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Araştırma Makalesi / Research Article

Comparison of Multi-Detector Computed Tomography Coronary Angiography with Invasive Coronary Angiography in Patients with Coronary Artery Disease

Koroner Arter Hastalığı Olan Hastalarda Çok Dedektörlü Bilgisayarlı Tomografi Koroner Anjiografi ile İnvaziv Koroner Anjiografinin Karşılaştırılması

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Abstract

Aim: This study aimed to investigate the accuracy of multi-detector computed tomography (MDCT) coronary angiography via comparing with the invasive coronary angiography (ICA).

Material and Method: Sixty-three patients (42 male, 21 female) that presented with chest pain and underwent MDCT, followed by ICA within one month were evaluated. The age of the patients ranged from 35 to 75 years. The coronary arteries were examined over a total of 15 segments according to American Heart Association classification. The detected stenoses of coronary artery were divided into four groups; non-obstructive (1-49%), significant stenosis (50-74%), high-grade stenosis (75-99%), and occlusion (100%). Segment-based and patient-based analyses were performed. The results of MDCT coronary angiography and ICA were compared. The sensitivity, specificity, positive predictive and negative predictive values were calculated by comparing the MDCT coronary angiography and ICA data.

Results: In the segment-based analysis, regardless of the stenosis rate, the sensitivity was 90.8%, specificity was 95%, positive predictive value was 82.7% and negative predictive value was 97.5%. In the segment-based analysis regarding the detection of ≥ 50% stenosis, the sensitivity specificity, positive predictive and negative predictive values were 89.6%, 95.9%, 59.0%, and 99.2%, respectively. In the patient-based analysis regarding the detection of ≥ 50% stenosis, the sensitivity was 96.2%, specificity was 66.6%, positive predictive value was 68.4%, and negative predictive value was 96%.

Conclusion: MDCT coronary angiography is an examination that can be used as a non-invasive method for patients in the low and medium risk group for coronary artery disease.

Keywords: Multi-detector computed tomography; invasive coronary angiography; coronary artery disease

Öz

Amaç: Bu çalışma, çok dedektörlü bilgisayarlı tomografi (ÇDBT) koroner anjiyografinin doğruluğunu, invazif koroner anjiyografi (İKA) ile karşılaştırarak incelemeyi amaçladı.

Materyal ve Metot: Göğüs ağrısı ile başvurup ÇDBT koroner anjiografi çekilen ve bunu takiben bir ay içerisinde İKA yapılan hastalar çalışmaya alındı. Çalışma grubumuzda yaşları 35-75 arasında değişen 42'si erkek, 21'i kadın toplam 63 hasta vardı. Koroner arterler American Heart Association sınıflamasına göre toplam 15 segment üzerinden incelendi. Tespit edilen koroner arter stenozları 4 gruba ayrıldı; non-obstrüktif (%1–49), anlamlı stenoz (%50–74), yüksek dereceli stenoz (%75–99) ve oklüzyon (%100). ÇDBT sonuçları İKA ile karşılaştırılarak segment bazlı ve hasta bazlı analizler yapıldı. Elde ettiğimiz veriler İKA sonuçları ile kıyaslanarak sensivite, spesifite, pozitif prediktif değer ve negatif prediktif değerleri hesaplandı.

Bulgular: Çalışmamızda segment bazlı analizde stenoz oranlarına bakılmaksızın yapılan değerlendirmede sensitivite %91.5, spesifite %95, pozitif prediktif değer %84.7 ve negatif prediktif değer %97.4, segment bazlı ≥ %50 stenozları saptamada sensitivite %89.6, spesifite %95.9, pozitif prediktif değer %59.0 ve negatif prediktif değer %99.2, hasta bazlı değerlendirmelerimizde ≥ %50 stenoz tespit etmede sensitivite %96.2, spesifite %66.6, pozitif prediktif değer %68.4 ve negatif prediktif değeri %96 bulduk.

Sonuç: ÇDBT koroner anjiografi, koroner arter hastalığı açısından düşük ve orta risk grubunda yer alan hastalarda non-invaziv bir yöntem olarak kullanılabilir bir tetkiktir.

Anahtar Kelimeler : Multi-dedektör bilgisayarlı tomografi; invaziv koroner anjiografi; koroner arter hastalığı

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INTRODUCTION

Cardiovascular diseases are one of the leading causes of death worldwide (1). The most common cardiovascular disease is coronary artery disease (CAD), which has the greatest mortality and morbidity rates (2). Invasive coronary angiography (ICA) is accepted as the gold standard in the diagnosis of CAD. It has significant advantages, such as having high spatial and temporal resolution and facilitating the use of additional interventional methods for treatment. However, ICA has an invasive nature and is costly, causes certain complications, and is insufficient in characterizing plaques. For these reasons, a non-invasive, more cost-effective imaging method with high diagnostic sensitivity was needed (3).

In the last years, multi-detector computed tomography (MDCT) coronary angiography has been increasingly used for the evaluation of CAD. MDCT coronary angiography is a non-invasive imaging method that has a high spatial and temporal resolution, can show anatomical details from multiple perspectives. MDCT coronary angiography can evaluate other anatomical structures of the heart as well as coronary arteries. In addition, it can distinguish the coronary artery wall-atherosclerotic plaque border and characterize plaques by providing three-dimensional and cross-sectional images rather than projection images (4). MDCT coronary angiography provides independent prognostic information on mortality and estimated cardiac events in patients with known or suspected CAD. The use of firstly MDCT coronary angiography is recommended for patients with a low or moderate risk of CAD (5).

In this study, we aim to evaluate the diagnostic accuracy of MDCT coronary angiography regarding ICA in the diagnosis of CAD.

MATERIAL AND METHOD

Patient Selection and Preparation

The retrospective study was approved by the Inonu University Medical Faculty Ethical Committee. (2015/16). 138 patients who underwent MDCT coronary angiography in the radiology department between February 2015 and January 2016 were included in the study. In the patients included in the study, ICA was performed within 1 month in the cardiology clinic after MDCT coronary angiography. Patients with contrast material allergy, renal failure, advanced heart failure, hyperthyroidism, epilepsy, respiratory distress, Reynaud's syndrome, atrioventricular block, were excluded from the study. In addition, forty-six patients with a history of bypass surgery and / or coronary artery stenting, 18 patients with a duration of more than 1 month between MDCT coronary angiography and ICA, and 11 patients with insufficient MDCT images due to motion, cardiac arrhythmia or respiratory artefacts were excluded from the study.

MDCT Protocol

The heart rate of pre-scan patients was aimed to be 70 beats / min. Beta-blocker therapy was administered to patients with a high heart rate under the supervision of a cardiologist. In all cases, before MDCT coronary angiography, unenhanced CT was performed to determine the calcium load (calcium score) of the coronary arteries. Calcium scoring was automatically calculated by software specifically designed to mark calcified areas. MDCT coronary angiography was performed with 64-slice (Aquillon; Toshiba Medical Systems) and 256-slice (Somatom Definition Flash; Siemens Healthcare) CT devices. The duration of the examination in the 64-slice MDCT device varied between the cases with the average duration being calculated as 7-10 sec. Imaging was undertaken in the routine spiral mode applying standard protocols. In the 256-slice CT device, three different imaging protocols were used according to the heart rate of the patients. The duration of imaging was between 5 and 8 sec. For patients with a heart rate of 60 beats / min or less, the Flash Spiral scan protocol was applied. In this mode, CT angiography images were obtained at a single heart rate with an extremely low dose of radiation. In patients without arrhythmia but having a heart rate of 60-90 beats / min., the adaptive prospective electrocardiogram (ECG)-triggered mode was used. The patients with arrhythmia or a heart rate of ≥ 90 were scanned using the routine spiral mode.

Before the MDCT procedure, scanogram images covering the carina and the base of the heart were used to determine the area to be scanned. Then, ECG-recorded helical images of the whole heart from the carina to the base were obtained during inspiration. A contrast agent (75-95 ml) with high iodine concentration (≥ 350 mg / mL) was administered using an autoinjector at a rate of 5 ml / sec for 64-slice scans and 6 ml / sec for 256-slice scans. Following the contrast enhancement, 50 mL saline bolus was injected at a rate of 5 mL / sec to reduce artefacts in the right heart and allow the examination of contrast material in dead spaces (line, antecubital vein and right heart). An automated dual-syringe injector (CT motion, Ulrich medical) was used for the administration of contrast medium and saline.

Invasive Coronary Angiography

Conventional coronary angiography was performed with the transfemoral Judkins approach, and the right coronary artery (RCA) and left main coronary artery branches were displayed in different projections. Stenosis rates were compared on two different planes with normal segments on the proximal side and recorded by a cardiologist that did not know the findings of MDCT coronary angiography.

Evaluation and Interpretation of Images

During imaging, the heart rate and ECG tracing were recording retrospectively for the spiral mode and prospectively for the adaptive mode. The images were then transferred to workstations for analysis (Syngo Via; Siemens Medical Solutions, Vitrea; Toshiba Medical Systems). Thin-axial data was used to obtain images in the formats of two-dimensional maximum intensity

projection (MIP), multiplanar reconstruction (MPR), and three-dimensional volumetric display. The MPR and MIP images were used to evaluate arterial lumens, arterial wall and heart chambers, and three-dimensional images were utilized to assess coronary artery anatomy and stenosis. The volumetric rendering technique was adopted to demonstrate the complicated anatomic three-dimensional characteristics of coronary arteries and to obtain details that might have been overlooked in the examination of images on the axial plane.

In the 64-slice CT procedure, reconstruction percentages corresponding to 35-40% in ECG tracing and 70% in left anterior descending (LAD) and left circumflex artery (LCX) coronary arteries were used for RCA. For the 256-slice CT images, the best systolic and diastolic reconstructions were automatically detected on the workstation. Thus, coronary arteries were examined in detail on images with minimal artefacts. All images were evaluated by a radiologist experienced in cardiovascular radiology. The coronary arteries were examined over 15 segments according to the American Heart Association (AHA) classification. On this basis, RCA consisted of segments 1-4, the left main coronary artery segment 5, LAD segments 6-10, and LCX segments 11-15.

Taking the stenosis-free luminal diameter proximal to the stenosis arterial segment as a reference, 50% ≥ narrowing of the luminal diameter in the stenosis segment was interpreted as obstructive CAD. The detected coronary artery stenoses were divided into four groups; normal, non-obstructive (1-49%), significant stenosis (50-74%), high-grade stenosis (75-99%), and occlusion (100%).

The data obtained were compared with the results of ICA, and the sensitivity, specificity, and positive and negative predictive values were calculated. Segment- and patient-based analyses were performed on the data. In the segment-based analysis, the sensitivity, specificity, and positive and negative predictive values were calculated for the detection of lesions in all segments regardless of stenosis rate and for identification of those that caused ≥50% and ≥75% stenosis. In the patient-based analysis, these values were calculated only for the determination of lesions that caused ≥50% and ≥75% stenosis. In the same analysis, the detection of stenosis by ICA and MDCT at the same segment level in a coronary artery was evaluated as an indication of a true positive case.

According to their morphology, plaques were characterized as calcified, soft or mixed. A plaque was considered to be soft if calcification was not observed or was minimal (0-130 HU), mixed if it was calcified but had soft components (> 130 HU), and calcified if the whole plaque was calcified (> 130 HU). ICA and MDCT images of 2 patients are shown in figures 1 and 2.

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0. Categorical variables were presented as counts and percentages. Sensitivity, specificity, positive predictive value and negative predictive value for MDCT to detect significant stenosis were calculated from the chi-square test of contingency.

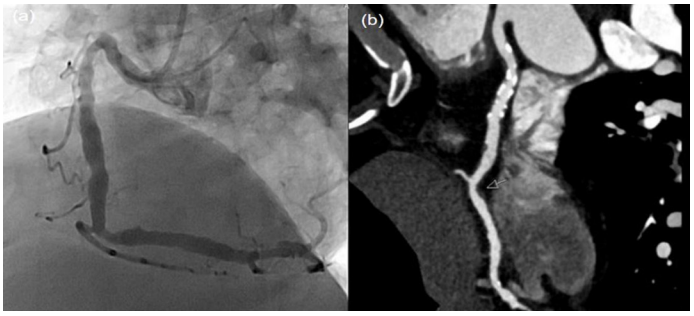

Figure 1. An ICA image (a) and MDCT curved MPR reconstruction image (b) of a 65-year-old male patient with a soft plaque that caused approximately 50% narrowing of the lumen following the RCA acute marginal branch. In addition, in the ICA image, at the proximal RCA level, calcified plaques causing luminal irregularity but no significant stenosis are observed.

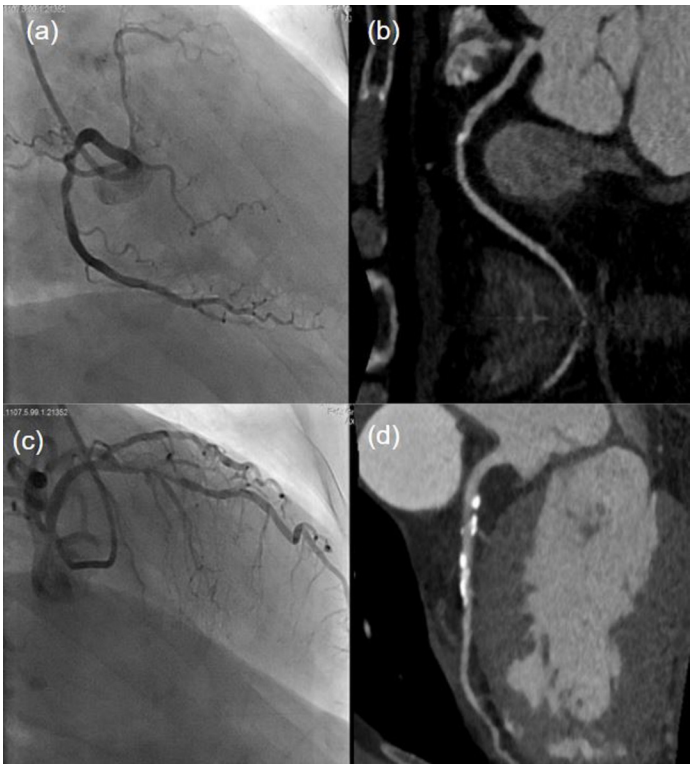

Figure 1. An ICA image (a) and MDCT curved MPR reconstruction image (b) of a 74-year-old female patient with a discrete calcified plaque that caused 50-74% narrowing of the lumen before the RCA acute marginal branch. In the same patient, the ICA (c) and curved MPR (d) images show a tubulary calcified plaque following LAD D1 causing 50-74% stenosis. Another calcific plaque is observed in the LAD proximal segment without significant stenosis.

RESULT

The sample of the study consisted of 63 patients, 42 male (42.6%) and 21 female (33.3%), aged 35 to 75 years. A total of 946 coronary arterial segments were evaluated by ICA, and stenosis was detected in 196 of these segments at various levels and rates. Of the segments with stenosis,

90.8% (n = 178, true positive result) were also detected by MDCT coronary angiography.

Using MDCT, stenosis was detected in 215 segments at various levels, of which 37 were evaluated as normal in ICA (false-positive result). A total of 712 segments were evaluated as normal (true-negative result) using MDCT coronary angiography and ICA. Eighteen segments were reported to be normal in MDCT coronary angiography but had stenosis according to ICA (false-negative result).

According to the findings of MDCT coronary angiography and ICA, obstructive CAD was not present in 851 of 945 segments. Six segments were evaluated as non-obstructive CAD or normal by MDCT coronary angiography but defined as obstructive CAD according to ICA. Both ICA and MDCT angiography revealed obstructive CAD in 52 segments. Thirty-six segments were identified as obstructive CAD by MDCT coronary angiography, but defined as non-obstructive CAD or normal by ICA.

Concerning the detection of segments with high-grade stenosis (75-99%) and occlusion (100%), we obtained the following results: Of the 945 segments, 911 had no high-grade stenosis or occlusion according to both MDCT coronary angiography and ICA; nine segments were evaluated as normal or having stenosis below 75% by MDCT coronary angiography but identified as high-grade stenosis or occlusion by ICA; 16 segments had high-grade stenosis or occlusion according to both imaging techniques; and nine segments were interpreted to have high-grade stenosis or occlusion by MDCT coronary angiography but evaluated as having less than 75% stenosis or being normal in ICA. Segment-based assessment results were summarized in tables 1 and 2.

In the patient-based assessment, the presence of stenosis above the specified threshold in any segment of coronary arteries revealed by both MDCT coronary angiography and ICA was interpreted as a true-positive case. Here, we assumed a threshold of ≥ 50% for obstructive CAD and ≥ 75% for severe stenosis. In the analysis of 63 patients, 27 patients were found to have ≥ 50% stenosis according to ICA, and 26 of these patients were also identified by MDCT coronary angiography (true-positive patient). There was only one patient (false-negative) who was evaluated as having ≥ 50% stenosis in ICA, but was not identified by MSCT coronary angiography. In the obstructive CAD analysis, 24 patients were evaluated as normal by both MDCT coronary angiography and ICA (true-negative patients). Twelve patients had ≥ 50% stenosis according to MDCT coronary angiography, but were evaluated as normal or having non-obstructive CAD by ICA (false-positive patients).

In the analysis of high-grade stenosis (≥ 75%), 16 patients were identified to have high-grade stenosis by ICA, of whom only 11 were also evaluated the same in MDCT coronary angiography. For the remaining five patients, MDCT coronary angiography revealed 50-74% stenosis in three patients and 1-49% stenosis in two patients. Forty-four patients were evaluated as having normal findings by both MDCT coronary angiography and ICA. Lastly, three patients that were found to have high-grade stenosis in MDCT coronary angiography were assessed as having normal findings or less severe stenosis in ICA. Concerning the characterization of plaques identified by MDCT angiography, 48.3% (n = 117) were mixed, 39.2% (n = 95) were calcified, and 12.3% (n = 30) were soft. Patient-

Table 1. The true-positive, true-negative, false-positive, and false-negative results of MDCT angiography for the detection of stenosis in all segments (segment-based assessment)

			ICA	
			STENOSIS PRESENT	STENOSIS ABSENT
MDCT coronary angiography	STENOSIS REGARDLESS OF RATE	PRESENT	178	37
		ABSENT	18	712
	≥ 50% STENOSIS	PRESENT	52	36
		ABSENT	6	851
	≥ 75% STENOSIS	PRESENT	16	9
			9	911

Table 2. The sensitivity, specificity, and positive and negative predictive values of MDCT angiography for the detection of stenosis (segment-based assessment)

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
STENOSIS REGARDLESS OF RATE	90.8%	95%	82.7%	97.5%
≥ 50% STENOSIS	89.6%	95.9%	59%	99.2%
≥ 75% STENOSIS	64%	99%	64%	99%

Table 3. The true positive, true negative, false positive and false negative results of MDCT in detecting ≥ 50% and ≥ 75% stenosis in all patients (patient-based assessment)

			ICA	
			STENOSIS PRESENT	STENOSIS
MDCT	≥ 50% STENOSIS		ABSENT	99.2%
		PRESENT	26	12
		ABSENT	1	24
	≥ 75% STENOSIS	PRESENT	11	3
		ABSENT	5	44

Table 4. The sensitivity, specificity, and positive and negative predictive values of MDCT angiography for the detection of ≥ 50% and ≥ 75% stenosis (patient-based assessment)

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
≥ 50% STENOSIS	96.2	66.6	68.4	96
≥ 75% STENOSIS	68.7	93.6	78.5	89

based assessment results were summarized in tables 3 and 4.

DISCUSSION

In our study, we found that MDCT coronary angiography provided high sensitivity and negative predictive values in the segment and patient-based analyzes.

ICA is the gold standard method in the diagnosis of CAD. In the presence of CAD, ICA shows the luminal diameter, stenosis rate, and luminal irregularity with high resolution (3, 6). An important advantage of ICA is that it facilitates the use of interventional procedures, such as balloon or stent placement in the stenotic region under emergency or elective conditions according to the clinical findings from the examination of the patient (6). However, since ICA indirectly displays the lumen of the coronary arteries secondary to contrast enhancement, it only provides information about the lumen and does not allow direct observation of the arterial wall. For this reason, ICA does not offer any insight into the character of an atherosclerotic plaque or its rupture tendency (7). Lumen stenosis is usually determined by the proportion of a stenotic segment to the normal segment proximal to the stenosis. In the presence of diffuse atherosclerotic CAD, if there is no normal arterial segment, ICA may underestimate the stenosis rate (6, 7). In addition, outward displacement of plaques (positive remodelling) may cause normal visualization of the luminal diameter despite the presence of significant CAD. Furthermore, the invasive nature of ICA brings certain risks, the severity of which is related to the skill and experience of the angiographer, the stability of the patient's clinical symptoms, and the diffuseness of CAD. The most important complications are stroke, myocardial infarction, and death (6-8). The high cost of ICA and the requirement of interventional procedures only in one third of cases are among the other disadvantages of this procedure. Therefore, a more cost-effective and non-invasive imaging method is necessary for diagnostic purposes (3, 6, 7).

MDCT coronary angiography has been used since 1998 to visualize vascular structures outside the coronary artery system with the advances in technology making it possible to visualize long-range and high-resolution images. Since the heart is a moving organ, MDCT started to be used for imaging coronary arteries only after the ECG tracing technology was introduced to MDCT devices (8). Involving the use of synchronous imaging with ECG and reconstruction methods, having a high spatial and temporal resolution, and being able to perform faster volume scanning, MDCT allows detecting coronary artery stenosis with high sensitivity at low pulse following appropriate preparations (8). Furthermore, features such as increased number of detectors, reduced gantry rotation period, decreased cross-sectional thickness, and increased X-ray utilization factor in MDCT devices have increased the use of MDCT coronary angiography in CAD imaging (7-9).

The advances in CT technology have eliminated the problems with temporal resolution, which is a critical parameter in the visualization of the heart, a moving organ. High diagnostic values have been achieved using 64-slice MDCT, and this method has been accepted as a non-invasive alternative to ICA in patients suspected of having coronary artery stenosis (10).

In a meta-analysis of 29 studies involving 2,024 patients and the comparison of MDCT with ICA, the sensitivity, specificity, and positive and negative predictive values of MDCT in detecting lesion were reported to be 81%, 93%, 67.8%, and 96.5%, respectively, regardless of the stenosis rate (11). Similarly, in the current study, we found 90.8% sensitivity, 95% specificity, 82.7% positive predictive value, and 97.5% negative predictive value.

Ehara et al. conducted a coronary angiography study using a 64-slice CT device and evaluated 884 segments in 69 patients, and reported that the sensitivity, specificity,

positive predictive value, and negative predictive value for ≥ 50% stenosis detection were 90%, 94%, 89%, and 95%, respectively (12). In another study, Hans et al. compared the findings obtained by 64-slice CT with ICA in 50 patients, and found that for ≥ 50% stenosis, the sensitivity, specificity, and positive and negative predictive values of MDCT were 81.8%, 97.7%, 88.9%, and 95%, respectively (13). In the segment-based analyses of the current study, when we compared the MDCA results with those of ICA in detecting ≥ 50% stenosis, we found 89.6% sensitivity, 95.9% specificity, 59.0% positive predictive value, and 99.2% negative predictive value. These results are similar to those reported by most of the MDCT coronary angiography studies conducted in recent years. Our positive predictive value was low because some of the segments evaluated as 50-74% stenosis in MDCT coronary angiography were interpreted as 1-49% stenosis by ICA. In another study conducted with 104 patients using a 256-slice MDCT device, segment-based analyses revealed 93.5% sensitivity, 95% specificity, 77.6% positive predictive value, and 98.7% negative predictive value for the detection of ≥ 50% stenosis (14). In our study, although we utilized both 64-slice and 256-slice MDCT devices, the former was used for the imaging of most patients. When we compare our results with the above-mentioned study that only used a 256-slice MDCT device, there are no significant differences. Similar to our results, their positive predictive value was also low. Today, MDCT coronary angiography is indicated for use in obstructive CAD in patients with low to moderate risk. This is supported by large scientific communities due to the high negative predictive value of MDCT angiography for obstructive CAD (5). In a multi-center study of 291 patients, although the negative predictive value was high, the positive predictive value was found to be low (15).

Alexander et al. evaluated 798 segments in 64 patients using 64-slice MDCT. According to their segment-based analysis, compared to ICA, the sensitivity and specificity of MDCT for the detection of ≥ 75% stenosis were 80% and 97%, respectively (16). Our segment-based analysis revealed 64% sensitivity, 99% specificity, 64% positive predictive value, and 99% negative predictive value for the detection of ≥ 75% stenosis. We consider that our lower sensitivity value is due to misinterpretations regarding stenosis rates. The segments that we evaluated as 50-74% stenosis in MDCT but defined as ≥ 75% stenosis in ICA reduced the sensitivity value. Therefore, despite the high sensitivity percentages for lesion detection, we obtained lower sensitivity in detecting stenosis rates. Similarly, the lower positive predictive value may be explained by the interpretation of some segments as ≥ 75% stenosis in MDCT coronary angiography but as 50-74% stenosis in ICA.

In a prospective and multi-center study of 230 consecutive patients presenting with chest pain but no previously known CAD, Budoff et al. investigated the diagnostic accuracy of 64-slice MDCT coronary angiography based on 50% and 70% threshold values (17). Their patient-based analysis on the data revealed 95% sensitivity, 83% specificity, 64% positive predictive value, and 99% negative predictive value for the detection of ≥ 50% stenosis. Similarly, for the detection of ≥ 70% stenosis, the sensitivity, specificity, and positive and negative predictive values were reported as 94%, 83%, 48%, and 99%, respectively. In another study conducted with 104 patients using 256-slice MDCT, the patient-based analysis showed 98.8% sensitivity, 50% specificity, 92.4% positive predictive value, and 87.5% negative predictive value for the detection of ≥ 50% stenosis (14). In our patient-based analysis, compared to ICA, we found the sensitivity, specificity, and positive and negative predictive values of MDCT to be 96.2%, 66.6%, 68.4%, and 96%, respectively for ≥ 50% stenosis detection and 68.7%, 93.6%, 78.5%, and 89%, respectively for ≥ 75% stenosis detection. We consider that the low positive predictive values for the ≥ 50% and ≥ 75% thresholds and the low sensitivity for the ≥ 75% threshold are not related to the detection of lesions, but are due to inaccuracies in determining the rates of stenosis they cause in the lumen.

Many studies investigating the accuracy of MDCT coronary angiography have reported high false-positive results and low positive predictive values. Among the factors that increase false positives are technical problems and motion artefacts that degrade image quality. Common high-density calcified plaques in coronary arteries not only make it difficult to evaluate MDCT coronary angiography but also limit the validity of the results. The presence of intense calcified plaques leads to an overestimation of lumen narrowing and false-positive results in stenosis rates (14). In this study, the fact that the majority of the patients had mixed and calcified plaques may have caused similar results.

While coronary artery plaques are visualized as regular or irregular filling defects in ICA images, MDCT coronary angiography allows for the characterization of plaques that cause luminal narrowing, thus clinically indicate more risky lesions. In this study, of the plaques identified by MDCT angiography, 48.3% (n = 117) were mixed, 39.2% (n = 95) were calcified, and 12.3% (n = 30) were soft. Studies have shown that soft-mixed plaques with surface irregularities or ulcerations are much more likely to cause acute coronary syndromes than calcified plaques (18).

CONCLUSION

In conclusion, this study revealed that MDCT coronary angiography provided high sensitivity and negative predictive values in the examination of segment-based and patient-based analyses. MDCT coronary angiography can be used as a suitable non-invasive diagnostic alternative to ICA in patients with known CAD or those included in the low or moderate risk groups. ***Congresses***

The study was represented as an e-poster at European Congress of Radiology in 2018.

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interests or potential conflicts of interest.

Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The study was approved by the Inonu University Medical Faculty Ethical Committee. (2015/16). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.*

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MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

Evaluation of Renal Vascular Variations in Routine Computed Tomography Examinations

Rutin bilgisayarlı tomografi incelemelerinde renal vasküler varyasyonların değerlendirilmesi

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Abstract

Aim: Anatomical variations of the kidney, including multiple renal arteries are crucial for renal and abdominal aortic surgery and renovascular hypertension. In this study, we aimed to investigate the frequency of multiple renal arteries in a Turkish population by evaluating the images of patients who underwent contrast-enhanced computed tomography (CT) for various reasons.
Material and Methods: Images of patients who underwent contrast abdominal computed tomography in our hospital due to various health problems were evaluated retrospectively. The presence, number, and exit levels of multiple renal arteries were examined.
Results: In the study, CT scans of 470 patients, aged between 18 and 69 years (43.7 ± 14.1) were analyzed retrospectively. Of the 940 kidneys evaluated, 113 had multiple renal arteries. Of the multiple renal arteries, 59 belonged to women and 54 to men, and the difference was found to be statistically insignificant. The incidence of multiple renal arteries was determined as 20.6% in evaluated cases and 12% in evaluated kidneys. The number and frequency of occurrence is 53 (47%) in the right kidney and 60 (53%) in the left kidney, respectively, and there is no significant difference between the two sides. Accessory renal arteries originated from the abdominal aorta between lumbar 1 vertebra (L1) and L4, except for 2 cases where they originated from the iliac artery.
Conclusion: The incidence of multiple renal arteries in the Turkish population was found at rates similar to the literature, using CT. CT is found to be a reliable method in detecting multiple renal arteries. Considering the presence of multiple renal arteries in CT examinations, we think that valuable information can be obtained in the investigation of renovascular hypertension.

Keywords: Multiple renal arteries; anatomical variations; computed tomography; renal vasculature

Öz

Amaç: Çoklu renal arter varlığı böbrek ve abdominal aorta cerrahisinde, renovasküler hipertansiyonda önemli bir rol oynar. Çeşitli nedenlerle kontrastlı bilgisayarlı tomografi (BT) yapılmış hastaların görüntülerini değerlendirerek Türk toplumunda çoklu renal arter sıklığını araştırmayı amaçladık.
Gereç ve yöntem: Çeşitli sağlık problemleri nedeni ile hastanemizde kontrastlı abdominal bilgisayarlı tomografi yapılmış hastaların görüntüleri geriye dönük olarak değerlendirildi. Çoklu renal arter varlığı, sayısı ve çıkış düzeyleri incelendi.
Bulgular: Çalışmada 470 hastanın BT taraması retrospektif olarak incelendi. Olguların yaş ortalaması 43.7±14.1 olup yaş aralığı 18-69 idi. Değerlendirilen 940 böbreğin 113'ünde çoklu renal arter mevcuttu. Çoklu renal arterlerin 59'u kadın, 54'ü ise erkek olup cinsiyetler arasında anlamlı farklılık yoktu. Değerlendirilen olgularda çoklu renal arter görülme sıklığı %20.6, değerlendirilen böbrekler için ise %12 olarak belirlendi. Görülme sayı ve sıklığı sırası ile sağ böbrekte 53 (%47) ve sol böbrekte 60 (%53) olup iki taraf arasında anlamlı farklılık yoktu. Aksesuar renal arterler iliak arterden köken aldığı 2 vaka dışında lomber 1-4 vertebralar (L1-L4) arası abdominal aortadan köken almakta idi.
Sonuç: BT ile Türk toplumunda çoklu renal arter sıklığı literatür ile benzer oranlarda tespit edilmiştir. Çoklu renal arter tespitinde BT güvenilir bir yöntemdir. BT incelemelerinde çoklu renal arter varlığının dikkate alınması ile renovasküler hipertansiyon araştırılmasında ve cerrahi girişimler öncesinde değerli bilgiler edinilebileceğini düşünmekteyiz.

Anahtar Kelimeler : Çoklu renal arter, anatomik varyasyon, bilgisayarlı tomografi, böbrek damarları

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INTRODUCTION

The renal arteries leave the lateral faces of the abdominal aorta at the level of L1-L2 vertebrae. The right renal artery (RLA) having an elongated track compared to the left renal artery (LLA), passes behind the inferior vena cava (IVC) (1,2). Renal arteries tend to appear with numerical variations, although they are usually found as one for each side. Along with their numbers, variations can also be seen in the levels of separation from the aorta. Moreover, course variations can be seen in renal veins, with less numerical variations (3-5). The knowledge of renal vascular variations and separation levels is crucial for the surgical management of various pathologies, interventional radiological procedures, and especially transplantation (6,7). In addition, to date, many studies suggested that the presence of multiple renal arteries may be associated with hypertension (8,9). There are studies, suggesting that renal artery variations are observed at higher rates in African blacks. Although the frequency of variation varies between 9% and 76% in various studies, the average rate, in general, is found to be 28% to 30% (3-5). Although there have been past studies about the renal vasculature variations including the Turkish community, the numbers are insufficient in terms of elucidating the literature. Studies conducted for the Turkish population have generally been conducted by detecting multiple renal arteries as an additional finding in those who undergo digital subtraction angiography (DSA) for another reason (3,5,10). There are studies examining renal vascular variations with computed tomography (CT) angiography (11). To our knowledge, to date, a comprehensive study for the detection of accessory renal arteries by routine abdominal CT, among the Turkish population was not reported.

There are differences in the definition of the accessory renal artery. In addition, in the presence of multiple renal arteries, if the diameters are similar, it may not be possible to define which artery is true and which artery is an accessory. Therefore, it can be said that it is correct to use multiple renal artery definitions as much as possible. In some studies, the number of arteries departing from the abdominal aorta was evaluated, whereas, in other studies, the number of renal arteries entering the kidney was evaluated. Therefore, there are studies with quite different rates of multiple renal arteries from each other (3-5,12). In our study, the presence of multiple renal arteries that separate from the aorta from different points and progress to the kidney were evaluated. In our study, we aimed to evaluate the frequency of multiple renal arteries by computed tomography. In addition, remarkable renal vein course variations were evaluated in the cases.

MATERIAL AND METHOD

Four hundred and seventy patients who underwent contrast-enhanced abdominal CT examinations in Fatih Sultan Mehmet Training and Research Hospital, between January 2019 and June 2019 were evaluated retrospectively. Examinations were performed with a 128-slice CT device (GE Healthcare Optima CT660, USA). In our hospital, routine abdominal CT examinations are performed with this device using the following parameters: fixed noise index of 30, 1.25 mm slice thickness, 120 kVp, and a gantry rotation time of 0.5 seconds. Repeated examinations, technically unsatisfactory arterial phases, artifact formations, total nephrectomy, kidney tumors, kidney anomalies, end-stage renal failure, vasculitis such as polyarteritis nodosa, and intra-abdominal pathologies that complicate evaluations were accepted as exclusion criteria from the study. All CT scans were examined by a radiologist with 14 years of CT experience as images in the axial and coronal planes. Remarkable renal vein variations were recorded together with multiple renal arteries (Figures 1 and 2). This retrospective study is not a clinical study on human subjects or laboratory experimental animals. The study was carried out with the protocol in accordance with the Declaration of Helsinki, and was submitted by the institutional review board with the approval number 17073117_050.06.

Statistical Analysis

Statistical Package for the Social Science 22 (version 22 for Windows; SPSS, Turkey) program was used for statistical analyzes. A chi-square test was used to compare the difference between males and females of double renal arteries and the difference between the right and left sides. Data were expressed as mean ± standard deviation. A p-value of <0.05 was considered statistically significant.

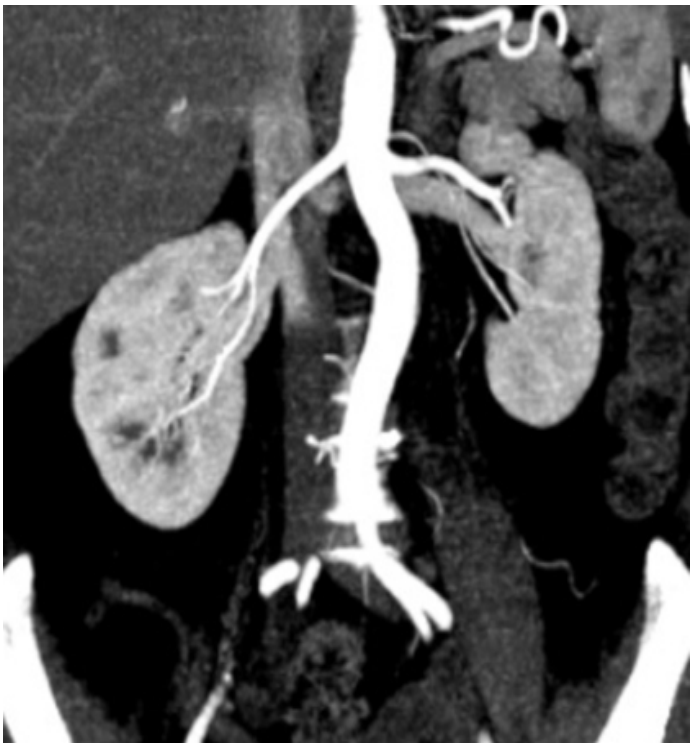

Figure 1. Double renal arteries are seen on the left. Thin diameter renal artery, which comes out from the top, crosses the other and extends to the lower half of the kidney

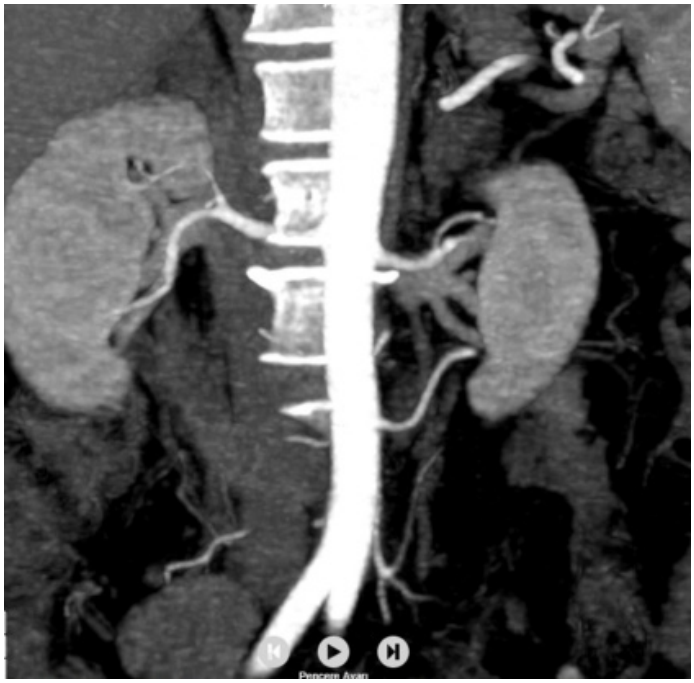

Figure 2. Two renal arteries that supply the left kidney

RESULT

Images of 470 patients who underwent contrast-enhanced abdominal computed tomography examination were retrospectively analyzed. 211 of the cases were male (44.9%) and 259 were female (55.1%). The mean age of male cases was 42.7 ± 14.7, while the mean age of female cases was 44.6 ± 13.6. The mean age of the patients was 43.7 ± 14.1 with the range 18-69. Of the 940 kidneys evaluated, 113 had multiple renal arteries. No patients were found to have more than two renal arteries on one side. 59 of the cases with multiple renal arteries were female and 54 were male, and the difference between each gender was noted to be statistically insignificant (p = 0.38). The incidence of multiple renal arteries in the evaluated kidneys was found to be 12%, and the incidence of multiple renal arteries was 20.6% in cases. The number and frequency of occurrence was 53 (47%) in the right kidney and 60 (53%) in the left kidney, respectively, and there was no significant difference between the two sides (p = 0.19). In 37 (7.9%) of the cases, there were multiple renal arteries in the right kidney, 44 (9.4%) in the left kidney, and 16 (3.4%) in the bilateral renal artery (Table 1). Of the 827 kidneys fed by one renal artery, 282 of the renal arteries originated from the level of the L1 vertebra (34.1%), 296 from the L1-L2 intervertebral disc level (35.8%), 243 from the L2 vertebra (29.4%), and 6 from the L3 vertebra (0.7%) (Table 2). Accessory renal arteries originated from the abdominal aorta between L1 and L4, except for 2 cases where they originated from the iliac artery. In addition, the retroaortic left renal vein variation was notified in 24 cases (5%), circumaortic left renal vein was found in 5 cases (1%) (Figure 3), and inferior vena cava transposition (Figure 4) (left-sided inferior vena cava) variation was seen in 1 case (Table 3).

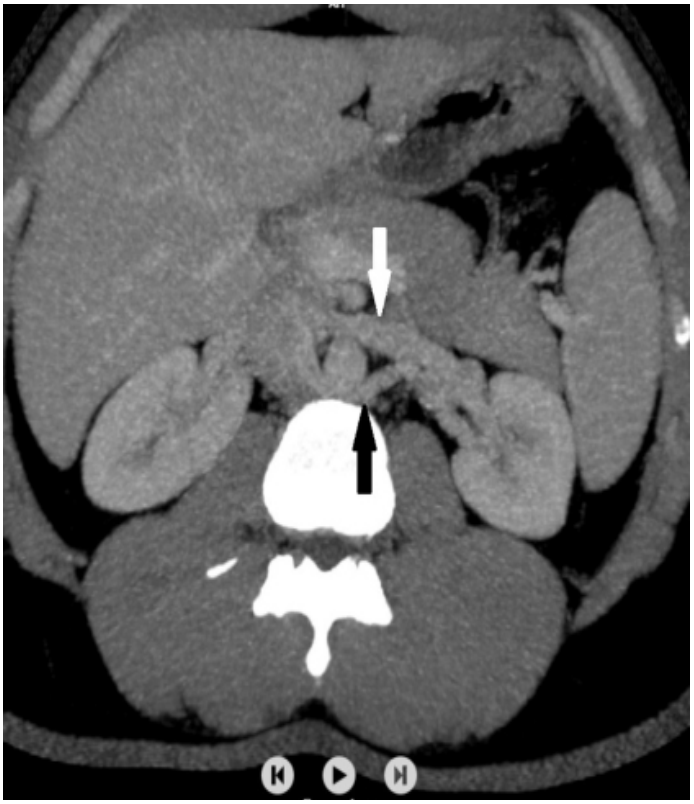

Figure 3. Axial CT image of the anterior branch (white arrow) and posterior branch (black arrow) of the circumaortic left renal vein

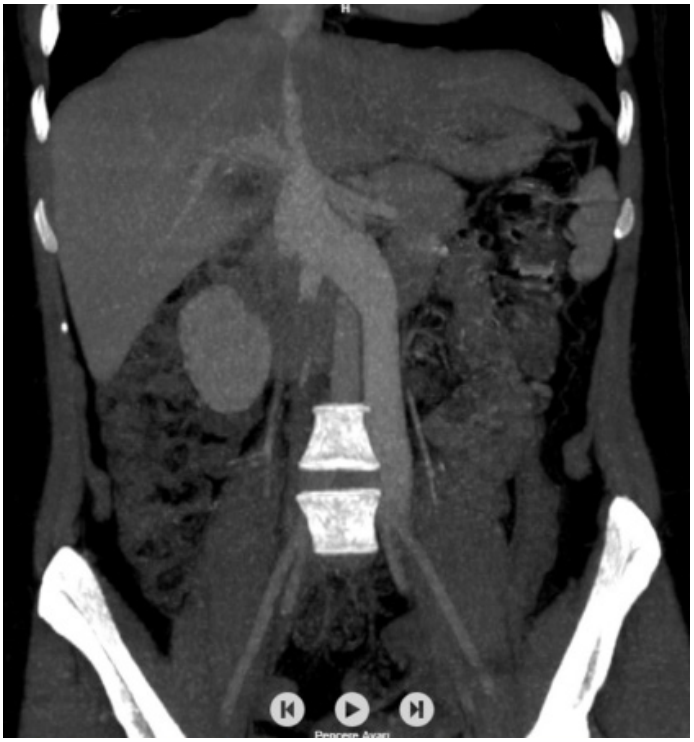

Figure 4. Transposition of inferior vena cava (Left-sided Inferior Vena Cava). The inferior vena cava, lying to the left of the aorta, crosses the aorta at the level of the renal veins and passes to the right

Table 1. Multiple renal arteries incidence rates

	Number (n)	Distribution (%)
Normal	373	79.4
Right-side multiple renal arteries	37	7.9
Left-side multiple renal arteries	44	9.4
Bilateral multiple renal arteries	16	3.4
Total	470	20.6

Table 2. Renal arteries origin levels

	Number (n)	Distribution (%)
L1 vertebra	313	33.3
L1-L2 intervertebral disc	326	34.7
L2 vertebra	273	29
L3 vertebra	17	1.8
L4 vertebra	9	1
Left iliac artery	2	0.2
Total	940	100

Table 3. Additional vascular variations

	Number (n)
Retroaortic left renal vein	24
Circumaortic left renal vein	5
Transposition of inferior vena cava (left-sided IVC)	1
Total	30

DISCUSSION

The differences in the number and exit points of the renal arteries from the aorta are explained by the embryological development of the mesonephric arteries (13). In the embryological period, these arteries form a vascular network on both sides of the aorta, between the 6th cervical and 3rd lumbar vertebrae, feeding the adrenal glands, kidneys, and gonads. With time, these arteries disappear by involution and a single mesonephric artery remains and takes over the circulation of the kidney. As a result of the persistence of the mesonephric arteries, more than one renal artery may arise that feeds the kidney (13). Renal arteries usually branch off from the aorta below the superior mesenteric artery. Renal arteries enter the kidney from the renal hilum. In the presence of more than one renal artery, additional renal arteries can enter the kidney from the hilum or parenchymal level. It is important to identify the presence of more than one renal artery, especially before surgical operations (14). There are studies about the number and variations of renal vascular structures that present with dissections, radiological examinations, and surgical findings. For the evaluation of vascular structures, DSA for arteries and venography for venous structures are accepted as the golden standard. However, with the development of technology and the fact that angiography is an invasive method, contrast-enhanced CT and magnetic resonance imaging provide results as successful as conventional angiography (15,16). In our study, we investigated the separation levels and numbers of renal arteries. We also evaluated conditions such as retroaortic course or circumaortic variation of the left renal vein. Although there are many studies on the number of renal arteries, few studies focused on exit levels and additional renal vein variations (5).

In our study, it was found that the renal arteries most frequently originated from the lateral of L1-L2 intervertebral disc level. More rarely, we encountered a small number of renal artery cases originating from the L3 vertebra level. Accessory renal arteries were observed to originate from the aorta between the L1-L4 vertebra, except for two cases that originated from the iliac artery. Similar results have been shown in other studies on this subject. Our findings were consistent with the literature information. Some studies reported the presence of renal arteries originating from the T12 vertebra level (17,18). Renal artery variations gain more importance due to increased renal transplantations, interventional radiological procedures, urological and vascular interventions (19-22). In addition, it has been reported in various studies that there is a possibility of a relationship between the presence of multiple renal arteries and hypertension. The

accessory renal artery generally has lower calibration and according to a hypothesis, the kidney segment fed by this artery secretes more renin than other renal parenchyma segments, causing hypertension (8,9,23,24). Atasoyu et al. reported in their study that the presence of an additional renal artery may cause hypertension (23). Of the 940 kidneys evaluated in our study, 113 had multiple renal arteries. Of the patients with multiple renal arteries, 58 were women and 53 were men. The incidence of multiple renal arteries in the evaluated kidneys was 11%, and multiple renal arteries were detected in 20.6% of the cases. The number and frequency of occurrence are 53 (47%) in the right kidney and 60 (53%) in the left kidney, respectively, and there is no significant difference between the two sides. Accessory renal arteries originated from the abdominal aorta between L1 and L4, except for 2 cases where they originated from the iliac artery.

Satyapal et al examined the incidence and morphometry of the accessory renal artery; and reported that 102 of 440 kidneys (23.2%) had accessory renal arteries and 40 of them were on the right side, where 62 of them were on the left side (20). In the study performed by Sevinç et al., they stated that the frequency of additional renal arteries was 22% (25). Sampaio et al., as a result of an anatomical evaluation of 266 kidneys, determined the additional renal artery rate as 30.4% and Bordei as 14% (21,26). In our study, the rate of multiple renal arteries was determined to be 20.6%, and it is in parallel with some studies, it is seen to be lower than in some studies. However, in some studies, the renal artery that diverges only from the aorta but enters the kidney more than one by branching early was evaluated as multiple renal arteries. In our study, arteries that separate from the aorta and reach the kidney independently were accepted as additional renal arteries. During the reporting of contrast-enhanced computed tomography, evaluation of the presence of additional renal artery is often overlooked. Similarly, the retroaortic course of the left renal vein and circumaortic variation may be ignored or overlooked in reporting. Because of the effects of venous variations on the function of the left kidney and the possibility of the presence of an additional renal artery to be associated with hypertension, the importance of the findings in our study was aimed to be emphasized. In addition, transplantation of a kidney with a single renal artery is technically easier and the rates of postoperative complications and kidney loss are lower than kidney transplantation with more than one renal artery (18,26).

The fact that CT angiography images optimized for imaging only the renal arteries were not used in our study can be considered as an important limitation. It is difficult to show very thin vascular structures with routine abdominal computed tomography. This may be the reason why 3 or more renal artery variations were not observed on one side in our study. In addition, the insufficient number of subjects can be mentioned as one of the limitations of our study for the evaluation made through routine CT examinations.

CONCLUSION

Our study aimed to investigate the incidence of vascular variations of the kidney, which is crucial for interventional radiological procedures and surgical approaches, with increasing frequency of application. It is seen that these variations can be successfully demonstrated with the contrast-enhanced computed tomography procedure. For this reason, the importance of evaluating these variations becomes evident when preparing computed tomography reports.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The study was carried out with the protocol in accordance with the Declaration of Helsinki, and was submitted by the institutional review board with the approval number 17073117_050.06.*

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MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

The Relationship Between Impulsivity Level and Neutrophil / Lymphocyte Ratio, Platelet/ Lymphocyte Ratio and Mean Platelet Volume in Individuals Diagnosed with Gambling Disorder

Kumar Oynama Bozukluğu Tanısı Olan Bireylerde Dürtüsellik Düzeyi Ile Nötrofil/Lenfosit Oranı, Platelet/ Lenfosit Oranı Ve Ortalama Trombosit Hacmi Arasındaki Ilişki

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Abstract

Aim: Gambling disorder (GD) is a mental illness with an increasing frequency in society that characterized by the urge to gamble despite negative consequences and desire to quit. In this study, we aimed to examine the mean platelet volume (MPV), neutrophil/ lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and the relationship between these values and impulsivity in patients with GD.

Material and Method: 42 patients diagnosed with gambling disorder and 42 healthy controls were included in this study. Sociodemographic data form, Barratt Impulsivity Scale Short Form (BIS-11-SF) were administered to all participants, and then a complete blood count was requested from these individuals. NLR, PLR and MPV were measured according to complete blood count.

Results: The mean BSI-11-SF total score of the patient group was found to be statistically significantly higher than the control group ($p < 0.05$). It was found that while the motor impulsivity scores of GD patients increased, the MPV values significantly decreased ($r=-0.33$, $p = 0.03$). There was no significant difference between the patient and control groups in terms of NLR ($p = 0.288$), PLR ($p = 0.377$) and MPV ($p = 0.883$) values. In addition, in the patient group, there was a weak negative correlation between age and motor impulsivity score and a weak negative correlation between motor impulsivity score and MPV ($r=-0.33$, $p=0.03$), ($r=-0.31$, $p=0.04$).

Conclusion: It was concluded that an individual's diagnosis with gambling disorder had a high level of impulsivity, but there was no relationship between gambling and complete blood count parameters. Further studies are needed to explain the etiopathogenesis of gambling disorder.

Keywords: Gambling Disorder; neutrophil/lymphocyte; platelet/lymphocyte; platelet volume; impulsivity; blood parameter

Öz

Amaç: Kumar Oynama Bozukluğu (KOB), olumsuz sonuçlarına ve bırakma arzusuna rağmen sürekli kumar oynama dürtüsünün görüldüğü toplumda sıklığı giderek artan ruhsal bir hastalıktır. Bu çalışmada KOB tanılı hastalarda ortalama trombosit hacmi (OTH), nötrofil/lenfosit oranı (NLO), trombosit/ lenfosit oranı (TLO) ve bu değerlerin dürtüsellik ile olan ilişkisini incelemeyi amaçladık.

Materyal ve Metot: Bu çalışmaya KOB tanılı 42 hasta ve 42 sağlıklı kontrol grubu dahil edildi. Tüm katılımcılara sosyodemografik veri formu, Barratt Dürtüsellik Ölçeği Kısa Formu (BIS-11-KF) uygulandı ve ardından bu kişilerden tam kan sayımı istendi. NLO, TLO ve OTH değerleri tam kan sayımına göre ölçüldü.

Bulgular: Hasta grubunun BSI-11-KF toplam puan ortalaması kontrol grubuna göre istatistiksel olarak anlamlı derece yüksek bulundu ($p<0,05$). KOB hastalarının motor dürtüsellik puanları arttıkça OTH değerlerinin anlamlı olarak azaldığı tespit edildi ($r=-0,33$, $p=0.03$). Hasta ve kontrol grubu arasında NLO ($p=0,288$), TLO ($p=0,377$) ve OTH ($p=0,883$) değerleri arasında anlamlı farklılık saptanmadı. Ayrıca hasta grubunda yaş ile motor dürtüsellik puanı arasında negatif yönde zayıf ilişki, motor dürtüsellik puanı ile OTH arasında negatif yönde zayıf ilişki saptandı ($r= -0,33$, $p=0,03$), ($r= -0,31$, $p=0,04$).

Sonuç: Kumar oynama bozukluğu tanısı mevcut kişilerin dürtüsellik düzeyinin yüksek olduğu ancak incelenen tam kan sayımı parametreleri ile kumar oynama arasında ilişkinin olmadığı sonucuna varıldı. Kumar oynama bozukluğunun etiyopatogenezi için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Kumar oynama bozukluğu; nötrofil/ lenfosit; trombosit/ lenfosit; trombosit hacmi; dürtüsellik; kan parametresi

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INTRODUCTION

Gambling disorder (GD) is a behavioral addiction that brings with it problems such as needing to gamble with more and more money in order to provide the desired pleasure, having difficulty quitting the gambling habit, borrowing to obtain money, lying (1). It is estimated that between 0.12% and 5.8% of adults experience problems due to gambling (2). Although an increasing number of neuroimaging and neurobiological studies have been carried out in recent years, the etiopathogenesis of gambling has not yet been fully elucidated (3). Since it is accompanied by impulsivity, pathological gambling disorder which manifests itself with features such as inattention, risk taking, novelty seeking, excitement and pleasure seeking, defined as not being able to prevent responding to an action is classified under the title of "Impulse-Control Disorders Not Elsewhere Classified" in DSM-IV-TR (4,5). It is known that inflammation is important in the pathogenesis of many psychiatric disorders accompanied by impulsivity (6, 7). Leukocyte counts and subtypes are some of the determinants of chronic inflammation (8, 9). NLR obtained by the ratio of neutrophil and lymphocyte counts to each other, is thought to be an important parameter that can be used in the follow-up of psychiatric disorders, as it is easy to obtain and inexpensive. It is known that suicide attempts are common in individuals with impulsive and aggressive behavior patterns and their NLR values are higher than healthy controls (10-12).

Platelets play a role in the inflammation process together with leukocytes and progenitor cells (13). The platelet/lymphocyte ratio (PLR) is calculated as the ratio of platelet to lymphocyte count and is a simple indicator commonly used in inflammation-related conditions such as cardiovascular diseases and chronic diseases (14). Avcil et al. investigated this rate in children with impulsivity and attention deficit, and suggested that inflammation may play a role in the pathogenesis of the disease, and therefore PLR can be used as a biomarker (15). Mean platelet volume (MPV) is used as a measure of platelet size and is known to be an indicator of platelet activity (16). MPV was found to be higher in patients with depression compared to the healthy control group (17), and lower in manic patients (18).

Recently, hematological parameters have also been investigated in substance addictions often accompanied by impulsive behaviors (19, 20). Neurobiological findings show that pathological gambling and drug addiction share common etiopathological pathways (21, 22). In our literature review, we could not find any studies examining NLR, PLR and MPV parameters in individuals diagnosed with gambling disorder, which is a behavioral addiction and whose etiopathogenesis has not been clarified yet. In the light of the studies we have given above, we investigated whether NLR, PLR and MPV values, which are easy and inexpensive options that can be suitable for routine use due to the possible relationship of the inflammation system with impulsivity, can be useful as a biomarker that can be used in early diagnosis and follow-up in patients with gambling disorder.

MATERIAL AND METHOD

E-97132852-050.01.04-10880 numbered ethics committee approval was obtained for this study from the Fırat University Non-Interventional Research Ethics Committee and all stages were carried out in accordance with the Declaration of Helsinki. In this cross-sectional study, 55 patients diagnosed with applied to the Fırat University psychiatry outpatient clinic and were treated as outpatients or inpatients and 42 healthy volunteer hospital employees who had not received psychiatric treatment before and had no history of systemic disease were included. After obtaining the approval of the ethics committee, the patients who were followed up with the diagnosis of gambling disorder from the Fırat University psychiatry clinic were called to the psychiatry outpatient clinic between 15.01.2021 and 05.02.2021, after written consent was obtained, the patients completed the scale and blood tests were taken. Persons who were unable to answer the questions asked, had a history of neurological disease, had hearing and speech impairment, had a history of alcohol and substance use in the last 6 months, and had additional psychiatric diagnoses other than GD and adjustment disorder in the past were not included in the study. In addition, a detailed history was taken and the patient registry system was reviewed to exclude systemic diseases that may affect hemogram values. Individuals with additional systemic disease were not included in the study. An interview was made by the psychiatrist in the psychiatry outpatient clinic. Eight of the participants did not accept to participate in the study afterwards, and 5 of them were excluded from the study because they filled the scale incompletely. Our sample group consisted of 42 male patients and 42 male healthy controls with similar sociodemographic characteristics as the patient group. Since male gender is a risk factor for GD and the lifetime prevalence of this disorder was found to be higher in males in gender studies, the sample group consisted entirely of male patients (23). Interviews were conducted in the psychiatry outpatient clinic in a structured manner according to DSM-5, with a duration of at least 30 minutes. Written consent was obtained from all participants before the evaluation. Sociodemographic data form prepared by us, Barratt Impulsivity Scale Short Form (BIS-11-SF) was applied to all participants. Afterwards, 5 cc venous blood samples were taken from the antecubital vein in a biochemistry tube for hemogram analysis from all of the participants and the samples were evaluated in the biochemistry laboratory of our hospital. The samples were studied with the "CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, U.S.A.)" device within half an hour and the results of the patients were uploaded to the patient registration system within two hours at the latest. According to this device, reference ranges are

2.1–6.1 (10e3/uL) for neutrophil, 1.3–3.5 (10e3/uL) for lymphocyte, 140-360 (10e3/uL) for platelet and 7- 9 fl for mean platelet volume (MPV).

Scales Used in the Study

1) Sociodemographic and Clinical Data Form: A sociodemographic and clinical data form prepared by us considering the aims of the study was used, in accordance with the information obtained through clinical experience and literature review. This form is a semi-structured form that includes sociodemographic information such as age, gender, marital status, educational status, occupation, place of residence, economic status, family structure.

2) Barratt Impulsivity Scale Short Form (BIS-11-SF): It was developed by Barratt in 1959 and its latest form, BIS-11, was developed in 1995. It is a 30-item self-report scale evaluated on a 4-point likert scale, with items 1=rarely/never; 2=sometimes; 3=often; 4=almost always/always. There are 3 subscales that do not overlap with each other: Attention Impulsivity (A), Non-Planning (NP), and Motor Impulsivity (M) (24). BIS-11-SF scores were found to be related to behavior and personality traits in studies conducted in normal populations. It is frequently used in psychiatric studies due to its simplicity and practicality. The Turkish validity and reliability study was performed by Tamam et al. (25) in 2008. In our study, the Cronbach alpha value was found to be 0.80.

Statistical analysis

Statistical analyzes were performed using the SPSS 16.0 (SPSS Inc., Chicago) package program. A p value below 0.05 was considered statistically significant. Whether the data showed normal distribution or not was examined with the Kolmogorov-Smirnov test. Student-t test was used for normally distributed continuous data, and chi-square test was used to evaluate categorical data. Pearson correlation analysis was performed to determine the relationship between the measurements.

RESULTS

While the mean age of the people included in the study was 34.35±10.25 in the patient group, it was 33.35±7.47 in the control group. Statistically significant differences were found in parameters such as economic status, occupation, presence of additional psychiatric disease, previous psychiatric treatment, smoking and alcohol use when the patient group and the control group were compared in terms of sociodemographic ($p<0.05$). There was no difference in terms of age, gender, marital status, educational status, place of residence and drug use. The comparison of the sociodemographic data of the patient group and control group is summarized in Table 1.

Table 1. Comparison of sociodemographic data

	Case group (n:42) n (%)	Control group (n:42) n (%)	P
Age	34.35 ± 10.25	33.35 ± 7.47	0.611
Gender			
Male	42 (%100)	42 (%100)	
Marital status			
Married	25 (%59.5)	22 (%52.4)	0.510
Single	17 (%40.5)	20 (%47.6)	
Education status			
Middle school and below	17 (%40.5)	9 (%21.4)	0.590
High school and above	25 (%59.5)	33 (%78.6)	
Residential area			
Village / District	14 (%33.3)	9 (%21.4)	0.221
City center	28 (%66.7)	33 (%78.6)	
Economical situation			
Low	33 (%78.6)	16 (%38.1)	0.001
Middle	9 (%21.4)	23 (%54.8)	
High	0	3 (%7.1)	
Occupation			
Not working	15 (%35.7)	6 (%14.3)	0.023
working	27 (%64.3)	36 (%85.7)	
Organic disease			
None	42 (%100)	42 (%100)	
Drug use			
None	42 (%100)	42 (%100)	

Presence of additional psychiatric disorder			
Available	9 (%21.4)	0	0.002
None	33 (%78.6)	42 (%100)	
History of previous psychiatric treatment			
Available	11 (%26.2)	3 (%7.1)	0.019
None	31 (%73.8)	39 (%92.9)	
Smoking			
Yes	40 (%95.2)	11 (%26.2)	0.000
No	2 (%4.8)	31 (%73.8)	
Alcohol and substance use			
Yes	8 (%19)	0	0.005
No	34 (%81)	42 (%100)	
Number of games played			
None	0	42 (%100)	
1	21 (%50)	0	
More than 1	21 (%50)	0	

Mean±SD= Mean±Standard Deviation. n (%)= Number and percent

BIS-11-SF scale and subscale scores are given in Table 2, and the BIS-11-SF total score of the patient group was found to be statistically significantly higher than the control group ($p<0.05$). All BIS-11-SF subscale mean scores were higher in the patient group than in the control group, and this difference was statistically significant ($p<0.05$).

No statistically significant difference was observed between the patient and control groups in terms of MPV, NLR and PLR values given in Table 3 ($p=0.833$, $p= 0.288$, $p=0.377$).

The correlation values between scale scores and parameters are given in Table 4. The relationship of the variables with each other was analyzed separately in both groups with the Pearson correlation test. In the patient group, there was a weak negative correlation between age and motor impulsivity score, a weak negative correlation between motor impulsivity score and MPV, and a strong positive correlation between NLR and PLR ($r= -0.33$, $p=0.03$), ($r= -0.31$, $p=0.04$), ($r=0.80$, $p<0.001$). In the control group, a weak positive correlation was found between motor impulsivity score and NLR ($r=0.34$, $p=0.02$).

Table 2. BIS-11-SF scale and subscale scores

	Hasta (n:42) Ort.±ss	Kontrol (n:42) Ort.±ss	P
Attention impulsivity score	26.42 ± 8.49	17.78 ± 5.51	0.000
Motor impulsivity score	29.07 ± 5.80	18.26 ± 4.65	0.000
Non-planning score	27.59 ± 8.47	20.21 ± 5.84	0.000
BIS-11-SF total score	83.09 ± 15.14	56.26 ± 9.64	0.000

Mean±SD= Mean±Standard Deviation

Table 3. Comparison of blood parameters

	Hasta (n:42) Ort.±ss	Kontrol (n:42) Ort.±ss	P
Ortalama trombosit volümü (OTH)	9.83 ± 1.38	9.77 ± 1.29	0.833
Nötrofil / Lenfosit oranı	1.72 ± 1.21	1.99 ± 1.10	0.288
Trombosit / Lenfosit oranı	98.07 ± 55.09	107.29 ± 38.64	0.377

Mean±SD= Mean±Standard Deviation

Table 4. Correlation values between scale scores and parameters

		Case group (n:42)				Control group (n:42)			
		Age	MPV	NLR	PLR	Age	MPV	NLR	PLR
Motor impulsivity	r	-0.330	-0.313	-0.234	0.021	0.021	0.192	0.340	0.100
	p	0.033	0.043	0.136	0.895	0.895	0.222	0.028	0.528
Non-planning	r	-0.120	-0.281	-0.249	0.255	0.255	-0.071	0.156	0.008
	p	0.449	0.072	0.112	0.103	0.103	0.656	0.325	0.960
Attention impulsivity	r	0.150	0.170	0.014	-0.260	-0.260	0.133	0.051	-0.090
	p	0.344	0.282	0.928	0.096	0.096	0.400	0.751	0.571
BIS-11-SF total score	r	-0.110	-0.182	-0.221	0.016	0.016	0.126	0.287	0.002
		0.489	0.249	0.160	0.920	0.920	0.426	0.065	0.991

MPV: Mean Platelet Volume, NLR: Neutrophil / Lymphocyte Ratio, PLR: Platelet / Lymphocyte Ratio

DISCUSSION

In this study, the level of impulsivity and some hemogram parameters were compared between patients diagnosed with GD and a healthy control group. In our study, we found that impulsivity was high in individuals diagnosed with GD, and mean platelet volumes decreased as motor impulsivity increased in this patient group. Chowdhury et al. (26) mentioned in a meta-analysis study that motor impulsivity may play a role in the pathogenesis of this disease in individuals diagnosed with gambling disorder. Altintas et al. (27) found no difference in the total score of impulsivity in 30 people diagnosed with GD compared to the control group. Again in 2015, the attention, motor and planlessness subgroup mean scores of the same scale in 51 men and 53 women diagnosed with GD were found to be similar to the control group (28). It has been shown that GD patients are less successful than healthy controls in providing impulse control due to the deterioration in the behavioral inhibition control system (29, 30). Although our sample group is small, it is in line with the studies in the literature that predominantly show the relationship between gambling disorder and impulsivity, supporting that impulsive behaviors are at the forefront in the clinic of these patients. In our study, NLR, PLR, and MPV values were also compared between patients diagnosed with GD and healthy controls. Although the impulsivity scores of the patients were significantly higher than the controls, we did not find a significant difference between the patient and control groups in terms of MPV, NLR and PLR ratios. Variable results have been reported in studies examining the relationship between impulsivity and hemogram parameters. In a study including male and female patients who showed impulsive personality traits and attempted suicide, the NLR value was found to be higher in the case group than in the control group (12). However, both NLR and PLR values in children diagnosed with attention deficit hyperactivity disorder (ADHD) were found to be similar to healthy controls (31). While an increased NLR level was found in patients with bipolar disorder with a history of suicide attempt, it was reported that NLR levels were not different in patients with bipolar disorder who did not attempt suicide compared to the healthy control group (32). In another study, PLR values were found to be lower in individuals diagnosed with opiate addiction compared to the control group, while in a study conducted in individuals diagnosed with alcohol use disorder, no difference was found between the patient and control groups in terms of PLR (33, 34). In a study that included patients diagnosed with autism, ADHD, and a control group, MPV values were compared between the groups and no significant difference was found (35). In another study, MPV values were found to be significantly higher in adults diagnosed with ADHD compared to the control group (36). In our study, we found that MPV values decreased significantly as the motor impulsivity scores of GD patients increased, in contrast to the diseases in which impulsivity was seen in the clinic. These inconsistent results suggest that it may vary due to the characteristics of the participants (eg, the effects of substances such as alcohol and opiates on blood parameters, the age of the patients, etc.). There are studies reporting that gambling disorder is not associated with education period and marital status (24, 37). In our study, no difference was found between the patients diagnosed with GD and the control group in terms of marital status and education period. This shows that the sociocultural level may not be protective in the occurrence of this disorder. It is known that pathological gambling is more common at younger ages (38). In our study, consecutive patients diagnosed with GD were young adults, consistent with the literature, and it was observed that motor impulsivity increased with decreasing age in the patient group (39). It has been found that gambling is more common in people with low

economic status in the USA (40). In this study, it was observed that the economic status of the patients was low. Smoking and gambling are often seen together (41). In the study, 95.2% of the patient group was smoking. We included patients who did not have a history of alcohol and substance use in the last 6 months, but 19% of the patients had a history of alcohol and substance use more than 6 months ago. The comorbidity of alcohol and substance use in individuals diagnosed with GD was found to be 19-50% (28). Our findings support other studies in this respect and remind us that other habits of patients should be questioned.

The most important limitation of our study is that the number of patients is relatively small and only hemogram parameters (not checking the testosterone level, lipid level, etc. that may be related to impulsivity) were examined. In addition, the patient group consists of patients who voluntarily applied to the psychiatry clinic for treatment. There is a need to identify patients with gambling disorder who do not apply for treatment and to conduct more extensive studies.

CONCLUSION

We think that this study will contribute to the development of new ideas about the relationship of GD with hematological parameters. However, more studies based on the cause-effect relationship are needed to fully explain this relationship and to develop new approaches on the follow-up and treatment of GD.

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Conflict of Interest: *There is no conflict of interest between the authors.*

Ethical Approval: *E-97132852-050.01.04-10880 numbered ethics committee approval was obtained for this study from the Fırat University Non-Interventional Research Ethics Committee and the study was conducted in accordance with the Declaration of Helsinki.*

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Araştırma Makalesi / Research Article

Monocyte to HDL Ratio in The Prediction of Carotid Artery Intima-Media Thickness

Karotis Arter Intima-Media Kalınlığının Tahmininde Monosit-HDL Oranı

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Abstract

Aim: In this study, we aimed to determine whether an increased monocyte count to high-density lipoprotein (MHR) would predict increased carotid intima-media thickness (IMT).
Material and Method: All consecutive subjects presenting to the cardiology outpatient clinic of our institute were enrolled in this cross-sectional study. Subjects with cardiovascular and inflammatory diseases were excluded. Subjects were divided into two groups according to carotid IMT: those with carotid IMT >0.9 mm (increased) and those with carotid IMT ≤0.9 mm (normal). The difference in MHR between the two groups was the primary outcome measure of the study.
Results: The MHR of the subjects with increased IMT was significantly higher than that of subjects with normal IMT (16.7 ± 5.7 vs. 12.8 ± 5.5, p <0.001). Logistic regression analysis demonstrated that age (OR: 1.202, 95% CI: 1.126-1.284, p<0.001) and MHR (OR: 1.190, 95% CI: 1.097-1.291, p<0.001) were significant predictors for a carotid IMT of >0.9 mm. ROC curve analysis revealed an MHR value of 13.4 as a cut-off in the identification of subjects that had increased IMT, with a sensitivity of 72% and specificity of 60.7%.
Conclusion: The inflammation marker MHR can be used as a simple and cost-effective marker to predict increased carotid IMT which is accepted as the indicator of subclinical atherosclerosis.

Keywords: Coronary artery disease, monocytes, high density lipoprotein, HDL, carotid intima-media thickness

Öz

Amaç: Bu çalışmada, artmış monosit sayısının yüksek yoğunluklu lipoprotein düzeylerine oranı (MHO)'nun artmış karotis intima-media kalınlığı (İMK)'yi yordayıp yordamayacağını belirlemeyi amaçladık.
Materyal ve Metot: Kurumumuzun kardiyoloji polikliniğine ayaktan başvuran ardışık tüm olgular bu kesitsel çalışmaya alındı. Kardiyovasküler ve enflamatuar hastalıkları olan olgular hariç tutuldu. Olgular karotis İMK'ye göre iki gruba ayrıldı: karotis İMK>0,9 mm (artmış) ve karotis İMK≤0.9 mm (normal) olanlar. MHO'daki iki grup arasındaki fark, çalışmanın birincil sonuç ölçütüdür.
Bulgular: Artmış İMK'ye sahip olguların MHO'su, normal İMK'ye sahip olgulardan anlamlı olarak daha yüksekti (16,7 ± 5,7'ye karşı 12,8 ± 5,5; p<0,001). Lojistik regresyon analizi, yaşın (OR: 1,202, 95% CI: 1,126-1,284; p<0,001) ve MHR (OR: 1,190, 95% CI: 1,097-1,291; p<0,001)'nin >0,9 mm'lik bir karotis İMK'si için önemli prediktörler olduğunu gösterdi. ROC eğrisi analizi, %72 duyarlılık ve %60,7 özgüllük ile 13,4'lük bir MHO kesme değerinin artmış İMK'nin saptanmasında kullanılabileceğini gösterdi.
Sonuç: Enflamasyon belirteci MHO, subklinik aterosklerozun göstergesi olarak kabul edilen artmış karotis İMK'sini tahmin etmek için basit ve maliyet-etkin bir belirteç olarak kullanılabilir.

Anahtar Kelimeler : Koroner arter hastalığı, monositler, yüksek yoğunluklu lipoprotein, HDL, karotis intima-media kalınlığı

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INTRODUCTION

Coronary artery disease (CAD) is the leading cause of morbidity and mortality worldwide. Despite the gradual decline in the mortality of CAD over the last decades, particularly in the western world, CAD is still responsible for one-third of all deaths among individuals older than 35 years (1-3). The overall disease burden and related morbidity and mortality of CAD have led to a search for solutions that could aid early diagnosis and management. It is now well-known that early diagnosis and interventions, even in subjects without symptoms, improves prognosis. Carotid artery intima-media thickness (IMT) is utilized as a non-invasive measurement of early atherosclerotic changes in the carotid artery wall. It is a surrogate marker for subclinical cardiovascular disease and cardiovascular events (4, 5). The ACCF/AHA guidelines recommend using carotid IMT for the assessment of individuals presenting with an intermediate risk of CAD (6). Despite its wide availability, measurement of carotid IMT is time-consuming and requires familiarity with the technique.

Since inflammation is one of the basic hallmarks of atherosclerosis, and the monocytes are a major component of the inflammatory processes during atherosclerosis, monocyte to high-density lipoprotein cholesterol (HDL) ratio (MHR) –which is associated with inflammation– has recently been investigated in subjects with atherosclerotic cardiovascular disease (7, 8). However, the role of MHR in the prediction of subclinical atherosclerosis has not been studied yet. Given the strong association between the inflammatory state and MHR, we hypothesized that MHR would be higher in subjects with subclinical atherosclerosis.

The present study aimed to compare MHR values in subjects with and without increased carotid IMT and determine whether increased MHR would predict increased carotid IMT.

MATERIAL AND METHOD

Study Design

All consecutive subjects aged between 30 and 60 years admitted to our institute's cardiology outpatient clinic, and between June 2017 and August 2017, were enrolled in this cross-sectional study. Subjects with diabetes mellitus, hypertension, or any structural or functional cardiovascular disease on cardiac examination and screening tests (including electrocardiography and echocardiography) were excluded from the study. To diminish any confounders that might influence monocyte levels, subjects with any hematological, immunological, or inflammatory disease that could result in monocytosis were excluded from the study, as well as patients with malignancies and those receiving corticosteroid therapy. The protocol was approved based on the ethical standards of the Declaration of Helsinki. The permissions and consents required for the study were obtained from the Adıyaman University Biomedical Research Ethics Committee (Approval number = 2017/3-7). Informed consent was obtained from the subjects.

Fasting venous blood samples were obtained, and the following parameters were measured: complete blood count, fasting glucose, urea, creatinine, C-reactive protein, and lipid profile (Olympus AU-640 analyzer, Mishima Olympus Co. Ltd, Shizuoka, Japan). At the Adiyaman University Training and Research Hospital biochemistry laboratory, hematological parameters were studied on the "CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, U.S.A.)" device. Existing cigarette smoking was defined as >10 cigarettes per day. Body mass index (BMI) was calculated using the standard formula of weight (kg)/ height squared (m2). A detailed medical history of each subject was also recorded. All participants underwent transthoracic echocardiography and carotid intima-media thickness measurement with a commercially available cardiac ultrasound system (Vivid E9, GE Medical Systems, Horten, Norway). The left lateral decubitus pose was used for all patients. All patients were examined in detail using the standard two-dimensional echocardiographic method. The same investigator performed all measurements.

Primary Outcome

Subjects were divided into two groups according to carotid IMT values: Those with a carotid IMT greater than 0.9 mm (increased IMT group) and those with a carotid IMT equal to or lower than 0.9 mm (normal IMT group) (9, 10). The difference in MHR values between the two groups and the relationships between MHR and carotid IMT values were the primary and secondary outcome measures of the study.

Statistical Analysis

All analyses were performed on SPSS version 21 (SPSS Inc., Chicago, IL, USA). The sample was divided into two based on the carotid IMT 0.9 mm. Student t-test was used to analyze the differences in numerical data between groups, and a chi-square test was used to analyze the differences of categorical data. Correlation analysis was performed to evaluate the relationship between carotid IMT and MHR, sociodemographic characteristics, and blood parameters. Logistic regression analysis was applied to measure the effect of age, smoking, BMI, and blood parameters on carotid IMT. ROC curve analysis has used the sensitivity and specificity of MHR for predicting carotid artery IMT. The values less than 0.05 were accepted to show statistically significant relationships.

RESULT

A total of 200 subjects (mean age 41.7 ± 8.6 years, 49.5% male) were enrolled in this cross-sectional study. Carotid IMT was >0.9 mm in 50 of the participants (mean carotid IMT 0.93 ± 0.1 mm) and was ≤0.9 mm in the remaining 150 participants (mean carotid IMT 0.56 ± 0.1 mm).

Demographic features and laboratory measurements of the study groups are presented in Table 1. Age, BMI, fasting glucose level, active smoking, total and LDL

cholesterol, monocyte count, and platelet count were significantly higher in subjects with increased carotid IMT than normal carotid IMT. The MHR of the subjects with increased carotid IMT was also substantially higher than that of subjects with normal carotid IMT values (16.7 ± 5.7 vs. 12.8 ± 5.5, p<0.001).

As shown in Table 2, correlation analysis revealed that carotid IMT was significantly correlated with MHR (r=0.325, p<0.001), age (r=0.893, p<0.001), monocyte count (r=0.261, p<0.001), fasting glucose (r=0.261, p<0.001), blood urea nitrogen (r=0.184, p<0.001), total cholesterol (r=0.356, p<0.001), LDL cholesterol (r=0.313, p<0.001), triglyceride level (r=0.293, p<0.001), leukocyte count (r=0.185, p=0.009), neutrophil count (r=0.148, p=0.037), lymphocyte count (r=0.153, p=0.037), whereas it was negatively correlated with HDL cholesterol level (r=-0.210, p=0.003).

Logistic regression analysis demonstrated that age (OR: 1.202, 95% CI: 1.126-1.284, p<0.001) and MHR (OR: 1.190, 95% CI: 1.097-1.291, p<0.001) were significant predictors for a carotid IMT of >0.9 mm (Table 3). ROC curve analysis revealed an MHR cut-off value of 13.4 to identify subjects with increased carotid IMT with a sensitivity of 72% and specificity of 60.7% (Figure 1).

Table 1. Sociodemographic and Clinical Variables of the Groups

	Carotid IMT ≤ 0.9 mm (n=150)	Carotid IMT > 0.9 mm (n=50)	p value
Age (year)	38.5 ± 6.6	51.4 ± 6.6	<0.001**
Gender, Female (n, %)	76 (50.7%)	25 (50%)	0.935
Smoking (n, %)	118 (78.7%)	49 (98%)	<0.001**
BMI (kg/m2)	28 ± 4.6	27.8 ± 3.4	0.010*
Carotid IMT (mm)	0.56 ± 0.1	0.93 ± 0.1	<0.001**
Glucose (mg/dL)	72.8 ± 26.4	125.5 ± 35.2	0.003*
BUN (mg/dL)	28 ± 8.7	29.4 ± 7.3	0.161
Creatinine (mg/dL)	0.73 ± 0.16	0.75 ± 0.19	0.156
Total Cholesterol (mg/dL)	180.8 ± 40.7	204.8 ± 42.2	0.002*
HDL Cholesterol (mg/dL)	43.3 ± 9.4	40.7 ± 7.7	0.052
LDL Cholesterol (mg/dL)	105 ± 30.6	122.2 ± 32.3	0.001*
Triglyceride (mg/dL)	157.8 ± 88.3	192.6 ± 115.4	0.060
WBC (/mm3)	8459.9 ± 1968.5	8948.3 ± 1740.3	0.069
Hemoglobin (g/dL)	15.7 ± 8.9	15.8 ± 11.7	0.289
Neutrophil Count (/mm3)	4891.6 ± 1574.1	5074.8 ± 1393.6	0.337
Lymphocyte Count (/mm3)	2637.9 ± 777	2886.8 ± 944.7	0.138
Monocyte Count (/mm3)	525.6 ± 187.4	657.6 ± 185.8	<0.001**
Platelet Count (x103/mm3)	251.2 ± 124.8	277.3 ± 92.1	0.133
MHR	12.8 ± 5.5	16.7 ± 5.7	<0.001**
CRP (mg/L)	0.43 ± 0.43	0.75 ± 0.19	0.014

Table 2. Correlations Between Carotid Artery IMT Value and Selected Variables

	Carotid IMT	
	r	p
MHR	0.325	<0.001**
HDL Cholesterol	-0.210	0.003*
Monocyte Count	0.261	<0.001**
Age	0.893	<0.001**
Gender	0.096	0.175
BMI	0.129	0.070
Smoking	-0.127	0.073
Fasting Glucose	0.261	<0.001**
BUN	0.184	0.009*
Creatinine	0.070	0.325
CRP	0.035	0.620
Total Cholesterol	0.356	<0.001**
LDL Cholesterol	0.313	<0.001**
Triglyceride	0.293	<0.001**
Leukocyte Count	0.185	0.009*
Hemoglobin	-0.012	0.871
Neutrophil Count	0.148	0.037*
Lymphocyte Count	0.153	0.030*
Platelet Count	0.037	0.601

Table 3. Logistic Regression Analysis Demonstrating the Predictors of Increased Carotid IMT

	Odds ratio	95% Confidence Interval	p value
Age	1.202	1.126-1.284	<0.001**
BMI	0.993	0.875-1.128	0.920
Smoking	0.083	0.051-1.202	0.083
Glucose	1.001	0.995-1.008	0.750
BUN	0.987	0.937-1.039	0.611
Total Cholesterol	1.010	0.986-1.034	0.415
LDL Cholesterol	0.987	0.963-1.012	0.316
Triglyceride	0.966	0.990-1.002	0.235
MHR	1.190	1.097-1.291	<0.001**

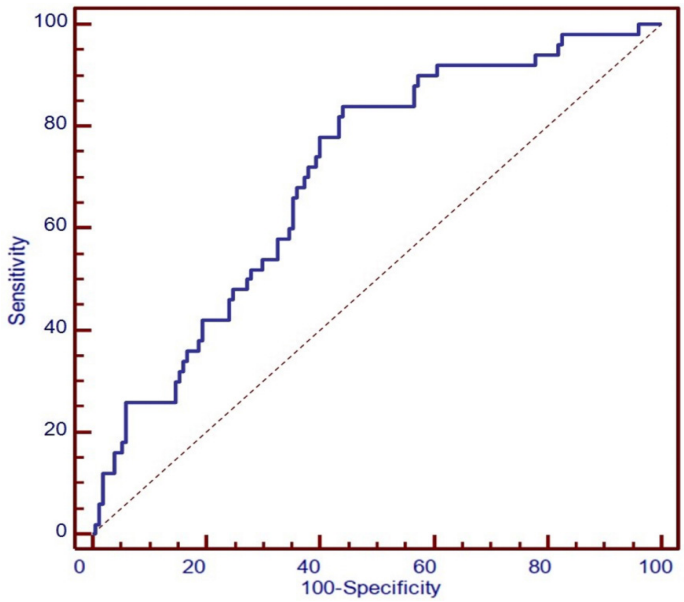

Figure 1. ROC Curve Demonstrating the Sensitivity and Specificity of Monocyte to HDL Ratio for Predicting Carotid Artery Intima Media Thickness

DISCUSSION

Results of the present study demonstrate that MHR is significantly higher in subjects with increased carotid IMT. In addition to the significant correlation between MHR and carotid IMT, MHR was an independent predictor of increased carotid IMT. Moreover, MHR can identify subjects with increased carotid IMT with relatively high sensitivity even though specificity was moderate. These results are promising, particularly when considering that they were obtained from a consecutively enrolled patient group that did not include those with known heart diseases.

Currently, CAD is accepted as a multifactorial disease, and the healing response to vascular injury is considered to allow the initiation and progression of the atherosclerotic plaque (9-11). The presence of hypercholesterolemia is the primary trigger for the initiation of atherosclerosis. In the next step, monocytes adhere to the vascular endothelium and migrate through mechanisms that involve VCAM-1 and selectins. Oxidation of the LDL promotes the secretion of the macrophage chemotactic protein 1. Monocytes change into macrophages within the arterial intima and express scavenger receptors, thus converting into foamy macrophages, which play a critical role in the occurrence and development of atherosclerosis (12). Beyond their activity inside the arterial wall, several immune stimulatory agents and cytokines presenting in blood circulation affect the circulating monocytes and, therefore, contribute to the pathogenesis of CAD and its complications (13). In this briefly explained the complex process, inflammatory activity is likely responsible for plaque instability which may promote plaque rupture, fissuring, or erosion; thus, resulting in the acute presentations of CAD such as unstable angına (14).

High-density lipoprotein, which has been acknowledged as an anti-atherosclerotic lipoprotein under normal physiological conditions, neutralizes the atherosclerotic role of the monocytes. Also, HDL provides various anti-atherosclerotic properties, independent from the monocyte-blocking functions (15-19). The atherosclerotic functions of the monocytes and monocyte-blocking properties possessed by HDL have led to the suggestion that MHR could be a valuable indicator of atherosclerosis. Tani et al. have demonstrated in an intravascular ultrasound study of 114 patients with established CAD that treatment with 40 mg pravastatin leads to a significant reduction in plaque volume and monocyte count in addition to a significant increase in HDL cholesterol level. Multivariate analyses revealed that the rise in serum HDL cholesterol and decreased monocyte count were independent predictors of plaque regression (19). Kundi et al. (20) have shown in 428 patients with stable CAD that MHR was significantly higher in patients with high Syntax scores (≥ 23) and that an MHR value >24 was predictive for a high Syntax score with a sensitivity of 66% and a specificity of 65.1%. Two studies conducted by Akboga et al. have reported that MHR could independently predict CAD as indicated by the high (≥ 23) Syntax score and saphenous vein graft stenosis of >50% (21, 22). Several studies also demonstrate the association between an increased MHR and stent thrombosis, stent restenosis, and no-reflow phenomenon after PCI of the infarct-related artery, in-hospital MACE, and even with in-hospital mortality and long-term mortality (23-26).

This study is the first to report the predictive role of MHR on carotid IMT. Our findings demonstrate that MHR value is significantly correlated with carotid CIMT and that an MHR value of >13.4 was predictive for increased carotid IMT (≥0.9 mm). Given its correlation with carotid IMT and its role in identifying increased carotid IMT, we suggest that the calculation of MHR can be used as a simple, cost-effective, and highly predictive marker of subclinical atherosclerosis. Combining MHR with carotid IMT in subjects with established CAD will probably increase the carotid IMT in predicting the early stages of atherosclerosis. Further studies are required to address the usefulness of the combination of MHR and carotid IMT in detecting subclinical atherosclerosis.

This study also has some limitations to be mentioned. Although we suggest that MHR values are predictive for the presence of subclinical atherosclerosis, this suggestion arises from the assumption that carotid IMT is a robust predictor for the early stages of atherosclerosis. However, the golden standard for detecting atherosclerosis is coronary angiography; however, the study population included in this study did not have CAD established by coronary angiography. Although this is a limitation concerning its usefulness in evaluating the degree of CAD and relationships with other parameters associated with CAD, it is also an advantage in determining its efficacy in previously healthy populations. Additionally, increased carotid IMT is currently accepted as an indicator of

endothelial dysfunction and early atherosclerosis; therefore, the correlation between MHR values and increased carotid IMT is very likely an indication of the presence of subclinical atherosclerosis.

CONCLUSION

The Monocyte-to-HDL ratio is significantly correlated with carotid IMT values. MHR also appears as an independent predictor of increased carotid IMT. We suggest that MHR can be used as a cost-effective and straightforward marker of inflammation for predicting the presence of increased carotid IMT, which is accepted as a reliable indicator of subclinical atherosclerosis.

The authors declare that this study has received no financial support.

Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *The protocol was approved based on the ethical standards of the Declaration of Helsinki. The permissions and consents required for the study were obtained from the Adıyaman University Biomedical Research Ethics Committee (Approval number = 2017/3-7). Informed consent was obtained from the subjects.*

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Araştırma Makalesi / Research Article

The Effect of Blood Groups on Infection and Prognosis of SARS-CoV-2

Kan Gruplarının SARS-CoV-2 Enfeksiyonu ve Prognozu Üzerine Etkisi

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Abstract

Aim: This study aimed to investigate the effect of blood groups on the risk and prognosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the infected/source cases and contact individuals.
Material and Method: This study was designed as a descriptive and retrospective study. The individuals who were in contact with the SARS-CoV-2main/source cases and followed at home were included in the study.The distribution of the participants according to their blood groups was assessed. Patients were divided into three groups as group 1 including source/main cases, group 2 including SARS-CoV-2contacts who were living in the same house with the source case and followed up, and group 3 including contacts who were followed up in the same house but did not develop SARS-CoV-2 during the follow-up.
Results: While the rate of Non-O blood group was the highest (n=365, 39.4%) in group 2the rate of O blood group was the highest (n=190, 42.8%) in group 3 (p:0.028). While the rate of Rh positive blood group was high in group 1 that of Rh negative blood group was higher in group 3 (p:0.000). For other variables, the presence of a chronic disease was more in group 1 (p:0.000). Rh (+) blood group (OR:0.464, p:0.010, %95 Cl: 0.306 ~ 0.703) was among the factors affecting the development of the infection.
Conclusion: Patients infected with SARS-CoV-2 mostly had A, Non-O blood group and Rh positivity. Having Rh (+) blood group may have increased the rate of infection development in high-risk household contacts. After patients in this blood group were detected as contacts a closer follow-up may be necessary to decrease morbidity.

Keywords: SARS-COV-2; ABO and Rh blood group; comorbid diseases

Öz

Amaç: Bu çalışmanın amacı, asıl/kaynak vakalar ve temaslı olan vakalarda kan gruplarının Ciddi Akut Solunum Yolu Sendromu 2 (SARS-CoV-2) riskini ve prognozu nasıl etkilediğini araştırmaktır.
Materyal ve Metot: Çalışmamız tanımlayıcı retrospektif olarak planlanmıştır. SARS-CoV-2 bulunan asıl/kaynak vakalar ile temaslı olup evde takip edilen bireyler dahil edilmiştir. Katılımcıların kan gruplarına göre dağılımları incelenmiştir. Hastalar 1.grup, kaynak/asıl vakalardan, 2.grup ev içi temaslı olup karantina sürecinde SARS-CoV-2 olan hastalar, 3.grup ev içi temaslı olup karantina sürecinde SARS-CoV-2 gelişmeyen bireyler olarak üç gruba ayrıldı.
Bulgular: Çalışmaya 1451 kişi dâhil edilmiştir. Yaş ortancası 41 idi. Gruplar arasında ABO kan grupları açısından fark yoktu ama A kan grubu 1. Grupta (% 45.4) en fazla orandaydı (p:0.61). Non-O kan grubu 2.grupta (%39.4) en fazla iken, O kan grubu da 3.grupta (%42.8) en fazla idi (p: 0.028). Rh pozitif kan grubu 1. grupta fazla idi. Rh negatif kan grubu 3. grupta daha fazla idi (p:0.000). Rh (+) kan grubu (OR:0.464, p: 0.010 ,%95 Cl: 0.306 ~ 0.703) ev içi temaslı olan vakalarda takipte enfeksiyon gelişmesini etkileyen faktörlerdendi.
Sonuç: SARS-CoV-2 ile enfekte olan hastalarda büyük oranda A, Non-O kan grubu ve Rh pozitifliği vardı. Yüksek risk taşıyan ev içi temaslılarda Rh (+) kan grubuna sahip olma enfeksiyon gelişme oranını artırmış olabilir. Bu kan grubundaki hastaların temaslı olduğu tespit edildikten sonra daha yakın takip edilmesi morbiditeyi azaltmak için gerekebilir.

Anahtar Kelimeler : SARS-COV-2;ABO ve Rh kan grubu; komorbid hastalıklar

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INTRODUCTION

Coronaviruses belonging to the Coronaviridae family are enveloped and non-segmented ribonucleic acid viruses that can cause infective diseases in humans and other mammals (1). They most commonly cause upper respiratory tract infections. Their previous types that caused fatal infections are Severe Acute Respiratory Syndrome-Coronavirus (SARS Co-V) and Middle East Respiratory Syndrome-Coronavirus (MERS Co-V) most commonly (2,3). Cases with a viral pneumonia-like disease of unknown cause were detected in Wuhan, China in December 2019. The virus could be detected as a result of the studies and it took place in literature as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4). Infected patients have had different clinical courses and the infection has been observed to have more severe course especially in people with a chronic disease (5). There is not a biological marker showing the clinical course and severity of the disease yet.

ABO blood groups are genetically coded antigens in structure of glycoprotein present on the surface of erythrocytes. Rh groups are another group of antigens and called positive or negative according to the presence or absence of D antigen (6). It has been revealed that differences in ABO and Rh blood groups are effective on clinical course of the disease in cardiovascular, oncologic and some infectious diseases (7,8). For example, it was reported that individuals with O blood group were more susceptible to vibrio cholerae and had more severe clinical course (9). Similar studies have been performed for SARS-CoV-2 as well and have revealed that people with A blood group are more susceptible to the infection (10). However, studies on this subject are not sufficient and their number is limited. This study aimed to investigate the effect of ABO, O and Non-O, and Rh blood groups on the risk and prognosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the infected/source cases and contact individuals.

MATERIAL AND METHOD

Study design and setting

This study was designed as a descriptive and retrospective study. Patients who were followed up at 'Erciyes University Faculty of Medicine Hospitals and Secondary Care Public Hospitals' and patients/individuals who were followed up/isolated in their home were included in the study. The case information was obtained by file scanning through the Public Health Management System (PHMS) records of the Turkish Ministry of Health and hospital records. This study consisted of three groups. Group 1 included SARS-CoV-2(+) source patients, group 2 included SARS-CoV-2(+) contacts who were living in the same house with the infected patient and followed up, and group 3 included SARS-CoV-2(-) contacts who were living in the same house with the infected patient and followed up. As contacts living in the same house with the infected patient are accepted as high-risk group for SARS-CoV-2infection, they were included in the study. Kin relationships were not preferred and therefore, partners were included in the study. Distributions of the participants according to ABO, O and Non-O, and Rh blood groups were assessed. Presence of a chronic disease, smoking history, being a healthcare worker, being followed up in home or hospitalizations and presence of pneumonia were also assessed.

Study participants

Individuals at the age of 18 and above (18-100) who were SARS-CoV-2(+), who were SARS-CoV-2(+) contacts and followed up and who were SARS-CoV-2(-) contacts and followed up were analyzed. Data of 1371 patients were obtained. As blood groups of 51 patients and information about the presence of a chronic disease and follow-up status in 29 patients could not be obtained, they were excluded. G*Power 3.1 analysis program was used for power analysis to determine the sample size in this study. Minimum number of the participants for the study was determined as 1,125 (α- value:0.05, ß-value:0.80).

Necessary institutional consents were obtained from Kayseri Local Health Authority, Department of Public Health Services. The approval of Erciyes University Medical Faculty Ethics Committee was obtained (Date: 02.12.2020; Decision No: 2020/615) and additionally, Turkish Ministry of Health approval was also obtained on 12th of May 2020 for this study as required.

Statistical Analysis

Statistical analysis was performed using SPSS 22 for Windows (IBM SPSS Inc., Armonk, NY, USA).In data analysis, frequency, mean, median and standard deviation, and minimum and maximum values were determined as descriptive data. Chi-square test was used in comparison of the categorical data. In numerical data, Mann Whitney U test was used for non-normally distributed groups. Logistic regression analysis was performed. $p<0.05$ was accepted as the statistically significant value.

RESULT

The study was conducted with 1,371 patients. Of these patients, 576 (48%) female and 795 (52%) male individuals were included in the study. Median age was 41 (18-91). There were 337 (24.6%) individuals in group 1, 516 (37.6%) in group 2 and 518 (37.8%) in group 3. The number of male individuals was 203 (60.2%) in group 1, 290 (56.20%) in group 2 and 302 (58.30%) in group 3. Median age was 42 (18-91) in group 1, 41 (18-89) in group 2 and 40 (18-87) in group 3. The rate of patients who had a chronic disease was 30% in the study. The rate of those who had pneumonia (pulmonary involvement) was 26.5%, that of those who were hospitalized was 25.3% and that of those who had smoking history was 28.2%. Only 97 individuals (7.1%) were healthcare workers. The rates of blood groups among all participants were 42.7% for A, 17.2% for B, 7.7% for AB and 32.4% for O. It was 67.6% for Non-O blood groups. While 90% were Rh

positive, 10% were Rh negative. The rate of presence of a comorbid disease was 30%. Total exitus rate in Group 1 and Group 2 was 2.4%. Demographic and clinical data of the groups were given in Table 1.

There was no statistical difference among the groups in terms of ABO blood groups. The rate of A blood group was the highest (45.4%) in group 1 and the rate of O blood group was the highest (36.7%) in group 3 (p:0.61). When the groups were assessed in terms of O and Non-O blood groups while the rate of Non-O blood group was the highest (39.4%) in group 2, the rate of O blood group was the highest (42.8%) in group 3 (p:0.028). When the groups were assessed in terms of Rh blood groups while the rate of Rh positive blood group was the highest (95%) in group 1, the rate of Rh negative blood group was significantly higher (15.30%) in group 3 (p:0.000) (Table 2).

In this study, 8.1% of the SARS-CoV-2(+) patients (group 1 and 2) had no symptoms. The most common symptoms were fever in 211 patients (24.7%), loss of smell in 113 patients (13.7%) and dyspnea in 88 patients (10.3%). There was no difference among ABO blood groups in terms of the symptoms (p:0.054). However, the most symptomatic group was O blood group (12.4%). Those in Non-O blood groups were less symptomatic (p:0.071). When Rh blood groups were assessed in terms of symptoms, Rh (-) blood group (13.7%) was more asymptomatic (p:0.001) (Table 3).

When pulmonary involvement was assessed, the rate of pneumonia (43%) was found proportionally higher in A blood group (p:0.801). The rate of the presence of pneumonia was high in Rh positive blood group (43.1%), but it was not statistically significant (p:0.186). The rate of hospitalization was higher in A blood group (45%) and it was the lowest in AB blood group (p:0.999). While mortality rate was proportionally higher in A blood group (51.5%), it was lower in O blood group (30.1%) (p:0.427). There was no difference between O and Non-O blood groups in terms of presence of pneumonia, hospitalization,mortality, presence of a comorbid disease, being a healthcare worker and smoking history. The rates of hospitalization (70.3%), mortality (78.8%) and presence of a comorbid disease (68.4%) were higher in Non-O blood group [(p:0.50), (p:0.51), (p:0.18), (p:0.37) (p:0.13), (p:0.28)]. There was no difference between Rh blood groups in terms of presence of pneumonia, hospitalization,mortality, presence of a comorbid disease, being a healthcare worker, and smoking history [(p:0.18), (p:0.19), (p:0.09), (p:0.31), (p:0.35), (p:0.42)]. The rate of Rh positive patients who were hospitalized (41.1%) was higher and the rate of presence of pneumonia (43.1%) and mortality (4.2%) was proportionally higher in that blood group.

When 1,034 contacts were assessed, the rate of A blood group was found proportionally higher in group 2 than in group 3 (p:0.65). The rate of Non-O (52.7%)blood group was higher in group 2 (p:0.007) and the rate of Rh (+) blood group (52%) was higher in group 2 than in group 3 (p:0.000). There was no difference between group 2 and 3 in terms of being a healthcare worker and smoking history (p:0.65 and p:0.376 respectively). While Rh (+) blood group (OR:0.464, p: 0.010, 95% Cl: 0.306 ~ 0.703) and presence of a comorbid disease (OR:4.57, p: 0.000, %95 Cl: 3.31 ~ 6.30) affected infection development during follow-up among contacts living in the same house with the source patient (Table 4). ABO and O and Non-O blood groups, age, gender, healthcare worker status and smoking were not among the factors affecting infection development (p:0.53 and p:0.156 respectively, p:0.957, p:0.477, p:0.141, p:0.476).

Table 1. Demographic and clinical data by groups

		Group 1	Group 2	Group 3
Gender	Male	203(60.2)	290(56.2)	302(58.3)
	Female	134(39.8)	226(43.8)	216(41.7)
Age (Years)	Median(min-max)	42(18-91)	41(18-89)	40(18-87)
Comorbid Disease	Yes	147(43.6)	63(12.2)	201(38.8)
Health Worker	Yes	44(13.1)	20(3.9)	33(6.4)
Smoking	Yes	95(28.2)	148(28.7)	143(27.6)
Pneumonia	Yes	267(79.2)	97(18.8)	-
Hospitalization	Yes	254(75.4)	93(18)	-
Mortality	Yes	29(8.6)	4(0.8)	-

Table 2. Distribution of patients according to blood groups

		Group 1 (337) N (%)	Group 2 (516) N (%)	Group 3 (518) N (%)	Total N (%)	P value
ABO group	A	153 (45.4)	231 (44.8)	201 (38.8)	585 (42.7)	0.13
	B	60 (17.8)	93 (18.0)	83 (16)	236 (17.2)	
	O	103 (30.6)	151 (29.3)	190 (36.7)	444 (32.4)	
	AB	21 (6.2)	41 (7.9)	44 (8.5)	106 (7.7)	
O and Non-O	O	103(30.6)	151(29.3)	190 (36.7)	444(32.4)	0.028
	Non-O	234(69.4)	365(70.7)	328(63.3)	927(67.6)	
Rh group	Positive	320 (95)	475 (92.1)	439 (84.7)	1234 (90)	0.000
	Negative	17 (5)	41 (7.9)	79 (15.3)	1371(10)	

Group 1: Source Case, Group 2: SARS CoV2(+) Contact, Group 3: SARS-CoV2(-) Contact
Chi-square test analysis was performed

Table 3. Distribution of symptoms according to blood groups

	A	B	O	AB	O	Non-O	Rh(+)	Rh(-)
Fever	108(51.2)	42(19.9)	50(23.7)	11(5.2)	50(23.7)	161(76.3)	197(93.7)	14(6.6)
Cough	30(42.9)	13(18.6)	20(28.6)	7(10)	20(28.6)	50(71.4)	64(91.4)	6(8.6)
Dyspnea	34(38.6)	16(18.2)	27(30.7)	11(12.5)	27(30.7)	61(69.3)	84(95.5)	4(4.5)
Fatigue	33(48.5)	10(14.7)	19(27.9)	6(8.8)	18(28.1)	46(71.9)	65(95.6)	3(4.4)
Backache	32(48.5)	12(18.2)	21(31.8)	1(1.5)	21(32.3)	44(67.7)	61(92.4)	5(7.6)
Loss of Smell	49(41.5)	25(21.2)	38(32.2)	6(32.2)	37(31.6)	80(68.4)	110(93.2)	8(6.8)
Loss of Taste	40(57.1)	7(10)	16(22.9)	7(10)	16(22.9)	54(77.4)	64(91.4)	6(8.6)
Sore Throat	13(39.4)	8(24.2)	10(30.3)	2(6.1)	10(30.3)	23(69.7)	32(97)	1(3)
None	23(33.3)	9(13)	32(46.4)	5(7.2)	32(46.4)	37(53.6)	61(88.4)	8(11.6)

Chi-square test analysis was performed

Table 4. Factors affecting development of infection in contacts

			95% C.I.for EXP(B)
Fever	p	Exp (B)	Lower	Upper
Rh(+) Blood Group	0.000	0.475	0.313	0.721
Comorbid diseases	0.000	4.57	3.31	6.30

Binary logistic regression analysis was performed

DISCUSSION

ABO and Rh blood groups play a vital role during blood transfusion and in several clinical practices. Their relationship with infectious, non-infectious and cancerous diseases has widely been investigated and various studies have been performed on this issue (11-14). Arac et al. reported in their study that the rate of A blood group was higher in those infected with SARS-CoV-2 infection compared with the normal healthy population (15). The rate of having A blood group is higher and the rate of having O blood group is lower in individuals who haveSARS-CoV-2infection (16). The prevalence of SARS-CoV-2 infection has been reported to be higher in Non-O blood groups (17). The data of this study were similar to the findings in literature.

Torun et al. analyzed blood groups of 86,797 individuals between January 2008 and September 2010 in their study showing the prevalence of blood groups in general population. Of the blood samples, 88.2% (n= 76,580) were Rh positive and 11.8% (n= 10,217) were Rh negative. The prevalences of A, O, B, and AB blood groups were 44% (n= 38,253), 33.3% (n= 28,904), 16.2% (n= 14,031), and 6.5% (n= 5,609) respectively (18).

Since the study by Torun et al.was conducted in the same region as this study, our data were found to be similar to the general population. A study conducted in Diyarbakir province showed that the Rh (+) ratio of PCR-positive patients was higher compared with the general population (15). The general population was not evaluated in this study. The infected/source and contact persons who were in the quarantine process formed the sample of this study.One of the factors affecting the SARS-CoV-2 positivity of people in contact during the quarantine process is the state of Rh (+) blood type.

In addition, the rate of a blood group was proportionally higher and that of Non-O blood group was significantly higher in group 1 and 2 (SARS-CoV-2(+) patients). The rate of contacts in whom SARS-CoV-2infection developed in group 2 was high similarlyto that in literature in terms of A and Non-O blood groups. This result suggests that the risk of developing SARS-CoV-2infection is high in A and Non-A blood groups. In studies assessing the relationship between Rh blood groups and SARS-CoV-2infection, the rate of Rh positive blood group was found significantly high. It was emphasized for Rh negative blood group that it could have a preventive effect against SARS-CoV-2(16,18). In this study, Rh positive blood group increased the risk of SARS-CoV-2infection, which suggests that Rh(-) blood group is preventive against SARS-CoV2.

ABO blood group may have an effect on symptoms inpatients with SARS-CoV2. Clinical symptoms of people with different blood types may be different after SARS-CoV-2infection. In the study by Wu et al., fever and cough were more in A blood group according to the distribution of symptoms ($p<0.05$ and p:0.05 respectively). Dyspnea was more in AB blood group ($p<0.05$). Fatigue and malaise were associated with A and O blood groups ($p<0.05$) (19). In this study, fever, cough, dyspnea, and other symptoms were more in patients with A, Non-O and Rh (+) blood groups, which is consistent with the data in literature. It is considered that clinical presentation of SARS-CoV-2infection is more severe in patients with A, Non-O and Rh (+) blood groups. In literature, there are studies investigating the effect of blood groups on clinical prognosis of patients. In the study by Juyi et al., the rate of hospitalization was higher in patients with A blood groups in SARS-CoV-2infection and in another study, the rate of Rh positivity was reported to be higher in patients hospitalized in the intensive care unit (ICU) (20,21). Our data are similar to findings in these studies. As individuals with A, Non-O and Rh (+) blood groups have more severe clinical course, they should be carefully followed up in terms of hospitalization.

There is no study revealing that there is a relationship between blood groups and pulmonary involvement (pneumonia) in SARS-CoV2. In this study, pneumonia was more in A, Non-O and Rh (+) blood groups, but there was no statistical relationship. In studies investigating the effect of blood groups on mortality in SARS-CoV-2infection, while it was reported that Rh (-) blood group decreased the risk of mortality and intubation, no significant relationship was found among blood groups and intubation or the risk of SARS-CoV-2infection and mortality in some studies (17,22,23). In this study, no relationship was found between mortality and blood groups. Other parameters such as having a comorbidity, smoking history and being a healthcare worker in SARS-CoV-2infectionhave also been assessed in studies. The risk factors that have commonly been mentioned and studied in SARS-CoV-2infection are age, gender and comorbid diseases such as hypertension, diabetes mellitus and cardiovascular disease. It has been revealed in China and Italy that hypertension and cardiovascular diseases increase the mortality rates (25-27). Presence of a comorbid disease causes breathing problems in patients and increase in mortality rate (27). Comorbidity rates in patients who are hospitalized in the intensive care unit (ICU) or who are exitus have increased up to 90% (28). In this study, comorbidities were significantly more in group 1 including source patients, which is consistent with findings in literature. It is considered that the risk of SARS-CoV-2infection increases in individuals with a comorbidity.

In a study in Latium, Italy, although the prevalence of SARS-CoV-2was low among healthcare workers they were infected 34 times more often compared with the general population. This was because of the increased risk in the workplace (29). It was observed in this study that being a healthcare worker did not increase the risk of SARS-CoV-2infection. There are also studies in which smoking is another risk factor and individuals' status of being infected with SARS-CoV-2has been assessed. The results of a meta-analysis performed in China have revealed that active smoking does not increase the risk of progression to a serious disease in SARS-CoV-2infection (30). In this study, findings on smoking were similar to those on non-smoking, which is consistent with the findings in literature.

CONCLUSION

The rate of developing the disease after contact with the infected patient was higher in individuals with Rh positive blood group. The prevalence of SARS-CoV-2infection was higher in A and Non-O blood groups. Clinical course was more severe in A, Non-O and Rh (+) blood groups. These individuals should be followed up more carefully, as their risk of being infected is higher. We think close follow-up of individuals especially with Rh positive blood group after contact with the infected person can decrease the

risk of complication development.

Limitations of this study are as follows: As SARS-CoV-2 has emerged as a new infection source there are no sufficient studies on this subject and further studies are needed. Other limitations in this study are as follows: most of the individuals were tested with PCR only once and file scanning was performed and criteria for hospitalization changed according to the current conditions.

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Conflict of Interest: *The authors declare that they have no competing interest.*

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Araştırma Makalesi / Research Article

Clinical Characteristics of Patients who Died Within a Year in a Tertiary Intensive Care Unit

Üçüncü Basamak Bir Yoğun Bakım Ünitesinde Bir Yıl Içinde Ölen Hastaların Klinik Özellikleri

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Abstract

Aim: The aim of this study was to find out the clinical characteristics of patients who died within a year in the intensive care unit (ICU) and to find out the association of ICU admission albumin, lactate levels and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of these patients who died with ICU length of stay.
Material and Method: The files of patients who died in the ICU (n:350) between January 2018 and December 2018 were examined retrospectively. The patients' demographic data and their clinical characteristics, ICU admission types (surgery or medical medicine), the units they were admitted in, reasons for admission, comorbidities, admission albumin and lactate levels, APACHE II scores and ICU length of stay were recorded. The association of patients' clinical characteristics with ICU length of stay and laboratory values was evaluated.
Result: The patients' mean age was 72.68±12.98 years, mean APACHE II score was 27.0±10.0, mean albumin value was 3.1±0.7 g/dL and mean lactate value was 4.1±3.3 mmol/L. It was found that albumin value was lower in patients admitted to ICU with mechanical ventilator (MV) need (p<0.001), and lactate value and APACHE II score were significantly higher in patients with post-cardiopulmonary resuscitation (p<0.001). Mean ICU length of stay was 28.24 ± 37.53 days. A weak positive correlation (r =0.172, p=0.001) was found between the patients' length of stay and albumin, and a weak negative correlation was found with the lactat (r = 0.121, p=0.023) and APACHE II scores (r = 0.151, p=0.001). A weak negative correlation was found between the patients' albumin and lactate (r =0.152, p=0.004), and APACHE II score (r =0.179, p=0.001), as well as a moderate positive correlation between lactate and APACHE II score.
Conclusion: Significant association was found between hypoalbuminemia, hyperlactatemia and high APACHE II scores and ICU length of stay in patients who died in ICU. More comprehensive studies are needed to show the effects of this association on effective use of ICUs.
Keywords: Intensive care; mortality; length of stay; hypoalbuminemia; hyperlactatemia

Öz

Amaç: Amaç: Bu çalışmada Yoğun Bakım Ünitesinde (YBÜ) bir yıl içinde mortalite gözlenen hastaların klinik özelliklerinin saptanması ve YBÜ'ye kabul esnasında albümin, laktat seviyelerinin ve Acute Physiology and Chronic Health Evaluation II (APACHE II) skorlarının YBÜ yatış süresi ile ilişkisinin belirlenmesi amaçlandı.
Materyal ve Metot: Çalışmada Ocak 2018 ve Aralık 2018 tarihleri arasında YBÜ'de mortalite gözlenen (n:350) hastaların dosyaları retrospektif olarak incelendi. Hastaların demografik verileriyle birlikte klinik özellikleri, YBÜ'ye kabul tipi (cerrahi veya dahili), kabul edildiği üniteleri, kabul nedenleri, komorbiditeleri, kabul albümin ve laktat seviyeleri, APACHE II skorları ve YBÜ yatış süreleri kayıt edildi. Hastaların klinik özelliklerinin YBÜ yatış süresi ve laboratuvar değerleri ile ilişkisi değerlendirildi.
Bulgular: Hastaların yaş ortalaması 72.68±12.98 yıl, ortalama APACHE II skoru 27.0±10.0, albümin değeri 3.1±0.7 g/dL ve laktat değeri 4.1±3.3 mmol/L olarak belirlendi. Mekanik ventilatör (MV) ihtiyacı nedeniyle YBÜ'ye kabul edilen hastalarda albümin değerinin daha düşük olduğu (p<0.001), laktat değerinin ve APACHE II skorunun post–kardiyopulmoner resusitasyon hastalarda anlamlı olarak daha yüksek olduğu saptandı (p<0.001). YBÜ yatış süresi ortalaması 28.24 ± 37.53 gündü. Hastaların yatış süresi ile albümin arasında zayıf pozitif korelasyon (r = 0.172, p = 0.001), laktat (r = 0.121, p = 0.023) ve APACHE II skorları ile zayıf negatif korelasyon bulundu (r = 0,151, p = 0,001). Hastaların albümin ile laktat (r = 0.152, p = 0.004) arasında ve APACHE II skoru (r = 0.179, p = 0.001) arasında zayıf negatif korelasyon ve laktat ile APACHE II skoru arasında (r =0,401, p<0.001) orta derecede pozitif korelasyon bulundu.
Sonuç: Bu çalışmada, YBÜ'de mortalite gözlenen hastalarda hipoalbuminemi, hiperlaktatemi ve yüksek APACHE II skorları ile YBÜ yatış süresi arasında anlamlı bir ilişki gözlendi. Bu ilişkinin YBÜ'lerin etkin kullanımına etkilerini göstermek için daha kapsamlı araştırmalar gereklidir.
Anahtar Kelimeler : Yoğun bakım; mortalite; yatış süresi; hipoalbuminemi; hiperlaktatemi

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INTRODUCTION

Intensive care units (ICU) are special units where critical patients are followed up closely and treated and their life functions are supported by advanced technological devices (1). Due to the increase in elderly population with comorbidities in the world and in our country, the need for ICUs has been increasing.

Management and performance assessment of ICUs can be affected by a large number of factors such as care process and organization (2). Unlike other departments of hospitals, ICUs are the units with the highest rate of mortality due to critical patients (3). Mortality rates in ICU vary depending on factors such as the underlying comorbidities of the patients, hospitalization indicators, advanced age, interventional procedures applied, the structure of ICUs and length of stay (LOS) (3,4). In European countries, ICU mortality rate is reported as between 6.7% and 17.8% (4), while it is reported as between 8% and 19% in USA (5). In our country, altough it varies according to most centers, ICU mortality rate is reported as between 3% and 51% (6-9). Although the current ICU bed capacity is sufficient in our country when compared with other countries, there are problems in the effective use of ICUs (10). Therefore, it is necessary to predetermine the patients who cannot make use of treatment in ICU, to know the factors that increase mortality rates and to provide an effective critical care triage. ICUs are becoming units where chronic patients who do not benefit from acute period treatment and whose LOS is prolonged due to advanced technological support therapies are hospitalized (11). Long LOS in ICU is associated with high mortality rate and negative complications (1). In addition, long LOS in ICUs may cause critical patients who may benefit from ICU not to receive healthcare services (12). On the other hand, finding out the clinical characteristics of critical patients who die and the factors related with length of stay is important for effective use of limited number of ICU beds during the current COVID-19 pandemic.

The primary objective of this study is to describe the clinical characteristics of patients who died within a year in the general intensive care unit of a regional tertiary hospital. The secondary objective of the study is to find out the association of ICU admission albumin, lactate levels and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of these patients who died with clinical parameters and ICU length of stay.

MATERIAL AND METHOD

Ethics Statement

Ethics committee approval of this study was taken from local Clinical Researches Ethics Committee in accordance with the Declaration of Helsinki (date: Jul 24, 2019; Approval No:134).

Design and Setting of the Study

This study was conducted by retrospectively examining the data of 350 (33.3%) of 1050 patients who were treated in ICU of a tertiary hospital between January 2018 and December 2018 and who met the inclusion criterion (>18 years of age). The IUC of this hospital is a closed system with 36 beds and provides advanced treatment service to all adult medical medicine and surgery critical patients.

Study Data

The data were obtained from patient files and hospital information system automation program. Patients' demographic data and their ICU admission type (surgery or medical medicine), units they were admitted in, reasons for admission, their comorbidities and length of stay were evaluated. APACHE II scores of all patients calculated on admission to ICU, their admission albumin and lactate values were recorded. The patients' reasons for admission to ICU were classified according to ICD-10 (International Classification of Diseases) codes. The patients who underwent resuscitation after cardiac or respiratory arrest were grouped as post-CPR (post-Cardiopulmonary Resuscitation). All patients were routinely consulted for medical departments (cardiology, respiratory disease or medical medicine) in the preoperative period. The presence of comorbidities in the patients was confirmed by examining the consultation records obtained during the patients' stay in ICU. The comorbidity status was divided into two categories: "Two or less comorbidities", "Three or more comorbidities". Those with Alzheimer's or Parkinson's disease as comorbidity were included in the neurodegenerative disease group. APACHE II scores were divided into two categories according to the median (27) value: "APACHE below 27 score", "APACHE above 27 score". The age group was divided into two categories as under 65 and above. The association of clinical variables with albumin, lactate levels, APACHE II score and length of stay in the ICU was examined.

Statistical analysis

All statistical analyses were performed using SPSS v.20.0 (IBM Corp., Armonk, NY, USA) software. Frequency, mean, standard deviation, percentage (%), median, and interquartile range (25-75 p) values were determined with the analysis of the data. Normality was assessed using the Kolmogorov-Smirnov test. The statistical difference between the two groups was evaluated using the Mann-Whitney U test and student t test and the Chi-Square test. Kruskal–Wallis test were used for analysis between groups at each time point for nonparametric continuous and ordinal data. Correlations between albumin, lactate level, APACHE scores, and length of stay were analyzed using the Spearman's correlation test for non-normally distributed variables and the Pearson distribution for normally distributed variables.

RESULT

Demographic and clinical characteristics of the patients

164 (46.9%) of the patients were male, while 186 (53.1%) were female and mean age was found as 72.68±12.98 (min=19, max=96) years. 273 (78%) of the

patients were aged 65 and older. Hypertension (46.6%), neurodegenerative disease (31.1%) and respiratory disease (30.6%) were the most common comorbidities.

The association of clinical characteristics with albumin, lactate levels and APACHE II score

It was found that mean ICU admission APACHE II score of the patients was 27.0±10.0, while their mean albumin value was 3.1±0.7 g/dL and mean lactate value was 4.1±3.3 mmol/L. It was found that the patients were most frequently admitted to the ICU from emergency service (64%). It was found that serum albumin (p=0.078) and lactate (p=0.256) levels of patients did not differ significantly in terms of the units patients were admitted to, while their APACHE II scores differed significantly and the highest APACHE II score was found in patients who were transferred from medical ICU. It was found that while 294 (84%) of the patients were admitted to ICU for medical causes, 56 (16%) were admitted for surgical causes. No significant differences were found in albumin and lactate values of the patients in terms of their ICU admission types and APACHE II score was significantly higher in medical patients (p=0.002). When ICU admission diagnoses were examined, it was found that albumin value was significantly lower in patients who needed MV (p<0.001), while lactate value and APACHE II score were significantly higher in post-CPR patients (p<0.001). Albumin values were found to be lower in the patient group aged 65 and older (p=0.002). In patients with APACHE II score above 27, it was found that albumin values were significantly lower (p=0.011) and lactate values were higher (p<0.001) (Table 1).

Table 1. The association of study variables with albumin, lactat levels and APACHE score

		Albumin Median (Q1-Q3)	p	Lactat Median (Q1-Q3)	p	APACHE II Median (Q1-Q3)	p
All Patients		**3.1 (2.6-3.6)**	**N/A**	**3.1 (1.8-5.2)**	**N/A**	**27 (19-35)**	**N/A**
Referring unit (n)	Emergency service (n=224)	3.12 (2.70-3.70)	0.078¥	3.00 (1.80-4.70)	0.256¥	25 (17-34)	<0.001¥
	Coronary ICU (n=24)	3.45 (2.80-3.80)		3.11 (1.71-4.75)		24 (19-35)	
	Medical ICU (n=37)	2.90 (2.50-3.30)		4.50 (2.53-6.90)		36 (28-38)	
	Palliative care unit (n=17)	3.22 (3.10-3.70)		2.36 (1.75-3.20)		26 (24-35)	
	Wards (n=48)	3.10 (2.50-3.45)		3.35 (1.60-5.74)		28 (24-34)	
Patient type (n)	Medical (n=294)	3.12 (2.60-3.60)	0.358‡	3.10 (1.80-5.70)	0.160‡	28 (21-36)	0.002‡
	Surgical (n=56)	3.20 (2.80-3.77)		2.59 (1.57-4.20)		23 (15-30)	
Admission diagnosis (n)	Sepsis (n=49)	2.90 (2.50-3.50)	<0.001¥	3.60 (2.20-6.30)	<0.001¥	24 (18-32)	<0.001¥
	Post-CPR (n=67)	3.00 (2.55-3.37)		5.10 (3.00-9.60)		36 (32-42)	
	Respiratory disease (n=52)	3.10 (2.52-3.47)		2.02 (1.49-3.43)		24 (18-32)	
	Need for MV (n=33)	2.70 (2.40-3.40)		4.70 (2.70-6.90)		32 (28-38)	
	Heart disease (n=25)	3.70 (3.20-4.10)		2.23 (1.20-3.00)		16 (12-25)	
	Neurologic disease (n=30)	3.60 (3.30-3.8)		3.30 (2.10-4.30)		26 (20-28)	
	Cerebral hemorrhage (n=15)	3.90 (3.10-4.00)		1.97 (1.50-4.20)		26 (22-29)	
	Acute kidney injury (n=17)	2.92 (2.60-3.30)		3.00 (1.90-4.10)		31 (28-36)	
	Trauma (n=22)	3.02 (2.80-3.61)		2.13 (1.47-3.36)		18 (14-24)	
	Abdominal surgery (n=12)	3.48 (2.30-4.06)		3.20 (1.80-5.01)		27 (18-33)	
	Other surgery (n=10)	2.95 (2.80-3.73)		2.45 (1.60-3.60)		13 (12-20)	
	Other medical disease (n=13)	3.13 (2.60-3.50)		3.20 (2.20-7.00)		30 (24-36)	
	Intoxication (n=5)	3.20 (2.50-4.20)		1.90 (0.50-3.40)		13 (10-17)	
Age groups (n)	Under 65 years (n=77)	3.40 (2.90-3.80)	0.002*	2.50 (1.68-4.42)	0.119‡	26 (20-32)	0.350*
	65 years and older (n=273)	3.10 (2.60-3.60)		3.20 (1.89-5.50)		28 (19-35)	
Comorbidity groups (n)	Two or less comorbidities (n=246)	3.10 (2.59-3.60)	0.070‡	3.00 (1.75-5.38)	0.744‡	28 (20-36)	0.113*
	Three or more comorbidities (n=104)	3.26 (2.80-3.73)		3.20 (1.90-5.06)		25 (18-34)	
APACHE II groups (n)	APACHE below 27 score (n=176)	3.20 (2.80-3.77)	0.011*	2.30 (1.50-3.46)	<0.001‡	19 (14-24)	<0.001*
	APACHE above 27 score (n=173)	3.10 (2.59-3.50)		4.40 (2.45-7.70)		35 (31-38)	

Significant p values are written in bold.
¥Kruskal–Wallis test ; *Mann-Whitney U test; ‡independent samples t-test

Table 2. The association of LOS with study variables

		Length of ICU stay			p value
		Median	Percentile 25	Percentile 75	
All Patients					
Gender	Male (n=164)	14	3	55	0.207‡
	Female (n=186)	7	3	39	
Referring unit	Emergency service (n=224)	8	3	38	0.509¥
	Coronary ICU (n=24)	10	3	52	
	Medical ICU (n=37)	25	3	45	
	Palliative care unit (n=17)	29	4	63	
	Wards (n=48)	11	4	50	
Patient type	Medical (n=294)	12	3	48	0.115*
	Surgical (n=56)	6	3	10	
Admission diagnosis	Sepsis (n=49)	6	3	24	<0.001‡
	Post-CPR (n=67)	8	2	46	
	Respiratory disease (n=52)	30	7	56	
	Need for MV (n=33)	4	3	12	
	Heart disease (n=25)	52	46	63	
	Neurologic disease (n=30)	14	5	56	
	Cerebral hemorrhage (n=15)	8	5	35	
	Acute kidney injury (n=17)	13	5	38	
	Trauma (n=22)	6	4	9	
	Abdominal surgery (n=12)	5	3	13	
	Other surgery (n=10)	5	3	8	
	Other medical disease (n=13)	35	4	62	
	Intoxication (n=5)	3	3	7	
Age groups	Under 65 years (n=77)	46	31	62	<0.001‡
	65 years and older (n=273)	6	3	25	
Comorbidity groups	Two or less comorbidities (n=246)	13	5	58	0.161‡
	Three or more comorbidities (n=104)	8	3	39	

Significant p values are written in bold.
¥Kruskal–Wallis test ; *Mann-Whitney U test; ‡independent samples t-test.

The association of LOS with study variables

The mean of LOS in the intensive care unit was 28.24 ± 37.53 (min=1, max=275) days. Among clinical factors admission diagnosis (p <0.001) and age groups (p <0.001) affected LOS. Those with heart disease had the highest LOS (52 days). It was determined that patients aged 65 and over had shorter LOS (6 days). The distribution of LOS based on clinical and nonclinical variables is demonstrated in Table 2.

The association between ICU length of stay and albumin, lactate and APACHE score

A weak positive correlation (r =0,172, p=0,001) was found between the patients' LOS and albumin, and a weak negative correlation was found with the lactat (r = 0,121, p=0,023) and APACHE scores (r = 0,151, p=0,001). A weak negative correlation was found between the patients' albumin and lactate (r =0,152, p=0,004), and APACHE II score (r =0,179, p=0,001), as well as a moderate positive correlation between lactate and APACHE II score (r =0,401, p<0.001) (Table 3) (Figure 1).

Table 3. Correlation between ICU length of stay, albumin, lactate and APACHE II score

		LOS	Albumin	Lactat
Albumin	r	0.172		
	p	0.001		
Lactat	r	-0.121	-0.152	
	p	0.023	0.004	
APACHE II score	r	-0.151	-0.179	0.401
	p	0.005	0.001	<0.001

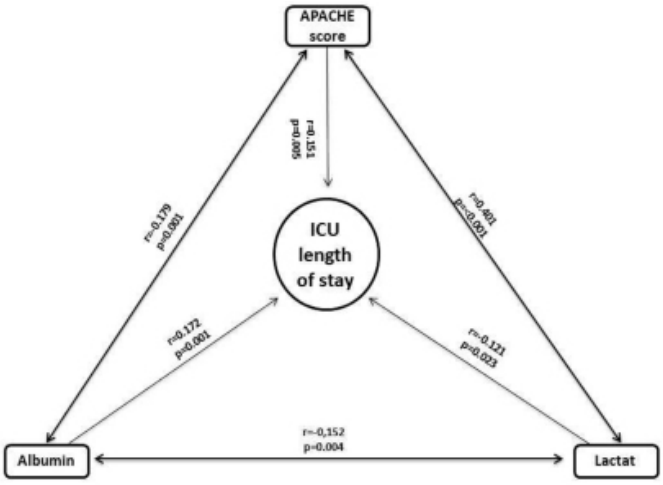

Figure 1. Relationship between length of stay in ICU, albumin, lactate and APACHE II score

DISCUSSION

ICUs are units where critical patients with high mortality rates are followed. When the literature is reviewed, it can be seen that while ICU mortality rates differ by centres, they vary between 23% and 51% (6-9). In this study, one-year mortality rate in ICU was found as 33.3%, in line with the literature. A great majority of these critical patients in ICU consist of elderly patients with chronic health problems and multiple organ failures (2,13,14). In this study, mean age of the patients who died was found as 72.68±12.98 years and 78% were in geriatric age (> 65) group. Although age is an important prognostic factor in critical patients in ICU (13); severity of the disease, reasons for admission to ICU and presence of comorbidities have been determined as risk factors more important than age in other studies (2,13,14).

A large number of studies have shown that hypoalbuminemia, hyperlactatemia and high APACHE II scores contribute to high mortality rates in critical patients in ICU (15,16). The relationship between these variables and mortality and LOS was examined in detail in this study. When the literature is reviewed, it can be seen that the significance of hypoalbuminemia in predicting increased mortality, increased MV time and increased ICU length of stay has been emphasized (15). In this study, mean ICU admission albumin level was found as 3.1 g/d L and hypoalbuminemia was found in geriatric patients with MV needs most frequently. Other than these, a positive significant relationship was found between albumin level and LOS.

Patients' reasons for admission to ICU are also effective on mortality and different reasons have been put forward in a large number of studies in literature (14,17-20). Although primary hospitalization indications have been reported as cardiovascular diseases (14), respiratory failure (17), gastrointestinal diseases (18), sepsis and stroke, reasons for admission vary in terms of patient population and ICU type. In the present study, primary hospitalization indications were found as post-CPR and MV need. In a large number of studies, it has been reported that MV need is increased in critical patients and this situation is associated with poor prognosis (21,22). The presence of hyperlactatemia and high APACHE II levels in this patient group support this situation. It was found that 84% of the patients were admitted to ICU with medical medicine reasons and LOS of these patients was higher in these patients when compared with those who were admitted with surgical reasons, although not statistically significant. Similarly, in their study, Meregalli et al. (23) reported that LOS in ICU was higher in medical patients when compared with surgical patients. Majority of the patients were transferred from the emergency service. It was found that the albumin level was the lowest and lactate and APACHE II level were the highest in patients transferred from in-hospital medical ICU. We think that the reason for this may be the fact that most of the patients were critical patients who needed MV after resuscitation.

The presence of comorbidities also has a negative effect on ICU results (13,14). In this study, almost all of the patients had at least one chronic disease and in line with the literature, the most common comorbidity was hypertension (46.6%), neurodegenerative diseases (31.1%) and respiratory diseases (30.6%) (18,24). However, no significant difference was found in ICU length of stay and other variables in terms of comorbidity groups.

It has been reported that mortality is higher in patients with long LOS in ICU and life span is shortened with LOS (25). In this study, ICU LOS was found to be shorter in patients with MV need and in elderly group. We think that high mean age in our study contributed both to high mortality rate and shorter mean length of stay. In addition, the causes in LOS and mortality are multi-factorial and vary according to ICU characteristics (26).

Another important result of the study is the result that ICU LOS has a positive significant relationship with albumin level and a negative significant relationship with lactate level and APACHE II score. Blood lactate level is one of the parameters used in predicting the prognosis of ICU patients. Hyperlactatemia is usually a multi-factorial condition due to tissue hypoxia that develops as a result of respiratory and circulatory disorders (23). Adıyaman et al. found that both mortality and IC LOS were significantly longer in patients with >2 mmol/L lactate (16). However, in our study it was found that lactate level had a negative association with IC LOS and positive association with APACHE II score. One of the ICU scoring systems used in predicting mortality is APACHE II, which is widely accepted around the world. It is evaluated in the first 24 hours of intensive care hospitalization and the values that deviate the most from the normal are taken (27). In our study, it was found that mean APACHE II score was high and had a negative association with IC LOS. In addition, albumin level was found to be low and lactate level was found to be high in the patient group with high APACHE score. Similarly, it was found in another study that serum

lactate level was significantly correlated with APACHE scores and associated with LOS (28). Based on all these results, we can say that there is a significant association between ICU admission albumin, lactate levels and APACHE scores and LOS in critical patients.

CONCLUSION

In this study, it was found that most of the patients who died in ICU were elderly patients with comorbidities. A significant association was found between hypoalbuminemia, hyperlactatemia and high APACHE II scores and ICU length of stay in these patients. Based on our results, knowing the factors related to mortality and length of stay in ICU and taking the necessary precautions may contribute to effective use of ICUs.

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Conflict of Interest: *The authors have no conflicts of interest to declare*

Ethical approval: *Ethics committee approval of this study was taken from local Clinical Researches Ethics Committee in accordance with the Declaration of Helsinki (date: Jul 24, 2019; Approval No:134).*

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Araştırma Makalesi / Research Article

Comparison of Auxiliary Diagnostic Methods in Pulmonary Embolism

Pulmoner Embolide Yardımcı Tanı Yöntemlerinin Karşılaştırılması

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Abstract

Aim: We investigated the importance of auxiliary diagnostic methods in cases when computed tomography pulmonary angiography (CTPA) cannot be used in pulmonary embolism (PE) with a high mortality rate.
Materials and Methods: Patients were selected after the exclusion criteria were applied in a sample created from a single center. A total of 86 patients included in our study were examined in terms of clinical features, auxiliary diagnostic methods, anticoagulant use, and hospitalization and discharge status according to the massive or segmental involvement of PE in CTPA.
Results: The mean age of the patients was 52.29±14.14 years. According to the CTPA results, there were 46 (53.5%) patients with massive involvement and 40 (46.5%) patients with segmental involvement. While there were 38 (82.6%) patients with massive involvement whose right chambers of the heart were dilated in echocardiography (ECHO) results, there were 19 (47.5%) patients with segmental involvement. There was a statistical significance between the massive involvement of CTPA and ECHO result (p=0.001).
Conclusion: ECHO may be preferred as an auxiliary radiological method in the diagnosis of PE in emergency departments (ED), especially in massive embolisms.

Keywords: Pulmonary embolism; massive; segmental; echocardiography

Öz

Amaç: Mortalite oranı yüksek pulmoner embolide (PE) bilgisayarlı tomografi pulmoner anjiyografinin (BTPA) kullanılamadığı durumlarda yardımcı tanı yöntemlerinin önemini araştırdık.
Materyal Metod: Hastalar tek merkezden oluşturulan bir örneklemde dışlama kriterleri uygulandıktan sonra toplanmış oldu. Çalışmamıza dahil edilen toplam 86 hasta BTPA'da PE'nin masif ya da segmental tutulumuna göre klinik özellikleri, yardımcı tanı yöntemleri, antikoagülan kullanımı ve yatış taburculuk durumuna göre incelendi.
Bulgular: Hastaların yaş ortalaması 52.29±14.14 yıl idi. BTPA sonucuna göre masif tutulumu olan 46 (%53.5) ve segmental tutulumu olan toplam 40 (%46.5) hasta vardı. Masif tutulumlarda ekokardiyografi (EKO) sonucunda sağ kalp boşlukları dilate olan 38 (%82.6) hasta varken; segmental tutulumlarda ise 19 (%47.5) hasta vardı. BTPA'nin masif tutulumu ile EKO sonucu arasında istatistiksel bir anlamlılık vardı (p=0,001).
Sonuç: Acil servislerde PE tanısında özelikle de masif embolilerde yardımcı radyolojik yöntem olarak EKO tercih edilebilir.

Anahtar Kelimeler: Pulmoner emboli; masif; segmental; ekokardiyografi

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INTRODUCTION

Acute pulmonary embolism (PE) is a common cause of acute-onset chest pain that occurs in the emergency department (ED) (1). Patients most frequently present with complaints of shortness of breath, chest pain, cough, hemoptysis, palpitation, tachypnea, and cyanosis (2). It is one of the most important causes of death in hospitalized patients and is responsible for approximately 15% of deaths. However, in case of late diagnosis or misdiagnosis, this rate can increase up to 30% (3).

Radiological methods such as chest radiography, ventilation/perfusion (V/P) scintigraphy, echocardiography (ECHO), computed tomography pulmonary angiography (CTPA), conventional pulmonary angiography, and magnetic resonance (MR) angiography are preferred for diagnosis. PE develops due to thromboisis in the deep veins of the legs in more than 3/4 of the cases (4). Color Doppler ultrasonography (CDUS) is the most commonly used imaging method in the diagnosis of DVT (5).

CT pulmonary angiography (CTPA) takes a significant place in the diagnosis of PE since it shows embolism directly and is a fast and non-invasive method (6). Furthermore, Wells scoring, which is the most preferred scoring method for PE diagnosis, is also applied (7). To date, many studies have been conducted on the relationship between the PE clinical picture and diagnostic methods (8,9).

In our study, we investigated which of the other auxiliary diagnostic methods such as posteroanterior chest X-ray (PA CXR), ECHO and lower extremity venous color doppler ultrasonography would be more helpful in diagnosing PE according to the CTPA result.

MATERIAL AND METHOD

This study was initiated after the ethics committee approval was obtained from Inönü University Scientific Research and Publication Ethics Committee with the decision dated 05.03.2019 and numbered 2019/5-9.

Case Selection and Data Collection

In this study, patients diagnosed with pulmonary embolism in the ED of a university hospital for a period of 1 year between 01.01.2018 and 31.12.2018 were examined. Pregnant women, patients with contrast material allergy and renal insufficiency were accepted as exclusion criteria. Patients with normal D-dimer levels (200-500 ng/ml) or D-dimer levels below normal (<200ng/ml) were not included in the study (10).

Eighty-six patients who were diagnosed with PE after the exclusion criteria were included in the study. Systemic physical examinations of the patients admitted to the ED were performed by emergency medicine specialists. Patients' age, sex, admission complaints, anticoagulant use, Wells scores, direct chest radiographs, ECHO, Doppler USG, CTPA (massive or segmental involvement), and hospitalization-discharge status were evaluated.

Statistical Analysis

The statistical analysis of the data obtained was carried out using the IBM SPSS (version 20.0; SPSS ™, Chicago, IL) program. The numerical data obtained by measurement were presented as mean and standard deviation, and the categorical data obtained by counting were presented as number (n) and percentage (%). Pearson's chi-square test was used for the statistical analysis of categorical variables, and the Mann-Whitney U test was used for the analysis of independent variables that did not exhibit normal distribution. The value of $p<0.05$ was considered significant in all tests.

RESULT

Our study was conducted with a total of 86 patients, 40 (46.5%) males and 46 (53.5%) females, after all exclusion criteria were applied. The mean age of the patients was 52.29±14.14 years. When we examined the patients according to their complaints, we observed that the most common complaint was shortness of breath, which was followed by chest pain, cough, syncope, hemoptysis, and leg pain, respectively (Table 1).

According to the patients' CTPA results (massive and segmental involvement), sex, Wells score classifications, PA CXR results, ECHO results, the presence of DVT on Doppler USG, anticoagulant drug use, and hospitalization status were statistically compared bythe chi-square test.

There were a total of 46 (53.5%) patients with massive involvement, according to the CTPA result. Of these, 22 (47.8%) were male, and 24 (52.2%) were female. Again, according to the CTPA results, 18 (45%) of 40 (46.5%) patients with segmental involvement were male, and 22 (55%) were female. No statistical significance was found between the CTPA result and sex (p=0.482) (Table 2).

The number of patients whose Wells score was accepted as moderate was 60 (69.8%), and the number of patients whose Wells score was accepted as high was 26 (30.2%). In massive involvement, there were 29 (63%) patients with a moderate Wells score and 17 (37%) patients with a high Wells score. In segmental involvement, there were 31 (77.5%) patients with a moderate Wells score and 9 (22.5%) patients with a high Wells score (p=0.111) (Table 2). On the PA CXR, the number of patients with infiltration was 59 (68.6%), the number of patients without infiltration was 14 (16.3%), and the number of patients with effusion was 13 (15.1%). In massive involvement, there were 37 (80.4%) patients with infiltration, 5 (10.9%) patients without infiltration, and 4 (8.7%) patients with effusion on the PA CXR. In segmental involvement, there were 22 (55%) patients with infiltration, 9 (22.5%) patients without infiltration, and 9 (22.5%) patients with effusion on the PA CXR (p=0.039) (Table 2).

While the number of patients with normal ECHO results was 29 (33.7%), the number of patients with dilated right heart chambers was 57 (66.3%). In massive involvement, there were 8 (17.4%) patients with normal ECHO results

and 38 (82.6%) patients with dilated right heart chambers. In segmental involvement, there were 21 (52.5%) patients with normal ECHO results and 19 (47.5%) patients with dilated right heart chambers (p=0.001) (Table 2). There were 50 (58.1%) patients without DVT and 36 (41.9%) patients with DVT in Doppler USG results. In massive involvement, there were 23 (50.0%) patients without DVT and 23 (50.0%) patients with DVT on Doppler USG. In segmental involvement, there were 27 (67.5%) patients without DVT and 13 (32.5%) patients with DVT on Doppler USG (p=0.077) (Table 2).

Among all patients, the rate of anticoagulant drug use was very low. There were only 16 (18.6%) patients using anticoagulants. In patients with massive involvement, there were 36 (78.3%) patients not using anticoagulants and 10 (21.7%) patients using anticoagulants. In segmental involvement, there were 34 (85%) patients not using anticoagulants and 6 (15%) patients using anticoagulants. Drug use had no statistical significance for both involvements (p=0.423) (Table 3).

The total number of patients hospitalized was 81 (94.2%), and the total number of patients discharged was 5 (5.8%). Forty-six (100%) of the patients with massive involvement were hospitalized. In segmental involvement, the number of patients hospitalized was 35 (87.5%), and the number of patients discharged was 5 (12.5%) (p=0.019) (Table 3).

Table 1. Complaints of the patients during admission to the ED

Complaints	Number	Percentage
Shortness of breath	52	60.4%
Chest pain	14	16.3%
Cough	12	13.9%
Syncope	4	4.7%
Hemoptysis	3	3.5%
Leg pain	1	1.2%

Table 2. Comparison of CTPA results with clinical variables

CTPA Result **Variables**		**Massive**	**Segmental**	**Total**	**p-value**
Sex	Male	22(47.8%)	18 (45%)	40 (46.5%)	0.482
	Female	24 (52.2%)	22 (55%)	46 (53.5%)	
Wells Scale	Moderate	29 (63%)	31 (77.5%)	60 (69.8%)	0.111
	High	17 (37%)	9 (22.5%)	26 (30.2%)	
PA CXR	With infiltration	37 (80.4%)	22 (55%)	59 (68.6%)	0.039
	Without infiltration	5 (10.9%)	9 (22.5%)	14 (16.3%)	
	With effusion	4 (8.7%)	9 (22.5%)	13 (15.1%)	
ECHO Result	Normal	8 (17.4%)	21 (52.5%)	29 (33.7%)	0.001
	Dilated right heart chambers	38 (82.6%)*	19 (47.5%)	57 (66.3%)	
Doppler USG	Without DVT	23 (50.0%)	27 (67.5%)	50 (58.1%)	0.077
	With DVT	23 (50.0%)	13 (32.5%)	36 (41.9%)	

PA CXR: Posteroanterior chest X-ray, ECHO: Echocardiography, USG: Ultrasonography, DVT: Deep vein thrombosis

Table 3. Comparison of the drug use and hospitalization variables according to CTPA results

CTPA Result		**Massive**	**Segmental**	**Total**	**p-value**
Drug Use Status	Using anticoagulants	10 (21.7%)	6 (15%)	16 (18.6%)	0.423
	Not using anticoagulants	36 (78.3%)	34 (85%)	70 (81.4%)	
Hospitalization Status	Hospitalization	46 (100%)	35(87.5%)	81(94.2%)	0.019
	Discharge	0(0%)	5(12.5%)	5(5.8%)	

The mean hospitalization duration in the services was 9.62 days, and the mean hospitalization duration in intensive care units was 3.30 days. All patients with massive involvement were admitted to the service or intensive care unit. However, five patients with segmental involvement were discharged outpatient without admission to the pulmonology service. Upon examining the hospitalization duration in the intensive care unit, we observed that 16 patients with massive involvement and 26 patients with segmental involvement were never admitted to the intensive care unit.

DISCUSSION

PE is a difficult-to-diagnose lung disease that causes about 300,000 deaths annually in the United States of America (11). It is very important to make a definitive diagnosis to prevent this fatal condition. It is difficult to diagnose PE without specific clinical and physical examination findings. Therefore, some diagnostic tests are needed. Arterial blood gas, D-dimer, biochemical markers, electrocardiography, and PA CXR contribute to the diagnosis, albeit limited, in patients with suspected PE (12).

PE is a potentially fatal disease resulting in obstruction of the lung blood flow and perfusion impairment due to an embolism (13). PE is also considered an acute complication of DVT (14). While DVT has an annual incidence of 0.1% in the general population, it has a rate of more than 1% in hospitalized patients (15). Especially in proximal DVTs, Doppler USG has a sensitivity of more than 90% and a specificity of 95%. However, DVT can be detected in approximately 30-50% of patients diagnosed with PE (16). In another study, bilateral lower extremity Doppler USG performed on patients diagnosed with PE revealed thrombus in the lower extremity in 44.4% of the cases (12). In our study, we detected DVT at a similar rate in 41.9% (n=36) of PE patients in line with the literature.

PE can be observed as mild shortness of breath and can even be asymptomatic, as well as leading to death as a result of sudden cardiac arrest (17). It has a wide clinical spectrum and can often occur with different combinations such as shortness of breath, pleuritic chest pain, respiratory failure, hypoperfusion, and hemodynamic instability (17). Hemoptysis and cough may also occur, but they are usually associated with other underlying causes (18). In our study, the most common complaint of the patients was shortness of breath, while the second most common complaint was chest pain.

The mean age of the incidence of the disease is 69.3±16.0 years, and there is no significant difference in terms of sex (19). However, although the sex ratios were close to each other in our study, the mean age was lower (52.29±14.14 years).

ECHO, which can be applied bedside by helping to diagnose PE in ED, is now indispensable. ECHO may show right ventricular dysfunction, although it cannot prove the embolism completely (20). In the study conducted by Mazen S et al., dilatation in the right ventricle (55%) and right ventricular dysfunction (85%) were observed in the ECHO evaluation of patients with suspected PE (p=0.001) (21). The right ventricular dilatation was observed most commonly in the ECHO evaluation of patients in our study (p=0.001).

Although PA CXR is not a priority for diagnosis, it can support other diagnostic methods. In a study, the most common chest radiography findings were parenchymal infiltration in 37.3%(n=22) and pleural effusion in 35.6% (n=21), but no finding was detected in 33.9% (n=20) of the patients (22). In our study, parenchymal infiltration was observed most commonly, at a rate of 68.6% (n=59), in line with the literature, on the PA CXR.

With technological advances in recent years, CTPA can directly show the thrombus in the pulmonary artery bed up to the segmental level (23). Although acute PE cannot be observed with the help of CTPA, which we prefer for definite and rapid diagnosis of PE in ED, it can show alternative diagnoses for the patient's clinical picture (24). In a study evaluating the detection of acute PE, when CTPA was compared with pulmonary angiography, which is the gold standard, it was observed that CTPA had 91% accuracy (25). In the study carried out by Erdal et al., it was reported that 68% (n=64) of the thrombus were central (main and lobar arteries), and 32% (n=30) were peripheral (segmental and subsegmental arteries) (22). Our study was quite compatible with the literature, and we detected massive embolism in 53.5% (n=46) of the patients diagnosed with PE and segmental embolism in 46.5% (n=40).

In the present study, we also compared the ECHO results according to whether PE was massive or segmental. The right heart chambers were dilated in 82.6% of patients with massive PE, while the right heart chambers were dilated in 47.5% of patients with segmental PE.

As a result of a study performed according to Wells scoring, 14.75% of the patients were evaluated as those with high probability, 52.46% as those with moderate probability, and 32.79% as those with low probability (26). In our study, there were no patients with low probability in the Wells scoring. The Wells score of most patients (69.8%) was moderate. There were more patients (63%) with moderate Wells scores in both massive and segmental involvement.

Especially the anticoagulant use status of patients also affects PE. The main goal of PE treatment after discharge is to prevent the recurrence of fatal or non-fatal venous thromboembolism (VTE) with oral anticoagulants (27). Although these agents are very effective in preventing VTE recurrence, new thromboembolic events occur at an estimated rate of 3.3% (28), while fatal PE occurs in 1.5% of patients under treatment (29). In another study conducted with 124 patients, 30 patients were diagnosed with pulmonary embolism according to the results of CTPA performed on 70 patients with moderate and high probability determined as a result of V/P scintigraphy. It

was observed that 24 (80%) of 30 patients diagnosed with PE were not using any drug for prophylaxis (30). In our study, 10 (62.5%) of 16 patients were using anticoagulants due to PE history. The remaining 6 (37.5%) patients were using anticoagulants for other reasons (atrial fibrillation-flutter, heart valve replacement, stroke, etc.). Of the total patients, only five patients died. Of these 5 patients who died, 4 did not have a history of anticoagulant use, and 1 patient was using anticoagulants due to previous PE. In light of this information in the literature (28,29), we can say that the use of oral anticoagulants significantly reduces the development of recurrent PE, especially the development of fatal PE.

In the study conducted by Baydın et al. with 102 patients, 21.6% of the cases were massive PE, and 78.4% were segmental PE. Moreover, all massive and segmental cases were hospitalized (31). In our patients, all of the patients with massive involvement (n=46) and those with segmental involvement (n=35), except for 5 patients (discharge), were hospitalized.

Limitation of the Study

The main limiting factor is that our study does not reflect the general population due to the small number of patients included. Furthermore, the fact that it could not be carried out in a multi-centered manner is also a limiting factor.

Finally, another limitation is that pulmonary angiography, which is known as the gold standard in diagnosis, could not be performed.

CONCLUSION

PE is a disease that is difficult to diagnose in ED. Although CTPA is most commonly used in diagnosis, we cannot use CTPA in patients with contrast material allergy and renal insufficiency and pregnant women. Among the auxiliary radiological methods in diagnosis, ECHO, which can be used as a non-invasive and bedside method with ease of application and accessibility, is now indispensable in ED, especially in the diagnosis of massive PE.

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Araştırma Makalesi / Research Article

Evaluation of Routine Coagulation Testing Requirements in Patients with Severe Epistaxis

Ciddi Epistaksis olan Hastalarda Rutin Koagülasyon Teslerinin Değerlendirmesi

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Abstract

Aim: There are studies about coagulation parameters are not required in the management of epistaxis. The aim of the present study was to investigate whether or not coagulation tests are required and its relationship with medications in severe epistaxis cases that require intervention.
Material and Method: The patients above 16 years who had presented to emergency department due to epistaxis, who had undergone anterior/posterior nasal packing or electro-cautery to the nasal mucosa were included the study. The demographic characteristics, blood count, coagulation test, anti-platelet and anti-coagulant medications, the procedures carried out for stopping bleeding, whether reversal treatment or blood transfusion was needed were recorded.
Results: A total of 469 patients, it was found that coagulation parameters had been tested in 141(30.2%). While PT, aPTT and INR values of the anti-coagulant using patients were significantly higher($p<0.001$, $p=0.003$, $p<0.001$, respectively), the platelet and hemoglobin values were not found to be associated with anti-platelet drug and anti-coagulant use($p=0.304$, $p=0.098$, respectively). The patients were allocated to two groups as those any parameter of whom was impaired or not. While a significant difference was found between the groups with regard to hemoglobin values($p=0.006$), no patients were determined to need reversal treatment or hemoglobin replacement.
Conclusion: Routine coagulation testing is not required for patients who have epistaxis that cannot be stopped with conservative methods and who are using anti-platelet drugs as it does not lead to a difference in treatment. Coagulation tests may not be performed in patients who use anti-coagulants based on the results.

Keywords: Epistaxis, nose-bleed, coagulation, antiplatelet

Öz

Amaç: Epistaksis yönetiminde koagülasyon testlerinin gerekli olmadığını gösteren çalışmalar mevcuttur. Bu çalışmanın amacı, müdahale gerektiren ciddi burun kanamalarında pıhtılaşma testlerinin gerekli olup olmadığını ve ilaçlarla ilişkisini araştırmaktır..
Materyal ve Metot: Çalışmaya Acil Servis'e burun kanaması ile başvurmuş 16 yaş üstü, anterior veya posterior burun tamponu konulan veya nazal mukozaya koterizasyon uygulnan hastalar dahil edildi. Hastalara ait demografik veriler, tam kan sayımı, koagülasyon testleri, kullandığı antikoagülan ve anti-trombosit ilaçlar, kanamayı durdurmak için kullanılan yöntem ve kan transfüzyonu veya koagülasyon bozukluğu için kan ürünü alıp almadığı kaydedildi.
Bulgular: Toplam 469 hastadan 141 (%30,2)'inin koagülasyon testlerinin çalışıldığı bulundu. Antikoagülan kullanan hastaların PT, aPTT ve INR değerleri anlamlı olarak yüksek bulunurken (sırasıyla $p<0,001$, $p=0,003$, $p<0,001$) trombosit ve hemoglobin değerlerinin anti-trombosit ve antikoagülan kullanımı ile ilişkili olmadığı bulundu (sırasıyla $p=0.304$, $p=0.098$). Hastalar herhangi bir koagülasyon veya kanama parametresinde bozulma olan ve olmayan olarak iki gruba ayrıldı. Hemoglobin değerleri açısından gruplar arasında anlamlı fark bulunurken ($p=0,006$), kan transfüzyonu veya koagülasyon bozukluğu için kan ürünü replasmanına ihtiyaç duyan hasta saptanmadı.
Sonuç: Konservatif yöntemlerle durdurulamayan epistaksisi olan ve antitrombosit ilaç kullanan hastalarda tedavide fark yaratmadığı için rutin pıhtılaşma testi yapılmasına gerek yoktur. Antikoagülan kullanan hastalarda sonuçlara göre pıhtılaşma testleri yapılmayabilir.

Anahtar Kelimeler : Epistaksis, burun kanaması, koagülasyon, antiplatelet

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INTRODUCTION

Epistaxis is among the most common causes of bleeding of head and neck origin in patients presenting to the emergency room. This condition is usually not complicated and rarely difficult to control. Most cases can be controlled with nasal compression and topical vasoconstrictors (1). Although severe epistaxis cases that cannot be stopped with conservative methods may be controlled with anterior or posterior nasal packing, balloon catheter or electrical and medical cautery; surgical interventions (endoscopic ligation, embolization) may rarely be required (2). Coagulation parameters including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT) and the international normalized ratio (INR) are still being tested in many centers besides the anamnesis and physical examination. However, some studies are available reporting that these tests are not necessary in the management of epistaxis, and it was concluded that these approaches increased the costs and the duration of hospital stay (3).

Many current studies include the whole epistaxis cases that can be controlled even with conservative treatments. The present study was conducted with the aim of investigating the necessity of coagulation tests and its relationship with the medications used.

MATERIAL AND METHOD

The present study was conducted at the Emergency Department of Okmeydani Research and Training Hospital, which is a tertiary center that accepts about 550,000 emergency room admissions annually. The data were retrospectively obtained from the electronic medical report system of the hospital. The patients above 16 years who had been admitted to emergency room due to epistaxis, who had undergone anterior/posterior nasal packing or electro-cautery to the nasal mucosa between June 2017 and May 2019 were retrospectively included in the study. The demographic characteristics of the patients, blood count parameters, coagulation test results, anti-platelet (acetyl salicylic acid, [ASA], clopidogrel, prasugrel, ticagrelor) and anti-coagulant medications (warfarin, rivaroxaban, dabigatran, apixaban, edoxaban) used by the patients, the procedures carried out for stopping the bleeding, whether or not reversal treatment or blood transfusion were needed were recorded. The patients whose bleeding could be controlled spontaneously or with conservative treatment (nasal compression, topical vasoconstrictor), who were below 16 years of age, pregnant, who had trauma-related hemorrhage and whose medications could not be determined via the pharmacy system of the ministry of health, were excluded from the study.

The coagulation parameters were accepted as impaired if the values were as follows: PT>14.2 sec, aPTT>33 sec, INR>1.2, platelet count<150,000. It was investigated whether or not there was an association between these values and drug use, and the association between the medication and coagulation parameters in patients in whom any parameter was impaired.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Okmeydani Training and Research Hospital, Istanbul, Turkey (Approval No. 1087).

Statistical Analysis

Statistical analyses were performed using the SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL, USA). In the comparison of the continuous variables between the two groups, the Mann Whitney U test was used for the variables that were not normally distributed, and the independent sample t test was used for the normally distributed continuous data. The Chi-square test or the Fisher's exact test was used for comparison of the categorical variables. For comparison of the continuous variables among three groups, the one-way variance analysis (ANOVA) was used for the normally distributed continuous variables and the Kruskal-Wallis test was used for the non-normally distributed continuous variables. The Post-hoc Tukey test, the Welch ANV or the Bonferroni correction was used for the subgroup comparisons.

RESULT

A total of 469 patients who had been admitted to the emergency room due to epistaxis and undergone one of anterior/posterior nasal packing or nasal mucosa cautery, were included in the study. Of these patients, 141 (30.2%) were determined to have been tested for coagulation parameters and enrolled in the study. 78 (%55.3) of the patient in the study were male. The mean age of the patients was 61,9 (± 19.0). The demographic and clinical characteristics of the patients have been presented in Table 1.

While 94 (66.7%) patients were not using any medications, 28 (20%) were using ASA and other anti-platelet combinations; 16 (11%) of them were using only ASA and 3 (2%) were using clopidogrel. Of the patients who were using anti-coagulants, 8 (5.6%) were using rivaroxaban and 6 (4.2%) were using warfarin. While the PT, aPTT and the INR values of the patients who were using anti-coagulants were significantly high (p>0.001, p=0.003 and p>0.001, respectively), the platelet and the hemoglobin values were not found to be related to anti-platelet and anti-coagulant use (p=0.304 and p=0.098, respectively).

Patients whose platelet count was low, INR value was high and the PT and aPTT were elevated, constituted a group, and the patients were allocated to two groups as those, any parameter of whom was impaired or not. While a significant difference was determined between these two groups with regard to the hemoglobin values (p=0.006), none of the patients whose coagulation parameter was impaired required reversal treatment and hemoglobin replacement (Table 2).

Table 1. Demographic and Clinical Characteristics of Patients

Parameters	All Patient (n=141)	No drugs (n=94)	Anti-platelets (n=33)	Anticoagulants (n=14)	p
Age, mean ± SD	61.9±19.0	60.5±21.9	63.3±9.0	66.2±19.1	0.002
Sex, male, n (%)	78 (% 55.3)	53 (% 56.4)	19 (% 57.6)	6 (% 42.9)	0.609
WBC(109/L), median(IQR)	8.76 ±3.01	8.10 (7.08-9.67)	8.49 (6.53-10.63)	9.14 (8.02-12.41)	0.091
Hb(g/dL), mean±SD	12.99 ±2.15	13.17±2.07	13.38±1.44	11.28±3.02	0.098
Plt(109/L), mean±SD	241.3±70.8	242.9±83.9	229.8±36.4	256.1±45.7	0.304
PT(sec), mean±SD	11.70(11.00-13.30)	11.77±1.35	11.51±1.41	28.69±8.94*,[a,b]	< 0.001
aPTT(sec), mean±SD	26.00(23.45-29.40)	26.31±61	24.79±2.98	41.61±12.52*,[a,b]	0.003
INR, median(IQR)	1.04 (0.96-1.16)	0.99 (0.95-1.12)	1.04 (1.01-1.12)	2.52(1.87-3.54)*,[a,b]	< 0.001
Intervention, n (%)					
Anterior Packing	103(%73.0)				
Anterior Packing + Cautery	7(%5.0)				
Anterior+PosteriorPacking	11(%7.8)				
Only Cautery	18(%12.8)				
Posterior Packing	2(%1.4)				

* p <0.05, a Versus no drugs, b Versus Anti-platelets used

Table 2. Relationship with any coagulation parameters impaired

Parameters	Normal(n=112)	Impaired (n=29)	p
Age, mean ± SD	56.3±19.2	69.7±16.3	0.001*
Sex; male, n (%)	61 (% 54.5)	17 (% 58.6)	0.688**
WBC (109/L), median (IQR)	8.65 (7.46-10.21)	7.85 (6.24-9.97)	0.281***
Hb(g/dL), mean (±SD)	13.33±1.73	11.71±2.84	0.006*
Reversal and Replecement Terapies	0	0	-

* Independent sample t test, ** Chi square test, *** Mann whitney u test

DISCUSSION

The present study including 141 patients investigated the patients whose coagulation test could be impaired without the absence of anti-coagulant and anti-platelet use or history of any medication. While the elevations in the INR values are related to anti-coagulant drugs, an association between this condition and the treatment given to the patient could not be demonstrated. Besides, a significant alteration was not observed in the tests of the patients who were receiving anti-platelet agents.

Many studies state that INR should be controlled in patients who are using warfarin and whose epistaxis does not respond to local measures (4,5). Similarly, discontinuation of anti-platelet drugs is not meaningful as their effect lasts up to 10 days besides knowing that discontinuation of anti-coagulants is not useful in acute hemorrhages.

Consulting with a hematologist or cardiologist may be needed for arrangement of treatment only when the hemorrhage is massive and cannot be stopped or in case of anti-coagulant over-dose (6). On the other hand, the rate of the need for reversing anti-coagulation was reported as only 0.15% yearly in epistaxis developing in patients using anti-coagulants in a large retrospective study (7). In our study, no patients required reversal and replacement therapy. Hence, it was concluded that coagulation testing could not be useful unless the presence of a bleeding that could not be controlled despite treatment even if the patients were using warfarin.

In the present study, the hemoglobin levels of the patients whose coagulation parameters were impaired were found to be significantly low. No patients required blood transfusion. In a large cohort of 591 patients, the need for blood replacement was investigated in patients with epistaxis and showed that only 2 out of 22 patients receiving replacement were using anti-coagulant and anti-platelet agents (8). A strong association was demonstrated between epistaxis surgery and blood transfusions, particularly posterior hemorrhages requiring surgical intervention (9). In our patient population, posterior tampon was applied to only 2 (1.4%) patients; this low rate may be the reason for not requiring replacement treatment.

Limitations

Our study has many limitations due to its retrospective design. Re-admissions of these patients could have been to other centers and this could not be evaluated due to limited access to data. The seniority of the clinicians who ordered the tests was not considered and we suggest that this could lead to a difference. However, the study was designed retrospectively as a prospective design could lead to bias. Although our patient population is relatively small, the population can be widened so as to include the patients who required surgical intervention and/or transfusion.

CONCLUSION

Routine testing of coagulation parameters is not necessary as it would not change the treatment in patients who are using anti-platelet agents and whose epistaxis cannot be controlled with conservative treatments. Based on our data, routine testing is not required in patients using anti-coagulants; however, studies are required conducted with larger populations including patients who use anticoagulants (particularly warfarin) for making this suggestion.

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Ethical approval: *The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Okmeydani Training and Research Hospital, Istanbul, Turkey (Approval No. 1087).*

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Araştırma Makalesi / Research Article

The Effect of Preoperative Nutritional Support on Postoperative Morbidity and Mortality in Patients With Gastric Cancer: A Single Center Retrospective Study

Mide Kanserli Hastalarda Preoperatif Nütrisyonel Desteğin Postoperatif Morbidite ve Mortalite Üzerine Etkisi: Tek Merkezli Retrospektif Veri Analizi

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Abstract

Aim: Weight loss and malnutrition are frequently observed in patients with gastric cancer. Therefore, nutrition is important, especially in patients with gastric cancer. In this study, we aimed to identify the effect of preoperative nutritional support on postoperative morbidity and mortality in patients with gastric cancer.

Material and Method: A total of 110 patients underwent gastrectomy due to gastric cancer between December 2015 and December 2019 were retrospectively analyzed. It was determined whether the patients were given preoperative and postoperative nutritional support. Clinicopathological features and short-term results were compared.

Results: Overall morbidity was 29.1% (n=32) in patients who underwent gastrectomy. It was observed that the rate of major complications increased statistically with increasing age (p<0.001). Comorbidity was also found to be a risk factor for major complications (OR 3.917, 95% CI 1.423-10.781; p=0.006). The incidence of complications increases especially in patients with a diagnosis of diabetes (OR 3.743, 95% CI 1.201-11.666; p=0.040). While anastomotic leak developed in 6.7% (n=2) of the patients who were taken preoperative nutrition, anastomotic leak developed in 10% (n=8) of the patients who were not taken nutritional support (p=0.588). Likewise, the relationship between the postoperative length of stay, postoperative complications and mortality of patients receiving preoperative nutritional support could not been proven.

Conclusion: The present study reveals that preoperative nutrition in patients with gastric cancer was not associated with improved morbidity and mortality rates. Large, multicenter prospective studies focusing on preoperative nutritional support are needed to uncover the exact relation of preoperative nutrition and morbidity-mortality rates in patients with gastric cancer.

Keywords: Gastrectomy; nutritional support; gastric cancer

Öz

Amaç: Mide kanserli hastalarda kilo kaybı ve malnütrisyon sıklıkla görülmektedir. Bu nedenle özellikle mide kanserli hastalarda beslenme önemlidir. Bu çalışmada mide kanserli hastalarda ameliyat öncesi beslenme desteğinin ameliyat sonrası morbidite ve mortalite üzerine etkisini belirlemeyi amaçladık.

Materyal ve Metot: Aralık 2015 ile Aralık 2019 tarihleri arasında mide kanseri nedeniyle gastrektomi yapılan toplam 110 hasta retrospektif olarak incelendi. Hastalara ameliyat öncesi ve sonrası beslenme desteği verilip verilmediği belirlendi. Klinikopatolojik özellikler ve kısa dönem sonuçları karşılaştırıldı.

Bulgular: Gastrektomi yapılan hastalarda genel morbidite %29.1 (n=32) idi. Yaş arttıkça majör komplikasyon oranının istatistiksel olarak arttığı görüldü (p<0.001). Komorbidite de majör komplikasyonlar için bir risk faktörü olarak bulundu (OR 3.917, %95 CI 1.423-10.781; p=0.006). Özellikle diyabet tanısı olan hastalarda komplikasyon insidansı artmaktadır (OR 3.743, %95 CI 1.201-11.666; p=0.040). Preoperatif beslenme alan hastaların %6.7'sinde (n=2) anastomoz kaçağı gelişirken, beslenme desteği almayan hastaların %10'unda (n=8) anastomoz kaçağı gelişti (p=0.588). Aynı şekilde preoperatif nütrisyon desteği alan hastaların postoperatif yatış süresi, postoperatif komplikasyonlar ve mortalitesi arasındaki ilişki kanıtlanamamıştır.

Sonuç: Bu çalışma, mide kanserli hastalarda ameliyat öncesi beslenmenin morbidite ve mortalite oranlarında iyileşme ile ilişkili olmadığını ortaya koymaktadır. Mide kanserli hastalarda ameliyat öncesi beslenme ile morbidite-mortalite oranları arasındaki kesin ilişkiyi ortaya çıkarmak için ameliyat öncesi beslenme desteğine odaklanan geniş, çok merkezli ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler : Gastrektomi; nutrisyonel destek; mide kanseri

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INTRODUCTION

Gastric cancer remains the fifth most common cancer type in worldwide and is the third leading cause of cancer-related deaths in the world (1). Gastrectomy is still remain as the main treatment method for gastric cancer though symptoms such as malabsorption, bacterial overgrowth, decreased gastric retention, rapid intestinal transit time and insufficient oral intake may occur in patients after surgery (2). Therefore gastrectomy is usually cause body weight loss in patients with gastric cancer. Weight loss in the first year after surgery was reported as 6% - 10% in patients who underwent subtotal gastrectomy and 15% - 18% in patients undergoing total gastrectomy (3,4). Preoperative malnutrition was reported as associated with increased morbidity (i.e. increased infection rate, delayed wound healing, pulmonary complications) and mortality in patients undergoing major surgery (5,6,7). Therefore, identification and treatment of malnutrition is important in the management of gastric cancer. Various guidelines such as ESPEN guidelines, German S3 Guidelines, and the North American Surgical Nutrition Summit recommend nutritional support for all patients with inadequate oral intake (8,9). Ding et al showed in a randomized controlled trial (RCT) of 106 patients who underwent gastrectomy that preoperative EN improves postoperative nutritional status, attenuates the inflammatory response, and facilitates recovery of patients (10). In this study, we aimed to identify the effect of preoperative nutritional support on postoperative morbidity and mortality in patients with gastric cancer.

MATERIAL AND METHOD

Demographics and Clinical Characteristics of The Patients

Patients underwent gastrectomy for gastric cancer between December 2015 and December 2019 were retrospectively analyzed. Patients that have the diagnosis of gastric adenocarcinoma and underwent R0 / R1 gastrectomy were included in the study. Patients who were considered inoperable and whose pathology result were not adenocarcinoma were excluded from the study. A total of 110 patients were detected. Patients' age, sex, comorbidities, American Society of Anesthesiology (ASA) scores, type of operation, TNM staging, histological type of tumor, presence of lymphovascular invasion, cerb-b2 positivity, preoperative level of albumin, whether preoperative or postoperative nutritional support was given, Clavien-Dindo scores, postoperative length of hospital stay, demographic and clinicopathological datas were collected. The study was approved by the ethics committee of the Ministry of Health University of Health Sciences Izmir Tepecik Training and Research Hospital (Approval number: 2020/9-2) and was adapted to the Helsinki Declaration.

Statistical Analysis

Statistical analysis were done with IBM SPSS Statistics software, version 25.0. As the descriptive statistics, the number of units (n), percent (%), mean ± standard deviation (x ´ ± ss), Median (Q1-Q3) values were given. Pearson Chi-Square and Ficher's exact test were used to evaluate categorical variables. The results are reported as Odds ratios (ORs) with 95% confidence interval (CI). The normal distribution of data's continuous variables were evaluated by Shapiro Wilk, normality test and Q-Q graphs. In the comparison of the continuous variables of the two groups, the Independent Sample T test was used for variables with normal distribution, and Mann-Whitney U test for variables that did not fit the normal distribution. $p<0.05$ value was considered statistically significant.

RESULT

Baseline Clinicopathological Characteristics

A total of 110 patients were found eligible for the inclusion criteria. The mean age was 61.4 ± 12.61 (range, 28-88) and 73 (66.4%) of the patients were male. 57 (51.8%) of the patients that underwent gastrectomy were had various comorbidities. 7 (6.4%) patients were ASA 1, 66 (60.0%) patients were ASA 2, 32 (29.1%) patients were ASA 3 and 5 (4.5%) patients were ASA 4. 12 (10.9%) of the patients were taken neoadjuvant therapy. The mean of preoperative level of albumin was 3.8 (SD ± 0.58) g/dL. Total gastrectomy was performed in 78 (70.9%) patients while subtotal gastrectomy was performed in 32 (29.1%) patients. R0 or R1 resection was performed to all patients. In pathological materials, the majority of patients were T4 (n=59, 53.6%) or N3 (n=44, 40.0%). Lymphovascular invasion was detected in 81 (73.6%) patients and cerb-B2 expression was found in 19 (17.3%) patients. 7 (6.4%) of the patients were operated due to emergency reasons.

32 (29.1%) of the patients were presented overall morbidity. While the most common complications were pulmonary complications such as atelectasis and pneumonia (13.7%), other complications were anastomotic leakage (9.1%), surgical site infection (3.6%), bleeding (1.8%), and cerebrovascular disease (0.9%). Postoperative complications of the patients were classified according to Clavien-Dindo Classification. According to this classification, 25 patients with score of 3 and above were grouped as the major complication group, and 85 patients who did not develop complications or scored 1 or 2 according to Clavien-Dindo were grouped as without major complications. The effect of the clinicopathological characteristics of the patients on major complications is summarized in Table-1.

It was observed that the rate of major complications increased statistically with increasing age ($p<0.001$). Comorbidity was also found to be a risk factor for major complications (OR 3.917, 95% CI 1.423-10.781; $p=0.006$). The incidence of complications increases especially in patients with a diagnosis of diabetes (OR 3.743, 95% CI 1.201-11.666; $p=0.040$). Also the rate of complications increases according to the number of comorbidities of the patients ($p<0.001$). The level of albumin which is used as an indicator of malnutrition, was found to be significantly lower in patients with complications ($p=0.001$). The

Table 1. The clinical and pathological features

	All patients (n=110)	without major complications (n=85)	with major complications (n=25)	p-Value
Age, years, mean ± SD	61.4 ± 12.61	59.0 ± 12.51	69.4 ± 9.37	<0.001
Gender, n (%)				0.776
Male	73 (66.4)	57 (67.1)	16 (64)	
Female	37 (33.6)	28 (32.9)	9 (36)	
Hypertension, n (%)	27 (24.5)	18 (21.2)	9 (36)	0.130
Diabetes mellitus, n (%)	15 (13.6)	8 (9.4)	7 (28)	0.040
Comorbidity, n (%)	57 (51.8)	38 (44.7)	19 (76)	0.006
ASA classification, n (%)				<0.001
1	7 (6.4)	7 (8.2)	0 (0)	
2	66 (60)	57 (67.1)	9 (36)	
3	32 (29.1)	20 (23.5)	12 (48)	
4	5 (4.5)	1 (1.2)	4 (16)	
ALB, g/dL, mean ± SD	3.8 ± 0.58	3.9 ± 0.51	3.4 ± 0.68	0.001
Neoadjuvant therapy, n (%)	12 (10.9)	11 (12.9)	1 (4)	0.291
Type of surgery, n (%)				0.101
Total gastrectomy	78 (70.9)	57 (67.1)	21 (84)	
Subtotal gastrectomy	32 (29.1)	28 (32.9)	4 (16)	
pT, n (%)				0.458
T1	10 (9.1)	9 (10.6)	1 (4)	
T2	11 (10)	10 (11.8)	1 (4)	
T3	30 (27.3)	22 (25.9)	8 (32)	
T4	59 (53.6)	44 (51.8)	15 (60)	
pN, n (%)				0.503
N0	26 (23.6)	21 (24.7)	5 (20)	
N1	16 (14.5)	14 (16.5)	2 (8)	
N2	24 (21.8)	19 (22.4)	5 (20)	
N3	44 (40)	31 (36.5)	13 (52)	
Tumor location, n (%)				0.110
Cardia	28 (25.5)	20 (23.5)	8 (32)	
Corpus	35 (31.8)	24 (28.2)	11 (44)	
Antrum	36 (32.7)	30 (35.3)	6 (24)	
Pylorus	11 (10)	11 (12.9)	0 (0)	
Lymphovascular invasion, n (%)	81 (73.6)	59 (69.4)	22 (88)	0.064
C-erb-B2 positivity, n (%)	19 (17.3)	16 (18.8)	3 (12)	0.555
Preoperative nutritional support, n (%)	30 (27.3)	21 (24.7)	9 (36)	0.265
Postoperative nutritional support, n (%)	78 (70.9)	54 (63.5)	24 (96)	0.002
Emergency operation, n (%)	7 (6.4)	3 (3.5)	4 (16)	0.046

complications were also found increased in patients that underwent emergency surgery (p=0.046).

Impact of Preoperative Nutritional Support on Postoperative Complications and Length of Hospital Stay

5 (4.5%) of the patients were received nutritional support only in the preoperative period, 53 (48.2%) of them were received nutritional support only in the postoperative period and 25 (48.2%) of them were received nutritional support both in the preoperative and postoperative periods. 27 (24.5%) patients were not received any nutritional support during the perioperative period. The effects of preoperative nutritional support on 30 patients' postoperative hospital stay, complications and mortality were summarized in Table-2. While anastomotic leak developed in 6.7% (n=2) of the patients who were taken preoperative nutrition, anastomotic leak developed in 10% (n=8) of the patients who were not taken nutritional support. However, it was not statistically significant (p=0.588). Likewise, the relationship between the postoperative length of stay, postoperative complications and mortality of patients receiving preoperative nutritional support could not been proven.

Table 2. The effect of nutritional support on mortality and morbidity

	All patients (n=110)	to get preoperative nutritional support (n=30)	not to get preoperative nutritional support (n=80)	p-Value
Postoperative length of hospital stay,				0.692
days, mean ± SD	12.3 ± 12.42	13.1 ± 14.58	12.0 ± 11.60	
Any complication, n (%)				0.123
Yes	32 (29.1)	12 (40)	20 (25)	
No	78 (70.9)	18 (60)	60 (75)	
Anastomosis leakage, n (%)				0.588
Yes	10 (9.1)	2 (6.7)	8 (10)	
No	100 (90.9)	28 (93.3)	72 (90)	
Clavien-Dindo classification, n (%)				0.227
0	78 (70.9)	18 (60)	60 (75)	
1	5 (4.5)	2 (6.7)	3 (3.8)	
2	2 (1.8)	1 (3.3)	1 (1.3)	
3	5 (4.5)	0 (0)	5 (6.3)	
4	10 (9.1)	5 (16.7)	5 (6.3)	
Mortality, n (%)				0.343
Yes	10 (9.1)	4 (13.3)	6 (7.5)	
No	100 (90.9)	26 (86.7)	74 (92.5)	

DISCUSSION

It is important to provide nutritional support in patients with gastric cancer in order to reduce postoperative complications and increase long-term quality of life. Early enteral nutrition should be initiated after surgery and adequate nutritional support should be given before surgery in patients with gastric cancer. Nutritional support for these patients can be provided enterally and parenterally. Although total parenteral nutrition (TPN) provides a significant benefit to surgical patients, it has many complications. Studies have proven that intestinal permeability increases in patients after surgical trauma and therefore there is a risk of bacterial translocation in patients receiving only TPN (11). It has also been found that enteral nutrition preserves intestinal integrity and reduces septic complications and hospital stay (12,13). Enteral nutrition is safer, cheaper and more physiological than parenteral nutrition. However, parenteral nutrition is mandatory in patients with gastrointestinal dysfunction.

Enteral immunonutrition (EIN) is an immune product enriched with arginine, glutamine, omega-3 fatty acids and ribonucleic acid. EIN is known as an alternative nutritional supplement that has emerged to modulate the metabolism and immune system and has attracted attention in recent years. However, its superiority over enteral nutrition is controversial. Gianotti et al. was compared the perioperative immunonutrition with standard enteral nutrition in patients undergoing major elective gastrointestinal surgery (14). This study showed that perioperative immunonutrition significantly reduced overall complications and length of hospital stay. However, it was found not associated with mortality. Song et al. reported in a meta-analysis that immunonutrition could effectively improve the nutritional and immunological

status of patients with gastric cancer who underwent surgical resection. On the other hand they couldn't find any association between immunonutrition and patients' postoperative complications and hospital stay (15).

It was shown that malnutrition can cause immunosuppression and poor prognosis in patients with gastric cancer. Therefore, nutritional support during the postoperative period is as important as preoperative nutrition. The ERAS protocol advocates that patients should take enteral nutrition as early as possible. However, some studies did not find a significant difference between early enteral nutrition and parenteral nutrition after total gastrectomy (16). Parenteral nutrition may be the only option especially for patients who are not suitable for enteral feeding. There are studies suggesting that parenteral nutrition can significantly improve patients' nutritional and psychological status, quality of life and immune functions (17). In addition, a study in an elderly patients undergoing surgery for gastric cancer showed that the combination of enteral and parenteral nutrition is superior to early enteral nutrition or total parenteral nutrition in promoting immune recovery (18). There are no separate guidelines for the management and treatment of elderly patients with gastric cancer. As expected, older patients typically have more medical comorbidities and higher American Society of Anesthesiologists (ASA) classification scores. Elderly patients should be evaluated carefully in the preoperative period considering the postoperative morbidity and mortality risks.

Fujiwara et al. (19) and Hsu et al. (20) reported higher rates of postoperative complications and mortality in elderly patients with gastric cancer. In our study it was observed that the rate of major complications increased statistically with increasing age. Also, age was found to be an independent factor negatively affecting postoperative mortality and morbidity in patients undergoing gastric resection. In our study, the increase in the number of comorbidities was also found to be associated with postoperative complications. We considered that this result is associated with the increase of various systemic diseases in elderly patients. When systemic diseases were examined separately, it was found that the incidence of complications increased in patients with diabetes mellitus. In a multicenter study, it was found that diabetic patients who underwent major surgery had a higher risk of infections and mortality than non-diabetic patients who had similar major surgery (21). There is an inverse correlation between serum levels of albumin and length of hospital stay and postoperative complications in patients with gastric cancer (22). We found that inverse correlation in our study either. This inverse correlation was due to both the decrease in albumin levels in the geriatric population and the fact that albumin was an indicator of malnutrition.

This study could not clearly show the effect of preoperative nutrition on postoperative mortality and morbidity. It is considered that the effect of preoperative nutrition could not be proven, since the majority of patients receiving preoperative enteral nutrition were malnourished patients and the risk of complications in this group was higher than other patients. However, age, albumin level, diabetes and the presence of more than one comorbidity were found to be factors affecting the postoperative prognosis in gastric cancer. These findings support other similar studies. The retrospective nature of this study caused some limitations. The lack of malnutrition or sarcopenic data such as body mass index of the patients, limited information about the perioperative diet regimen of the patients, the difference in surgical experience and surgical resection types determine the limits of this study. Prospective randomized studies are needed to overcome these problems and to examine preoperative nutrition in more detail.

CONCLUSION

The present study reveals that preoperative nutrition in patients with gastric cancer was not associated with improved morbidity and mortality rates. This result may stem from retrospective nature of this study and its limitations. Large, multicenter prospective studies focusing on preoperative nutritional support are needed to overcome these limitations and uncover the exact relation of preoperative nutrition and morbidity-mortality rates in patients with gastric cancer.

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Araştırma Makalesi / Research Article

Evaluation of the Correlation Between the Severeness of Lung Involvement and Fatty Liver Disease in Covid-19

Covid-19'da Akciğer Tutulumu Şiddeti İle Yağlı Karaciğer Hastalığı Arasındaki İlişkilerin Değerlendirilmesi

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Abstract

Aim: The aim of the study is to investigate whether there is a correlation between the severity of pneumonia and fatty liver disease in COVID-19.
Material and Method: In this study chest computed tomography (CT) images of 168 patients who were confirmed to be COVID-19 positive according to nasopharyngeal swab specimens were evaluated. The severity of pneumonia and the presence of hepatic steatosis were evaluated on CT images.
Results: The patients were aged between 26 and 89, and the mean age was 63.6 ± 12.4 years. 101 (60.1%) of the patients were male. Hepatic steatosis was observed in 51 (30.4%) patients. No significant difference between the severity of pneumonia and hepatic steatosis on CT (p = 0.715) was found. No significant difference was found in the presence of hepatic steatosis in patients who died because of COVID-19 compared to patients who recovered (p = 0.938).
Conclusion: This study revealed that there is no relationship between the severity of COVID-19 pneumonia and hepatic steatosis.

Keywords: COVID-19, chest CT, hepatic steatosis, lung

Öz

Amaç: Çalışmanın amacı, COVID-19'da pnömoni şiddeti ile yağlı karaciğer hastalığı arasında korelasyon olup olmadığını araştırmaktır.
Materyal ve Metot: Bu çalışmada nazofarengeal sürüntü örneklerine göre COVID-19 pozitif olduğu doğrulanan 168 hastanın göğüs bilgisayarlı tomografi (BT) görüntüleri değerlendirildi. BT görüntülerinde pnömoninin şiddeti ve hepatik steatoz varlığı değerlendirildi.
Bulgular: Hastaların yaşları 26 ile 89 arasında olup, yaş ortalaması 63.6 ± 12.4 yıl idi. Hastaların 101'i (%60.1) erkekti. 51 (%30.4) hastada hepatik steatoz gözlendi. BT'de pnömoni şiddeti ile hepatik steatoz arasında anlamlı fark saptanmadı (p = 0.715). COVID-19 nedeniyle ölen hastalarda hepatik steatoz varlığında iyileşen hastalara göre anlamlı fark saptanmadı (p = 0.938).
Sonuç: Bu çalışma, COVID-19 pnömonisinin şiddeti ile hepatik steatoz arasında bir ilişki olmadığını ortaya koymuştur.

Anahtar Kelimeler: COVID-19, göğüs BT, hepatik steatoz, akciğer

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INTRODUCTION

Corona virus disease 2019 (COVID-19), an acute respiratory disease, was first detected in Wuhan, China in December 2019 and then spread throughout China and the world (1). COVID-19 has a wide clinical spectrum from asymptomatic cases to cases resulting in acute severe respiratory failure requiring intensive care (2).

In a study conducted in China, it is found that the average age is 47, the disease is more common in men, and 23.7% of patients have at least one concomitant chronic disease (such as hypertension, diabetes, chronic obstructive pulmonary disease (3). The median incubation period of COVID-19 is 5 to 6 days, symptoms may occur within 2-14 days after contact, and infectiousness may begin 1-2 days before symptoms (4).

Although different COVID-19 symptoms may also be observed: fever, coughing, gastrointestinal diseases, headache, conjunctival hyperemia, nasal congestion, sore throat, increased secretion, sputum, malaise, hemoptysis, nausea vomiting, diarrhea, stomach pain, myalgia, rash, decreasing taste and smelling are among those reported. (3). The correlation between non-alcoholic fatty liver disease (NAFLD) and COVID-19 has been investigated in the limited availability of studies (5). In the post-mortem liver biopsy studies in patients who died from COVID-19, microvesicular steatosis accompanied by over activation of T cells is shown (6).

How liver abnormalities can affect virus infection is still unknown. The genetics, lifestyle, and underlying comorbidities of the person infected with the virus may also be critical in understanding the follow-up process of patients with liver damage. The present study aims to retrospectively evaluate the chest computed tomography (CT) of PCR (+) COVID-19 patients to investigate whether there is a correlation between the severity of pneumonia and fatty liver disease.

MATERIAL METHOD

CT images of 168 patients, who were randomly selected from inpatients with SARS-CoV-2 positive nasopharyngeal sampling, non-contrast thoracic tomography, and with no chronic liver disease hospitalized in Malatya Training Research Hospital in September, October, and November 2020, were evaluated by two radiologists.

The CT scans of the patients were performed using a 16-slice multidetector CT (Philips Medical System, MX). The tube voltage was 110 kV. Two radiologists retrospectively evaluated the CT images through picture archiving and communication systems (PACS). Radiologists were unaware of the clinical findings and prognoses of the patients.

Liver density was measured as Hounsfield unit (HU), excluding vessels and bile ducts as much as possible from the right lobe of the liver to an area of 150 mm2 (Fig. 1). If the density of the liver was at least 10 HU lower than the density of the spleen or if the liver density was below 40 HU, it was accepted as hepatic steatosis. CT images were also evaluated for the severity of pneumonia. The lung involvement area was evaluated as stated in the articles of Pan at all (7). Subsequently, the patients were divided into four groups according to the severity of pneumonia as 1-25%, 26-49%, 50-75%, and > 75%.

Intensive care unit (ICU) treatment and mortality evaluated as an indicator of poor prognosis. It was thought that the patients treated in the ICU had a worse prognosis than the patients who did not receive intensive care treatment, and the patients who died compared to the patients who recovered. Whether the patients had comorbid diseases was checked at the information system of the hospital.

Ethical approval was obtained from the Malatya Turgut Özal University Clinical Research Ethics Committee (Approval No. 2021/37).

Strengths and Limitation

In view of the strengths of our meta-analyse, we followed a strict technique and did not change from the pre-study protocol, except for the addition of mortality in our research. First of all, We excluded patients with additional diseases such as a malignant mass in the liver, hydatid cyst, patients with a malignant mass in the lung and those receiving chemotherapy due to other malignant tumoral diseases, and we did not include these patient groups in our study. Secondly, studies in the literature are still limited on this subject. Finally, the studies were retrospective and were conducted in a limited number of patients.

Statistical analysis

IBM SPSS Statistics for Windows 22.0 was used to perform the analysis of the data, and P-values were calculated using the chi-square test and analysis of variants (ANOVA). P <0.05 value was considered significant.

RESULT

The patients are aged between 26 and 89, and the mean age was found to be 63.6 ± 12.4 years. 101 (60.1%) of the patients were male. 116 (69%) patients were treated in the inpatient treatment unit and 52 (31%) patients in the intensive care unit. 122 (72.6%) patients recovered and were discharged. 108 (64.3%) patients had an accompanying comorbid disease such as diabetes mellitus, hypertension, heart failure. Hepatic steatosis was observed in 51 (30.4%) patients.

The patients were divided into 4 groups according to the severity of pneumonia. The mean age of the groups was similar, and no significant difference was found between the groups in terms of mean age (p = 0.170). Additionally, no difference was found between the groups in terms of comorbid diseases (p = 0.987).

Although the incidence of hepatic steatosis increased in accordance with the percentage of involvement in the groups categorized after their severity of pneumonia, no significant difference was found between the groups in terms of hepatic steatosis (p = 0.715). The frequency of

steatosis according to the lung involvement rate groups is present in Table 1.

The incidence of hepatic steatosis increased with age, and this was statistically significant (p <0.001). There was no significant difference between men and women in terms of hepatic steatosis between those with and without comorbid diseases. The values of p respectively: p= 0.821, p = 0.438.

Although the rate of hepatic steatosis was slightly higher in patients treated in the ICU compared to those not treated in the ICU, it was not statistically significant (p=0.938). The rate of hepatic steatosis was slightly higher in patients who died due to COVID-19 compared to patients who recovered however it was not statistically significant (p=0.697) (Table 2).

Table 1. Hepatic steatosis incidence rates in groups according to the severity of pneumonia

Lung involvement	HS present n(%)	HS absent n(%)	Total n(%)	P value
1 - 25%	17(25.8)	49(74.2)	66(100)	
26-49%	13(31.0)	29(69.0)	42(100)	
50-75%	10(33.3)	20(66.7)	30(100)	0.715
>75%	11(36.7)	19(63.3)	30(100)	
Total	51(30.4)	117(69.6)	168(100)	

Lung involvement: Percentage of lung involvement according to the severity of pneumonia; HS: Hepatic steatosis; n: number of patients

Table 2. The incidence of hepatic steatosis according to the prognostic characteristics of the patients.

	HS present n(%)	HS absent n(%)	Total n(%)	P value
ICU hospitalization	16(30.8)	36(69.2)	52(100)	0.938
Non-ICU hospitalization	35(30.2)	81(69.8)	116(100)	
Death	15(32.6)	31(67.4)	46(100)	0.697
Recovering	36(29.5)	86(70.5)	122(100)	

HS: Hepatic steatosis; n: number of patients; ICU: Intensive care unit

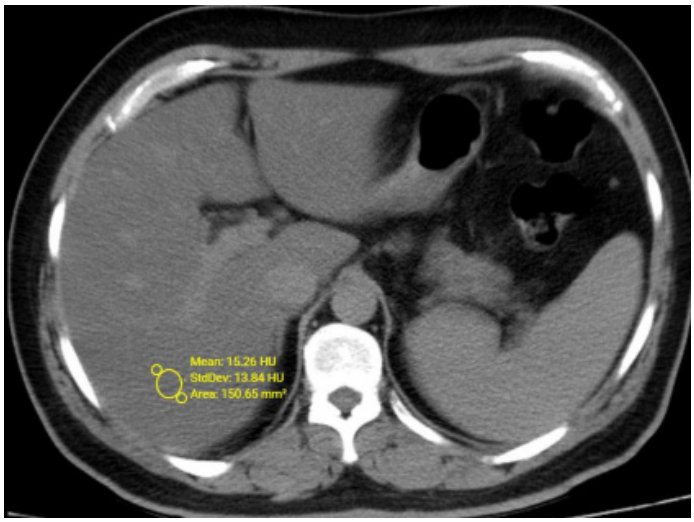

Figure 1. Axial CT image showing measurement of hepatic steatosis in the liver.

DISCUSSION

The pathogenesis of gastrointestinal symptoms and liver injury due to COVID-19 is still investigated. The glycoprotein spikes (S protein) on the outer surface of SARS-CoV-2 bind to the ACE2 (Angiotensin-Converting Enzyme 2) receptor of the host cells, therefore allowing the virus to enter the cell (8). Although ACE2 is not expressed in Kupffer cells, hepatocytes, and the endothelium of liver sinusoids, it has been shown in studies conducted in a culture medium that ACE2 expression is produced in hepatocytes by hypoxia. This situation is thought to indicate the damage to the liver in hypoxia condition occurring in COVID-19 (9). In our study, hepatic steatosis was observed in only 30.8% of the patients treated in the intensive care unit and 30.2% of the inpatients. These results suggest that hepatic steatosis has no effect on disease severity in COVID-19.

Hepatic steatosis is a deposition of fat in hepatocytes. Although the most common cause of hepatic steatosis is

non-alcoholic fatty liver disease, many other causes such as alcoholism, chronic viral hepatitis, drug toxicity, storage diseases, obesity, autoimmune-hereditary diseases, and malnutrition may lead to fatty liver (10).

It has been reported in studies that COVID-19 infection is more common in individuals with chronic diseases, and it has a more severe course. In a study published in Wuhan in January 2020, it was found that about half of the patients have at least one chronic disease (11). Comorbidities such as hypertension, diabetes, asthma, chronic obstructive pulmonary disease and cardiovascular diseases are also more common among severe COVID-19 patients (12). In this study, similar to other studies, the rate of comorbid diseases was high, and it was found to be 64.3%.

It is thought that a proinflammatory response to viral infection may increase in obesity due to weak immune system activity. In a study, it has been asserted that in the case of hepatic steatosis in the liver, it increases inflammation and may cause liver damage (13). However, in our study, there was no statistically significant difference in the rate of hepatic steatosis among the patients who were treated in the intensive care unit and the service and died. We think that it would not be valid to associate the issue that hepatic steatosis causes an increase in inflammation and worsen the patient's condition only with hepatic steatosis.

In a liver autopsy study in the literature, steatosis was observed in 8 of 14 patients, and it is thought that the observed fatty liver disease may be associated with metabolic diseases, and it has been suggested that there is not enough evidence to support the correlation between COVID-19 infection and the development of fatty liver disease (14). In a study, it was found that liver enzymes were abnormally high in COVID-19 patients. It has been reported that the reason for this may be due to systemic inflammation caused by the virus (15). In a study on how COVID-19 disease can affect the liver in patients with and without liver disease, it has been shown that pre-existing liver disease has little effect on getting COVID-19 infection (16). As stated in the previous studies, the fact that hepatic steatosis in COVID-19 disease was not found to be a significant difference in deceased intensive care and deceased service patients in our study, suggests that it should not be seen as a risk factor alone.

It was found that the presence of fatty liver disease in hospitalized patients who were COVID-19 positive, was not associated with adverse outcomes, and there was no difference in mortality classified by age, and fatty liver was observed in significantly young patients at admission (17). On the contrary, in our study, we found that the incidence of hepatic steatosis increases as age increase. It is thought that this is due to genetic and cultural differences. In our study, no significant difference was found between the groups in terms of hepatic steatosis. It would not be accurate to say that hepatic steatosis increases the severity of pneumonia. For this reason, we think that the presence of hepatic steatosis alone cannot constitute a risk factor in terms of the course of the disease.

CONCLUSION

It would not be accurate to claim the hepatic steatosis the only risk factor in COVID-19 disease and that it worsens the course of the disease. We think that knowing all the comorbid factors that worsen the course of the disease will provide better control over the disease and the treatment should be administered accordingly.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *Ethical approval was obtained from the Malatya Turgut Özal University Clinical Research Ethics Committee (Approval No. 2021/37).*

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Araştırma Makalesi / Research Article

Terminal Care and Death Through the Eyes of Turkish Nursing Students: A Qualitative Research Study

Türk Hemşirelik Öğrencilerinin Gözünden Yaşam Sonu Bakim Ve Ölüm: Bir Kalitatif

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Abstract

Aim: This study was aimed to determine the thoughts and feelings of nursing students emerging during the provision of care to terminally ill patients.
Material and Method: It is a qualitative study. The study population consisted of 12 students who volunteered to participate in the study. Data were collected using a semi-structured interview form and focus group interview technique. Descriptive and content analysis techniques were used for the data analyses.
Results: The study found out that the majority of the students defined death as a "sad ending" and "loss". Some students stated that they kept an attitude of acceptance, while others stated that they experienced intense feelings of fear when they encountered death. The students stated that they generally felt sorry for the patient, felt ineffective, and experienced an intensification of their fears of death when providing care for terminally ill patients. Furthermore, all of the students said that terminal care should aim to "minimize pain and provide an abundance of resources".
Conclusion: This study shows that nursing students need to get more education about terminal care and that further qualitative studies should be conducted to investigate the feelings of nursing students from various aspects.

Keywords: Nurse, student, terminal period, death

Öz

Amaç: Araştırma, terminal dönem hastalarına bakım veren hemşirelik öğrencilerinin bakım sırasında yaşadıkları duygular ve ölüm hakkındaki düşüncelerini belirlemek amacıyla planlanmıştır.
Materyal ve Metot: Araştırma nitel desende tasarlanmıştır. Araştırma grubunu, çalışmaya katılmaya gönüllü olan 12 öğrenci oluşturmaktadır. Veriler yarı yapılandırılmış görüşme formu ve odak grup görüşmesi tekniği ile toplanmıştır. Verilerin analizinde, betimsel analiz ve içerik analizi tekniği kullanılmıştır.
Bulgular: Araştırmada, öğrencilerin büyük çoğunluğu ölümü "Hüzün verici bir son ve kayıp" olarak tanımlamıştır. İlk defa ölümle karşılaştıklarında bazı öğrenciler kabullenici bir tutum sergilediğini, bazıları ise korku duygusunu yoğun olarak yaşadıklarını ifade etmişlerdir. Öğrenciler, terminal dönem hastalarına bakım verirken genellikle hasta için üzüldüklerini, çersizlik hissettiklerini ve kendi adlarına da ölüm korkularının arttığını belirtmişlerdir. Ayrıca öğrencilerin tamamı, terminal dönem bakımın amacının, "az ağrı ve refah içinde ölüm" şeklinde olması gerektiğini söylemiştir.
Sonuç: Bu araştırma, hemşirelik öğrencilerinin terminal dönem bakımı konusunda daha fazla eğitime ihtiyaçları olduğunu ve bu konuda öğrencilerin duygularının farklı boyutlarıyla da ele alındığı nitel çalışmaların artırılması gerektiğini göstermektedir.

Anahtar Kelimeler : Hemşire, öğrenci, terminal dönem, ölüm

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INTRODUCTION

"Death" is a universal phenomenon that happens unexpectedly regardless of the social position or the situation the person is in. Death is a concept difficult to define. In the face of death, humans attribute many meanings to death and react accordingly (1). When the reaction to death is excessive, immoderate or pathological; anxiety levels of people increase and adjustment to the environment is disturbed (2). When the response to death is an attitude of acceptance, the person can live a life to apply his or her values, alleviating the death anxiety.

Due to the technological advances and parallel medical innovations, death is considered a disease or a condition to be struggled against rather than being perceived as a natural process. For this reason, death can be considered as an event within a hospital. Nurses spend most of their time with patients in hospitals, therefore, they are constantly posed to face death. This is why nurses define terminal care and the process of death as one of the most challenging aspects of their profession (3). Several conditions complicate the death process, including the progressive deterioration of the patient's condition, difficulties in treating the symptoms, and the helplessness feelings of the patient's relatives (4, 5). Death is a challenging process and terminal care mainly aims to ensure the physical and psychological comfort of the patient to increase the quality of life (6). In order to raise awareness in nurses responsible for the provision of care, they should be trained and supervised on the physical, emotional, intellectual, social, and spiritual dimensions of end-of-life care throughout their education (2). Furthermore, students should be trained primarily to identify and control their emotions (7,8). Özer et al.'s study (2015) on student nurses found that assuming the care provider role for a terminally ill patient caused anxiety and that the reason of the anxiety was not related to the fear of death of the student nurses but occurred due to their feelings of inadequacy and helplessness in informing and directing the patient (9). In studies conducted abroad (9-11) students reported that their feelings of helplessness were caused by getting insufficient training about how to prepare the patient to death. Despair negatively affects students' provision of care to patients in the process of death. In a study performed by Şahin et al. (2016), 62.2% of nursing students stated that they would not like to provide care to a terminally ill patient (4). In a study by Youssef (2016), it was reported that 83.3% of nursing students developed negative feelings and thoughts towards terminal care patients and their families (12).

First of all, the students' feelings and thoughts about death should be identified in all aspects so that the students can effectively communicate with terminal care patients; manage their emotions, help themselves relieve feelings of helplessness, provide a standard care appropriately, and ensure that patients die in dignity. This study is expected to contribute to the literature by identifying student nurses' feelings and thoughts about death based on the results obtained from in-depth interviews. The aim of this study is to identify the feelings and thoughts of student nurses about the provision of care to terminally ill patients in Turkey.

MATERIAL AND METHOD

Type of Research

This study has aimed to comprehensively investigate the student nurses' feelings and thoughts about death during care provision to terminally ill patients and to compile a holistic view of the participants, it has been designed as a focus group study, which is one of the qualitative research methods.

Focus group interviews have been selected as a qualitative research method since they are one of the most appropriate methods to identify the feelings, thoughts, perceptions, and attitudes of individuals. Furthermore, focus group interviews provide in-depth information and allow brainstorming by using group dynamics (13). All senior student nurses, who volunteered to participate in the study, were included in the study without using any pre-specified method for participant selection.

Population and Sample of the Research

The study was carried out in a vocational healthcare high school in Central Anatolian Region in Turkey. Focus group interviews were conducted with the participating students in the meeting room at scheduled times. The interviews were carried out between 25.11.2018 and 29.11.2018.

Study Group: In compliance with the study design, the study group consisted of 12 fourth-grade nursing students, comprising 4 men and 8 women, volunteered to participate in the study. Male students were given the 'M' code (M1-4). Female students were given the 'F' code (F1-8). The students attended the 2017-2018 academic year at the time of the study and they provided care to terminally ill patients during their education. The students were coded to facilitate the documentation of the findings. The aliases of the students could be found on their ID badges during the interviews.

Inclusion criteria in the research: Inclusion criteria are being a 4th grade student, providing care to a terminal-period patient during their education and volunteering to participate in the study.

Exclusion criteria in the research: Students of 1st, 2nd and 3rd years and 4th year students who did not provide terminal period patient care were not included in the study.

Data Collection

There was a U-shaped table in the meeting room, allowing the participants to see each other. Appropriate environmental conditions (noise, light, temperature, ventilation, etc.) was ensured in the meeting room so that the interviews were conducted comfortably and trustfully. Before starting the interviews, refreshments and equipments (drinking water, pencil, paper, etc.) were

put on the table for the use of the participants. The comments of the students were recorded by a smartphone after obtaining their consent. Before the interviews, the meeting room was prepared by the investigator. Interviews were conducted in two sessions outside the class hours of the students. Each session took 30-40 minutes, considering the suitability of the students. All 12 students were present at the interviews.

The focus group interviews were moderated by an investigator. Additionally, another investigator was present during the interview to note the verbal and non-verbal statements of the students and the investigator, too. During the interviews, it was explained to the students that they could revisit the previous question and that they were allowed to express their ideas freely.

Data Collection Instruments

Introductory Information Form

The introductory information form consisted of three questions to document the age and gender of the students and the time when they encountered terminally ill patients.

Interview Form

A semi-structured interview form was used in the study to reveal the students' experiences in depth. The interview form was developed using the information obtained from the literature review (14-17) and by using the sub-dimensions (Neutral Acceptance, Escape Acceptance, Escape from Death and Fear) of the Attitude To Death Scale (15). There are four open-ended questions in the interview form. Interview questions were as follows:

1-What does death mean to you?

2-What did you feel at your first encounter with death?

3- How did you feel when providing care to the terminally ill patient?

4-In your opinion, what should be the main purpose of care provided during the terminal period?

Data Analysis

The characteristics of patients were analyzed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Percentages, frequencies, means, median, standard deviations, and ranges were used to define sociodemographic sample characteristics. Content analyses were used for the qualitative data. Content analysis is one of the most commonly used methods in qualitative data analyses. Content analysis is primarily used for analyzing the written and visual data obtained from the focus group interviews. The data summarized and interpreted in the descriptive analysis is more deeply analyzed in the content analysis (18). The data obtained in the descriptive analysis were further analyzed by three investigators using content analysis so that any potentially unnoticed concepts and themes would be unfolded. The data analysis was carried out in the following four steps:

Step 1: The frequency and percentages were calculated using the quantitative data.

Step 2: By reading the interview reports of each participant repeatedly, the investigators identified the following themes, including the meaning of death, emergent feelings at the first encounter with death, the feelings experienced during the provision of care to the terminally ill patient, and the purpose of providing care to a patient in the terminal period.

Step 3: The identified themes were categorized according to the sub-dimensions of the Attitude To Death Scale (Neutral Acceptance, Escape Acceptance, and Fear and Avoidance of Death). Then, these themes were interpreted interactively, unfolding new concepts.

Step 4: At this final step, the themes and codes were summarized in a Table 1.

Table 1. Themes and Codes Associated With the Student's Feelings and Thoughts About Death During Provision of Care to Terminally Ill Patients

Themes	Codes
Theme 1. Meaning of Death	A sad ending and loss
Theme 2. Emergent Feelings at the First Encounter With Death	Neutral Acceptance, Escape Acceptance, and Fear and Avoidance of Death
Theme 3. The Feelings Experienced During The Provision of Care to the Terminall Ill Patient	Neutral Acceptance, Escape Acceptance, and Fear and Avoidance of Death
Theme 4. The Purpose of Providing Care to A Patient in the Terminal Period has been identified.	Neutral Acceptance, Escape Acceptance, and Fear and Avoidance of Death

Ethical consideration

To conduct the study, the permission of the institution and the approval of the Ethics Committee of the Bozok University were obtained (Approval date: 06.06.2018) Before commencing the interviews, the volunteering students were informed about the study and an "Informed Consent Form For Volunteers" was signed by the students who agreed to participate in the study.

Limitations of Research: This study had certain limitations. First, the limitations of the study are that it was conducted with a small group of students and it was conducted after a few years following the students' experiences. The latter made it difficult for the students to remember their memories and feelings at that time.

RESULT

The results are discussed in two sections. The first section addressed the quantitative findings including the descriptive characteristics of the students. The second section addressed the qualitative findings comprising the answers of the students to the interview questions.

Sample Characteristics

Table 2 presents the descriptive characteristics of the students. Of the participating students, 75% were women and they first encountered a terminally ill patient after they became a student nurse. The mean(median) age of the students was 20.41±1.16(20).

Table 2. Sample Characteristics (N=12)

Sample Characteristics	n	Percentage
Gender		
Female	8	75.0
Male	4	25.0
Mean Age (years) (X± SD)(min-max) (median)		20.41±1.16 (19-23) (20)
First Encounter with A Terminall Ill Patient		
Before Undergraduate Education	4	25.0
After Undergraduate Education	8	75.0
Total (N)	12	100.0

Note. SD = standard deviation.

Qualitative Findings

The findings in this section were examined after being categorized under the following themes; including the meaning of death, emergent feelings at the first encounter with death, the feelings experienced during the provision of care to the terminally ill patient, and the purpose of providing care to a patient in the terminal period.

Theme 1: Meaning of Death

When the students were asked what death meant to them, the majority described it as "A sad ending and loss ". The definitions of death by the students are as follows:

"A sad ending and loss" (M1, M2, M3, F2, F6, F8)

"Salvation" (M4)

"A new beginning" (F1, F3, F4)

"Transition to Eternity" (F5)

"Real life" (F7)

Theme 2: Emergent Feelings at the First Encounter With Death

When students were asked to describe the feelings they experienced when they first encountered death, some of them informed that they kept an accepting attitude and some reported that they experienced a feeling of intense fear. The responses of the students are presented below under three codes including neutral acceptance, escape acceptance, and fear and avoidance of death:

a) Neutral Acceptance (M2, M3, F1, F2, F4, F5, F7)

"I thought that; one day, I will experience death, too. I felt that death was not as far away as I thought" (F1)

"It occurred to me that there might be an end to the life lived" (M2)

b) Escape Acceptance (F3)

"When I first encountered death, I felt very sorry. However, I later realized that it was salvation from mundane sufferings." (F3)

c) Fear and Avoidance of Death (M1, M4, F6, F8)

"At my first encounter with death, I intended to address it as a normal situation until when that frightening feeling inflicted me. Thinking that I might not find the patient in my next call was the scariest thought" (M1).

"I was scared. I didn't feel sorry for person who died; rather, I felt sorry for the relatives because it was sad to survive after the death of a deceased person" (M4).

Theme 3: The Feelings Experienced During The Provision of Care to the Terminall Ill Patient

When students were asked to describe the feelings they experienced while caring of the patient in the terminal period, some students accepted the situation and perceived death as a salvation from the disease. However, most of the students informed that they usually felt sorry for the patient and that experience aggravated their fear of death.

a) Neutral Acceptance (M4, F1, F4)

"I realized that I felt sorry for the patient, but it didn't scare me. Rather, I considered it as a condition that would happen to everyone eventually" (M4).

"I knew death was the end for everyone. When I thought that the patient could have been my mother or father, I felt sad. Then, I continued to provide appropriate care to the patient. It was a pleasant feeling to be helpful and make the patient comfortable" (F4).

b) Escape Acceptance (M3, F3, F5)

"I thought that medicine was insufficient to relieve the pain and sufferings of patients and I wondered why it could not cure the diseases. This made me think that every ephemeral being would die one day for a reason. I felt terribly sorry" (M3)

"My patient had cancer and was in terrible pain, having no expectations from life. I thought death could be the only salvation for that patient. I thought that someday I would be in this patient's position. If I were the patient, I'd like to die, too." (F3)

c) Fear of Death (M1, M2, F2, F6, F7, F8, F9)

"To see a patient dying; to whom I provided care, scared me terribly and gave me pain. I felt that I provided empty solace to my patient; however, I saw that the person in front of me had not given up life, yet. This made me think that one could never give up life." (M1)

"I felt very sorry at times and I was sometimes terribly desperate. I was tired of trying not to show these feelings." (F7)

"The patient's respiratory distress and vulnerability scared me so much. I was very upset seeing that he/she lived in this condition. However, I tried to ensure that the patient would not feel that way at all."(M2)

Theme 4: Purpose of Patient Care in Terminal Period

All of the students said that the purpose of the care in the terminal period should be to "minimize pain and provide an abundance of resources". The expressions of the participating students are as follows:

F3 "It is to ensure that the patient was made comfortable and his/her sufferings were relieved, even making the death process free of any suffering. Thereby, people, who suffered too much, at least would not suffer when they die."

M3 "To ensure that the patient's pain is diminished, he/she would die in peace and comfort, and he/she was assisted to enjoy himself/herself with the loved ones."

F5 "Care in the terminal period should minimize the pain of the patient, allow the patient to spend the end-of-life period peacefully at home, and the basic needs of the patient should be met".

DISCUSSION

The responsibility to sustain life is attained to student nurses during their education. Accordingly, nursing students assume responsibility for patient survival. However, the unpreventable character of death causes nursing students to experience negative emotions such as anxiety (19). American Association of Colleges of Nursing Palliative Competencies and Recommendations (2016) emphasizes that nursing students should be given training on end-of-life care (20). This way, student nurses can have the opportunity to elaborate attitudes towards their death and cope with end-of-life care problems.

Knowing the meaning of death for student nurses helps understand students' perspectives against death, determining the communication level of the patient. In our study, most of the students described death as a sad ending and loss. In the study conducted by Selçuk ve Avcı (2015) on university students, 82.3% of the students defined death as the beginning of a new life [21]. Bilge, Embel, and Kaya (2013) report that students, who will be future healthcare professionals, believe that death is a real and impending issue to be accepted and that death is a transition to another life after death (22). Our study results are different from those of the previously published studies in the literature. We can argue that this difference occurred because the participating students' perspectives about death were affected by the perspectives of the Central Anatolian population in Turkey.

Our study found out that the students experienced a neutral acceptance at their first encounter with death. A literature review of the studies from our country and abroad reveals that neutral acceptance is a widely used approach as shown by the Kumar et al. (2014) study and Bilge et al. (2013) study, investigating the students' attitudes towards death (22, 23). The similarity of our research findings to the literature indicates that nurses providing care for terminally ill patients encounter death frequently, perceiving death as a natural event that should be experienced and accepted.

In our study, the fear of death was the most common feeling experienced by the students during the provision of care for the terminally ill patient. Yılmaz and Vermişli (2015) found that, in young intensive care nurses, death anxiety was higher and their attitudes towards death were more negative compared to experienced nurses (24). A study on student nurses reported that during the provision of end-of-life care, 17.2% of students experienced 'sadness' and 10.2% 'could not recognize their feelings (25). In a study by Özer et.al (2015) on student nurses, it was determined

that the end-of-life care generated anxiety and angry (9). This anxiety may be the reflection of insufficiency and helplessness feelings of student nurses due to not knowing how to direct the patient and what to say. This finding might reflect insufficient professional experiences of student nurses and insufficient training provided to them during the undergraduate education, aiming to train them about how to approach death and how to cope with death-associated feelings.

Every individual has the right to receive effective care and treatment until the very last moment of his or her life. The nursing profession requires providing effective care to patients and helping to relieve their pain until the end of their lives (8, 26, 27). During the provision of care to terminally ill patients, the responsibilities of nurses include relieving the sufferings of terminally ill patients and their families, providing adequate medical care, avoiding the use of methods with no additional benefits, making the patient comfortable, and providing adequate emotional and spiritual support. In the study by Gurkan, Gumus, and Dodak (2011), 79.6% of student nurses stated that painful interventions applied to patients should be discontinued. In line with the information in the literature and the study findings of Gurkan, Gumus, and Dodak (2011), all of the participating student nurses in our study stated that the aim of terminal care should be to "minimize the suffering of the patient and provide an abundance of resources"(28).

CONCLUSION

The results of this study indicate that death affects all aspects of life, including physical, social, and psychological areas. We revealed that death and palliative care has common negative effects on students, regardless of cultural diversity. This finding might reflect insufficient professional experiences of turkish student nurses and insufficient training provided to them during the undergraduate education, aiming to train them about how to approach death and how to cope with death-associated feelings.

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Araştırma Makalesi / Research Article

Assessment of Occupational Fatigue in Healthcare Professionals During the COVID-19 Pandemia

COVID-19 Pandemisi Sürecinde Sağlık Profesyonellerinin Mesleki Yorgunluklarının Değerlendirilmesi

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Abstract

Aim: This study aimed to determine the level of occupational fatigue in healthcare professionals during the COVID-19 pandemic process and assess some variables considered to have a relationship with it.
Material and Method: This study used a descriptive cross-sectional design and was carried out on physicians and nurses between June and July 2020. The study data were collected using a questionnaire with items questioning some socio-demographic data of the healthcare professionals, characteristics of their workplace and working conditions, and contact with patients with COVID-19, and the items of the Occupational Fatigue-Exhaustion Recovery Scale. The study group consisted of 308 females and 98males. In non-normal distributions, the Mann-Whitney U test was used for variables with two groups and Kruskal–Wallis-H test for variables with more than two groups.
Results: The mean scores of the healthcare professionals from the chronic fatigue and acute fatigue sub-domains of the Occupational Fatigue Exhaustion Recovery Scale were 60.65±29.10, 65.52±21.64 and 45.09±19.1, respectively. In the study group, fatigue levels were higher in women who were aged 49 years or younger, had weekly working hours of more than 40 hours, and came into contact with COVID 19 patients every day..
Conclusion: The fatigue and burnout levels of healthcare professionals who are directly involved in the care of patients with COVID-19 during the pandemic process were above moderate levels, and the level of their recovery was at a moderate level. It is recommended that necessary administrative initiatives should be taken to improve healthcare workers' rights, whose working conditions are getting more difficult in the pandemic environment, their needs for rest should be planned, and that working environments that will ensure that not only the risk of contamination but also the risk factors that will arise due to fatigue are under control should be created.

Keywords: Covid 19, Pandemia, Fatigue, Healthcare Professionals

Öz

Amaç: Bu çalışma ile COVİD 19 pandemisi sürecinde sağlık çalışanlarının mesleki yorgunluk düzeylerinin saptanması ve ilişkili olduğu düşünülen bazı değişkenlerin değerlendirilmesi amaçlanmıştır.
Materyal ve Metod: Çalışma, Haziran-Temmuz 2020 tarihleri arasında hekim ve hemşireler üzerinde yapılan kesitsel tanımlayıcı bir araştırmadır. Çalışmanın amacına uygun olarak literatürden de faydalanılarak bir anket form hazırlanmıştır. Anket form, sağlık çalışanlarının bazı sosyodemografik özelliklerini, çalışma yeri ve çalışma koşulları ile ilgili bazı özellikleri, COVİD 19 hastaları ile temas hakkındaki bazı bilgileri ve Mesleki Yorgunluk Tükenmişlik Toparlanma Ölçeğinin maddelerinden oluşmaktadır. Çalışma grubunu oluşturanların 308'i kadın, 98'i ise erkektir. Veriler normal dağılım göstermediğinden iki guruplu değişkenler için Mann-Whitney U testi, ikiden fazla guruplu değişkenler için Kruskal-Wallis-H testi kullanıldı.
Bulgular: Sağlık çalışanlarının Mesleki Yorgunluk Tükenmişlik Toparlanma Ölçeğinin Kronik Yorgunluk, Akut Yorgunluk Toparlanma Alt boyutlarından aldıkları puanlar sırasıyla 60.65 ± 29.10, 65.52±21.64 ve 45.09 ± 19.1, puan idi. Çalışma grubunda kadınların, 49 yaş ve altı yaş grubunda olanların, haftalık çalışma süresi 40 saatten fazla olanların, COVİD 19 hastaları ile her gün temas edenlerin yorgunluk düzeyleri daha yüksek bulunmuştur.
Sonuç: COVID-19 hastalarının bakımıyla doğrudan ilgilenen sağlık profesyonelleri, pandemi sürecinde yorgunluk, tükenmişlik düzeylerinin orta düzeyden daha fazla olduğu, toparlanma düzeylerinin ise orta düzeyde olduğunu bildirdiler. Pandemi ortamında çalışma şartları daha da zorlaşan sağlık çalışanlarının haklarının iyileştirilmesi, dinlenme ihtiyaçlarının planlanarak, sadece bulaşma riski değil yorgunluğa bağlı oluşacak risk faktörlerin kontrol altına alınmasını sağlayacak çalışma ortamlarının oluşturulmasına yönelik idari çalışmaların yapılması önerilmektedir.

Anahtar Kelimeler: Covid-19, Pandemi, Yorgunluk, Sağlık Profesyonelleri

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INTRODUCTION

The COVID-19 pandemic, which started in Wuhan city, China in December 2019 and has affected the whole world since then, has been declared as an international public health emergency by the World Health Organization (WHO) (1). COVID-19 belongs to the virus group that causes Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (2). It causes severe acute respiratory tract infections, progresses as asymptomatic, mild, or severe symptomatic, and can be fatal with factors such as advanced age and underlying diseases (3).

The occupational group that is considered to be at high and very high risk for COVID-19 infection by OSHA (Occupational Safety and Health Administration) includes healthcare workers. Those who carry out aerosol-generating procedures (intubation, cough induction, bronchoscopy, mouth-throat-nose examination, ophthalmological examinations, central catheter placement, use of nebulizers, cardiopulmonary resuscitation, oxygen therapy, non-invasive ventilation, examinations involving some dental procedures, or invasive specimen collection), physicians, nurses, and other healthcare workers were defined as risk groups (4).

The health sector constitutes the most important step of the crisis. The crisis has physical, mental, and social effects on healthcare workers. Healthcare workers is exposed time pressure, low social support, high workload, uncertainty about patient treatment, and emotional impact. Therefore, health workers are at high risk of experiencing distress, fatigue, burnout, and mental and physical discomfort. Healthcare workers face a higher risk for stress and COVID-19 transmission compared to other segments of society since they work in the same environment with people who are infected or likely to be carriers (5).

In particular, the anxiety about transmitting the disease to their relatives negatively affects the physical and mental health of healthcare workers. Daily cases of infection and death, uncertain working hours, and having to work with COVID-19 cases regardless of the field of specialization are factors that increase the risk of fatigue, burnout and depression of healthcare professionals (6-9).

To work more efficiently, it is important that people feel good both mentally and physiologically. There are over 59 million healthcare workers in the world. Therefore, research in this field will be guiding to provide healthcare workers with more effective psychological support in the field. This pandemic has once more revealed that society needs healthcare workers and their performance of healthcare practices happily and healthily (10). This study aimed to determine the occupational fatigue levels of healthcare workers during the COVID 19 pandemic and to evaluate some variables thought to be related to it.

MATERIAL AND METHOD

Participants

This study used a descriptive cross-sectional design and was carried out with physicians and nurses between June and July 2020. The study population consisted of physicians and nurses across Turkey. According to the April 2020 data, the total population of the physicians and nurses was 165,363 and 204,969, respectively. For this study, the sample size was calculated as a minimum of 386 individuals at a 90% confidence interval using the known universe sample size calculation model. Eventually, 406 individuals who agreed to participate in the study formed the study group. While creating the sample, we targeted participants who were healthcare professionals working actively during the pandemic process and volunteered to participate in the study. Participants were determined using the virtual snowball (chain) sampling method, which is among the purposive sampling methods. The study data were collected using Google forms, designed in the form of an online self-report. A questionnaire form was developed based on the literature by the purpose of the study.

Measures

The 20-item questionnaire consisted of questions about socio-demographic(age, gender, the city of residence, level of education, marital status, number of children, chronic diseases) data of the healthcare professionals, characteristics of their workplace, and working conditions (occupation, institution, unit, total work experience, weekly working hours, mode of work, number of patients served daily), regarding contact with patients with COVID-19 (frequency of contact with patients with COVID-19, frequency of contact with family during the pandemic, type of accommodation, whether the participant or a family member was diagnosed with COVID-19), and the items of the Occupational Fatigue-Exhaustion Recovery Scale.

The Occupational Fatigue-Exhaustion Recovery Scale (OFER)

The Occupational Fatigue-Exhaustion Recovery Scale was developed by Winwood et al. in 2005 to measure occupational fatigue (11). Its Turkish validity and reliability study was carried out by Havlioğlu et al. in 2019 (12). Cronbach's alpha coefficient of the scale is 0.93 for chronic fatigue, 0.82 for acute fatigue, and 0.75 for recovery subscale. In this study, Cronbach's alpha was found to be 0.92 for chronic fatigue subscale, 0.73 for acute fatigue subscale, and 0.78 for recovery subscale. The scale consists of 15 items and three sub-dimensions, namely, chronic fatigue (items 1-5), acute fatigue (items 6-10), and recovery (items 11-15). Items 9, 10, 11, 13, and 15 are negative statements, which are inversely scored. It has a 7-point Likert-type rating structure with options 0 = strongly disagree, 1 = disagree, 2 = somewhat disagree, 3 = neither agree nor disagree, 4 = somewhat agree, 5 = agree, and 6 = strongly agree. The scale does not have

an overall score, and scores are calculated separately for each subscale (item-total scores / 30 x 100). A score between 0 and 100 is obtained for each subscale. A high score on the chronic and acute fatigue subscales indicates increased occupational fatigue, and a high score on the recovery subscale indicates recovery between shifts. A score between 0 and 25 shows low fatigue, 25-50 medium / low fatigue, 50-75 medium / high fatigue, and 75-100 high fatigue.

Ethical considerations

At the outset, the ethical approval of Eskisehir Osmangazi University Social and Human Sciences Scientific Research and Publication Ethics Committee was obtained (date: 27.04.2020 and issue: 11869). In addition, the study protocol was approved by the Ministry of Health of Turkey as it involved the COVID-19 pandemic.

Statistical analysis

The data obtained were analyzed using the SPSS Statistical Software Package. Shapiro-Wilk test was used to test the normal distribution of the data.In non-normal distributions, the Mann-Whitney U test was used for variables with two groups and Kruskal–Wallis-H test for variables with more than two groups. The statistical significance valuewas accepted as $p<0.05$.

RESULT

The study group consisted of 308 females and 98 males. Their ages ranged between 20 and 61, with a mean value of 35.46 ± 9.21 years. The scores obtained by the healthcare professionals from the chronic fatigue subscales of the Occupational Fatigue-Exhaustion Recovery Scale ranged between 0 and 100, with a mean score of 60.65 ± 29.10 (median: 66.7). Their scores from the acute fatigue subscale ranged between 6.67 and 100, with a mean score of 65.52 ± 21.64 (median: 66.7). For the recovery subscale, the scores ranged from 0 to 100, and the mean score was 45.09 ± 19.11 (median: 50.0). In the study group, women had higher levels of chronic and acute fatigue. Those who were aged 49 or younger had higher acute fatigue levels than those aged 50 and over. The acute fatigue levels of participants with a chronic disease history and the recovery levels of those with no chronic disease history were higher ($p<0.05$ for each). The distribution of the scores obtained by the study group from the subscales of the Occupational Fatigue-Exhaustion Recovery Scale by some sociodemographic characteristics is given in Table 1.

Table 1. The distribution of the scores obtained by the study group from the subscales of the Occupational Fatigue-Exhaustion Recovery Scale by some sociodemographic characteristics

Sociodemographic characteristics	n	The subscale scores of the Occupational Fatigue-Exhaustion Recovery Scale		
		Chronic fatigue subscale Median (min.-max.)	Acute fatigue subscale Median (min.-max.)	Recovery subscale Median (min.-max.)
Gender				
Male	98	53.3 (3.3-100.0)	56.6 (10.0-100.0)	50.0 (0.0-100.0)
Female*	308	70.0 (0.0-100.0)	66.7 (6.7-100.0)	46.7 (0.0-100.0)
Test value (z; p)		**2.752; 0.006**	**2.816; 0.005**	**1.206; 0.228**
Age group				
29 or younger	143	63.3 (10.0-100.0)	60.0 (6.7-100.0)	50.0 (0.0-100.0)
30-39	108	66.7 (0.0-100.0)	70.0 (10.0-100.0)	46.7 (3.3-100.0)
40-49*	130	70.0 (0.0-100.0)	68.3 (30.0-100.0)	43.3 (0.0-93.3)
50 or older*	25	50.0 (13.3-100.0)	53.3 (13.3-96.7)	53.3 (10.0-76.7)
Test value (KW; p)		**4.186; 0.242**	**10.603; 0.014**	**8.621; 0.035**
Profession				
Physician	142	63.3 (0.0-100.0)	66.7 (10.0-100.0)	46.7 (0.0-100.0)
Nurse	264	66.7 (0.0-100.0)	66.7 (6.7-100.0)	50.0 (0.0-100.0)
Test value (z; p)		**0.069; 0.945**	**0.082; 0.935**	**0.199; 0.842**
History of chronic disorder				
Yes	81	66.7 (0.0-100.0)	70.0 (23.3-100.0)	43.3 (3.3-83.3)
No	325	66.7 (0.0-100.0)	63.3 (6.7-100.0)	50.0 (0.0-100.0)
Test value (z; p)		**1.178; 0.239**	**2.220; 0.026**	**2.499; 0.012**
Total	**406**	**66.7 (0.0-100.0)**	**66.7 (6.7-100.0)**	**50.0 (0.0-100.0)**

*The group creating the difference

Of the participants in the study group, 231 worked in hospitals of the Ministry of Health, 108 in university hospitals, 41 in private hospitals, and 26 in primary healthcare institutions. The professional seniority ranged from 1 to 38 years, with a mean value of 12.54 ± 9.18 years. The participants reported that the number of patients they gave care daily varied between 2 and 150, with a mean value of 27.91 ± 27.60 patients. The recovery level of those working in Family Health Centers was higher than those working in other institutions. The chronic fatigue level of those who worked more than 40 hours a week was higher, and the recovery level between shifts among those who worked day and night shifts was lower than those who worked only day shift and only night shift. The distribution of the scores obtained by the study group from the subscales of the Occupational Fatigue Exhaustion Recovery Scale by some of the working conditions is given in Table 2.

Table 2. The distribution of the scores obtained by the study group from the subscales of the Occupational Fatigue Exhaustion Recovery Scale by some of the working conditions

Some working conditions	n	The subscale scores of the Occupational Fatigue-Exhaustion Recovery Scale		
		Chronic fatigue subscale Median (min.-max.)	Acute fatigue subscale Median (min.-max.)	Recovery subscale Median (min.-max.)
The Hospitals				
The Ministry of Health	231	70.0 (0.0-100.0)	70.0 (10.0-100.0)	46.7 (0.0-100.0)
University	108	58.3 (0.0-100.0)	68.3 (6.7-100.0)	50.0 (0.0-76.7)
Private	41	70.0 (0.0-100.0)	60.0 (10.0-100.0)	46.7 (0.0-100.0)
Primary healthcare*	26	56.7 (3.3-100.0)	56.7 (30.0-100.0)	56.7 (20.0-80.0)
Test value (KW; p)		**4.010; 0.260**	**5.833; 0.120**	**15.025; 0.002**
Pandemicpolyclinic	52	70.0 (13.3-100.0)	73.3 (0.0-100.0)	41.7 (0.0-100.0)
Pandemic service	62	73.3 (0.0-100.0)	70.0 (23.3-100.0)	50.0 (0.0-93.3)
Pandemic intensive care	48	60.0 (0.0-100.0)	70.0 (6.7-100.0)	45.0 (3.3-100.0)
Emergency department	43	56.7 (6.7-100.0)	56.7 (26.7-100.0)	50.0 (0.0-73.3)
Clinical services	133	66.7 (0.0-100.0)	66.7 (13.3-100.0)	46.7 (0.0-100.0)
Others	68	61.7 (0.0-100.0)	58.3 (16.7-100.0)	53.3 (6.7-86.7)
Test value (KW; p)		**6.541; 0.257**	**9.221; 0.101**	**10.306; 0.067**
Professional seniority (year)				
4 and fewer	92	63.3 (3.3-100.0)	63.3 (6.7-100.0)	50.0 (0.0-100.0)
5-9	90	63.3 (0.0-100.0)	65.0 (23.3-100.0)	46.7 (3.3-100.0)
10-14	72	70.0 (6.7-100.0)	70.0 (10.0-100.0)	46.7 (3.3-100.0)
15-19	53	56.7 (0.0-100.0)	66.7 (30.0-100.0)	46.7 (0.0-80.0)
20 or more	99	66.7 (0.0-100.0)	63.3 (13.3-100.0)	46.7 (0.0-93.3)
Test value (KW; p)		**1.853; 0.763**	**1.483; 0.830**	**1.528; 0.822**
Weekly working hours (hour)				
40 and fewer	239	60.0 (0.0-100.0)	66.7 (6.7-100.0)	50.0 (0.0-100.0)
41 or more*	167	76.7 (0.0-100.0)	70.0 (10.0-100.0)	43.3 (0.0-100.0)
Test value (z; p)		**3.575; 0.001**	**1.003; 0.316**	**1.924; 0.054**
Work shifts				
Day	129	66.7 (0.0-100.0)	63.3 (10.0-100.0)	50.0 (3.3-100.0)
Night	10	63.3 (16.7-100.0)	75.0 (30.0-86.7)	53.3 (20.0-86.7)
Day-night*	267	66.7 (0.0-100.0)	70.0 (6.7-100.0)	46.7 (0.0-100.0)
Test value (KW; p)		**0.019; 0.991**	**3.027, 0.220**	**7.416; 0.025**
Daily number of patients				
9 or fewer	113	63.3 (0.0-100.0)	63.3 (6.7-100.0)	50.0 (3.3-100.0)
10-29	137	63.3 (0.0-100.0)	66.7 (10.0-100.0)	46.7 (0.0-93.3)
30-49	66	71.7 (6.7-100.0)	66.7 (26.7-100.0)	48.3 (0.0-80.0)
50 or more	90	71.7 (0.0-100.0)	66.7 (13.3-100.0)	46.7 (0.0-100.0)
Test value (KW; p)		**4.622; 0.202**	**1.201; 0.753**	**0.457; 0.928**
Total	**406**	**66.7 (0.0-100.0)**	**66.7 (6.7-100.0)**	**50.0 (0.0-100.0)**

* The group creating the difference

Of the participants, 66 reported that they had no contact with patients with COVID-19, 240 had contact with them every other day, and 100 had contact with these patients every day. The number of those who had not been seeing their family was 145, and the number of those who tested positive for COVID-19 was 12. Chronic and acute fatigue levels of those in the study group who contacted COVID-19 patients every day were found to be higher. Chronic fatigue levels of those who were diagnosed with COVID-19 disease were found to be lower. Table 3 shows the distribution of the scores of the study group from the subscales of the Occupational Fatigue-Exhaustion Recovery Scale by some features regarding contact with patients with COVID-19.

Table 3. Distribution of the scores of the study group from the subscales of the Occupational Fatigue-Exhaustion Recovery Scale by some features regarding contact with patients with COVID-19

Some features regarding contact with patients with COVID-19	n	The subscale scores of the Occupational Fatigue-Exhaustion Recovery Scale		
		Chronic fatigue subscale Median (min.-max.)	Acute fatigue subscale Median (min.-max.)	Recovery subscale Median (min.-max.)
The status of contact with patients with COVID-19				
None	66	66.7 (0.0-100.0)	60.0 (23.3-100.0)	50.0 (3.3-83.3)
Every other day	240	63.3 (0.0-100.0)	65.0 (6.7-100.0)	50.0 (0.0-100.0)
Every day*	100	76.7 (0.0-100.0)	73.3 (23.3-100.0)	46.7 (0.0-93.3)
Test value (KW; p)		**9.004; 0.011**	**10.079; 0.006**	**4.371; 0.112**
Place of accommodation after work				
Home with family	308	66.7 (0.0-100.0)	66.7 (10.0-100.0)	46.7 (3.3-100.0)
Hotel / Guest House	19	56.7 (6.7-96.7)	50.0 (36.7-100.0)	50.0 (20.0-63.3)
Home alone	79	63.3 (6.7-100.0)	63.3 (6.7-100.0)	50.0 (0.0-100.0)
Test value (KW; p)		**1.438; 0.487**	**4.387; 0.112**	**1.657; 0.437**
History of diagnosis with COVID-19				
Yes*	12	48.3 (6.7-83.3)	53.3 (30.0-100.)	53.3 (26.7-73.3)
No	394	66.7 (0.0-100.0)	66.7 (6.7-100.0)	48.3 (0.0-100.0)
Test value (z; p)		**2.101; 0.036**	**1.258; 0.208**	**1.032; 0.302**
The family member that tested positive for COVID-19				
Yes	87	70.0 (0.0-100.0)	66.7 (6.7-100.0)	50.0 (0.0-100.0)
No	319	66.7 (0.0-100.0)	66.7 (10.0-100.0)	50.0 (0.0-100.0)
Test value (z; p)		**1.038; 0.299**	**0.941; 0.347**	**0.241; 0.809**
Total	**406**	**66.7 (0.0-100.0)**	**66.7 (6.7-100.0)**	**50.0 (0.0-100.0)**

*Farkyaratangurup

DISCUSSION

The number of healthcare workers affected by COVID-19 is at a substantial level. To date, there are limited publications and reports on healthcare workers and COVID-19. There is a need for a detailed examination of the situation of healthcare workers in the COVID-19 process (13). In the study, healthcare professionals who are directly involved in the care of patients with COVID-19 during the pandemic process reported that their fatigue and burnout levels were above the moderate level and that the level of their recovery was at a moderate level. In previous studies on healthcare workers, fatigue levels were found to be high, similar to our study results (11,14,15,16) Frontline healthcare workers face problems due to increased workload, busy working schedules, and increased exposure to positive cases (17). At the same time, this study was carried out in the first months of the emergence of the COVID-19 pandemic in Turkey. Many uncertainties, such as the working order not yet established, may have increased the fatigue in healthcare workers.

In the study group, both chronic and acute fatigue levels of females were higher than those of males. It was reported that regarding a higher susceptibility or vulnerability to diseases among health professionals, all mental disorder measurements in female healthcare workers were associated with more severe levels (18). This can be explained by the fact women are under more institutional and social expectation pressure than normal depending on the roles they undertake both in the institutions they work and in social life and with the increase in the time and workload in the health institutions they work during

the pandemic period. In the study of Polat and Coşkun (2020) on health workers during the pandemic process, the anxiety and depression levels of female workers were found to be significantly higher. This study supports the predisposition of female health workers to mental disorders (19).

The acute fatigue levels of the participants in the 49-and-younger age group were higher than those in the 50-and-older age group. Similar to our study, Yu et al. found that older or more experienced nurses had lower acute fatigue levels compared to younger or less experienced nurses (20). Tang et al. found that work-related accumulated fatigue was higher in healthcare workers aged between 30 and 45 years old (15). Recovery levels were found to be higher in the 50-and-older age group compared to those in the 40-49 age group. Possible causes of these situations can be explained by the fact that healthcare workers get exhausted more, their body resistance weakens, they have difficulty in showing performance, and that they start losing sensitivity due to long periods of work.

When the scores were compared by occupational groups, chronic fatigue, acute fatigue, and recovery scores of physicians and nurses were found very close to each other, and there was no statistical difference between them. This can be explained by the fact that all occupational groups in the health sector have been affected by the pandemic process and that especially physicians and nurses, who provide one-to-one care to patients and spend most of their time with patients, have been affected more than others.

There was no difference between the chronic fatigue and acute fatigue levels of the study group in terms of the institutions where they worked. The recovery level of those working in family health centers was higher compared to those working in other institutions. There are no night shifts in family health centers in our country, which may be the reason for the high recovery levels due to regular working shifts.

Chronic fatigue was higher in those who worked for more than 40 hours a week. This was due to more intense working conditions, more working hours, having one-on-one contact with too many patients, and spending less time in social life. Some studies showed that high working hours led to mental effects on healthcare workers (21,22).

The inter-shift recovery level of participants who worked day and night was found to be lower than those who worked only during the day and only at night. In a study on nurses working shifts in the USA, Chen et al. found high levels of acute fatigue and moderate recovery and chronic fatigue (23). Hazzard et al. found moderate levels of chronic fatigue, acute fatigue, and recovery in nurses (24). Healthcare workers who work in shifts work more shifts and overtime during the COVID-19 pandemic. Reduced rest periods due to excessive night shifts may be the reason for low recovery levels.

In the study group, the participants who came into contact with patients with COVID-19 every day had higher levels of chronic fatigue and acute fatigue. This is traumatizing for healthcare professionals who see that many patients who are infected with the virus and need intensive care cannot survive during the pandemic process (25). Kannampallil et al. (2020) also stated that the exposure of healthcare workers, who are at the forefront of care during the COVID-19 pandemic, to infected patients caused their level of stress and burnout to increase (26). In addition, healthcare workers are vulnerable to the risk of infection under pandemic conditions, which leads them to worry that they can be infected or they can transmit the virus to their families and friends. In addition, during this period, physicians and nurses provide care to individuals at risk of death, witness their physical and mental pain, and may reflect the difficulties they experience to employees inappropriately. Moreover, both sick individuals and healthcare professionals are isolated, their sharing is restricted, and they cannot come together with their family members, all of which may make up a risk factor for exhaustion.

The physicians and nurses in our study who tested positive for COVID-19 were found to have lower chronic fatigue levels. This can be associated with general occupational fatigue rather than chronic fatigue experienced due to the pandemic process.

When the literature was examined, there were no studies investigating the relationship between similar variables and occupational fatigue. Therefore, these results are new to the literature.

CONCLUSION

In conclusion, fatigue levels in the study group were higher in women who were aged 49 years or younger, had weekly working hours of more than 40 hours, and came into contact with COVID 19 patients every day. Healthcare professionals have significant responsibilities in managing large-scale public health events such as the COVID-19 pandemic. However, while healthcare professionals strive to provide professional care in this process, they also have to struggle with factors predisposing occupational exhaustion, such as being at risk of infection in the work environment, working long and intense hours, protecting the health of those around them, and physical/psychological fatigue and tension. It is important and necessary to plan the needs of healthcare personnel for rest, establish working and resting environments that will control not only the risk of contamination but also other risk factors due to insomnia and fatigue, create working and resting environments, reschedule working hours, and carry out supportive administrative work to reduce fatigue and burnout levels.

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Araştırma Makalesi / Research Article

Pre- and Post-Natal Endotoxin Exposures: Effects on Leucocyte Ratios and Levels of IL-1β, TNF-, Gonadotropins and Corticosterone in Female Rats

Prenatal Ve Postnatal Endotoksin Maruziyetleri: Dişi Sıçanlarda Lökosit Oranları Ve IL-1β, TNF-α, Gonadotropin Ve Kortikosteron Seviyeleri Üzerindeki Etkileri

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Abstract

Aim: The aim of this study is to investigate the long-term effects of prenatal and postnatal endotoxin exposure on hematological parameters, blood cytokines (TNF-α, IL-1β), gonadotropins and corticosterone levels in female rats.
Material and Method: Pregnant rats were injected intraperitoneally sterile saline (SF) or endotoxin (LPS) on days 17-18 of pregnancy. Following birth, female pups were subdivided into two groups and injected either sterile saline (SF, n=17) or endotoxin (LPS, n=17) on postnatal day 60 and four experimental groups were formed (SF+SF, SF+LPS, LPS+SF and LPS+LPS). Blood samples were taken 4 hours after final injection. Plasma levels of IL-1β, TNF-α, corticosteron, LH, FSH and blood leucocyte ratios were evaluated.
Results: Neutrophil % ratio was higher but lymphocyte % ratio was lower in SF+LPS, LPS+SF and LPS+LPS groups than SF+SF group. Corticosterone, LH and FSH levels were not different between the groups but TNF-α level of LPS+LPS groups was higher than SF+SF and LPS+SF groups. IL-1β level of SF+LPS group was higher than SF+SF and LPS+SF groups.
Conclusion: The results suggest that prenatal and post-pubertal endotoxin exposure programs cytokine level neutrophil and lymphocyte percentages without affecting hypothalamo-pituitary-adrenal and –gonadal axes.

Keywords: Prenatal endotoxin, postnatal endotoxin, neutrophil, lymphocyte, IL-1β, TNF-α, corticosterone, gonadotrophins.

Öz

Amaç: Bu çalışmanın amacı doğum öncesi ve doğum sonrası endotoksin maruziyetinin dişi sıçanlarda hematolojik parametreler, kan sitokinleri (TNF-α, IL-1β), gonadotropinler ve kortikosteron seviyeleri üzerindeki uzun vadeli etkilerini araştırmaktır.
Materyal ve Metot: Gebe sıçanlara gebeliğin 17-18. günlerinde intraperitoneal olarak steril salin (SF) veya endotoksin (LPS) enjekte edildi. Doğumdan sonra dişi yavrular iki gruba ayrılarak doğum sonrası 60. günde steril salin (SF, n= 17) veya endotoksin (LPS, n= 17) enjekte edildi ve dört deney grubu oluşturuldu (SF+SF, SF+LPS, LPS+SF ve LPS+LPS). Son enjeksiyondan 4 saat sonra kan örnekleri alındı. Plazma IL-1β, TNF-α, kortikosteron, LH, FSH düzeyleri ve kan lökosit oranları değerlendirildi.
Bulgular: Nötrofil % oranı SF+LPS, LPS+SF ve LPS+LPS gruplarında SF+SF grubuna göre daha yüksek ancak lenfosit % oranı daha düşüktü. Kortikosteron, LH ve FSH düzeyleri gruplar arasında farklı değildi ancak TNF-α düzeyleri LPS+LPS gruplarında SF+SF ve LPS+SF gruplarından daha yüksekti. SF+LPS grubunun IL-1β düzeyi SF+SF ve LPS+SF gruplarından daha yüksekti.
Sonuç: Prenatal ve post-pubertal endotoksin maruziyetinin, hipotalamo-hipofiz-adrenal ve -gonadal eksenleri etkilemeden sitokin düzeyi, nötrofil ve lenfosit yüzdelerini programladığı belirlenmiştir.

Anahtar Kelimeler : Prenatal endotoxin, postnatal endotoxin, nötrofil, lenfosit, IL-1β, TNF-α, kortikosteron, gonadotropinler.

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INTRODUCTION

There is a commensalist/mutualist balance between bacteria and the host and disruption of this balance may cause diseases in the latter. Accordingly, bacterial infections cause inflammatory reactions by stimulating the immune system (1) and change blood parameters, various hormonal responses, and inflammatory parameters such as interleukin 1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) (2). Number and type of leukocytes may also be influenced by the bacterial infections (3).

The effects of maternal infections on the development of postnatal or adulthood infections are not well known. Available data suggest that some maternal stress factors during pregnancy may re-program offsprings development and health status of the offsprings (4). This condition known as "fetal programming" is also thought to modify the responses of the offsprings to infections later in the life (4, 5).

Bacterial cell wall consitituents, namely endotoxins or lipopolysaccharides (LPS), are used to mimic bacterial infection. LPS-activated inflammatory response increases cytokines like IL-1β and TNF-α (2) and changes leukocyte differential counts (6). This stresful maternal condition might also re-program offsprings' hypothalmo-piutitary-adrenal or –gonadal axes (HPA and HPG, respectively) and may cause changes in corticosterone or gonadotrophins. However, this response might be modified by prenatal exposure to endotoxins. Therefore, we hypothesized that prenatal exposure to endotoxins would modify responses to post-pubertal endotoxins in adult female pups in terms of hematological parameters, levels of blood TNF-α, IL-1β, corticosterone and gonadotrophins (LH and FSH). In fact, the selected parameters were those which were either inflammation-related (hematological parameters, levels of blood TNF-α, IL-1β) or stress-related (corticosterone and gonadotrophins), which were both associated with effects of endotoxine exposure.

MATERIAL AND METHOD

Ethics Committee Approval

All procedures were conducted according to the guidelines of the Animal Research Ethics Committee of Inonu University Medical Faculty (2011/A-65) and carried out according to the guiding principles of the declaration of Helsinki.

Experimental Animals

This study was conducted on female pups obtained from 10 six month-old Sprague-Dawley pregnant rats (weight: 200-250 g) were purchased from and housed in our Experimental Animal Unit (Inonu University, Malatya, Turkey). They were housed under controlled conditions (12 h light:12 h dark; 22 ± 2 °C) and supplied with food and water ad libitum. For pregnancy to occur, 2 female and 1 male rats were kept in the same cage. Vaginal smears were taken daily at 09.00-11.00 h and were observed by light microscope for detection of spermatozoa to ensure a successful pregnancy. The day of observation of spermatozoa was accepted as the day 0 of pregnancy, and thereafter the animals were taken into individual cages. Injections (saline or LPS) outlined below were carried out on the day 18 of pregnancy (prenatal injection). The day of delivery was recorded and on postnatal day 21, female pups were divided into cages, each containing 4 pups. Second injections outlined below (saline or LPS) were applied at 9 a.m on the postnatal day 60. Exactly 4 h after the second injections animals were weighed, sacrificied and blood samples were taken for the determination of gonadotropins (LH, FSH), corticosterone, IL-1beta, TNF-alpha, whole blood counting.

Experimental Groups

Pregnant rats were injected either saline or LPS on day 18 of the pregnancy (prenatal injection) and the pups born to these rats were injected saline or LPS on postnatal day 60. Finally four groups of pups were formed as outlined in Table 1. Body weights of the rats were measured by scales to determine the dose of LPS. Lipopolysaccharide (LPS, Escherichia coli serotype 0111:B4, Sigma L-2630) in a volume of 0.05 ml and at a dose of 50 µg/kg was prepared with physiological saline solution and was administered intraperitoneally by using an insulin injector (10). Similarly, sterile physiological saline solution (0.9% NaCl) was administered intraperitoneally at 0.05 ml of by using an insulin injector. Experimental protocol is also esummarized in Figure 1.

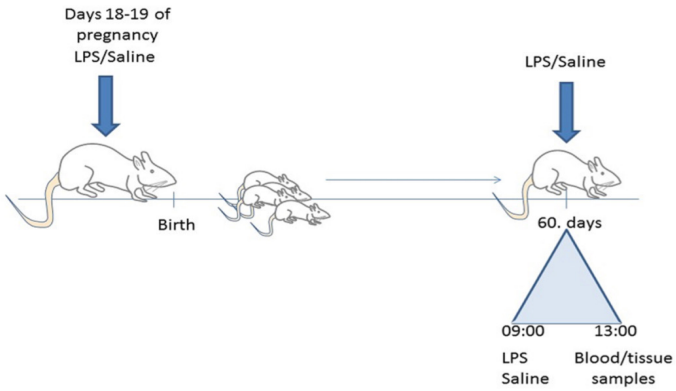

Figure 1. Experimental design. Pups born to mothers injected with LPS/saline on the gestational day 18 were assigned into a total of 4 groups including 8-9 rat pups per group and their blood and tissue samples were taken 4 hours after the injections at 9.00 am on the postnatal day 60.

Hematological Parameters

Hematological parameters were measured manually by using Thoma slides (Marienfeld, Germany). Air dried blood smears stained with May-Grünwald-Giemsa were used to find out differential leukocytes counts (7).

Serum cytokine and hormone concentrations

Serum TNF-α, IL-1β and corticosterone levels were determined by rat-specific commercial ELISA kits

(Booster, USA and Sun Red, China, respectively). Serum LH and FSH concentrations were carried out according to Pappa et al (1999) (8) as modified by Ozgocer et al., (2015) (9). Briefly, 96-well immunoplates (Nunc, Roskilde, Denmark) were coated with rat LH, rat FSH. Serum samples or standards were preincubated with primary antibodies and were then transferred into coated plates for competition with antigens on the solid phase. Plates were washed and the secondary antibody conjugated to streptavidin peroxidase was added into each well. Following washing, the color was developed by using tetramethylbenzidine as the substrate. Plates were read at 450 nm using a plate reader (Biotek, Synergy HT, USA). Rat LH and FSH antigens and primary antibodies (rabbit anti-rat LH and rabbit anti-rat FSH) were obtained from Dr. A.F. Parlow (NIDDK, NIH, USA). Secondary antibodies (goat anti-rabbit IgG) conjugated to streptavidin peroxidase was purchased from Sigma (Sigma-Aldrich, Taufkirchen, Germany). Sensitivity of the assays was 1 ng/ml for LH, 2 ng/ml for FSH and corticosterone 10 ng/ml for corticosterone. Inter- and intra-assay coefficients of variations were below 8 % for both LH and FSH and below 10 % for corticosterone.

Statistical Analysis

IBM SPSS Statistics 22.0 program was used for statistical analysis of data of parameters of all groups. The data were given in median (min-max) or mean (SD). Shapiro-Wilk test was performed to examine whether or not the data met normal distribution. Kruskal-Wallis test was used for between-groups comparison of the data. On the other hand, Conover test was used for paired comparison of groups. The value of $p<0.05$ was accepted statistically significant.

RESULT

Body weights, hematologic parameters, hormonal parameters and cytokines examined in the study were presented in the following Table 2, Figure 2 and Figure 3. Body weight of the pups in LPS+SF group was significantly lower than SF+SF and SF+LPS groups but not from LPS+LPS group (Figure 2). Results regarding hematologic parameters of blood samples taken 4 hours after lipopolysaccharide (LPS) or saline (SF) injection on the postnatal day 60 are shown in Table 2. Hematocrite (%) was highest in LPS+SF group (p=0.012) but WBC count did not differ between the groups. SF+SF group tended to have lower neutrophil counts (p=0.060) but neutrophil ratio (%) was significantly lower in the SF+SF group (p=0.001). Lymphocyte count was the highest in SF+LPS (p=0.049) but lymphocyte ratio (%) was highest in SF+SF group (p=0.001). Basophil and monosit count and ratios were indifferent between the groups (p>0.05)

Hormonal parameters and cytokines

Figure 3 shows the results regarding hormonal and cytokine parameters of blood samples taken 4 hours after lipopolysaccharide (LPS) or saline (SF) injection on the postnatal day 60. No statistical difference was observed between the groups in terms of LH, FSH and concentrations (p>0.05; Figure 3(a), Figure 3(b) and Figure 3(c). Serum TNF-α level was significantly higher in LPS+LPS group than SF+SF and LPS+SF groups (p=0.004; Figure 3(d). Serum IL-1β level of SF+LPS group was higher than SF+SF, LPS+SF and LPS+LPS groups (p=0.032 Figure 3(e).

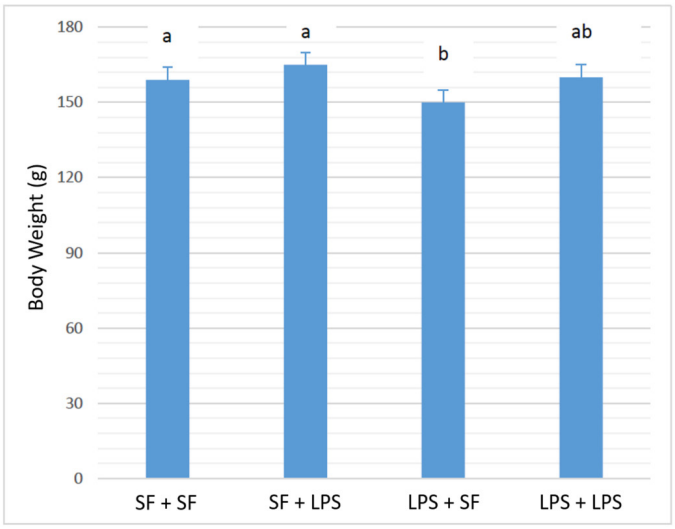

Figure 2. Effects of prenatal and postnatal LPS or saline exposure on body weight of the offsprings. The data were presented as Mean±SE and different letters indicate a significant difference at alpha level of $p< 0.05$.

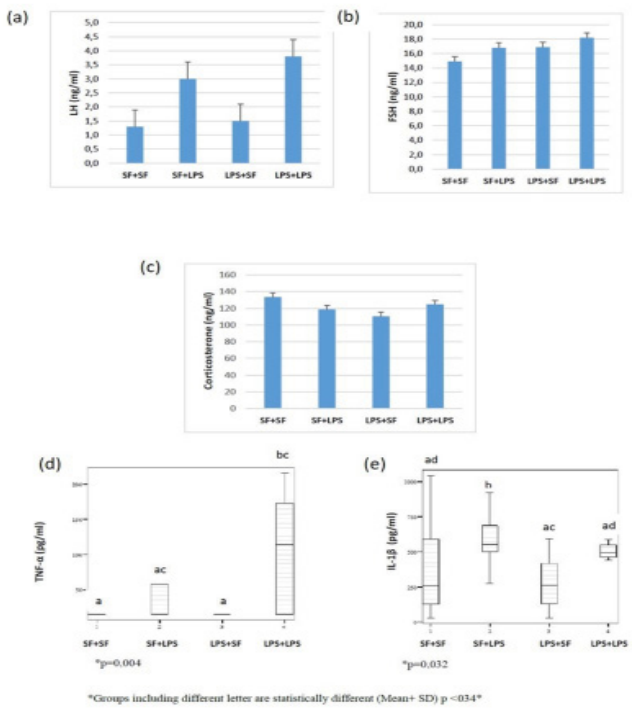

Figure 3. The Effects of LPS or saline on (a) LH, (b) FSH, (c) Corticosterone, (d) TNF-α, (e) IL-1β levels in blood sample taken 4 hours after lipopolysaccharide (LPS) or saline (SF)

Table1. Experimental groups and numbers of pregnant rats and pups used. On the day 18th of pregnancy, pregnant rats were either injected with saline (serum physiologic, SF; n=5) or LPS (n=5) and pups born to these mothers divided into two groups and injected with saline or LPS on postnatal day 60 (n=8 or 9 per four groups of experimental animals formed)

Number of Pregnant rats	Maternal injection on day 18th of pregnancy	Postnatal injection on day 60	Groups	Number of female pups
5	Saline	Saline	SF + SF	9
		LPS	SF + LPS	9
5	LPS	Saline	LPS + SF	8
		LPS	LPS + LPS	8

Table 2. Hematologic parameters of blood samples taken 4 hours after lipopolysaccharide (LPS) or saline (SF) injection on the postnatal day 60

	SF+SF	SF+LPS	LPS+ SF	LPS+LPS	p*
Hematocrit (%)	42±3[a]	41±3[a]	47±3[b]	41±4[a]	.012*
WBC count (#)	6000±2247	5733±1705	8517±2998	6288±2748	.289
Neutrophils count (#)	1059±642[a]	2308±1213[b]	2644±1445[b]	2426±1580[b]	.060
Neutrophils %	16±4[a]	39±11[b]	30±9[b]	34±17[b]	.001*
Lymphocyte count (#)	4218±1340[a]	2733±947[b]	4671±1703[a]	2584±1519[ab]	.049*
Lymphocyte %	72±6[a]	48±11[b]	56±11b	56±17[b]	.001*
Eosinophil count (#)	20±31[a]	9±27[b]	76±44[c]	54±61[bc]	.017*
Eosinophil %	0.1±0.3[a]	0.3±0.5[ab]	1.0±0.6[c]	0.9±0.9[bc]	.024*
Bazofil count (#)	390±197	344±120	541±206	334±234	.241
Bazofil %	6±1	6±2	7±1	6±1	.516
Monosit count (#)	330±186	341±143	478±226	268±219	.207
Monosit %	5±2	6±2	6±2	4±1	.224

*Groups including different letter are statistically different (Mean + SD).
Different letters indicate a significant difference at alpha level of p< 0.05.
WBC: White blood cell

DISCUSSION

This study showed that pups born to mothers injected with LPS during pregnancy had lower postnatal body weights. Wang et al. used daily LPS (50 µg/kg) injection protocol between days 13-17 of pregnancy and found out that prenatal weight decreased in male and female rats (10). Hodyl et al. (2007) injected LPS (200µg/kg) on days 16, 18, 20 of pregnancy and observed decreased prenatal weight and birth weight (6). Bernardi et al. (2010) injected LPS (250 µg/kg) on day 21 of pregnancy and found out decreased weight on postnatal day 2 (11). Altogether, these data suggests that prenatal maternal LPS injections generally decreases body weights of pups. On the other hand, it has been showed that injection of 0.12 µg/g LPS on day 17 pregnancy did not affect weight of pup in the first months following birth (12) or even increased body weight (13). However, in these two studies, the dose of LPS was either very low (12) or very high (13). It could be speculated that different doses of LPS might have triggered distinct immune mechanisms affecting body wieght regulation axes in opposing ways (14). It is also known that the day of pregnancy also modifies responses given to LPS injections (15).

In this study, hematocrite value differed between the experimental groups. It was the highest in LPS+SF group, suggested a prenatal programming for hematocrite value. Furthermore, this programming appears to be obscured by the second LPS injection (LPS+LPS group). Similar hematocrite levels in SF+SF group and SF+LPS group strengthens this hypothesis. In a study carried out by Kao et al. (2006), LPS was injected at 10000 µg/kg dose and blood samples were taken at 0.5, 1, 2, 3, 4, 5 and 6 hours after the injection. Hematocrite value decreased within the first 1 hour after injection but then it returned to normal level (16). When the data of the present study were examined in this perspective (SF+LPS group), it could be considered that hematocrite values increased and then returned to normal level in blood samples taken at 4th hour after postnatal LPS injection.

In this study, prenatal and/or postnatal immune stimulations by LPS increased neutrophil rate (%) but decreased lymphocyte ratio (%). Similarly, Hodly et al. (2007), determined that lymphocyte count decreased significantly in 4 hours after LPS injection on the postnatal day 50 following prenatal LPS administration (on gestational days 16, 18, and 20) without influencing neutrophil count. On the other hand, Doursout et al. (2013), found that neutrophil count was the highest 6 hours after male rats were injected with 35000 µg/kg LPS (17). In the

present study, LPS injections were determined to increase neutrophil count or rate (%) both in the acute period and in the long term. In that respect, increased neutrophil count in the group not receiving the second LPS injection (i.e. LPS+SF group) suggests a prenatal programming. In a study conducted by Zager et al. (2013) (18), they injected LPS to rats on the prenatal day 17 and found that their neutrophil activities did not change on the postnatal day 70, and concluded it had no impact on neutrophil-mediated innate immunity. On the contrary, in the present study, a single dose of LPS injection in the prenatal period seemed to permanently program program permanently the number and ratio of defense cells in the pups during postnatal period. In this context, while neutrophil percentage was two times higher, lymphocyte percentage decreased by 1/3. Increased neutrophil count in the present study might be due to delayed apoptosis. This might be supported by the fact that increased neutrophil lifespan might be due to delayed apoptosis (19, 20). In fact, exposure to LPS was determined to delay neutrophil apoptosis and to increase neutrophil count (21, 22). It seems crucial to conduct further investigation for the effects of prenatal LPS injection on the cascades of apoptosis.

In the present study, corticosterone level was not found to be different in both prenatal and postnatal period in LPS or saline groups. Hodly et al. (2007), stated that LPS injection of 200 µg/kg on the prenatal day 20 increased prenatal corticosterone level (6). In the one study conducted, they found that prenatal LPS injection did not affect serum corticosterone level of rat pups (23). However, in another study injected 50, 300, 500 µg/kg doses of LPS to rats on the prenatal days 15, 16, and 17 and found out that higher doeses increased but lower doses did not affect corticosterone levels on postnatal days 40 and 80 (24). Accordingly, the dose used in the present study was equal to the low dose of LPS applied by Enayati et al. (2012) suggesting that at lower doses of LPS, prenatal injections does not affect corticosterone levels during postnatal period.

Gonadotropin secretion in the adulthood was not affected by pre- or post-natal endotoxin exposures. This might be due to negative and postive feedback effects of hypothalamo-pituitary-gonadal axis. Thus, any possible change in LH or FSH was probably rectified by the feedback effects governed by the hypothalamus. By the time the second injection of LPS was carried out, all female pups had already reached puberty. This suggest that they had a fully functional HPG axis governing these feedback mechanisms. In this study, postnatal, but not prenatal, LPS injections increased TNF-α and IL-1β levels. It is known that LPS injections increases both parameters immediately following injections. For example, LPS injections at 100 µg/kg dose level increased TNF-α and IL-1β levels 3 hours post-injection (16). Lasala and Zhou (2007) injected 500 µg/kg LPS or saline on the prenatal day 18 and took blood samples of pups born from these rats 2 hours post-injection of LPS or saline on the postnatal day 21 (25). They observed that TNF-α and IL-1β levels were significantly higher in groups receiving postnatal LPS following prenatal saline (25). Similarly, rat pups which had maternal prenatal exposure to LPS (200 µg/kg) had increased TNF-α and IL-1β levels 4 hours post-injection on postnatal day 50 (6). On the other hand, Solati et al., reported that 1, 5, and 10 µg/kg doses of LPS administered on the prenatal day 10 did not cause any change in TNF-α and IL-1β levels of male rats on the postnatal day 21 (26). Dose of LPS used in the present study is known to induce immune response (10, 24, 27-29). On the other hand, the dose of prenatal LPS used by Hodly et al. was higher but that of Solati et al. was lower than the dose used in the present study (6). Therefore, it is might be possible that postnatal cytokine response does not occur if the dose administered in prenatal period is lower than 200 µg/kg. In a study conducted in humans, induction of second trimester placental tissue with endotoxin has been reported to provide tolerance to repeated ednotoxins (30). In a study conducted in mice, it was reported that exposure to endotoxins such as LPS during fetal development may be protective against an inflammatory disease in adulthood (31).

CONCLUSION

In conclusion, the present study suggests that (1) a prenatal programming against endotoxin immune challenge occurred in terms of body weights of pups and percentages of neutrophils and lymphocytes, that (2) postnatal endotoxin challenge increases TNF-α and IL-1β levels, but pre- and post-natal challenges does not appear to influence hypothalamo-pituitary-adrenal and –gonadal axes at the LPS doses applied in the current study.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *All procedures were conducted according to the guidelines of the Animal Research Ethics Committee of Inonu University Medical Faculty (2011/A-65) and carried out according to the guiding principles of the declaration of Helsinki.*

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MEDICAL RECORDS-International Medical Journal

Araştırma Makalesi / Research Article

Long-Term 32-Hours Continuous Shifts Increases Progesterone, IL-1β, TNF-α, IL-6, Eosinophil Count and Attention Performance in Female Pediatric Resident

Uzun Süreli 32 Saatlik Aralıksız Vardiyalar, Kadın Pediatri Asistanında Progesteron, Il-1β, Tnf-a, Il-6, Eozinofil Sayısı ve Dikkat Performansını Artırır

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Abstract

Aim: The study aimed at assessing effects of long-term 32-hours continuous shifts on leptin, melatonin, sex hormones, IL-1β, TNF-α, IL-6, hematological parameters, sleep quality and attention performance in female pediatric residents (FPR).
Materials and Methods: FPR working under 32 hours continuous shifts (08:00-08:00h after 08:00-17:00h, n=10) were compared to female health professionals working in day-time hours (08:00-16:00h, n=10). Vital parameters, glucose, leptin, melatonin, estrogen, progesterone, IL-1β, TNF-α, and IL-6 concentrations, complete blood count (CBC) and erythrocyte sedimentation rate (ESR) were measured. The participants were also requested to fill in sleep quality questionnaires and visual attention test.
Results: In the study; eosinophil ratio (p=0.015), hemoglobin (p=0.010), hematocrit (p=0.012), progesterone (p=0.008), TNF-α, (p=0.000), IL-1beta and (p= 0.003) IL-6 levels (p= 0.000) were found significantly higher in FPR. In addition, it was found that FPR had difficulty in waking up in the mornings (p = 0.000), had bad dreams (p = 0.040), and had poor sleep quality (p = 0.010). FPR had better attention performance (p=0.000).
Conclusion: Although attention performance was higher in FPR, data suggest that long-term continuous 32-hour shift system activates inflammatory response, disturbs ovarian steroid production and reduces sleep quality. Alltogether, these may culminate in inflammatory diseases or reproductive problems.

Keywords: Sleep, long-term continuous shift system, female, cytokine, hormone, hematological parameters

Öz

Amaç: Çalışmada, kadın pediatri asistanlarında uzun süreli 32 saatlik aralıksız vardiyaların leptin, melatonin, seks hormonları, IL-1β, TNF-α, IL-6, hematolojik parametreler, uyku kalitesi ve dikkat performansı üzerine etkilerininin değerlendirilmesi amaçlamıştır. FPR).
Materyal ve Metot: 32 saat sürekli vardiyada (08:00-08:00 sonrası 08:00-17:00, n=10) çalışan FPR, gündüz saatlerinde (08:00-16: 00 saat, n=10) çalışan kadın sağlık profesyonelleri ile karşılaştırılmıştır.
Bulgular: Çalışmada; eozinofil oranı (p=0.015), hemoglobin (p=0.010), hematokrit (p=0.012), progesteron (p=0.008), TNF α, (p=0.000), IL-1beta ve (p= 0.003) IL-6 düzeyleri (p= 0.000) FPR'de anlamlı olarak yüksek bulundu. Ayrıca FPR'nin sabahları uyanmakta güçlük çektiği (p=0,000), kötü rüyalar gördüğü (p=0,040) ve uyku kalitesinin kötü olduğu (p=0,010) bulundu. FPR daha iyi dikkat performansı gösterdi (p=0.000).
Sonuç: FPR'de dikkat performansı daha yüksek olmasına rağmen, veriler uzun süreli sürekli 32 saatlik vardiya sisteminin inflamatuar yanıtı aktive ettiğini, over steroid üretimini bozduğunu ve uyku kalitesini azalttığını göstermektedir. Hep birlikte, bunlar iltihaplı hastalıklar veya üreme sorunları ile sonuçlanabilir.

Anahtar Kelimeler: Uyku, uzun süreli aralıksız vardiya sistemi, kadın, sitokin, hormon, hematolojik parametreler

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INTRODUCTION

The twenty-four-hour service has become an indispensable part of working organizations due to the ever-changing demands of modern societies (1). Since the national health services provide 24 hour service for patients, the shift system and night work have become an important part of these organizations (2). Today, one in five working in Europe works on a night shift lasting more than twenty hours (3). In 1990, the international labor organization set new and radical standards for working organizations due to the negative impact of long or abnormal working hours on health (3). Although shift work is economically and socially important, disrupts the normal functioning of biological rhythms and contributes to social problems and the deterioration of sleep and health of shift workers (4) and negatively impact work performance (5).

Sleep is known to be important forh health and functional capacity (6). Sleep disturbance is a significant problem for shift workers due to the prevalence rate and the occupational and health consequences with which it is associated (7). Shift and night work may have negative effects on health, possibly due to the effects of sleep-wake cycle, eating, exercise behaviors, thermogenesis, hormone secretion and blood pressure levels (8). People working in shift system; increased blood pressure and heart rate reduction (9), increased cardiovascular morbidity and mortality and gastrointestinal disease rates (10). Sleepers and reproductive dysfunctions (10), lower working performance and risk of occupational accidents were found to be high in people working on night shifts (11). In their study, Born et al. found increased levels of hemoglobin and hematocrit, leucocyte, red blood cells, platelet counts, monocytes, natural killer cells and subgroups of lymphocytes in people with sleep deprivation (12). Plasma IL-6 and TNF-α levels were found to be high in all sleep-deprived nights (13). The shift system or long hours of work can cause problems by severely disrupting family and marital responsibilities (3). The effects of shift work on the human body may vary according to gender (14). The negative effects of the shift system, and especially the night shift on women, may be higher than their male counterparts due to home responsibilities, menstrual cycle deterioration and stress (3).

When we examine the publications about shifts up to the present, we have not found any studies investigating the long-term shift programs such as 32 hours. Recent research has focused on the potential health effects of shift work on sleep deprivation, cardiovascular disease, and metabolic disorders. (15). The present study, effects of 32 hours continuous shifts in FPR on their leptin, melatonin, sex hormones, IL-1β, TNF-α, IL-6, hematological and vital parameters, sleep quality and attention performance were examined.

MATERIAL AND METHOD

Ethical consent and participants

Approval for the study was obtained from the local ethics committee (Malatya Clinical Ethics Committee, No:2016/197). The participants consisted of female pediatric resident (FPR, 32 hours continuous shifts) and female health care professional (nurses, day-time workers) and working in the hospital. Groups were matched for menstrual phase. The study included healthy, regular cycling and non-smokers aged between 18 and 40 years.

Experimental design

The research consists of two groups of female participants working in the hospital: day-time workers (called as day-time shifters, n=10, 08:00-16:00 h, 37±1 year-old, 71±3 kg, 166±2 cm) and female pediatric resident (called as 32 hours continuous shifts, n=10, from 08:00 h to 17:00 h in the day after, 29±1 year-old, 65±5 kg, 158±7 cm) as outlined in Figure 1. Their vital parameters such as blood pressure (systolic and diastolic), pulse rate, respiratory rate, skin temperatures (forehead) and blood glucose levels were measured at 08:00, 16:00, 08:00 and 16:00 h during the 32-h continuous shift. These time points were similar for day time-shifters. FPR, started a normal shift in the next day following a 16 h resting period and above parameters were re-assessed at 08:00 h in the beginning of next morning. Blood samples were taken at 08:00 h at the end of 16 hours of rest after 32-hours of work schedule and were used for whole blood hematological parameters and erythrocyte sedimentation rate (ESR). Concentrations of cytokines (IL-1β, TNF-α, IL-6) and hormones (leptin, melatonin, estradiol, progesterone) in blood plasma were measured. Questionnaires [Pittsburgh Sleep Quality Index (PSQI), Karolinska Sleep Questionnaire (KSQ), State and Trait Anxiety Inventory (STAI)] and attention performance test (tracking test) were used in the study.

Evaluation of vital findings

Prior to evaluation of vital signs, participants rested in a sitting position for 5 minutes. Respirations and pulse rates were counted for 15 seconds and multiplied by four to calculate their rate per minute. For this purpose, pulse rate measurement was performed by placing three fingers between the bone and tendon on the radial artery in the participants, and chest movement was used for respiratory rate determination. Arterial blood pressure measurement was done indirectly using an automatic digital blood pressure monitor (Omron, M6 comfort, China). Proximal skin temperature was measured using a non-contact (without touching the skin) infrared digital thermometer (Mesilife, DT-8806, Mesitaş, Turkey). Blood glucose level was measured before the main meal by blood glucose monitoring system (Clever Chek, TD-4222, Germany) using venous blood.

Venous blood collection

Venous blood was drawn by a 10 ml injector with a

20-gauge needle and then transferred into two vacuum tubes with K3 ethylenediaminetetraacetic acid (EDTA). One of the tubes was centrifuged to obtain plasma, while the other tube was sent to the laboratory to determine the complete blood count (CBC) and erythrocyte sedimentation rate (ESR). CBC parameters were measured (Table 2 and Table 3).

Hormone and cytokine ELISA protocol

Plasma melatonin, leptin, estradiol, progesterone, TNF-α, IL-1β and IL-6 concentrations were measured by commercial enzyme immunoassay test kits (Fine Test, China). Plates were read using a microplate reader (Biotek, Synergy HT, USA) at 450 nm.

Visual trial test

The visual attention level of the participants was determined by means of a mark-making test consisting of numbers from 1 to 25 randomly distributed on an A4 paper. After the participants were informed about the test procedure, they were asked to complete the test. The first and last numbers were marked with a circle, making it easier for the participants to start and stop. With the aid of a stopwatch, the time used to complete the trail making test was recorded.

Table 1. Vital findings in women working in different shift types (day-time work and 32 hours continuous shifts). Values are presented as mean ± standard error

Vital parameters	32 h continous	p	
Respiration (number/min)	21±1	22.7±0.8	0.137
Pulse (heart beat/min)	74±3	76.3±1.8	0.488
Systolic Blood Pressure (mmHg)	106±3	98.0±2.7	0.057
Diastolic Blood Pressure (mmHg)	72±2	68.9±2.6	0.420
Glucose (mg/dl)	100±4	99.8±3.0	0.905
Body Temperature (oC)	36.5±0.1	36.5±0.1	0.853

Table 2. Complete blood count (CBC) in women working in different shift types (day-time work and 32 hours continuous shifts). Values are presented as mean ± standard error

CBC parameter	Day-time work	32 h continous shift	p
Leukocyte # (109/L)	6.770±0.427	7.484±0.559	0.323
Erythrocyte # (1012/L)	4.491±0.106	4.69±0.08	0.146
Haemoglobin (g/dL)	12.1±0.3	13.3±0.2	0.010
Hematocrit (%)	37.6±0.9	40.7±0.6	0.012
MCH (pg)	27.1±0.6	28.3±0.5	0.128
MCHC (g/dL)	32.3±0.5	32.6±0.3	0.597
RDW (%)	13.7±0.4	13.2±0.1	0.203
PCT (%)	0.3±0.0	0.3±0.0	0.829
MPV (fL)	11.1±0.3	11.0±0.2	0.803
PDW (%)	13.6±0.8	13.5±0.5	0.849
NRBC #	0.001±0.001	0.001±0.001	1.100
NRBC %	0.010±0.010	0.010±0.010	1.100
MCV (fL)	83.8±1.1	86.8±1.3	0.101
Platelet count (109/L)	284.2±17.0	281.9±21.6	0.934

MCH: Mean corspuscular hemoglobin
MCHC: Mean corpuscular hemogrlobin concentration
RDW: Red cell distribution width
PCT: Platecrite
MPV: Mean platelet volüme
PDW: Platelet distribution width
NRBC: Nucleated red blood cell
MCV: Mean corpuscular volume

Table 3. Leukocyte formula and erythrocyte sedimentation rate in women working in different shift types (day-time work and 32 hours continuous shifts). Values are presented as mean ± standard error.

Vital parameters	Day-time work	32 h continous shift	p
Lymphocyte Count # (109/L)	2.074±0.172	2.524±0.299	0.208
Percentage of lymphocytes %	31.4±2.7	33.5±2.3	0.563
Number of monocytes#(109/L)	0.484±0.030	0.505±0.044	0.699
Percentage of monocytes %	7.3±0.5	6.8±0.5	0.469
Neutrophil count # (109/L)	4.065±0.422	4.2±0.3	0.798
Neutrophil percentage %	59.1±2.9	56.5±2.1	0.465
Number of basophils (109/L)	0.051±0.006	0.056±0.008	0.633
Percent of basophil %	0.8±0.1	0.7±0.1	0.883
Eosinophil count # (109/L)	0.091±0.011	0.190±0.035	0.015
Percentage of eosinophils %	1.4±0.1	2.5±0.4	0.013
Neutrophil / lymphocyte ratio	2.2±0.2	1.8±0.5	0.480
Sedimentation (mm/h)	11.7±3.5	7.4±2.6	0.338

Statistical analyses

Statistical analyzes were performed using statistical software (Minitab 17, USA). Anderson-Darling test was used to control the normal distribution of the data. Data that did not show normal distribution were converted to log 10 data for normal distribution. Normally distributed data after this transformation were analyzed by Student's t-test. Non-normally distributed data and non-parametric data were analyzed using the Kruskal-Wallis test. Pearson test or Spearman Rho were used for normal or non-normally distributed data, respectively, for correlation analysis. $p<0.05$ was considered statistically significant.

RESULT

Demographic characteristics, vital signs, hematological parameters, inflammatory cytokine responses, metabolic and reproductive hormone levels, attention test findings, sleep parameters and regression analysis values are presented below.

Vital signs

Vital parameters are presented in Table 1. There was no difference between the groups in terms of respiratory rate, blood pressure, pulse rate, blood glucose and proximal skin temperature ($p>0.05$).

Hematological findings

CBC values are presented in Table 2 by group. Number of leukocyte, erythrocytes, number NRBC, MCH, MCHC, RDW, PCT, MPV, PDW, MCVand platelet were not different among the groups ($p>0.05$). However, we found that women working in 32 hours continuous shifts had higher hemoglobin concentration (13.3±0.2 vs 12.1±0.3; $p=0.010$), higher hematocrit concentration (40.7±0.6 vs 37.6±0.9; $p=0.012$; Table 2).

The leukocyte, neutrophil/lymphocyte ratio, and sedimentation numbers and percentages are presented in Table 3 by group. Counts of lymphocyte, monocytes, neutrophil, basophils and percentages of lymphocytes, monocytes, neutrophils and basophils did not differ among the groups ($p>0.05$). Moreover, neutrophil/lymphocyte ratio and sedimentation did not differ between groups ($p>0.05$). However, eosinophil count was higher in 32 hours continuous shifts (0.190±0.035) than day-time (0.091±0.015; $p = 0.011$; Table 3); percentage of eosinophils was higher in 32 hours continuous shifts (2.5±0.4) compared to day-time (1.4±0.1; $p = 0.013$; Table 3).

Plasma melatonin, leptin, estrogen and progesterone enzymeimmunoassays

Plasma melatonin, leptin, estrogen and progesterone concentrations of the experimental groups are shown in Figure 2. Melatonin, leptin and estrogen concentrations did not differ among the groups ($p>0.05$; Figure 2a, Figure 2b, Figure 2c respectively). Progesterone concentration was higher in 32 hours continuous shifts (5,433±1,60) than day-time work group (3,533±0,7; $p=0.008$, Figure 2d).

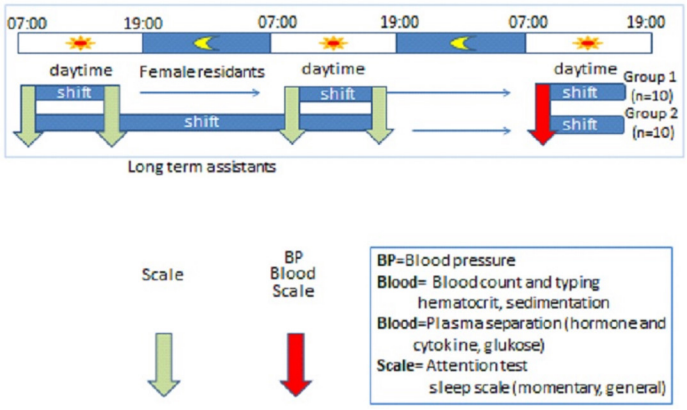

Figure 1. Design of the study. The women in Group 1 (n=10) had a normal day-time work while Group 2 had a 32 hours continuous shift (n=10) followed by a normal day- time work schedule. In the beginning and at the end of each daytime shift, vital parameters such as blood pressure (systolic and diastolic), pulse rate, respiratory rate, body temperature and blood glucose were measured. At the end of 16 hours of rest after 32-hours of work, blood samples were taken for the measurements of cytokines (IL-1beta, TNF-alpha, IL-6), hormones (leptin, melatonin, estrogen, progesterone), whole blood hematological parameters and erythrocyte sedimentation rate (ESR). Questionnaires (state and trait anxiety, sleep duration and quality) and attention performance test were also completed by the participants

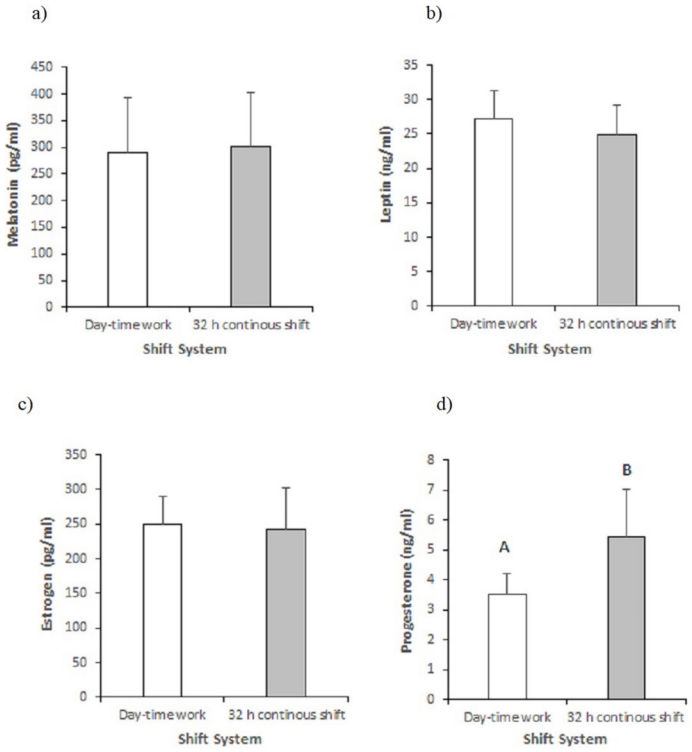

Figure 2. Melatonin (a), leptin (b), estrojen (c) and progesterone (d) concentrations in women working in different shift types (day-time work and 32 hours continuous shifts). Values represents as mean ± standard error. Groups with different capital letters differ significanly

IL-1β, TNF-α and IL-6 enzymeimmunoassays

Plasma IL-1β, TNF-α and IL-6 concentrations by group are

presented in Figure 2. IL-6 levels were higher in 32 hours continuous shifts (1.62±0.49) than that of day-time shift (0.48±0.13; p=0.000; Figure 3a). IL-1β levels were higher in 32 hours continuous shifts (16.9±3.02) than that of day-time shift (12.8±2.11; p=0.003; Figure 3b). TNF-α levels were higher in 32 hours continuous shifts (4.88±1.91) than that of day-time shift (2.09±0.68; p=0.000; Figure 3c).

Attentional performance test evaluations

Attentional performance assessed via the trail making test did higher in 32 hours continuous shifts (30.0±1.43) than that of day-time shift (22.1±0.8; p=0.000; Figure 4).

Sleep duration and quality

FPR under 32 hours continuous shifts they have difficulty in awakening (p=0.000), woke up later in the morning (p=0.009), had longer duration of sleep (p=0.001), low quality sleep (p=0.010), had bad dreams and (p=0.006) and (p=0.040) compared to day-time workers.

Correlations

In the study, the results of regression analysis of attention test, melatonin, leptin, estrogen, progesterone, IL-6, TNF-alpha and IL-1beta in women working in day-time shift and 32 hours continuous shifts are presented (Table 4). In the study, positive correlation were found between IL-6 and progesterone (r2 = 0.521, p = 0.019), IL-1beta and IL-6 (r2=0.644, p=0.003), TNF-alpha and progesterone (r2=0.509, p=0.022), TNF-alpha and IL-6 (r2=0.532, p=0.016) (Table 4).

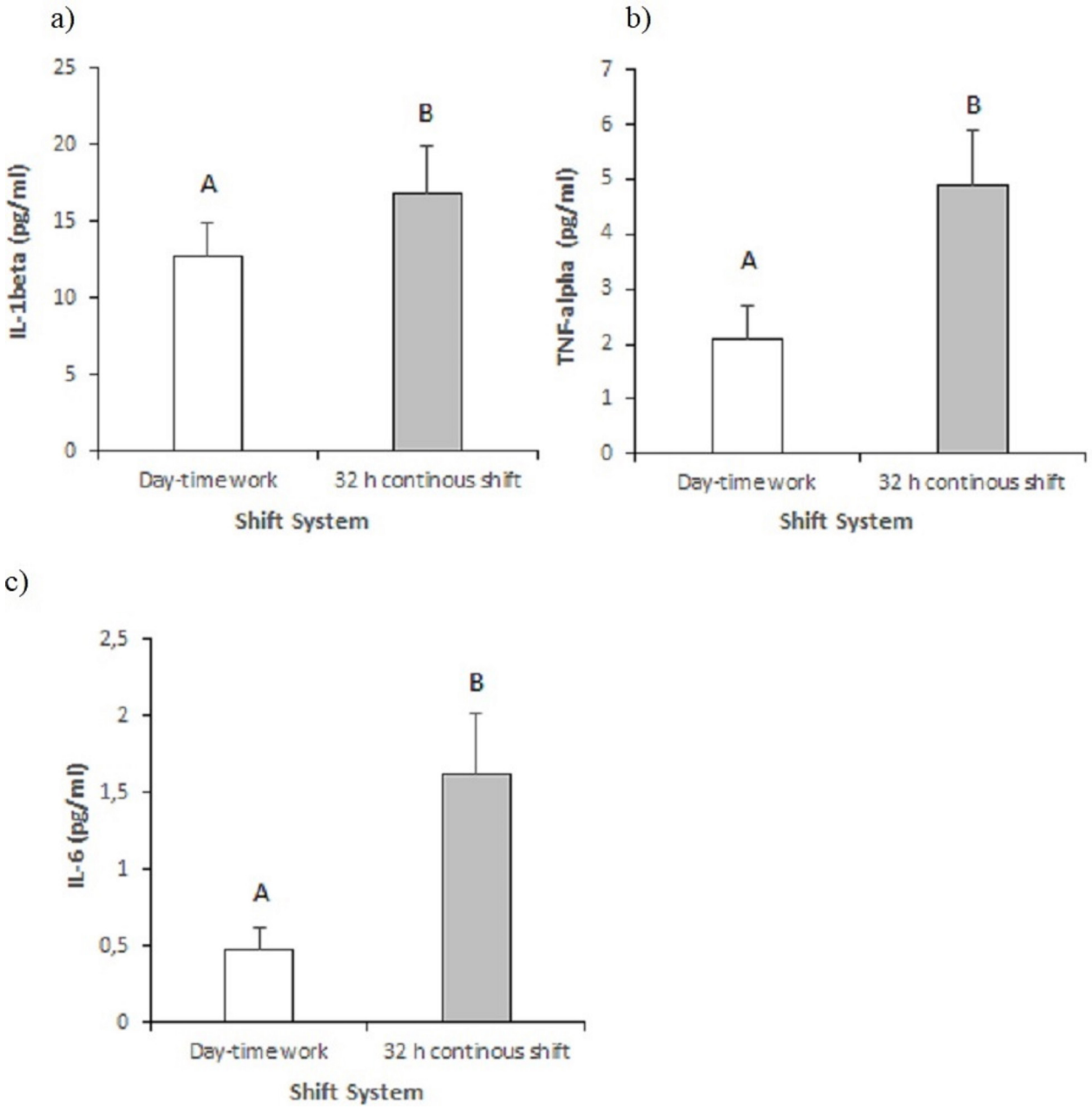

Figure 2. IL-1β (a), TNF-α (b) and IL-6 (c) concentrations in women working in different shift types (day-time work and 32 hours continuous shifts). Values represents as mean ± standard error. Groups with different capital letters differ significanly.

Table 4. Correlations among hormones and cytokines and duration trial test

Regression Analysis	Attention Test	Melatonin	Leptin	Estrogen	Progesterone	IL-6	IL1beta
Melatonin	-0.030						
	0.900						
Leptin	0.141	0.140					
	0.552	0.557					
Estrogen	-0.030	-0.047	-0.294				
	0.901	0.843	0.209				
Progesterone	-0.106	-0.049	-0.142	0.196			
	0.655	0.837	0.551	0.408			
IL-6	-0.437	-0.012	-0.205	0.093	0.521		
	0.054	0.961	0.386	0.697	0.019		
IL-1beta	-0.112	-0.016	0.007	0.043	0.406	0.644	
	0.648	0.947	0.978	0.861	0.085	0.003	
TNF-alpha	-0.275	-0.098	-0.087	-0.135	0.509	0.532	0.400
	0.241	0.680	0.717	0.571	0.022	0.016	0.089

*Intracellular: Pearson correlation P value

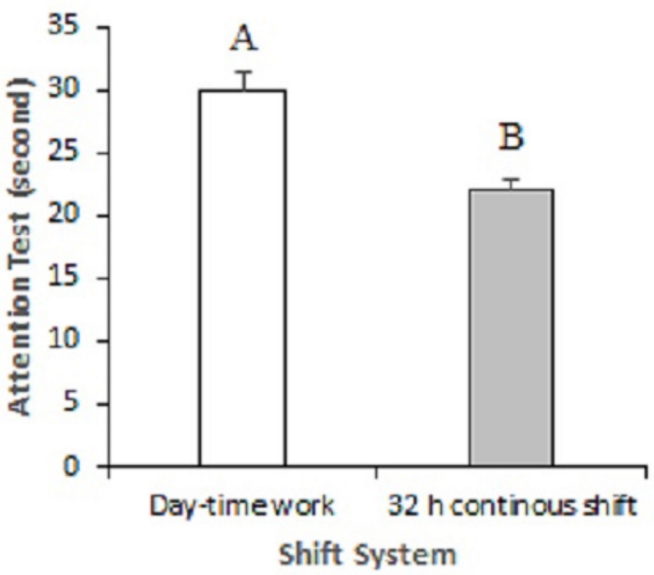

Figure 4. End of the shift trial test durations in women working in different shift types (day-time work and 32 hours continuous shifts). Values represents as mean ± standard error. Groups with different capital letters differ significanly (p=0.000).

DISCUSSION

This study compared the 32 hours continuous shifts and day-time shifts in women working in health sector and found out that night shifts and its duration had profound effects on various physiological parameters including CBC parameters, attention performance, sleep duration and quality, inflammatory and hormonal parameters. All these changes suggest that, in long term, there might be dentrimental effects of night-shift works on health the female healthcare workers. Also, it is thought that it may be useful to keep shift schedules short and to include rest periods. Moreover, it is thought that it may be useful to keep shift schedules short and to include rest periods.

Long-term shift system did not affect vital signs

Heart rate, respiratory rate, blood pressures, body temperature and glucose concentration was within normal limits and did not different between the groups, which is also reported by other shift system (16). However, there are some studies emphasizing that there is a relationship between shift work and development of hypertension and cardiovascular disease (15).

Long-term 32h shift was associated with increased hemoglobin, hematocrit and eosinophils

The 32 hours continuous shift system in FPR did not affect the number of red blood cells, white blood cells and platelets. For all that hemoglobin and hematocrit were found to be higher, although within normal range, in FPR who had 32 hours continuous shift system. Coglianese et al. found in their study that high hematocrit might be associated with increased heart disease (17). Sorlie et al. studied the risk of hematocrit on coronary heart disease and found out that high hematocrit level may be an independent potential risk factor contributing to coronary heart disease (18).

The 32 hours continuous shift system in FPR did not affect the number of lymphocytes, neutrophils, basophils and monocytes, but increased the number and percentage of eosinophils. Eosinophils are uncommon white blood cells and their activity is primarily related to the destructive infection and asthma (19). In this study, the high percentage and counts of eosinophils in the women under 32 hours continuous shift system may be indicative of increased allergic sensitivities (20). In addition, the long-lasting sleeplessness and

non-physiologic working hours may be the contributing factors to increased activity of the immune system (21).

Long-term 32 h shift system working did not affect plasma melatonin, leptin and estrogen levels but increased progesterone levels

In terms of melatonin level, there was no statistically significant difference between women working in 32 hours continuous shift system and women working in day shift. In the current study, we measured melatonin levels in the most standardized time for both groups (i.e. at 08:00 h in the next day-time work) as the FPR under 32 hours continuous shift are exposed to light in the other times. But this time point of melatonin measurement also coincided with its lowest diurnal level. Nevertheless, similar to our findings, Sack et al. found no difference in the level of melatonin between shifts and daytime work. They have emphasized that the reason for this may be the development of adaptation (22) and may be applicable in this study as well.

The leptin concentration was similar between the groups. In addition, there was no correlation with body mass index. In fact, it has been reported that shift-work increases body fatness and body mass index (23). In the current study, almost all residents had consciousness about good health and well being. They exercised measures such as walking, avoiding fast-food types, taking high nutritional consumption and taking care not to consume food late. It is probable that these types of measures prevented a higher body fat composition and increased leptin in the current study.

Estrogen concentration was not different between the groups but progesterone concentration was higher in women working in 32 hours continuous shift system. Night shift or shift system may cause different health problems (8), including reproductive problems (24). In women, night shifts are reported to shorten or prolong menstrual cycle, or increase menstrual pain (25), or may be associated with increased risk of miscarriage (26). In the current study, increased progesterone concentration might perturb reproductive function. In line with this, recently, Blake et al (2017) observed that lower progesterone and higher estrogen levels predicted higher assertiveness which safeguards indicrimante mate selectivity (27).

Long-term 32 h shift system increases plasma IL-1β, TNF-α and IL-6

In the present study, the levels of IL-6, IL-1beta and TNF-alpha were found to be higher in women working in long-term continuous shift system. Sleep is an important regulator of the immune system (21). Thus sleep deprivation may alter the immune response (28). Therefore, the cytokine level may vary depending on the sleep and wake cycle (29). The studies generally showed an increase in cytokine level after sleep deprivation (30). On the other hand, there were no differences in TNF-alpha, IL-6 (31) and IL-1beta among the groups as a result of some studies in which the shift system and daytime workers were compared (31). Although there are different results in literature review regarding shift system and immune functions, it is seen that there is an increase in cytokine level in general judicial shift system employees. Similar results were obtained in the current study. The presence of a strong significant increase in all three of the cytokines in the workers of 32 hours continuous shift system (IL-6 levels p=0.000, Figure 3a; IL-1β levels, p=0.003, Figure 3b; TNF-α levels, p=0.000; Figure 3c) supports the significant negative effects of this shift system on the immune system. Therefore, the long-term continuous shift system seems to be risk for the immune system. Negative consequences on the immune system may lead to serious diseases such as diabetes (32), cardiac diseases (33), obesity (32) and cancer (32). For this reason, care must be taken in the regulation of shift system programs.

Long-term shift system working increased visual attention

The level of attention was found to be better in women working in 32 hours continuous shift system than in women working in day shifts. In a study on sleep deprivation, it was found that the wakefulness levels of the group who were sleepless and tired during the day were higher than the inpatient group, and this was attributed to the relatively increased sympathetic nervous system activity (34). However, there are studies that find different results. In some studies, it has been emphasized that working in night shifts may have negative effects on performance and increase the risk of accidents (35) and impair cognitive functions (36). However, in the present study, long-term insomnia may have a positive effect on employees. As a matter of fact, the level of attention was found to be much better for night shift workers than for those working at day. Yang et al. similarly they found that there was an increase in attention levels in their study of patients with insomnia (37).

Long-term shift system working increased sleep duration but reduced sleep quality

In the study, women working in 32 hours continuous shift system compared to working women in day shift; they woke up later, had more bad dreams, had worse sleep quality and were more difficult to wake up. On the other hand, it was determined that women working in 32 hours continuous shift system woke less at night to use the toilet. However, when the opinion of the participants on this condition was obtained, it was found that they did not feel the bladder tension due to the increase in sleep depth due to being very tired. In the night shift workers, tiredness (38), inadequate sleep, decreased sleep quality and efficacy, sleep disturbances (38) are more common than day workers. The findings obtained from the present study are also very similar to the literature data. Therefore, taking into account the number of working years and the total number of seizures per month in the organization of night shift work programs and ensuring appropriate

rest periods may reduce the potential negative effects on night shift women.

IL-6 was correlated with visual attention, IL-1beta, progesterone and TNF-α

In the present study, a positive relationship between IL-6, IL-1beta and TNF-alpha suggests that the cytokine stress response may be similar (39). A positive relationship between IL-6 and TNF-alpha and progesterone suggests that the cytokine response may be related to progesterone in case of insomnia. As a matter of fact, it is emphasized that there may be an interaction between sex hormones and cytokines in some studies (40).

CONCLUSION

Although it may be considered that there is a positive change in hematolytic parameters and attention test in contrast to expectations in women working in 32-hours continuous shift system, it may be thought that these changes may have occurred as a result of deep stress activation. Indeed, such a shift system appears to increase the levels of cytokines (TNF-alpha, IL-1beta, IL-6) and progesterone and cause sleep problems. For this reason, it is considered that keeping shift programs as short as possible and adding rest periods to short-term shift programs may be useful.

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Conflict of Interest: *The authors declare that they have no competing interest.*

Ethical approval: *Ethics committee approval of this study was taken from local Clinical Researches Ethics Committee in accordance with the Declaration of Helsinki (Approval = 2016/197).*

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Araştırma Makalesi / Research Article

The Evaluation of Protein Oxidation in The Rats Which Induced Diabetes by Streptozotocin

Streptozotosin Diyabeti Oluşturulan Ratlarda Protein Oksidasyonunun Değerlendirilmesi

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Abstract

Aim: Diabetes mellitus (DM) is a chronic disorder and characterized by the development of long-term complications. Methylglyoxal (MGO), a precursor of advanced glycation endproducts (AGE), is detoxified in the organism by Glyoxalase through Glyoxalese I (GLO I) and GLO II.This study was aimed to investigate AGE formation in a diabetic rat model induced by streptozotocin (STZ) and the possible role of melatonin MEL which is a powerful antioxidant in this mechanism.
Materials and Methods: Four study groups, each containing ten Sprague Dawley rats, were defined as control, MEL, STZ and STZ-MEL. STZ and STZ-MEL groups were given a single 50 mg/kg dose of STZ to induce diabetes. MEL, 25 mg/kg was given intraperitoneally to MEL and STZ-MEL groups on a daily basis for 42 days. At the end of study, the levels of MGO, GLO I and GLO II enzymes were also determined in only tissue samples.
Results: Blood and urine glucose levels were found to be high in rats ($p<0.05$). STZ group had been shown to have higher tissue MGO levels and lower GLO I and GLO II activities ($p<0.05$). MEL treatment had suppressed high levels of MGO and increased enzymatic activities in STZ-MEL group.
Conclusion: In this study, we have shown that reducing MGO tissue levels in chronic diabetes to almost normal level and that the GLO system suppressed in diabetic rats are preserved with MEL,GLO I and GLO II activities increased. It has been shown that STZ induced diabetic rats had high MGO levels and the supression of GLO detoxification system indicates that AGE formation in diabetes is inevitable. Therefore, the usage of antioxidants such as MEL may be suggested to prevent diabetic complications.

Keywords: Diabetes mellitus, Methylglyoxal, Protein Oxidation

Öz

Amaç: Diabetes mellitus (DM) uzun süreli komplikasyonların gelişmesi ile karakterize kronik bir hastalıktır. İleri glikasyon son ürünleri (AGE) öncüsü olan metilglikoksal (MGO) Glioksalaz 1 (GLO 1) ve GLO 2 ile Glioksalaz tarafından organizmada detoksifiye edilmektedir. Bu çalışmada amaç streptozotosin (STZ) ile indüklenen diyabetik rat modelinde AGE oluşumunu araştırmak ve güçlü bir antioksidan olan melatonin (MEL)'in bu mekanizmadaki güçlü antioksidan rolünü araştırmaktır.
Materyal ve Metot: Her biri on adet Sprague Dawley ratları içeren dört çalışma grubu kontrol, MEL, STZ ve STZ-MEL olarak tanımlandı. STZ ve STZ-MEL gruplarına diyabeti indüklemek için tek doz 50 mg / kg STZ verildi. 25 mg / kg MEL, 42 gün boyunca MEL ve STZ-MEL gruplarına günlük intraperitoneal olarak verildi. Çalışmanın sonunda sadece doku örneklerinde MGO, GLO 1 ve GLO 2 enzimlerinin düzeyleri tespit edildi.
Bulgular: Ratlarda kan ve idrar glikoz düzeyleri yüksek bulundu ($p<0.05$). STZ grubunun daha yüksek doku MGO düzeylerine ve daha düşük GLO I ve GLO II aktivitelerine sahip olduğu ($p<0.05$) gösterilse de MEL tedavisi, yüksek MGO düzeylerini ve STZ-MEL grubunda artmış enzim aktivitelerini baskıladı.
Sonuç: Bu çalışmada, kronik diyabetteki MGO doku düzeylerinin neredeyse normale düştüğünü ve diyabetik sıçanlarda GLO sisteminin baskılanmasının MEL, GLO 1 ve GLO 2 aktiviteleri ile korunduğunu gösterdik. STZ kaynaklı diyabetik sıçanların yüksek MGO seviyelerine sahip olduğu ve GLO detoksifikasyon sisteminin baskılanmasının diyabet hastalığında AGE oluşumunun kaçınılmaz olduğu gösterilmiştir. Bu nedenle, MEL gibi antioksidanların kullanımı, diyabetik komplikasyonları önlemek için önerilebilir.

Anahtar Kelimeler: Diyabetes mellitus, Metilglioksal, Protein oksidasyonu

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INTRODUCTION

Diabetes mellitus (DM) is a set of metabolic diseases characterized by hyperglycemia induced by defects in insulin secretion, insulin action, or both (1). Although hyperglycemia is widely acknowledged as the most important risk factor for the development of diabetes complications, it is still debated which pathogenic mechanisms produce these complications. Many complex mechanisms such as increased carbonyl stress (2), oxidative stress (3) and the formation of advanced glycation end products (AGE) (4) are responsible for the development of diabetes complications. According to the classification made in 1980 by the committee of experts formed by the World Health Organization (WHO) and the Diabetes federation, two main forms of diabetes, namely TYPE 1 (Insulin-dependent IDDM) and Type 2 (Insulin-independent NIDDM) diabetes were defined, and the definitions of "juvenile" and "adult" diabetes were used in the naming of these forms (5).

Studies on experimental animals plays an important role in the understanding of diseases, the direction of treatments, and the discovery of new treatment methods. The animals most commonly used as diabetes models are rats, cats, dogs, cows, rabbits, and mice (6). Alloxan and streptozotocin (STZ) are chemical agents that are preferably used in the formation of experimental diabetes today (7). Despite the fact that their mechanisms differ, it is suggested that both have cytotoxic effects via free oxygen radicals (FOR) (8).

Oxidative stress is defined as the disruption of the balance between oxidant-antioxidant systems in the organism in cases where reactive oxygen species (ROS) is overproduced or antioxidant mechanisms are insufficient (9). Cross-linking reactions that can occur within or between molecules have been stated to have an association with protein oxidation and glycation reactions.

Glycation is the nonenzymatic covalent bonding of reducing sugars, primarily glucose, to amino groups of proteins. It's called "Maillard." In glycoxidation, reactive intermediates (ά-oxoaldehydes) such as methylglyoxal (MGO), glyoxal (GO), and 3-de-oxyglucocone (3-DG) are formed as the second step of Maillard reactions (10). MGO is a three-carbon aldehyde with a double carbonyl group that can be derived from carbohydrates, lipids, and even proteins in the organism. The main pathways responsible for MGO degradation in the organism are the glyoxalase detoxification system and alpha-keto aldehyde dehydrogenase pathway found in the cytosol of all cells (11). The glyoxalase system, which uses reduced glutathione (GSH) as a cofactor, has two different enzyme activities: Glyoxalase I (GLO I), Glyoxalase II (GLO II). MGO has been proposed as the most important precursor in the formation of AGE in recent years, and this view is supported by high plasma and/or tissue MGO levels in diabetic patients and experimental diabetes models (12).

In addition to its known effects on endocrine function and circadian rhythm, melatonin (MEL), a pineal gland hormone, has also been shown to have antioxidant activity in vitro and in vivo studies (13). It has been reported that it can protect the organism from the negative effects of diabetes and prevent oxidative damage in diabetic rats although the effect of MEL on AGE formation is still unknown (14).

The aim of this study is to assess the glyoxalase detoxification system as well as the MGO levels that cause AGE formation in an experimental diabetes model, as well as to look into the possible interaction of a strong antioxidant such as melatonin on these mechanisms.

MATERIAL AND METHOD

Erciyes University School of Medicine's Animal Care and Use Committee has approved all the experimental protocols (Approval number: TT-03-07;03/32).

Study group consisted 40 male Sprague Dawley rats, 4-5 months old, weighing 250-350 g. Experimental study was conducted in Erciyes University Hakan Çetinsaya Experimental Research Application and Research Center.

Induction of diabetes A single dose of freshly prepared STZ (50 mg/kg, dissolved in 0.1 M cold citrate buffer, pH 4.5) was administered for the induction of DM in overnight-fasted rats. Rats were tested for the induction of DM after 3 days of STZ administration by evaluating their fasting blood glucose levels via a commercial glucometer (Medisense Optium, Abbott, Switzerland). Only rats with fasting blood glucose levels > 200 mg/dL were included in the present study.

Experimental design Forty male rats were divided into four groups (n =10 per group) as follows: Control Group:Normal control (negative control without any treatment, CONT); Melatonin Group,:Only 25 mg/kg Melatonin administration, MEL); Streptozotocin Group,;Diabetic rats, STZ; Streptozotosin+Melatonin Group,;Diabetic rats treated with melatonin at 25 mg/kg for 6 weeks (STZ + MEL)

Liver homogenates;The liver of the treated rats were rinsed with isotonic saline, and their homogenates were prepared immediately (10% [w/v] in 0.1 M phosphate-buffered saline, pH 7.4) using a tissue homogenizer. Their supernatants were prepared by centrifugation and were used to measure MGO,GLO I,GLO II parameters.

MGO levels in liver tissue were determined employing the method developed by Cooper. The principle of the method is based upon measuring the color intensity of phenylhydrazones formed by MGO with dialdehyde structure and 2,4-dinitrophenylhydrazine (DNPH) at 550 nm (15). The method developed by Mannervick was used for the determination of tissue GLI I activity The methods principle is based upon the fact that S-d-lactoylglutathione (SLG) formation by GLO I, which catalyzes the conjugation of GSH and MGO, at 240 nm as a time dependent increase in OD (16).The method

developed by Racker was employed for the determination of tissue GLO II activity. The principle of the method is based upon monitoring the decrease in OD at 240 nm due to the conversion of SLG to lactate by GLO II (17). GLO I and GLO II activities and MGO levels were determined in liver tissues obtained from rats.

Statistical comparisons were conducted utilizing SPSS for Windows l0.0 software package. ANOVA and post-ANOVA (Scheffe procedure) tests were performed. The level of significance was accepted as $p<0.05$ in all statistical comparisons.

RESULT

Results showed that there was no significant difference between the control and MEL groups in terms of tissue MGO and GLO I and GLO II activities. In the STZ group, MGO levels were found to be significantly higher, while GLO II activity significantly decreased, and GLO I activity have shown a more significant decrease than only the MEL group. The increase in MGO values in the STZ-MEL group was also found to be statistically significant. When STZ and STZ-MEL groups were compared, it was observed that MGO levels decreased with the effect of MEL, but could not reach the levels of the control group. On the other hand, it was determined that the GLO II activity in the STZ-MEL group reached levels of the control and MEL groups.

All data of the study groups were presented in Table 1.

Table 1. Liver MGO,GLO I and GLO II levels in rats forming the study groups

GROUPS	MGO (nmol/mg pt)	GLO I (U/mg pt)	GLO II (U/mg pt)
CONT	1.41±0.027	0.084±0.017	0.049±0.018
MEL	1.44±0.31	0.095±0.02	0.051±0.018
STZ	3.34±0.43*[a]	0.061±0.019[a]	0.024±0.008*[a]
STZ-MEL	2.12±0.26*[ab]	0.074±0.044	0.054±0.018[b]

CONT=Control, MEL=Melatonin, STZ=Streptozotocin, Values are given as mean±S.D., for ten rats per group. Values are statistically significant at $p<0.05$; Statistical significance was compared with in the groups as follows: a) diabetic STZ rats groups were compared with normal control rats, b) STZ+MEL

DISCUSSION

Unclear remains how and under which pathological mechanism hyperglycemia poses the most important risk factor in the development of DM complications. Even if the experimental models used to understand this disease do not meet the real conditions in which human diabetes occurs, they are very advantageous in terms of showing the diabetic state biochemically, hormonally, and morphologically (18).

Considering the mechanisms associated with the pathogenesis of diabetes complications, it is seen that these mechanisms, which are based on different foundations, overlap with each other.

The complexity of the physiopathology of diabetes becomes more apparent when considering the fact that oxidative stress accelerates the formation of AGEs, in addition to the fact that AGE formation causes oxidative stress, and that lipid peroxidation products such as malondialdehyde (MDA), which are formed as a result of oxidative stress, are also an reactive carbonyl compounds (RCC), thus causing carbonyl stress (10).

MGO is a reactive dicarbonyl intermediate and a precursor of AGEs. Significant amount of evidence can be regarded as the increase of MGO levels in diabetic patients (19). MGO can be very cytotoxic making stable adducts. Its concentration levels are found to be significantly higher in the plasma of diabetic patients and diabetic animal tissues. (20) MGO is a physiological substrate of the glyoxalase system, as well as being a physiological α-dicarbonyl compound derived from glycolytic intermediates produced during the Maillard reaction. In this system, which utilizes reduced glutathione as a cofactor, MGO is converted to D-Lactate via SLG intermediates (21). In the experimental models, the significance of MGO in terms of endothelial dysfunction in diabetes was presented an increase in oxidative stress (22). According to Nemet et al. (23), it was shown that whole blood and plasma MGO levels, which were found to be high in both diabetic groups, were statistically significant only in plasma when MGO whole blood and plasma levels of patients with Type I and Type II diabetes were compared. MGO levels were similarly found to be high in kidney, lens, and blood samples from rats with STZ diabetes (24). However, Ohmori et al. (25) reported that MGO levels were low in liver tissues and high in skeletal muscle of rats 72 hours after the alloxan administration. Discrepancies in tissue MGO results in the literature can be attributable to methodological differences as well as experimental diabetic circumstances such as dose and duration.

In this study, liver tissue MGO levels were found to be high in the diabetic rat group. The glyoxalase system, which is common in almost every tissue of the organism and catalyzes the detoxification of MGO, may also affect MGO levels. Any suppression of this detoxification system can be the cause of the increase in MGO levels.

Although there are many studies in the literature investigating the effect of diabetes on GLO I and GLO II activities, the findings obtained from these studies differ.

According to Brouwers et al. in rats having Stz diabetes, GLO-I activity was found to be significantly increased in multiple tissues of all transgenic rats compared to wild-type (WT) littermates (26).

There are studies that reported the GLO I activity to be high in skeletal muscle (27) but low in liver (28) in

diabetic rats. GLO II activity was similarly discovered to be normal in the tissues of small intestine (29) and high in skeletal muscle (30) but low in kidney (31) and liver (32). Both GLO I and GLO II activities were found to be reduced in the liver tissue of diabetic rats in this study, which is consistent with some of the current literature. These data can be interpreted as partially supporting the increase in MGO levels.

Melatonin is a hormone that is produced by the pineal gland. It plays the role of antioxidant in the oxidant-antioxidant imbalance that could be the result of diabetes (33) .The previous studies conducted by Montilla et al. have revealed that melatonin decreased hyperglycemia and hyperlipidemia in rats with STZ-induced diabetic (34) Yavuz et. al stated that Melatonin protect the rats' β-cells from the destructive effects of STZ. The treatment of melatonin (200 µg/ kg/d, ip) for 3 days before the induction of diabetes and then the treatment of melatonin every day for 4 weeks restored the morphology and β-cell insulin levels, and increased major decrease of glutathione peroxidase activity in pancreatic tissue (35).

MGO levels were lower in the melatonin group than in the STZ+MEL group in our study, although GLO I and Glo II levels were higher.

CONCLUSION

The fact that the GLO detoxifying mechanism is suppressed, in addition to high MGO levels in the diabetes model produced with STZ, indicates that AGE generation is inevitable in diabetes when all of the findings of this study are evaluated together the literature. In the prevention of these highly complex pathogenic mechanisms; According to the results of the study, it has been found that melatonin has the protective feature against oxidative stress and decreased the severity of STZ-induced diabetes.

Congresses The study has been presented at the '1th National Congress of Dr Safiye Ali ' between August 6-7, 2021.

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Conflict of Interest: *The authors declare that they have no competing interest.*

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MEDICAL RECORDS-International Medical Journal

Olgu Sunumu/ Case Report

Acral Melanoma Presenting with Lung Invasion and a Giant Inguinal Mass

Akciğer İnvazyonu Ve İnguinal Bölgede Dev Kitle İle Prezente Olan Akral Melanom

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Abstract

Although malignant melanoma is a rare type of skin cancer, it accounts for most skin cancer-related deaths. Foot lesions may be ignored by both patients and clinicians and could therefore lead to advanced disease. An acral melanoma may also be confused with a pressure ulcer and result in a late diagnosis. The need to perform a skin biopsy should therefore be considered when dealing with protracted wounds. In this report, we present the case of an 84-year-old female patient with malignant melanoma, which was diagnosed late, recurred in the same area following surgery, and caused lung metastasis and a giant inguinal mass.

Keywords: Acral melanoma, atypical presentation, giant inguinal mass

Öz

Malign melanom, nadir görülen bir cilt kanseri türü olmasına rağmen cilt kanserlerine bağlı ölümlerin çoğunluğunu oluşturur. Ayaktaki melanomlar hem hasta hem de klinisyen tarafından önemsenmeyebilir ve sonrasında hasta metastatik lezyonlar ile prezente olabilir. Ayrıca bu yaralar basınç ülseri ile karıştırılabilir ve bu durum tanının gecikmesine neden olabilir. Uzun süre iyileşmeyen ayak yaralarında cilt biyopsisi yapılması gerektiği unutulmamalıdır. Biz bu yazıda; opere edilmesine rağmen ayağın aynı bölgesinde nüks eden, akciğer metastazı ve inguinal bölgede dev kitleye neden olan, akral melanomlu 84 yaşında bir kadın hastayı sunduk.

Anahtar Kelimeler : Akral melanom, atipik prezentasyon, dev inguinal kitle

INTRODUCTION

Although malignant melanoma is a relatively rare disease, it is one of the deadliest forms of skin cancer. Malignant melanoma accounts for only 4% of all skin cancers, yet it is responsible for about 79% of skin cancer-related deaths. Metastatic malignant melanoma is considered the most aggressive form of skin cancer (1-3).

Malignant melanoma has a better prognosis in females than in males. Women generally have thinner tumors because cutaneous melanoma in females is mainly localized in the extremities where it can be detected at an earlier stage and more easily. Women also tend to accept health advice better, and when a lesion occurs, they seek out a clinician earlier than men (4, 5). Some experts also think that estrogen may play a possible protective role in melanoma (6).

Previous studies have raised the possibility of an especially poor prognosis in cases of acral melanoma. Foot lesions are often ignored by both patients and clinicians, so this special group of patients may receive inadequate treatment because of a delayed diagnosis or misdiagnosis (1, 7-9). Even when noticed early, the possibility of melanoma might not be considered immediately. In cases of persistent foot ulcers, early biopsy is vital to exclude other causes of the ulcers, especially in the presence of atypical ulcer symptoms such as pigmentation and granulation tissue (10).

In this report, we present a case of a patient with acral melanoma and a fatal prognosis. The growth started as a small skin lesion in the plantar region of the foot and grew rapidly. Despite surgery, it relapsed in the same area and caused a lung invasion as well as a giant metastatic mass in the inguinal region.

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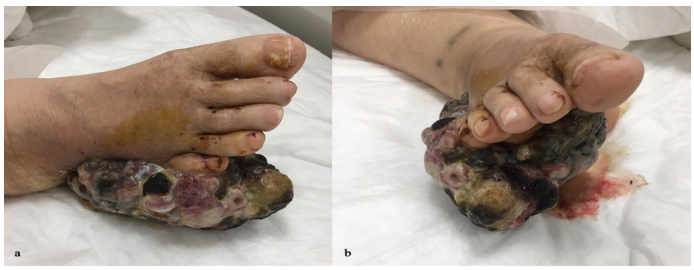
CASE REPORT

An 84-year-old female patient was admitted because of a largely expansive acral melanoma on her right foot and a giant metastatic mass in the right inguinal area. The lesion first appeared as a small brown spot on the right foot plantar region in 2011. A year later, an ulceration occurred on this lesion, and transparent drainage was apparent. In 2014, the patient presented at the hospital with complaints of a rapidly growing lesion and purulent drainage.

The lesion, which had turned into a mass on the skin, was resected, and skin tissue transplantation was performed on the resected area. A histological evaluation of the mass revealed malignant melanoma. Positron emission tomography scanning of the patient showed multiple metastases in the lung and inguinal lymph nodes. Because the patient was 79 years old at the time, the relatives of the patient declined chemotherapy. The patient had no complaints for three years following the surgical resection. However, the lesion and drainage subsequently reappeared in the same area. The lesion had been small in the operation site but had spread over a larger area during the course of the three years.

At her presentation to our hospital, the patient showed an infected mass, which covered half of the plantar face of the foot and extended to the dorsal region (Figures 1a, 1b). In the previous six months, the lymph nodes in the right inguinal region had become a giant metastatic mass (Figure 2a). The medical state of the patient was critical, and oral intake was reduced. She was experiencing severe respiratory distress due to diffuse metastatic masses and consolidations in the lung (Figure 2b). Despite all possible interventions, the patient died.



Figures 1a, 1b. A malignant melanoma mass at first presentation to our clinic; the mass subsequently spread from the plantar region to the dorsal side of the right foot.

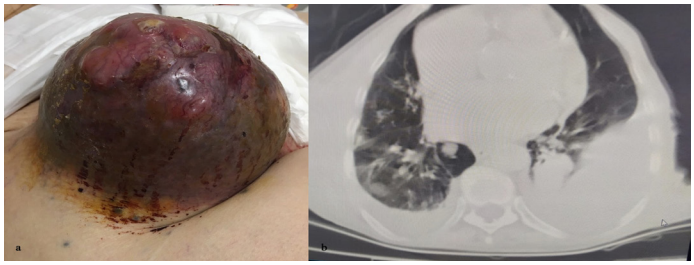


Figure 2a. Metastatic lymph nodes that merged into a giant mass in the right inguinal region **Figure 2b.** Diffuse metastatic masses, consolidations, and bilateral pleural effusion in the lung

DISCUSSION

In this report, we have presented the case of an 84-year-old woman with an acral melanoma. She underwent surgery but had a recurrence of the disease over a nine-year period. The patient's relatives declined chemotherapy following the melanoma diagnosis. During a follow-up, she showed lung metastasis and a giant metastatic mass in the inguinal region.

The most important prognostic factor in malignant melanoma is the thickness of the tumor (depth of invasion) in millimeters. Other important factors include the level of invasion, ulceration, regression, host lymphocytic inflammatory response, mitotic index, angiolymphatic invasion, microsatellitosis, and growth phase (radial or vertical) (11). According to the cancer rankings by gender in the United States, malignant melanoma is the fifth most frequent cancer in men and the seventh most frequent cancer in women (12). It is not seen as frequently as basal cell and squamous cell carcinomas, but melanoma causes more deaths than any other skin cancer (13, 14).

Approximately 33% of melanomas arise in the lower limbs. Screening of the lower extremities and feet is therefore important for the early detection of melanoma. Foot and ankle melanomas are located in less visible parts of the body, so delays in diagnosis are possible (15). Furthermore, melanoma tends to resemble ulcerative lesions of the foot and ankle.

When compared with ulcerations associated with trauma or diabetic or alcoholic neuropathy, invasive melanoma may not show distinguishable visual features. A biopsy should therefore be performed to exclude malignancy in any ulcerations or suspicious lesions that do not heal with standard care. Effective treatment of melanoma is possible with a diagnosis of limited disease (16, 17).

Some concerns have been raised that primary melanoma of the foot could be linked to a worse disease course. Previous studies have indicated that the anatomical area of the foot is an independent factor affecting the prognosis of melanoma. The 5-year survival rate for melanoma on all parts of the body is 91.7%. By contrast, invasive melanoma of the foot has a 5-year survival rate of only 68.4%. A previous report indicated that 54.4% of the foot melanomas in the study sample had already reached a depth of >2 mm by the time of diagnosis, and 48.4% of these had positive sentinel lymph node involvement (16).

Several studies have shown that the generally poor prognosis of patients with foot melanoma may result from the different characteristics of the tumor biology. Melanomas occurring on the hands and feet are linked to worse prognostic and biological factors regardless of the lentiginous histologic type (18). Minagawa et al. found that plantar melanoma of the foot occurred more frequently in locations exposed to mechanical stress, especially the heel and forefoot. These are also the areas of the foot most susceptible to the development of

calluses and pressure ulcers (19).

Initial biopsies in 54.4% of invasive melanoma lesions have been reported as >2 mm deep, and 29% have been found to be ulcerated. The diagnosis and treatment of melanomas of the foot may be delayed because of confusion with other diseases that tend to induce pedal ulcerations, such as diabetes, neuropathy, and peripheral vascular disease. However, the prevalence of metastatic disease and the 5-year mortality rate increases in lesions deeper than 1 mm; the application of screening methods and increased patient awareness of this disease are therefore crucial for patient survival (14-16).

CONCLUSION

Malignant melanoma is a relatively rare type of skin cancer, yet it has a high mortality rate. Melanomas of the plantar area of the foot can be confused with pressure wounds related to other disorders and might therefore be ignored. This could lead to diagnosis long after the metastatic form has developed. The patient in our case study was not concerned about the foot ulcer, and it was therefore diagnosed in the metastatic stage. Early and aggressive treatment could help increase the overall 5-year survival rates of patients with acral melanoma.

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MEDICAL RECORDS-International Medical Journal

Olgu Sunumu/ Case Report

Removal of a Maxillary Third Molar Displaced in the Infratemporal Fossa using an Intraoral Approach

İnfratemporal Locaya Deplase Olmuş Maksiller Üçüncü Molar Dişin İntraoral Yaklaşım İle Çıkartılması

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Abstract

Removal of an impacted maxillary third molar can be challenging for both dental clinicians and oral surgeons. Frequently encountered complications include infection, pain, swelling, root fractures, trismus, and haemorrhage. In addition, unexpected displacement of the maxillary third molar may be encountered during the extraction process. This case report presents a maxillary third molar displaced to the infratemporal fossa, as well as removal of the tooth following 1 month, along with the causative factors. The roles of orthopantomography and dental volumetric tomography scans in determining the localization of the tooth are discussed, together with different surgical options and risks for surgical removal of the tooth from the infratemporal fossa.

Keywords: Displacement, extraction, infratemporal fossa, third molar

Öz

Gömülü maksiller üçüncü molar dişinin cerrahi olarak çıkarılması hem diş hekimleri hem de çene cerrahları için zor olabilmektedir. Sık karşılaşılan komplikasyonlar arasında enfeksiyon, ağrı, ödem, kök kırıkları, trismus ve kanama bulunur. Bu komplikasyonlara ek olarak, çekim sırasında maksiller üçüncü azı dişi anatomik boşluklara deplase olabilmektedir. Bu olgu sunumunda çekim esnasında infratemporal fossaya deplase olan bir maksiller üçüncü molar dişi ve 1 ay sonrasında intraoral yaklaşım ile bölgeden uzaklaştırılması nedensel faktörlerle birlikte bildirilmiştir. Dişin lokalizasyonunu belirlemede ortopantomografi ve dental volumetrik tomografinin rolü, farklı cerrahi seçenekler ve dişin infratemporal fossadan cerrahi olarak çıkarılması sırasında oluşabilecek riskler tartışılmaktadır.

Anahtar Kelimeler : Yer değiştirme, diş çekimi, infratemporal fossa, üçüncü molar

INTRODUCTION

One of the most frequently performed operations in oral and maxillofacial surgery is removal of the upper third molar. However, the procedure is associated with complications, including maxillary tuberosity fracture, root fractures, prolapse of the buccal fat pad, and displacement of the tooth into the maxillary sinus, infratemporal fossa, lateral pharyngeal, or pterygomandibular spaces or other tissue cavities (1,2). Undesirable displacement of the maxillary third molar to neighbouring tissue cavities is a rarely cited but frequently observed complication (1-3). This clinical report describes the location and delayed surgical removal of an impacted maxillary third molar that was accidentally displaced into the infratemporal fossa.

CASE REPORT

A 20-year-old woman was referred to the Istanbul University Faculty of Dentistry, Department of Oral and

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Maxillofacial Surgery, by a dental clinician who had unsuccessfully attempted to remove the left maxillary third molar under local anaesthesia on the preceding day (Figure 1). During intraoral examinations, the tooth could not be detected; thus, it was suspected to have been displaced upwardly through the infratemporal fossa (ITF) or buccal space. The patient had facial swelling on her left side, local pain during mandibular movements, and trismus. Mouth opening was limited to 1 cm. Visual activity and all other aspects of head and neck examinations were normal. Immediately, an orthopantomogram was taken, which showed that the left maxillary third molar had been displaced superiorly and posteriorly, possibly into the ITF (Figure 2).

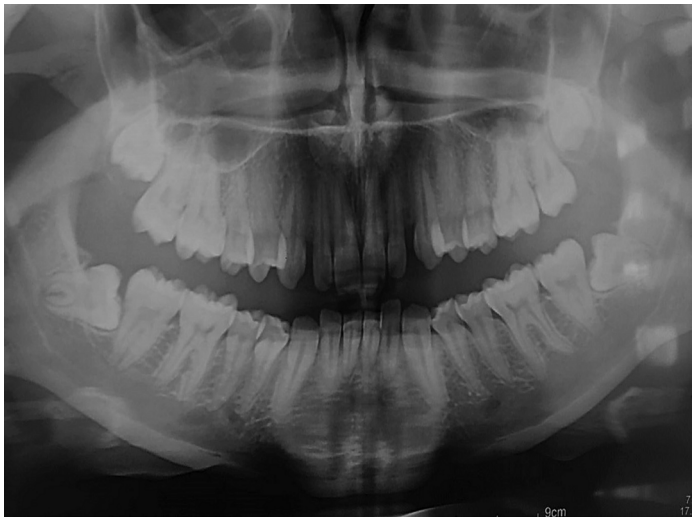

Figure 1. Orthopantomogram of the patient before extraction of upper left 3rd molar

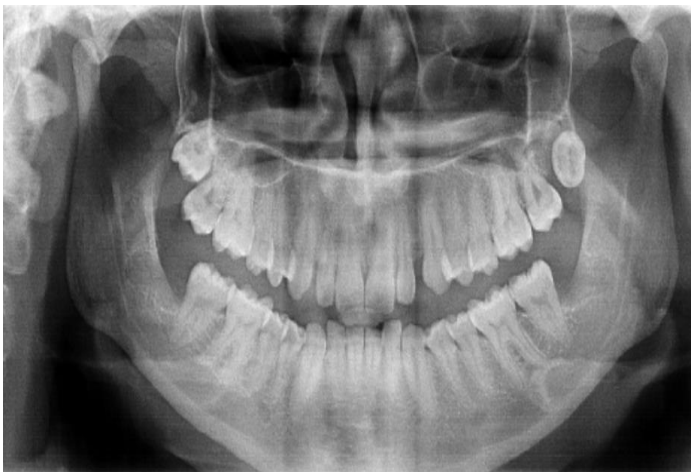

Figure 2. Orthopantomogram of the patient following the removal attempt of upper left 3 rd molar

The patient was administered 1 g amoxicillin and 1 g clavulanic acid (every 12 h), as well as a nonsteroidal anti-inflammatory drug (as needed) for 1 week to prevent infection. Seven days later, the patient showed improved mouth opening, however it remained insufficient for surgical intervention; pain remained on the left side of her face. She was instructed to return for consultation 3 weeks later. In addition, she was asked to return immediately if symptoms worsened.

Three weeks later, the patient showed no symptoms. To localize the exact location of the tooth, a dental volumetric tomography (DVT) scan was performed with 1 mm cross-sections. Axial and coronal cross-sections showed that the third molar had been displaced into the ITF (Figure 3 a and b).

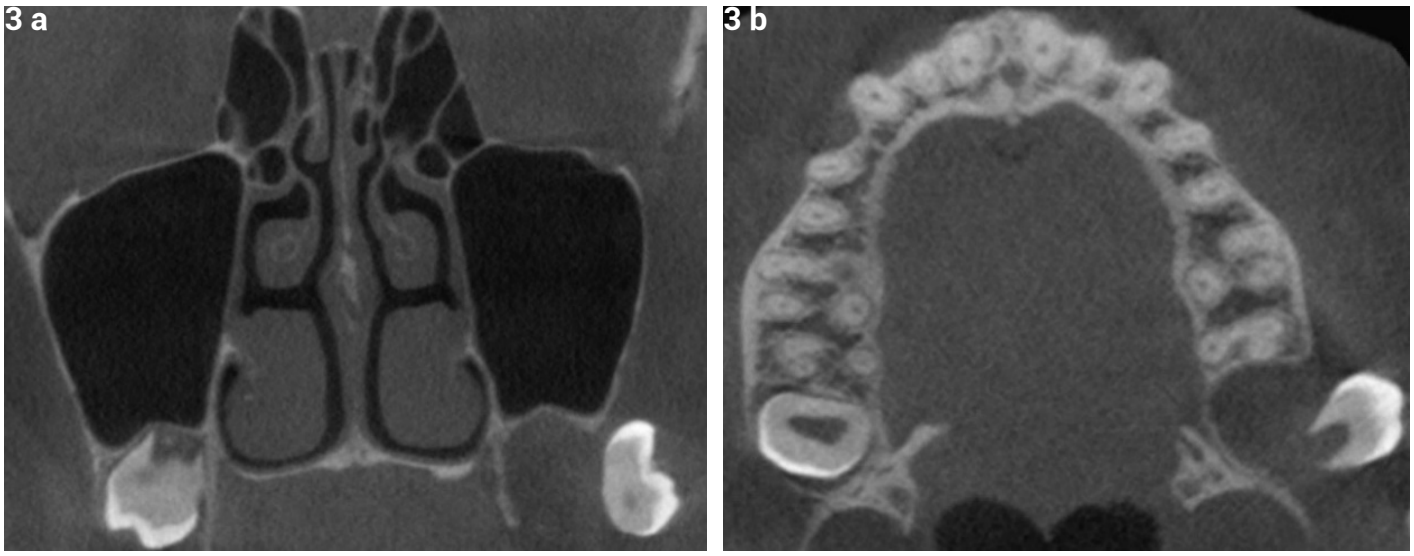

Figure 3 a. Coronal DVT sections of the displaced tooth. **b.** Axial DVT sections of the displaced tooth

Under local anaesthesia, the needle of a 2 cc dental syringe was used to probe the tissue slightly through the assumed tooth-bearing area to better determine its location and movement direction. When the needle

reached the approximate topographic position of the tooth and stabilization of the tooth in soft tissue had been confirmed, a small incision was made parallel to the fibres of the buccinator muscle. With the aid of a blunt surgical scissor, the muscle fibres were dissected and the enamel of the displaced third molar was observed (Figure 4). A haemostat was used to grip and pull the tooth from the anatomical cavity (Figure 5 a and b).

Deep layers of muscle fibres were irrigated with 0.5% saline solution. The incision was primarily closed with a 3–0 silk suture material and the patient received the same medical regimen that had been administered during the postoperative period. No postoperative complications occurred during follow-up period.

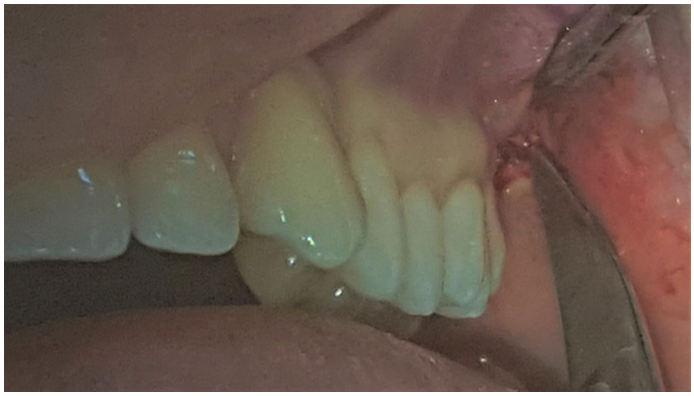

Figure 4. Dissection of the muscle fibers

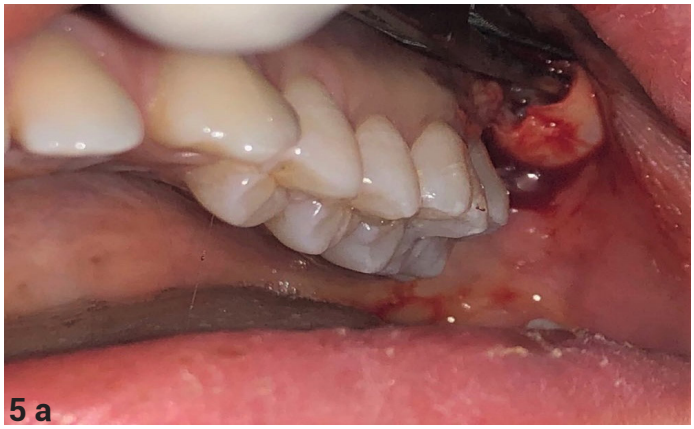

Figure 5 a. Hameostat holding the displaced tooth **b.** Removal of upper 3rd molar from infratemporal fossa

DISCUSSION

Lack of anatomical knowledge, poor radiographic examination, insufficient experience with regard to the basic principles of oral surgery techniques, and limited regional visibility may cause maxillary third molars to be displaced towards neighbouring anatomical cavities during their removal (1-5). The ITF is surrounded by the maxilla, styloid process, greater wing of the sphenoid bone, lateral pterygoid plate, and ramus. Moreover, it is occupied by pterygoid muscles, mandibular nerve branches, chorda tympani, maxillary artery, and pterygoid venous plexus (6). During the removal of a maxillary third molar, elevator misuse or application of excessive force may cause displacement of the tooth to the ITF through the periosteum. Further removal attempts may displace the tooth into the skull base, which poses a risk of irreversible morbidity (7,8). Radiographic investigations are recommended soon after displacement to eliminate the risk of damaging other anatomic areas (e.g., the orbit) (9). In the present case, panoramic radiographs taken on the next day showed that the displaced tooth had not moved superiorly through the orbit or skull base.

A patient with a displaced tooth into the ITF might be asymptomatic or might have symptoms of infection,

such as trismus, facial swelling, and pain. Mandibular movements may be limited due to the presence of a fibrous capsule around the displaced tooth. In some cases, diplopia has been reported due to paresis of the superior rectus nerve (1,2,5,9). The patient in the present case had facial swelling and exhibited limited mouth opening upon arrival at our clinic; however, she did not have any other comorbidities, such as visual distortion or diplopia. Some researchers support attempts to initiate migration of the displaced tooth in anatomical cavities until the time of operation (1,6). This is particularly useful for patients with underdeveloped teeth that exhibit no root formation. However, some authors10 have suggested that migration cannot be achieved due to the presence of fibrous tissue capsulation around the displaced tooth.

Selvi et al. advised a patient to chew gum on a regular basis, to stimulate migration of the tooth inferiorly through the oral cavity; they observed downwards movement of the displaced tooth (1). Another study revealed that radiographic images should be taken immediately before surgery, as the tooth can move into the ITF over time, as well as in accordance with jaw movements (6). The patient in the present case had a small amount of root formation and reported pain during mouth opening movements. Therefore, migration risk was considered low, and chewing gum was not advised because of pain during jaw movement.

Localization of the displaced tooth into the ITF is essential for an appropriate surgical approach; however, it is difficult because radiographic features of the tooth may overlap with other anatomical structures. For that reason, identification of the displaced tooth into the ITF requires radiographs to be taken on several planes (6,7). Based on the increasing technological capabilities and low radiation doses involved in image acquisition, DVT has become an important facet of diagnosis. Campbell et al. reported a new technique that enabled retrieval with an active navigation image guidance system (9). Light-emitting diode mask and computed tomography data are used to localize the displaced tooth. Our DVT scans in two different planes (axial and coronal) clearly identified the tooth withinto the ITF, positioned laterally to the lateral pterygoid plate.

Notably, some clinicians prefer to delay the operation for several weeks, such that the fibrous tissue capsule may immobilize the tooth. Without the formation of a fibrous capsule, the tooth may be further displaced into deeper anatomical locations during the operation. In the present case, we delayed the operation for 4 weeks to ensure the formation of fibrous capsule around the displaced tooth.

Many techniques have been suggested to reach a third molar that has been displaced into the ITF. These techniques include resection of the coronoid process, Gillies approach to access the displaced molar, trans-sinusoidal approach via Caldwell-Luc fenestration, hemicoronal incision, and use of an 18-gauge spinal needle to exert pressure on the displaced tooth (4,6,11,12). In the present case, we used the needle of a 2 cc dental syringe to establish the location and movement of the tooth. When we confirmed that the tooth was not mobile within the soft tissue, we began the operation. A small incision through the buccal vestibule was performed intraorally, following blunt dissection. Then the tooth was reached through this pathway.

CONCLUSION

Prevention of maxillary third molar displacement into anatomical cavities can be achieved using distal retractors after the flap has been raised. In the present case, removal of the tooth from the ITF was not particularly difficult through the intraoral incision, as the tooth was immobile due to the presence of the fibrous capsule. We recommend that patients be referred to an oral and maxillofacial surgeon if they experience maxillary third molar displacement into an anatomical cavity.

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MEDICAL RECORDS-International Medical Journal

Olgu Sunumu/ Case Report

Spinal anaesthesia experience in a patient with progressive supranuclear palsy using MAO-B inhibitor

MAO-B İnhibitörü Kullanan Progresif Supranükleer Palsi'li Hastada Spinal Anestezi Deneyimi

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Abstract

Progressive supranuclear palsy (PSP) is a rare clinical syndrome characterized by postural instability and mild dementia. The classical clinical picture of PSP includes severe gait and balance disorder, general bradykinesia, frontal dementia, visual disorders, dysarthria and dysphagia. Aspiration pneumonia is the leading cause of death in advanced PSP. We aimed to present our experiences in a 72-year-old patient with PSP using MAO-B inhibitor as an update for anaesthesiologists. We recommend that it should be taken into consideration that patients with PSP have a high risk of aspiration due to dysphagia and use of various medical treatments with high drug interaction and regional anaesthesia should be preferred. At the same time, we recommend the careful use of opioids during general or regional anaesthesia if the drug cannot be discontinued in patients using MAO-B inhibitor.

Keywords: Progressive supranuclear palsy, MAO-B inhibitor, anaesthesia

Öz

Progresif supranükleer palsi (PSP), postural instabilite ve hafif demans ile karakterize nadir bir klinik sendromdur. PSP'nin klasik klinik tablosunda şiddetli yürüme ve denge bozukluğu, genel bradikinezi, frontal demans, görme bozuklukları, dizartri ve disfaji vardır. Bu hastalarda disfajinin neden olduğu aspirasyon pnömonisi başlıca ölüm nedenidir.
MAO-B inhibitörü kullanan 72 yaşındaki PSP hastasındaki spinal anestezi deneyimlerimizi sunmayı amaçladık. PSP'li hastalarda disfaji nedeniyle aspirasyon riskinin yüksek olması, ilaç etkileşimi yüksek olan çeşitli medikal tedaviler kullanıyor olmalarının göz önünde bulundurulmasını ve anestezi tercihinin rejyonel anesteziden yana yapılmasını önermekteyiz. Aynı zamanda MAO-B inhibitörü kullanan hastalarda eğer ilaç kesilemiyor ise genel ve rejyonel anestezi sırasında opioidlerin dikkatli kullanılmasını önermekteyiz.

Anahtar Kelimeler : Progresifsupranükleer palsi, MAO-B inhibitörü, anestezi

INTRODUCTION

Progressive supranuclear palsy (PSP) is a rare clinical syndrome characterized by postural instability and mild dementia. Its mean onset age is 62, the prevalence is 5-6 people per 100000. Main clinical symptoms are severe gait and balance disorder, general bradykinesia similar to Parkinson's disease, frontal dementia, visual disorders due to vertical gaze palsy, spastic/ataxic dysarthria and dysphagia leading to aspiration. In this picture, especially dysphagia is a very common symptom causing aspiration pneumonia. Aspiration pneumonia is the major cause of death in advanced PSP (1). Anaesthesia management of patients with PSP is important because they use drugs that are likely to interact with anaesthetic and analgesic agents. We aimed to present our experiences in a PSP patient using MAO-B inhibitor as an update for anaesthesiologists.

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CASE REPORT

An emergency operation due to femur fracture was planned for the 72-year-old female patient who was diagnosed with PSP two years ago. She used rasagilin 1 mg/day and had no other systemic disease. She had undergone various operations due to nasal fractures, humerus fracture, and radius fracture because of frequent falls. She had balance and gait disorder, vertical gaze restriction, dysarthria and Parkinsonism as PSP symptoms. She did not have any dementia signs. In the airway examination of the patient, Mallampati score was 2, mouth opening and neck movements were sufficient. The patient was taken on the surgery table and monitored: Arterial blood pressure was 120/70 mmHg, heart rate was 80/min, SpO2 was measured as 97%.

It was decided to apply combined epidural spinal anaesthesia to the patient. After 15 mg hyperbaric bupivacaine was given to subarachnoid space with needle-through-needle method, the epidural catheter was withdrawn due to the intravascular placement and the operation was started with spinal anaesthesia. No sedative agents and opioids were used during the operation. Intermittent oropharyngeal aspiration was performed due to secretion from the rim of the mouth. During the 60-minute-long operation, hemodynamic parameters of the patient were stable. At the end of the operation, she was sent complication-free to the inpatient service. In the service, pain control was provided with intramuscular 75 mg diclofenac and intravenous 1 gr paracetamol.

DISCUSSION

Surgery and anaesthesia are planned in a great majority of PSP patients due to various reasons. Anaesthesia management is important in patients with PSP since there is a possibility of difficult airway, the risk of aspiration pneumonia is high and interaction of the drugs they use with anaesthetic agents.

Emergency surgeries may be required due to the injuries caused by imbalance and frequent falls in patients with PSP. These reasons require keeping the information about anaesthesia management up-to-date in patients with PSP. The presented case had a history of several surgeries due to frequent falls. We performed an emergency operation on the patient with femur fracture due to fall.

In patients with PSP, due to the presence of dysphagia and weak sputum excretion, care should be taken to prevent aspiration pneumonia in perioperative management. Patients under general anaesthesia have higher risk of developing postoperative pulmonary complication than regional anaesthesia (2). Preferring regional anaesthesia to general anaesthesia in patients with PSP may reduce the risk of postoperative pulmonary complications, but it does not eliminate the risk completely (3). In the presented case report, general anaesthesia was not preferred in the patient on whom lower extremity surgery was planned; regional anaesthesia was preferred as anaesthesia management. Despite this, it was found that the patient's swallowing function was insufficient and oropharyngeal secretions were aspired intermittently during the operation.

There is no effective treatment that can fully control PSP symptoms. For this reason, levodopa, benzodiazepines, acetyl cholinesterase inhibitors, antidepressants or treatments for the patient's current symptoms may be preferred (4). Rasagiline and other MAO-B inhibitors are also used in PSP patients due to Parkinsonism signs (5). Care should be taken about the interactions of anaesthetic agents that may be used in these patients due to their various drug uses.

A hypermetabolic state may develop with tremor, sweating, fever, hypertension and tachycardia when MAO-B inhibitors and some opioids are used together. It is recommended to discontinue MAO-B inhibitors 2 weeks before surgery due to their interactions with especially high dose fentanyl and pethidine (6,7). There are also studies which report that in non-cardiovascular surgeries, it is safe to give anaesthesia before MAO-B inhibitor is not discontinued in case of avoiding the known drug interactions (8). In this case report, the drugs were not discontinued since an emergency surgery was planned; therefore, opioid use was avoided. Combined spinal epidural anaesthesia was planned to reduce using postoperative opioids; however, epidural catheter was withdrawn due to intravascular location and the operation was completed with spinal anaesthesia. Postoperative analgesia was provided to the patient with non-steroidal anti-inflammatory drugs.

Another issue that should be paid attention is the possibility of difficult airway in patients with PSP. In addition to studies reporting difficult airway due to cervical contracture, there are also studies which report the difficulty of putting on laryngeal airway mask (9,10). Our patient's preoperative assessment did not have any examination finding that predicted difficult airway and cervical extension was not limited. This may be due to the fact that the patient had been diagnosed for 2 years. Since the operation was continued with regional anaesthesia, an apneic condition that required airway control was not experienced. However, it should be kept in mind that airway management might be difficult in patients with PSP.

CONCLUSION

As a conclusion, we recommend that it should be taken into consideration that patients with PSP have a high risk of aspiration due to dysphagia and use of various medical treatments with high drug interaction and regional anaesthesia should be preferred. At the same time, we recommend the careful use of opioids during general or regional anaesthesia if the drug cannot be discontinued in patients using MAO-B inhibitor.

Financial disclosures: *All authors report no financial interests or potential conflicts of interest.*

Conflict of Interest: *The authors declare that they have no competing interest.*

Informed Consent: *The patient's relatives provided their consent for the publication of the content of this report.*

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