing TAP and ESP blocks in terms of postoperative analgesia after total abdominal hysterectomy, the incidence of postoperative nausea and vomiting was higher in the TAP block group than in the ESP block group. However, it was not statistically significant (40). In our study, in parallel with these studies, there was no statistically significant difference between the groups regarding postoperative nausea, vomiting, and other side effects. We did not come across a similar study that evaluated all complication rates in the literature. In this respect, we think that our work is specific.

This is the first study in which the postoperative analgesic efficacy of patients classified as ESP block, TAP block, and control group in cesarean section operations was compared, unlike the studies in the literature.

After all, we observed that ESP and TAP blocks provided effective analgesia compared to the control group; ESP block provided more effective analgesia than TAP block and increased patient satisfaction.

Study limitations

The limitations of our study are that patients were followed up only for the first 24 hours in the postoperative period, and therefore we could not evaluate the long-term pain scores and complications of the methods used, limited data on the efficacy of ESP block for postoperative analgesia after cesarean delivery, and we did not perform dermatomal examination to determine the level of sensory block due to the persistence of spinal anesthesia effects.

Conclusion

Our study compared the analgesic efficacy of TAP and ESP blocks applied for postoperative pain treatment after cesarean section operations. We found that ESP block prolonged the time required for the first analgesic compared to TAP block, significantly reduced postoperative tramadol consumption in the first 24 hours, lower VAS scores, and increased patient and surgeon satisfaction. We believe that in the future, USG-guided ESP block will be one of the analgesia methods that can be used, especially in cesarean section and other lower

abdominal surgeries, as knowledge and experience increase. For this reason, we think that more studies are needed in this regard.

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Ethical Approval: The study protocol was approved by the Harran University Faculty of Medicine Ethics Committee no: 2021.04/17

Author Contributions: Concept: MKE, MAB Literature Review: MAB, MKE Design: MKE, MAB Data acquisition: MAB, MKE Analysis and interpretation: MKE, MAB Writing manuscript: MAB, MKE Critical revision of manuscript: MKE, MAB

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Original Article

The Role of Amino Acids in Knee Osteoarthritis

Diz Osteoartritinde Amino Asitlerin Rolü

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Abstract

Background: Osteoarthritis is an important public health problem and the most common musculoskeletal disease in the World. The pathogenesis and etiology of osteoarthritis is still unclear. We aimed to make an amino acids analysis that will contribute to the pathogenesis, diagnosis and treatment of knee osteoarthritis.

Materail and Methods:The study included according to the radiological grading scale of Kellgren-Lawrence, 30 patients at Grade 1-2; Group 1 (Grade 1-2), 30 patients at Grade 3-4; Group 2 (Grade 3-4), 30 healthy controls; Group 3. We compared between groups age, sex, body mass index, Western Ontario and McMaster Universities, Short form-36 findings, and plasma-free amino acid levels.

Results:A comparison of the serum norvaline, leucine, isoleucine, allo-isoleucine, cystathionine, phenylalanine, 1-methyl hystidine, arginine, alanine, cystine, valine, threonine, and tryptophane levels of the knee osteoarthritis and control groups compared a statistically significant difference (p=0.001, p=0.001, p=0.001, p=0.001, p=0.044, p=0.003, p=0.001, p=0.035, p=0.010, p=0.011, p=0.001, p=0.001, p=0.003).

Conclusions

We consider that, norvaline leucine; isoleucine, allo-isoleucine, cystathionine, phenylalanine, 1-methyl hystidine, arginine, alanine, cystine, valine, threonine, and tryptophane amino acids could be, as potential systemic serum biomarkers for diagnosis of knee osteoarthritis.

Key words: Knee Osteoarthritis, Amino Acid Levels, Kellgren-Lawrence

ÖZ

Amaç: Osteoartrit dünyada en sık görülen kas iskelet sistemi hastalığı olup önemli bir halka sağlığı sorunudur. Osteoartritin patogenezi ve etiolojisi hala belirsizdir. Diz osteoartritinin patogenezi, tanı ve tedavisine katkı sağlayacak bir Amino asit analizi yapmayı amaçladık.**Gereç ve Yöntem:** Çalışmaya, Kellgren-Lawrence radyolojik evreleme ölçeğine göre grup 1, evre 1-2 olan 30 hasta; grup 2, evre 3-4 olan 30 hasta; grup 3, 30 sağlıklı kontrol dahil edildi. Gruplar arasında yaş, cinsiyet, vücut kitle indeksi, Western Ontario ve McMaster Üniversiteleri Osteoartrit İndeksi, Short form-36 ve plazma serbest amino asit düzeylerini karşılaştırıldı.**Bulgular:** Diz osteoartritli ve kontrol gruplarının serum norvalin, lösin, izolösin, allo-izolösin, sistatyonin, fenilalanin, 1-metil histidin, arginin, alanin, sistin, valin, treonin ve triptofan düzeyleri karşılaştırıldığında istatistiksel olarak anlamlı fark bulundu (p=0.001, p=0.001, p=0.001, p=0.001, p=0.044, p=0.003, p=0.001, p=0.035, p=0.010, p=0.011, p=0.001, p=0.001, p=0.003).**Sonuçlar:** Norvalin, lösin izolösin, allo-izolösin, sistatyonin, fenilalanin, 1-metil histidin, arginin, alanin, sistin, valin, treonin ve triptofan amino asitlerinin, diz osteoartritinin tanısında potansiyel sistemik serum biyobelirteçleri olabileceğini düşünüyoruz.

Anahtar Kelimeler: Diz Osteoartriti, Amino Asit, Kellgren-Lawrence

Highlights

- No study in which all amino acids were examined, in the literature.
- Norvaline, leucine, isoleucine, allo-isoleucine, cystathionine, phenylalanine, MHIS1, arginine, alanine, cystine, valine, threonine and tryptophan levels were low in knee OA.
- These amino acids may have an important role in the etiogenesis and pathogenesis of knee OA.
- These AAs can be used as potential systemic serum biomarkers.

Introduction

Osteoarthritis (OA) is a degenerative disease that results in progressive cartilage destruction in heavily loaded joints as a result of certain genetic, mechanical, and biochemical factors (1). It is an important public health problem and the most common musculoskeletal disease in the world (2). It is most commonly observed in the knee joint and causes pain and disability (3,4). The incidence of OA increases by age. Particularly, It is more common in women over 50 years old than men (5). In the USA, it is predicted that 14 million people, including 3 millions of ethnic minorities, have a symptomatic knee OA (6).

The pathogenesis and etiology of OA is still unclear. Some genetic and environmental factors such as natural immune system, occupational exposure, obesity, ethnic origin and physical activity play a significant role in OA pathogenesis (7). There is no efficient approach to stop, eliminate or delay OA's progress.

Metabolism has an important effect on the development and progression of many diseases (8). In recent years, metabolomics (Lipids, small peptides, amino acids (AA), vitamins and nucleic acids) analyses have been performed to determine OA phenotypes and to examine biochemical indicators (9,10). Analysing metabolisms of body AAs under physiological and pathological conditions contributes to defining pathological mechanisms of some diseases and diagnosing and treating them (11).

We aimed to analyze serum free AA that will contribute to the diagnosis, prevention and treatment of knee OA. This study examines the relationship between radiological severity and serum free AA levels in patients with knee OA.

Materials and Methods

Sample , Ethics

The study was approved by the Ethics Committee of Clinical Research of Harran University (HRU/20.06.25). Written consent was obtained from all participants.

This study were include 60 patients with bilateral knee pain who were diagnosed with primary knee OA according to American College of Rheumatology (ACR) criteria and 30 healthy controls. Patients were evaluated according to the radiologically according to the Kellgren-Lawrence (K-L) scale divided into two groups and healthy controls. Group 1 included patients KL grade 1-2, group 2 included KL grade 3-4 and group 3 included healthy controls.

The patients who had primary knee OA but were younger than 40 years or older than 60 years, the patients with systemic inflammatory or autoimmune diseases, the patients who have had glucocorticoid injection into their knee joint in the last three months or hyaluronic acid injection in the last six months, the patients who underwent total knee arthroplasty or other knee surgeries, and the patients with malignancies exclude in the study.

Data collection

Age and gender were recorded. Body mass index (BMI) was calculated. Clinical severity was determined according to the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), while overall quality of life was measured using the Short Form-36 (SF-36) questionnaire.

5-ml blood samples were taken from patient groups and healthy controls into edta tubes. The collected samples were taken to a biochemistry laboratory in cool-packs. They were centrifuged at 5000 rpm for 10 mins. The supernatant body in the tubes was gently transferred into Eppendorf tubes through pipettes. Each plasma sample was first named and numbered and then transfused into numbered tubes. The samples were kept at -80°C till the day the study was conducted.

JASEM amino acid kits were used in the study. To analyse plasma-free AA profile, the samples removed from -80°C refrigerator were cooled at room temperature. Then, 50µl was taken into sterile Eppendorf tubes. Onto these tubes, 50µl of Internal Standard solution in amino acid kits were added. Each tube was carefully vortexed at 5 seconds. Later, 700µl of Reagent-1 in kits were added into vortexed tubes. The tubes were carefully re-vortexed at 15 seconds. The re-vortexed tubes were centrifuged at 3000 rpm for 5 mins. The supernatant body of the samples was gently taken from centrifuged tubes and transfused into HPLC vials through sterile pipettes. Then, for analysis, they were placed onto the tray in HPLC part of LC-MS/MS device (Shimadzu 8045, Japan) and scanned. As mobile phase, Mobile Phase-A and Mobile Phase-B in AA kits were used. Restek LC Columns was used as column.

Statistical analysis

SPSS 22.0 software (SPSS® for Windows Chicago, IL, USA) was used for statistical analysis. An evaluation of the distribution of the numerical data was performed using the Shapiro-Wilk test. When the distribution of the numerical data was normal or skewed, an independent-sample t-test or Mann-Whitney U test was used,

respectively. A Chi-Square test was used to compare categorical data. Results with a p value of <0.05 were considered statistically significant.

Results

Average ages and BMI of the groups are presented in **Table 1**. Average ages of group 1, group 2 and group 3 are 52.26±5.43; 53.20±4.87; 45.56±3.92 years. BMI of the groups are 33.15±5.86 kg/m²; 35.37±6.11 kg/m²; 27.64±4.67 kg/m², respectively. There was a statistically significant difference age and BMI were lower in the control group when compared to patient groups. (p<0.005, p<0.005).

Group 1 include 27 (90%) women and 3 (10%) men. Group 2 included 26 (86.67%) women and 4 (13.33%) men. Group 3 had 10 (33.33%) women and 20 (66.67%) men. While the ratio of women was higher in patient groups, the ratio of men was higher in healthy controls. There was a statistically significant difference (p<0.005). Comparisons of gender among groups are presented in **Table 1**.

Table 1. Age, BMI and gender in groups

	Group 1	Group 2	Group 3	p
Age(years)	52.26±5.43	53.20±4.87	45.56±3.92	0.001
BMI(kg/m²)	33.15±5.86	35.37±6.11	27.64±4.67	0.001
Gender				
Female	27(90%)	26(86.67%)	10(33.33%)	0.001
Male	3(10%)	4(13.33%)	20(66.67%)	

WOMAC index and SF-36 data are presented in Table 2. WOMAC index analysis was not conducted for healthy controls. However, WOMAC score was found to be 49.33±22.28 in Group 1 and 57.75±17.19 in group 2. WOMAC scores weren't, significant difference between group 1 and group 2 (p=0.139). The difference between the groups was significant according to the findings of subgroups of SF-36 such as physical role limitations, emotional role limitations, social functionality, physical functionality, vitality, general mental health, pain and general health perception (p<0.005, p<0.005, p< 0.005, p<0.005, p<0.005, p<0.005, p<0.050, p<0.050 respectively). It was found that SF-36 findings were higher in healthy controls than in patient groups with relatively lower scores.

Table 2.WOMAC total score and SF-36 subgroup scores

	Group 1	Group 2	Group 3	p
WOMAC	49.33±22.28	57.75±17.19	-	0.139
SF-36 Physical functioning	54, 75±24, 84	33, 16±19, 27	86, 00±26, 40	0.001
SF-36 Vitality	43, 66±20, 59	40, 16±15, 72	64, 33±22, 15	0.001
SF-36 Mental health	55, 86 ±1, 71	49, 73±17, 40	68, 26±18, 28	0.001
SF-36 Pain	45, 32 ± 22, 57	32, 42±22, 71	77, 41±22, 17	0.001
SF-36 General health perception	39,16 ± 17.37	34,75±15,26	62, 66±14, 12	0.001
SF-36 Role limitations (emotional problems)	37.77 ± 45.26	25.55±35.75	88.88±28.14	0.001
SF-36 Role limitations (physical problems)	39.16±42.89	25.83±33.78	85.83 ±29.12	0.001
SF-36 Social functioning	63.81±23.29	55.75±27.66	87.50±19.42	0.001

The analysis on AA levels in knee osteoarthritis which are significant presented in **Table 3**. The analysis on AA levels in knee osteoarthritis which are significant presented in **Table 3**. Regarding levels of norvaline, leucine, isoleucine, allo-isoleucine, cystathionine, phenylalanine, MHIS1, arginine, alanine, cystine, valine, threonine, and tryptophane, significant differences were observed among groups (p<0.001, p<0.001, p<0.001, p<0.001, p=0.044, p=0.003, p<0.00, p=0.035, p=0.010, p=0.011, p<0.001, p<0.001, p=0.006, respectively). When the difference among groups was examined, it was seen that levels of all parameters were lower in patient groups than those of healthy controls. However, for other AAs examined in the study, statistically significant difference was not observed among groups. Findings for these AAs are also presented in **Table 4**.

Table 3. AA's, which is a significant difference between groups

	Group 1	Group 2	Group 3	p
Norvaline	4.53±1.07	4.34±1.14	7.27±2.52	0.001^a
Leucine	190.12±53.23	185.72±43.25	268.27±99.76	0.001^b
Isoleucine	61.63±24.04	63.29±22.60	95.49±38.14	0.001^c
Allo-isoleucine	22.81±8.01	22.88±7.61	34.84±14.00	0.001^d
Cystathionine	0.87±0.45	0.93±0.47	1.25±0.76	0.044^e
Phenylalanine	86.48±27.81	86.51±17.07	109.84±31.80	0.003^f
Mhis1	7.23±3.67	7.18±3.18	13.69±9.15	0.001^g
Arginine	51.17±30.97	53.65±35.78	80.82±50.23	0.035^h
Alanine	381.05±117.42	424.48±120.16	498.55±166.49	0, 010ⁱ
Cystine	35.92±18.44	37.59±24.56	50.62±18.09	0, 011ⁱ
Valine	231.48±69.43	228.89±64.88	328.14±100.19	0, 001^j
Threonine	133.00±40.96	118.41±59.95	198.12±97.09	0.001^k
Tryptophane	65.20±19.84	67.20±17.62	83.42±27.46	0.006^l

Abberivations:^asignificant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^bsignificant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^csignificant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^d significant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^esignificant difference was observed between group 3 and group 1 and group 2 (p=0.005, p=0.001), ^f significant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^g significant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^h significant difference was observed between group 3 and group 1 and group 2 (p=0.007, p<0.00) ⁱ significant difference was observed between group 3 and group 1 and group 2 (p=0.003, p=0.001), ^j significant difference was observed between group 3 and group 1 and group 2 (p=0.023, p=0.031), ^k significant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.001), ^l significant difference was observed between group 3 and group 1 and group 2 (p=0.001, p=0.002)

Table 4. AAs with no significant difference between groups

	Group 1	Group 2	Group 3	p
Aspartic acid	18.95±7.29	16.11±6.75	21.41±10.13	0.071
Carnosine	0.84±0.82	0.88±1.08	2.53±4.72	0.530
Ethanolamine	11.30±3.95	11.01±3.45	10.68±5.73	0.703
Gaba	0.26±0.15	0.24±0.11	0.27±0.16	0.984
Homocitrullin	2.03±1.88	1.98±1.29	2.71±1.93	0.212
Trans_4_OHProline	6.20±2.82	6.79±3.30	6.06±2.13	0.699
Orthophosphorylethanolamine	12.52±10.11	12.96±12.01	10.59±8.85	0.754
Glutamine	749.18±172.47	720.81±117.62	800.12±203.56	0.187
Glutamic acid	73.63±36.65	80.37±28.87	89.19±51.68	0.428
Glycine	200.26±147.57	223.52±93.79	216.59±138.12	0.352
Histidine	134.19±62.17	137.09±57.66	161.97±64.62	0.168
Lysine	201.78±41.29	208.48±49.04	243.69±76.51	0.053
Methionine	35.74±9.80	34.95±6.93	43.49±17.16	0.172
Ornithine	184.41±54.96	192.97±57.33	205.99±91.92	0.802
Proline	419.72±222.51	450.03±175.31	471.36±246.74	0.427
Serine	133.03±55.57	130.04±43.50	146.05±72.88	0.813
Taurine	44.70±16.95	46.75±18.10	46.39±22.80	0.878
4-OH Proline	7.79±3.78	8.82±4.13	7.38±2.77	0.334
5-OH-Lysine	1.20±1.75	1.04±0.58	1.26±1.11	0.388
Asparagine	90.86±24.36	94.50±23.49	95.80±29.60	0.889
Citrulline	43.64±16.50	42.21±13.69	51.23±18.06	0.162
Tyrosine	123.83±39.37	130.09±30.83	143.42±44.78	0.123
MHIS3	10.63±10.70	8.30±9.05	16.11±17.81	0.070

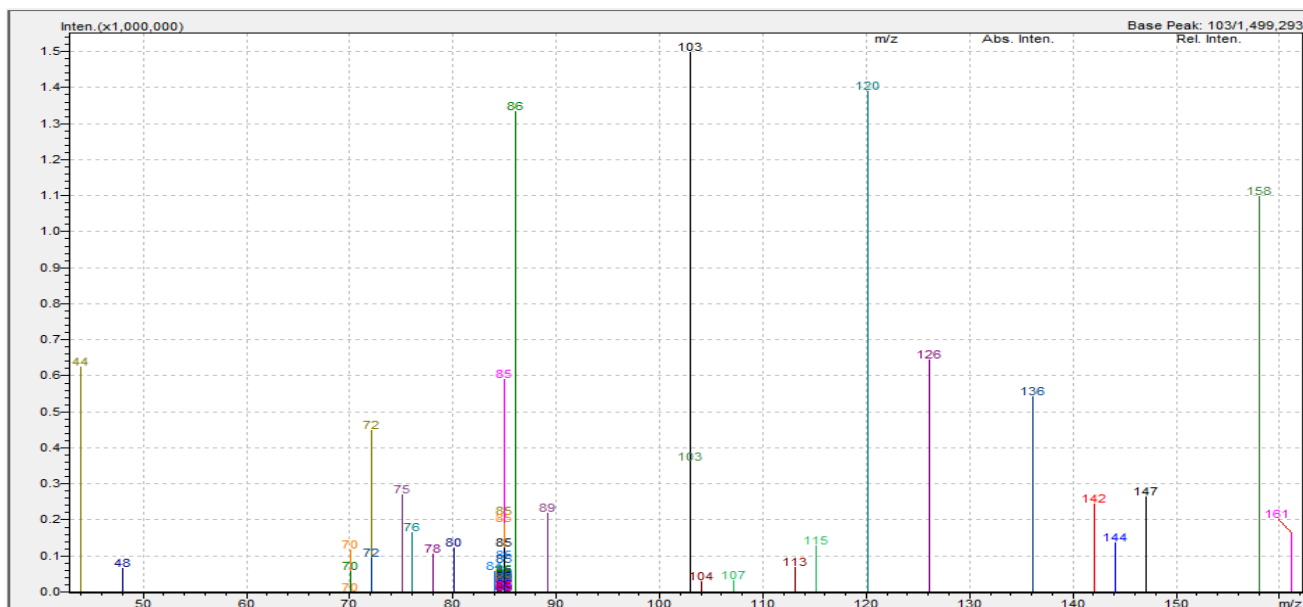


Figure 1.LC-MS/MS analysis parameters

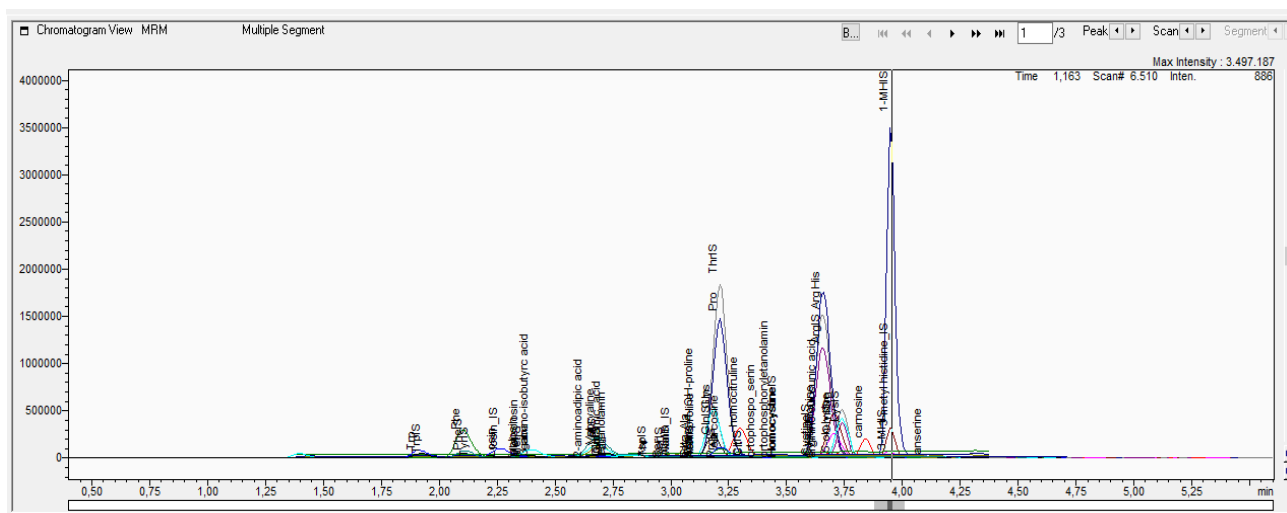


Figure 2.LC-MS/MS analysis parameters peak image

Discussion

In this study, serum norvaline, leucine, isoleucine, allo-isoleucine, cystathionine, phenylalanine, 1-methyl histidine (MHIS1), arginine, alanine, cystine, valine, threonine and tryptophan levels were low in knee osteoarthritis. It can be thought that the deficiency of these amino acids may be effective in the etiology and pathology of knee OA.

Comparison of our data with other studies is difficult because of the small number of studies on AA in knee OA.

In a recent study, amino acids such as arginine, asparagine, leucine, phenylalanine and serine were high (12). We found the opposite in our study. This may be due to the fact that the other study included hip osteoarthritis. This may be due to the difference in the pathophysiology of hip OA and knee OA.

The study suggested that combined supplementation of allopurinol and L-arginine significantly inhibited inflammatory markers and these supplements could be very effective in OA cases (13). It has been reported that OA patients had lower arginine concentrations in their plasma, arginine / asymmetric dimethyl arginine and higher symmetrical dimethylarginine concentrations compared to healthy controls (14). Similarly, our study showed that lower levels of arginine in the patient groups. The Arginine supplementation can be effective.

Carnitine is a quaternary ammonium cation synthesized in the liver and kidney from the amino acids lysine and methionine; in a study concluded that supplementation improved the clinic in women with OA (15). We

did not observe any difference between the study groups for lysine and methionine amino acid levels. The lack of difference does not mean that it is not be used as a supplement.

A study reported that ratio of the branched-chain amino acids (BCAA; valine, leucine and isoleucine) to histidine were associated with knee OA and that valine and isoleucine levels increased in knee OA (16). Another study showed that increased cytokine levels resulting from an increase in BCAA concentration increase the rate of joint collagen degradation leading to OA (17). In contrast to the studies in literature, the concentrations of BCAAs such as valine, leucine and isoleucine were significantly decreased in patients with knee OA when compared to healthy controls in our study. This can be due to the differences between the material and method in the studies.

It is thought that the increase in glycine, proline and leucine concentrations increases the synthesis of type II collagen and thus the joint cartilage matrix is regenerated (18). In our study, glycine, proline and leucine levels were higher in the healthy group. This result supports the literature.

Threonine, homoserine, and allotreonine concentrations are increase after mechanical overload (19). In our study, glycine, serine and threonine concentrations was increase in patient groups with higher body mass index compared to healthy controls. However, glycine and serine concentrations was not statistically significant difference between the patient groups and the control group. However, plasma threonine concentration was found to be lower in both patient groups compared to the control group.

While 4-OH proline, glycine and histidine levels decreased, tryptophan levels increased in OA patients compared to healthy controls in a study (20). However, 4-OH proline, glycine and histidine levels did not change in our study, tryptophan levels were found to be lower in the patient groups. This is due to the differences between the material and method in the studies.

Kinurenic acid which is a metabolite of tryptophan, is thought to contribute to chronic inflammation in OA (21). Contrary to the study in literature, plasma tryptophane levels were found to be lower in patients with knee OA in our study.

Glutamate and aspartate levels in synovial fluid were 54 and 28 times higher in patients with synovitis than healthy controls. Therefore, it is considered that glutamate and aspartate contribute to arthritis pathogenesis in humans (22). Further studies indicate that glutamate and aspartate have significant impacts on activating inflammatory mediators such as (RANTES) protein, IL-8, TNF- α , which are expressed and secreted in synovial liquid of patients with inflammatory arthropathies including active rheumatoid arthritis, acute gout and symptomatic OA (23). In our study, although plasma aspartic acid and glutamate concentration was lower in patient groups than control group, the difference was not meaningful. This can be differences only plasma free AA levels were examined in our study. However, a combined study on the levels of synovial liquid or intra-articular tissues could have presented more useful findings.

Aging is the most powerful risk factor for OA. But, it is not an enough cause for OA (24). In our study, average age was higer in patient groups when compared to control group, confirming other studies in literature which argue that aging increases osteoarthritis.

There is a relationship between the incidence and prevalence of knee OA with BMI (25). Similarly, another study showed that obese women with a BMI of 30 to 35 kg / m² had a four-fold higher risk of OA than non-obese women (26). Consistent with other studies in the literature, our study showed higher BMI in patient groups.

The OA is more common in men younger than 50 years old, its prevalence increases in women older than 50 years old (27). Therefore, knee OA prevalence is higher in women than men (6). However, the incidence and prevalence of OA become equal for both men and women at around 80 years old (28). Chu et al. found that knee OA prevalence is higher in women in all grades of the disease (29). In our study, gender distribution was observed difference between control group and patient groups which confirmed previous studies. Whereas the ratio of women was higher in patient groups, the number of men was higher in control group. Thus, findings confirm the claim that aging increases knee OA risk in women.

A significant correlation has been demonstrated between WOMAC scores and the radiological severity of knee OA. It has been suggested that there are significant differences in function, pain, and flexibility among patients with the same radiographic scores (30). In another study of 114 patients with knee OA, it was argued that K-L grading could not be associated with WOMAC pain sub-scoring (31). Similarly, in our study, no meaningful relation was found between radiological severity of knee OA and WOMAC score. These findings suggest that radiological severity of knee OA is not always compatible with clinical severity and symptoms.

Patients with severe knee OA had lower mean quality of life subscales (32). In a similar study, patients with knee OA were found to have lower scores on all sub-dimensions of SF-36 compared to healthy controls (33). In our study, SF-36 scores were found to be higher in the control group than in the patient group. According to

the findings of SF-36 sub-dimensions such as physical role limitations, emotional role limitations, social functionality, physical functionality, vitality, general mental health, pain and general health perception, the difference between the patient groups and the control group was found to be significant. Higher scores on SF-36 sub-dimensions indicate better health (34). Our findings confirming the studies in the literature also show that knee OA affects the quality of life. Thus, the quality of life can be increased and kept at an optimum level by determining the risk factors that cause the progression of OA, taking measures against it and organizing effective treatment.

Study limitations

There are some limitations in our study. For example; plasma free AA levels may be affected, such as comorbidities of patients, diet and medical treatments. Therefore, the findings of our study may be affected by these factors. In addition, only AA level in plasma was examined in our study. However, a combined study on the levels of synovial fluid or intra-articular tissues may provide more useful findings. Since our sample set is not very large, it lacks the high statistical power that can be provided by a larger population.

Conclusions

Norvaline, leucine, isoleucine, allo-isoleucine, cystathionine, phenylalanine, MHIS1, arginine, alanine, cysteine, valine, threonine and tryptophan levels were low in knee OA. Therefore, we conclude that these amino acids may have an important role in the etiogenesis and pathogenesis of knee OA. In conclusion, we think that these AAs can be used as potential systemic serum biomarkers and may be useful as dietary supplements in knee OA.

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Author Contributions: Concept: NA, SS Literature Review: NA, SS, IK, AG Design: SS, Data acquisition: NA, SS, IK, AG Analysis and interpretation: SS Writing manuscript: NA, SS Critical revision of manuscript: IK, AG

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