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There are no title and abstract sections. Does not contain figures and tables. It should be stated which article (number, date) is dedicated and the name, institution and address of the author should be found at the end. The reply to the letter is given by the editor or the authors of the article, again published in the journal.

Contents

Editorial

Dear colleagues,

It gives me great pleasure to announce the third issue of Northwestern Medical Journal in 2023, at third year of publication.

We totally have ten scientific articles for you in this issue. Kayılıoğlu et al. reviewed transient loss of consciousness, while Afşin et al. analyzed tuberculosis in patients using biological disease-modifying antirheumatic drugs. Urakçı et al. investigated the factors predicting pathological complete response to neoadjuvant chemotherapy in patients with non-metastatic muscle invasive urothelial bladder cancer. Odabaşı Tezer et al. evaluated dentinal defects after canal root preparation with different rotary and reciprocal systems. Kalyoncuoğlu et al. assessed the hygiene habits and awareness of the removable denture wearer geriatric population. Yabalak studied the efficacy and safety of carotid stenting under ticagrelor and acetylsalicylic acid dual antiplatelet therapy. Yıldız et al. probed the knowledge and awareness of Turkish dentists about temporomandibular disorders. Deniz et al. investigate dthe serum procalcitonin levels in open heart surgery and its relationship with mortality and morbidity. The muscle volumes in COVID-19 penumonia patients were analyzed quantitatively by Kalfaoğlu. Bozkurt Yavuz presented a case report of Rose Bengal test positive Crimean Congo hemorrhagic fever patient.

We sincerely appreciate the valuable input from our readers, authors, reviewers, and publisher. We eagerly anticipate your important contributions to our upcoming issues.

Best regards,
Prof. Ahmet Ural, M.D.
Editor-in-chief

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Original Article

Transient loss of consciousness: Neurally-mediated syncope, psychogenic syncope or epilepsy? A cross-sectional study

Geçici bilinç kaybı: nöral aracılı senkop, psikojenik senkop veya epilepsi? Kesitsel bir çalışma

Hülya Kayılıoğlu, Özlem Yayıcı Köken

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ABSTRACT

Aim: This study aimed to define important clinical and laboratory features that may be useful in the differential diagnosis of pediatric patients who presented with temporary loss of consciousness and in whom cardiac causes had been excluded, especially in the differentiation of convulsive syncope and epileptic seizure.
Methods: The records of patients presenting with temporary loss of consciousness and in whom cardiac causes had been excluded, were retrospectively evaluated. All patients were grouped according to their diagnosis and the data were evaluated comparatively.
Results: Six-hundred-and-twelve patient files were evaluated, and 350 patient files were included in the study. 68.6% of the patients were diagnosed with vasovagal syncope, 13.1% were diagnosed with psychogenic pseudosyncope and 18.2% of the patients were diagnosed with epilepsy. In addition, compared to other subgroups, the patients in the epilepsy group were younger ($p<0.001$), the total number of attacks was lower ($p<0.001$), the attacks lasted longer ($p<0.001$), post-attack symptoms were more common ($p<0.001$), and urinary incontinence and motor movements were more frequent ($p<0.001$).
Conclusion: The incidence of epilepsy was found to be significantly higher than expected in the pediatric patients presenting with transient loss of consciousness without cardiac reasons. Patient age, number and duration of attacks, presence of urinary incontinence and motor movements may also be important in the differential diagnosis of transient loss of consciousness. This study indicates that the management of transient loss of consciousness needs to be tailored to pediatric patients.

Keywords: Epilepsy, syncope, syncope unconsciousness, urinary incontinence, vasovagal

ÖZ

Amaç: Bu çalışmada, geçici bilinç kaybı ile başvuran ve kardiyak nedenler dışlanmış pediatrik hastaların ayırıcı tanısında, özellikle konvülziv senkop ve epileptik nöbet ayrımında yararlı olabilecek önemli klinik ve laboratuvar özelliklerin tanımlanması amaçlanmıştır.
Yöntem: Geçici bilinç kaybı ile başvuran ve kardiyak nedenler dışlanan hastaların dosyaları geriye dönük olarak incelendi. Tüm hastalar tanılarına göre gruplandırıldı ve veriler karşılaştırmalı olarak değerlendirildi.
Bulgular: Altı yüz on iki hasta dosyası değerlendirildi ve 350 hasta dosyası çalışmaya dâhil edildi. Hastaların %68,6'sına vazovagal senkop, %13,1'ine psikojenik psödosenkop ve %18,2'sine epilepsi tanısı konuldu. Ayrıca epilepsi grubunda diğer alt gruplara göre; hastaların daha küçük yaşta olduğu ($p<0.001$), toplam atak sayısının daha az olduğu ($p<0.001$), atakların daha uzun sürdüğü ($p<0.001$), atak sonrası semptomların daha uzun sürdüğü ($p<0.001$), idrar kaçırma ve motor hareketlerin daha sık görüldüğü saptandı ($p<0,001$).
Sonuç: Bu çalışma ile geçici bilinç kaybı ile başvuran kardiyak nedenler dışlanmış pediatrik hastalarda epilepsi insidansı beklenenden oldukça yüksek bulundu. Geçici bilinç kaybının ayırıcı tanısında hastaların yaşı, atak sayısı ve süresi, idrar kaçırma ve motor hareketlerin varlığı açısından sorgulanması önemlidir. Bu çalışma, geçici bilinç kaybı yönetiminin pediatrik hastalara göre uyarlanması gerektiğini açıkça ortaya koymaktadır.

Anahtar kelimeler: Bilinç kaybı, epilepsi, senkop, üriner inkontinans, vazovagal senkop

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INTRODUCTION

Transient loss of consciousness (TLOC) is a common problem in children and adolescents, given the fact that approximately 15% of the population experiences it at least once before the age of 18. Syncope can be defined as TLOC and postural tone due to cerebral hypoperfusion (1).

These patients are often referred to pediatric cardiology and neurology clinics for recurrent syncopal episodes and many tests are performed on these patients (2,3).

The majority of syncope in the pediatric population is related to neurally-mediated syncope (NMS). Vasovagal syncope (VVS) is the most frequent form of NMS (1).

Importantly, the diagnosis of epilepsy can be made in some of the children who are being evaluated for syncope. Therefore, the distinction between NMS and other more serious diseases (eg epilepsy and cardiac diseases) should be carefully made in patients presenting with syncope-like symptoms (4).

Detailed clinical guidelines for syncope have been published. However, there are still difficulties encountered in the diagnosis and patient management (5,6). Many unnecessary tests are being performed to exclude rare important conditions (epilepsy, cardiac causes), and all patients who experience temporary changes in consciousness are referred to the pediatric cardiology and pediatric neurology departments (4).

The difficulty of the differential diagnosis of epilepsy can be better understood when it is considered that convulsive activity can also occur in patients with syncope. It has been reported that 74,000 patients were misdiagnosed with epilepsy in England in 2007 and the coexistence of convulsive syncope and epileptic activity was partly responsible for this situation (7).

This study aimed to define important clinical and laboratory features that may be useful in the differential diagnosis of pediatric patients who presented with temporary loss of consciousness and in whom cardiac causes had been excluded, especially in the differentiation of convulsive syncope and epileptic seizure.

MATERIALS AND METHODS

This is a retrospective study conducted in the department of pediatric neurology. Ethical approval for the study was obtained from the Ethics Committee Number 1 of the Ankara City Hospital (E1-20-577). The study was conducted in accordance with the Declaration of Helsinki.

The files of all pediatric patients who were admitted to pediatric neurology clinics due to TLOC were evaluated. All the patient files evaluated in the study belonged to patients managed and treated by the authors. The inclusion periods were therefore varied.

Files of patients who did not undergo an adequate cardiological evaluation and who were diagnosed or suspected of cardiac syncope were excluded from the study. In addition, files of the patients with known neurological disorders or with insufficient hospital records were also excluded from the study.

Demographic and clinical characteristics and laboratory results of the patients were obtained from the files (Table 1, Table 2).

The American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society 2017 guidelines were used for syncope classification (1).

Initial and serial awake and sleep electroencephalogram (EEG) recordings (obtained with Nihon Kohden -Tokyo, Japan- and Neurosoft -Ivanovo, Russia- using 18 channels with the scalp electrodes distributed according to the 10-20 system) of patients who had motor movements during the episode or post-ictal consciousness changes or had first- or second-degree relatives with epilepsy, were reassessed by two pediatric

neurologists who were blinded to the patients' clinical data. EEG recordings less than 20 minutes were not included in the study.

Normally distributed variables between two independent groups were compared using the Student's t-test. The Mann-Whitney U test was used for the comparisons of non-normally distributed data. Differences in the normally distributed variables among more than two independent groups were analyzed by one-way ANOVA. The Kruskal-Wallis test was used for comparisons of the non-normally distributed data. The post hoc least significant difference or Conover's non-parametric multiple comparison tests were used to determine which group differed from the others.

RESULTS

Six-hundred-and-twelve patient files were evaluated. Three-hundred-fifty patient files were included in the study, considering the exclusion criteria (Figure 1). The mean age of the patients was 147.0 (±50.2) months old and 196 of the patients were girls (56.0%). The neurological examination of all patients was unremarkable.

The patients were categorized into three groups: Vasovagal syncope (VVS), epilepsy and psychogenic pseudosyncope (PPS), and their clinical and laboratory results are presented in Table 1.

Among the patient groups, the epilepsy patients were the youngest, while the PPS patients were

Table 1. Demographic data and clinical findings of the patients.

	VVS (n: 240)	Epilepsy (n: 64)	PPS (n: 46)	P-value
Age (years) (n, %)*				
7–9	63 (26.3%)	23 (35.9%)	1 (2.2%)	
10–14	107 (44.6%)	27 (42.2%)	22 (47.8%)	**0.002[b]**
>15	70 (29.2%)	14 (21.9%)	23 (50%)	
Gender (female/male) (n)*	130/110	26/20	40/24	0.489
Family history of epilepsy (n, %)*	19 (7.9%)	18 (28.1%)	12 (26.1%)	**<0.001[a,b]**
Number of attacks (n, %)*				
1	94 (39.2%)	25 (39.1%)	11 (23.9%)	
2	85 (35.4%)	28 (43.8%)	16 (34.8%)	**<0.001[a,b,c]**
3	38 (15.8%)	8 (12.5%)	2 (4.3%)	
>3	23 (9.6%)	3 (4.7%)	17 (37.0%)	
Time between episodes (days, mean ± SD)[β]	10.6 ± 6.2	24.2 ± 8.7	2.3 ± 1.3	**<0.001[a,b,c]**
Relation with position (n, %)*				
Standing for long periods	175 (72.9%)	7 (10.9%)	6 (13,0%)	
During physical activity	4 (1.7%)	9 (14.1%)	8 (17.4%)	**<0.001[a,b,c]**
Sitting	11 (4.6%)	12 (18.8%)	2 (4.3%)	
Lying down	18 (7.5%)	13 (20.3%)		
Independent of position	32 (13,3%)	23 (35.9%)	30 (65.2%)	
Triggers with emotional and painful stimulus*	203 (84.5%)	3 (4.7%)	40 (86.9%)	**<0.001[a,c]**
Prodromal symptoms (n, %)*	209 (87.1%)	22 (34.4%)	22 (47.8%)	**<0.001[a,b,c]**
Unknown	23 (9.6%)	14 (21.9%)		
Duration of syncopes (n, %)*				
>2 min	8 (10.3%)	24 (75.0%)	7 (35.0%)	**<0.001[a,b,c]**
<2 min	70 (89.7%)	8 (25.0%)	13 (65.0%)	
Urinary incontinence (n, %)*	8 (3.3%)	24 (37.5%)	1 (2.2%)	**<0.001[a,c]**
Seizure-like motor movements (n, %)*	33 (13.8%)	44 (68.8%)	15 (32.6%)	**<0.001[a,c]**
Change in skin color (n, %)*				
Pallor	140 (58.3%)	-	-	
Cyanosis	14 (5.8%)	25 (39.1%)	8 (17.4%)	**<0.001[a,b,c]**
Post-episodic symptoms (n, %)*	24 (10.0%)	35 (54.7%)	9 (19.6%)	**<0.001[a,b,c]**

*Categorical data were described as number of cases (%) and compared using the Pearson's chi-square test or fisher's exact test. * Continuous variables were expressed as either the mean ± SD or the median, and compared using the Kruskal Wallis test[β]. The Conover-Inman test was performed for binary comparisons among the groups and statistical significance was accepted as P < 0.05. Significant differences were found between: a) neurally mediated syncope vs. epilepsy, b) neurally mediated syncope vs. Psychogenic pseudosyncope (PPS) and c) PPS vs. epilepsy. Statistically significant P-values are represented by bold font. VVS:Vasovagal syncope; PPS: Psychogenic pseudosyncope.*

the oldest (p=0.001). The rate of positive family history for epilepsy was similar in the epilepsy and PPS groups (28.1% and 26.1%, respectively), while it was very low in the VVS group (7.9%, p<0.001).

When the total number of episodes (syncope or seizures) since admission was evaluated, it was seen that 95.4% of the epilepsy group, 90.4% of the VVS group, and only 63.3% of the PPS group had three or fewer episodes (p<0.001).

All 64 patients who were diagnosed with epilepsy had abnormal EEG recordings. Considering the clinical features and EEG findings, 57 patients were diagnosed with generalized epilepsy (89.1%), while the remaining seven with focal epilepsy. However, only 35 of the patients who were diagnosed with epilepsy had postictal confusion (54.7%). The remaining patients had suspected convulsive syncope but were diagnosed with epilepsy based on their EEG recordings.

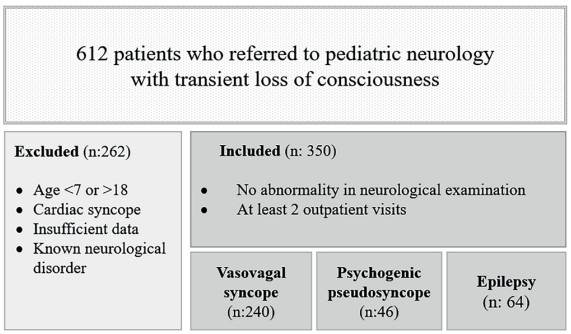

Figure 1. Study flowchart.

Post-episodic symptoms were significantly more common in the epilepsy group (p<0.001). Standing posture during the episode was observed in 72.9% of the patients in the VVS group, and in 10.9% and 13% of the patients in the epilepsy and PPS groups, respectively (p<0.001). VVS was triggered by an emotional or painful stimulus in 84.5% of patients, which is significantly more common in the other groups (p<0.001). The effect of a hot environment was not statistically significant among groups.

In the PPS and VVS groups, episodes were shorter than two minutes in 65% and 89.7% of the patients, respectively, while epileptic seizures were significantly longer than two minutes in 75% of the epilepsy group (p<0.001). Urinary incontinence and motor movements were more frequent during epileptic seizures (p<0.001).

Seizure-like motor movements were more common in the epilepsy group (p<0.001) but these movements were also reported in 32.6% of the PPS patients. Pallor was more common in the VVS group (p<0.001), while cyanosis was more common in the epilepsy group (p<0.001). Only eight patients had changes in skin color in the PPS group (17.4%). Lip and tongue injuries or head trauma during episodes were statistically similar among groups, which were reported in 25% of the epilepsy group, 14.1% of the VVS group, and 10% of the PPS group.

Table 2. Laboratory results of the patients in each group.

	VVS (n: 240)	Epilepsy (n: 64)	PPS (n: 46)	P-value
Hemoglobin (mean ± SD)$^{\beta}$ (mg/dl)	13.5 ± 1.6 (13.60)	13.8 ± 1.1 (13.25)	13.2 ± 1.3 (13.90)	0.809
Hematocrit (mean ± SD)$^{\beta}$ (%)	41 ± 3.9 (38.6)	40.6 ± 3.1 (37.4)	42.1 ± 4.7 (39.4)	0.901
MCV (mean ± SD) $^{\beta}$ (fl)	89.4 ± 68.6 (82.6)	85.6 ± 4.5 (84.9)	82.1 ± 3.9 (79.7)	**0.015**^{b,c}
RDW (mean ± SD)$^{\beta}$ (fl)	14.1 ± 1.3 (13.8)	13.8 ± 0.7 (13.4)	14.7 ± 1.1 (14.4)	**0.011**^{a,c}
Iron (mean ± SD)$^{\beta}$ (µg/dl)	65.2 ± 36.8 (57.0)	71.3 ± 27.7 (71.0)	60.2 ± 36.6 (66.0)	0.411
Ferritin (mean ± SD)$^{\beta}$ (ml/ng)	22.3 ± 17.9 (16.9)	18.7 ± 12.1 (20.0)	9.4 ± 9.3 (7.3)	**0.018**^{a,c}
TSH (mean ± SD)$^{\beta}$ (µU/ml)	2.4 ± 1.6 (2.1)	2.6 ± 1.0 (2.7)	1.6 ± 0.7 (1.5)	**0.020**^{c}
Free T4 (mean ± SD)$^{\beta}$ (pg/ml)	1.3 ± 0.5 (1.2)	3.9 ± 5.6 (1.4)	1.3 ± 0.2 (1.4)	0.089
Vitamin B12 (mean ± SD$^{\beta}$ (pg/ml)	351.1 ± 183.6 (309.0)	340.3 ± 139.3 (280.0)	315.8 ± 90.4 (289.5)	0.573

Continuous variables were expressed as either the mean ± SD or the median, and compared using the Kruskal Wallis test $^{\beta}$ The Conover-Inman test was performed for binary comparisons among the groups and statistical significance was accepted as P < 0.05. Significant differences were found between: a) VVS vs. epilepsy, b) VVS vs. PPS, and c) epilepsy vs. PSS. Statistically significant P-values represented by bold font. MCV: mean corpuscular volume; PPS: Psychogenic pseudosyncope; RDW: red cell distribution width. TSH: thyroid stimulating hormone; VVS:Vasovagal syncope.

Table 2 summarizes the results of the laboratory findings. Ferritin levels were significantly lower in the PPS group and highest in the VVS group (p=0.018).

Cranial magnetic resonance imaging (MRI) was performed in 176 patients to determine the structural etiology of TLOC. However, none of these findings could be associated with the clinical findings.

DISCUSSION

Loss of consciousness in pediatric patients is a major source of concern for the patients and their families, especially until life-threatening causes are ruled out (8).

Clinical guidelines for syncope in pediatric patients should be used routinely (5,6). In a retrospective study, it was shown that the patients were evaluated more systematically and effectively after the use of the diagnostic approach algorithm for syncope in the pediatric emergency department (9). Effective use of guidelines in the emergency department in clinical practice can facilitate patient management.

The most striking finding in our study was that the diagnosis of epilepsy was seen at a rate of 18%. A study on pediatric patients with unknown origin of syncope showed that 4 out of 18 patients (22.2%) were diagnosed with epilepsy at long-term follow-up (10).

All the patients who were diagnosed with epilepsy in our cohort had abnormal EEG recordings. This stresses the importance of the EEG in distinguishing convulsive syncope from epileptic seizure. The American Heart Association recommends EEG recording and monitoring of vital signs at the same time as the tilt test, but does not recommend routine EEG recording in patients whose medical history and physical examination does not indicate neurogenic etiology (1,6). A detailed history is crucial for the evaluation of patients with loss of consciousness. Since younger children may not be able to express the period prior to, during, and after the episode, and the lack of a witness can make it impossible to have a clear understanding of the situation.

Another important issue is how to distinguish convulsive syncope from epileptic seizures based on clinical findings. Although myoclonic jerks in the extremities and locked jaw are common in neurogenic syncope, similar findings can also be observed in other groups due to cerebral hypoxia, which is defined as convulsive syncope. In a previously mentioned study, in which simultaneous EEG recordings were performed with the tilt test, myoclonic jerk was observed in the upper extremities in 25% of the patients during the episode (11). In patients with motor movements, whether these movements occur before or after loss of consciousness is a guide to diagnosis. While motor movements are observed after loss of consciousness in convulsive syncope, motor movements begin simultaneously with loss of consciousness in epileptic seizures (8). Capturing this detail in the patient's history may assist the diagnosis.

Postictal confusion, which is a feature of epilepsy but is absent in convulsive syncope, can also be seen as a key point in making this distinction. One of the interesting findings of our study was that only 54.7% of the epilepsy patients had postictal confusion. The remaining patients were thought to have convulsive syncope initially but were finally diagnosed with epilepsy based on the EEG recordings.

As a result, our study suggests that EEG has an important place in the management of TLOC in the younger age group. For this patient group, it may be necessary to review the EEG indications for future guidelines.

On the other hand, we found that urinary incontinence was significantly higher in the epilepsy group compared to the other groups. The rate of urinary incontinence in non-epileptic patients was found to be around 3%. Additionally,

in another retrospective study, the incidence of urinary incontinence in patients with psychogenic nonepileptic seizures was found to be 12% (12). In our study, this rate was found to be as high as 37.5% in epileptic patients. A pooled analysis of data from the literature showed that the presence of urinary incontinence is not indicative of whether an episode is epileptic (13). However, this may be due to the fact that only patients with loss of consciousness accompanied by motor movements were evaluated in this study.

We found that the patients in the PPS group had significantly lower ferritin levels, lower MCV, and higher RDW. There is not enough information on this in the current medical literature.

Post-episodic neuroimaging was performed in 176 of the patients with a history of TLOC, however, imaging did not provide any specific findings in any of the patients. This again demonstrates that imaging does not contribute to the diagnosis in patients with TLOC and normal neurological examination (14).

The strength of our study is that the number of patients was statistically large enough to easily capture the differences. If the clinical features had been evaluated separately, significant differences between the main causes of TLOC could have been detected. However, the retrospective nature of the study limits the power of the information obtained. Long-term follow-up would be valuable to obtain more accurate clinical results.

In this study, patients between the ages of 7 and 18 with loss of consciousness were evaluated, and the incidence of epilepsy was found to be significantly higher than expected. This result indicates that the management of transient loss of consciousness needs to be tailored to pediatric patients.

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Original Article

Tuberculosis in patients using biological disease-modifying antirheumatic drugs

Biyolojik hastalık modifiye edici antiromatizmal ilaç kullanan hastalarda tüberküloz

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ABSTRACT

Aim: In rheumatic diseases, the possibility of developing tuberculosis (TB) increases due to both the disease itself and the biological disease-modifying antirheumatic drugs (bDMARDs) used for treatment. In our study, we aimed to investigate the causes and risk factors of TB infection in patients using bDMARDs for rheumatological diseases.
Methods: Demographic, radiological, laboratory data, tuberculin skin test (TST) results, duration of disease, and medications used in TB patients were recorded in 531 patients who were using bDMARD with the diagnosis of rheumatologic disease.
Results: TB developed in 5 (0.9%) of 531 patients. TB was detected in 10% of the anakinra users, 2.4% of the infliximab users, 1.4% of the certolizumab users, 1.2% of the etanercept users, and 0.9% of the adalimumab users. The mean duration of bDMARD use until TB development was 28 months. All the cases were female, and the mean age was 53.8 years.
Conclusion: Our study highlights the importance of routine chest X-ray, cervical-supraclavicular lymphadenopathy (LAP) examination, annual TST follow-up, and symptom questioning in TST-negative or anergic patients using bDMARDs.

Keywords: bDMARD, rheumatologic disease, tuberculin skin test, tuberculosis

ÖZ

Amaç: Romatolojik hastalıklarda hem hastalığın kendisi hem de tedavi için kullanılan biyolojik hastalık modifiye edici antiromatizmal ilaçlar (bDMARD) nedeniyle tüberküloz (TB) gelişme ihtimali artmaktadır. Çalışmamızda romatolojik hastalıkları nedeniyle bDMARD kullanan hastalarda gelişen TB enfeksiyonunun nedenlerini ve risk faktörlerini araştırmayı amaçladık.
Yöntem: Romatolojik hastalık tanısıyla bDMARD kullanan 531 hastadan TB gelişenlerde demografik, radyolojik, laboratuar verileri, tüberkülin cilt testi (TST) sonuçları, hastalık süresi ve kullandığı ilaçları kaydedildi.
Bulgular: 531 hastanın 5'inde (0.9 %) TB gelişti. Anakinra kullananların 10%'unda, infliximab kullananların 2.4%'ünde, sertolizumab kullananların 1.4%'ünde, etanercept kullananların 1.2%'sinde ve adalimumab kullananların 0.9%'unda TB saptandı. TB gelişene kadar geçen ortalama bDMARD kullanım süresi 28 aydı. Olguların tamamı kadın ve ortalama yaş 53.8 idi.
Sonuç: Çalışmamız bDMARD kullanan TST negatif veya anerjik olguların rutin akciğer grafisi, servikal-supraklavikular LAP muayenesi, yıllık TST takibi ve semptom sorgulamasının önemini vurgulamaktadır.

Anahtar kelimeler: bDMARD, tüberküloz, romatolojik hastalık, tüberkülin cilt testi

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INTRODUCTION

The suppression of the immune system with the accompanying autoimmune disease or immunosuppressive treatments (such as glucocorticoids or anti-TNF agents) may reactivate silent infections in the granuloma tissue. While there are many studies (1) showing that the risk of infection has increased since the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) for the treatment of rheumatological diseases such as rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA), there are also studies reporting that treatment with bDMARDs does not significantly increase the risk of infection (2). It is also known that autoimmune diseases may increase the risk of infection by causing dysfunction in the immune system (3).

Tuberculosis (TB) is one of the diseases that can affect all organs, most commonly the lungs, and cause significant morbidity and mortality worldwide (4). Latent tuberculosis infection is investigated before giving immunosuppressive treatment in rheumatic diseases. The effects of immunosuppressive treatment and autoimmunity can cause false negative tuberculin skin test (TST) results. Therefore, a negative TST result should be considered suspicious, and these patients should be carefully monitored for atypical TB presentation. Anti-TNF therapy should be avoided until active TB is ruled out or treated if detected (5). This issue is very important, especially in Türkiye where the prevalence of latent TB is high. In our study, we aimed to investigate the causes and risk factors of TB infection in patients using bDMARDs for rheumatological diseases.

MATERIAL AND METHODS

The bDMARDs used by the patients included in our study were: etanercept, adalimumab, infliximab, golimumab, abatacept, rituximab, tocilizumab, certolizumab, secukinumab, and anakinra. Patients using targeted synthetic DMARDs (tofacitinib, baricitinib) were also included in the study. Demographic, radiological, laboratory data, TST test results, duration of disease, and medications used in patients who developed TB among 531 patients reciveing bDMARD treatment with the diagnosis of rheumatological disease in the Rheumatology outpatient clinic between February 2019 and December 2022 were recorded. Approval was obtained from the ethics committee of our institution for our study (no: 2023/28, date: 21.02.2023).

RESULTS

The drug distribution of 531 patients using bDMARD with the diagnosis of rheumatologic disease was as follows; abatacept: 11, adalimumab: 113, baricitinib: 27, etanercept: 85, golimumab: 93, infliximab: 41, rituximab: 39, secukinumab: 66, certolizumab: 73, tofacitinib: 57, tocilizumab: 33, and anakinra: 10 people. Some patients had a history of more than one bDMARD use. The general characteristics of the patients are shown in Table 1.

TB developed in 5 patients (0.9%). TB was detected in 1 (10%) of the anakinra users, 1 (2.4%) of infliximab users, 1 (1.4%) of the certolizumab users, 1 (1.2%) of the etanercept users, and 1 (0.9%) of the adalimumab users. The mean duration of bDMARD use until TB development was 28 months. All the cases were female, and the mean age was 53.8 years. Since the Bacillus Calmette-Guérin (BCG) vaccine was routinely

Table 1. General characteristics of patients using biologic agent therapy.

Age	51 (19-86)
Gender (F/M)	300 /231
Disease duration (years)	8 (1-44)
Diagnosis	**n (%)**
Rheumatoid arthritis	215 (40.5%)
Ankylosing spondylitis	213 (40.1%)
Psoriatic arthritis	33 (6.2%)
Vasculitis	24 (4.5%)
Overlap syndrome	23 (4.3%)
Sjogren's syndrome	6 (0.9%)
Undifferentiated spondyloarthritis	3 (0.6%)
Systemic sclerosis	1 (0.2%)
Other	14 (2.6%)

Table 2. Demographic, laboratory, radiological, and clinical findings of patients diagnosed with tuberculosis.

	Case 1	Case 2	Case 3	Case 4	Case 5
Gender	Female	Female	Female	Female	Female
Age (year)	67	64	69	33	36
Rheumatological disease	RA	RA	Psoriatic Arthritis	Still's Disease	Behcet's Disease
Rheumatological disease duration	6 years	5 years	3 years	1 year	15 years
History of TB	no	no	no	no	no
TB theme	No	no	no	no	no
TST (mm)	2	anergic	anergic	15	2
Chest X-ray before bDMARD	Normal	Normal	Normal	Hilar fullness	Normal
BCG scar	yes	yes	yes	yes	yes
INH prophylaxis	no	no	no	unknown	no
bDMARD	Etanercept	Infliximab	Certolizumab	Anakinra	Adalimumab
bDMARD duration used until TB develops	5 years	4 years	2 months	6 months	2 years
Immunosuppressive drug	sulfasalazine, leflunomide, prednisolone	methotrexate, prednisolone, leflunomide	methotrexate, prednisolone, leflunomide	methylprednisolone	Azathioprine, Cyclosporine, prednisolone
Previous bDMARD use	no	Tofacitinib	no	no	Infliximab
Symptom	cough	no	dyspnea, fatigue	dyspnea	cough, sputum
Radiology in the diagnosis of TB	cavity	cavitary nodule, infiltration	infiltration	normal	Hilar LAP
Diagnostic method	Microbiology (Sputum culture)	Microbiology (Sputum culture)	Microbiology (Gastric lavage)	Pathology (Lymph node biopsy)	Pathology (Lymph node biopsy)
ARB	negative	negative	negative	unknown	unstudied
Mycobacteria culture	reproduction (+)	reproduction (+)	reproduction (+)	unknown	unstudied
Mortality	no	no	yes (1st month)	no	no
Comorbidity	DM, HT, asthma, OSAS	goiter	HT, dementia	HT, CRF	Bipolar

RA: rheumatoid arthritis, TB: tuberculosis, INH: isoniazid, BCG: bacillus Calmette-Guérin, TST: tuberculin skin test, bDMARD: Biological Disease-Modifying Antirheumatic Drug, ARB: acid-resistant bacteria, DM: diabetes mellitus, HT: hypertension, OSAS: obstructive sleep apnea syndrome, CRF: chronic renal failure, LAP: lymphadenopathy.

administered during childhood in Türkiye, all the cases had at least one BCG scar. The clinical findings of each case are shown in Table 2 and presented in detail below.

Case 1, GK

A 67-year-old female patient, who has been followed up with the diagnosis of RA for 6 years, had diabetes mellitus (DM), hypertension (HT), asthma, and severe obstructive apnea syndrome diagnoses. TST of the patient who used prednisolone, leflunomide, and sulfasalazine before using etanercept was evaluated as 2 mm. Isoniazid (INH) prophylaxis was not given to the patient who had a normal chest X-ray and had no TB contact. Since the control TST was anergic 3 years later, it was evaluated as anergic again when the booster reaction test was performed. On a thorax CT taken upon detection of nodules on a chest X-ray during routine control, a 22x23 mm nodule was observed in the middle lobe of the right lung (Figure 1a). The nodule was measured as SUV max 2.0 in PET-CT, and when wedge resection was performed, the pathology was reported as necrotizing granuloma, anthracosis, and rheumatoid nodule. Prednisolone, leflunomide, and etanercept treatment were continued. When the patient was admitted with cough complaints in the 5th year of anti-TNF treatment, centrally located cavitary lesions in the right lung were observed on a thorax CT (Figure 1b), and sputum was negative for acid-resistant bacteria (ARB), but M. tuberculosis reproduction was detected in mycobacterial culture. Anti-tuberculosis (HRZE: isoniazid, rifampicin, pyrazinamide, ethambutol) treatment was started by continuing with

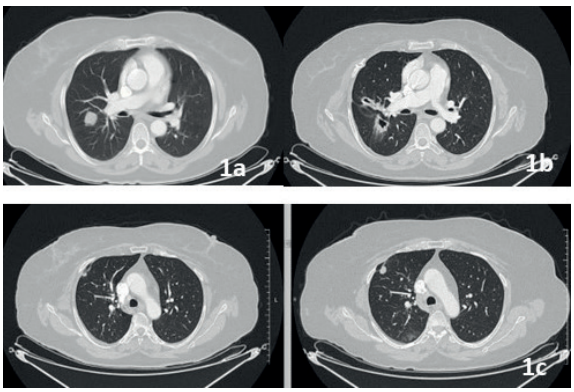

Figure 1. a: 22x23 mm nodule in the middle lobe of the right lung on the thorax CT, b: Cavity lesions on the thorax CT, c: Progression of the peripheral nodule in the right upper lobe on the thorax CT.

prednisolone, one of the rheumatic drugs. A transthoracic tru-cut biopsy was performed 1 year after the end of the treatment due to the detection of the progression of the peripheral nodule in the right upper lobe on a thorax CT during the follow-up (Figure 1c). A transthoracic fine needle biopsy was performed but was not diagnostic; therefore, wedge resection was performed, and the pathology result was reported as granuloma with caseification necrosis. However, rituximab and steroid treatment were continued, considering that the patient had no clinical complaints, CRP and sedimentation were normal, and sputum ARB was negative, considering that it might be secondary to tuberculosis infection of the granuloma tissue.

Case 2, SE

A 64-year-old female patient had been followed up with the diagnosis of RA for 5 years and had goiter as an additional disease. INH prophylaxis was not used because the patient who used tofacitinib for 4 years was found to have anergic TST two times. Prednisolone 10 mg and leflunomide were also continued. It was learned that the patient had previously used methotrexate and discontinued the drug. Since the patient's arthritis was not under control, infliximab and methotrexate treatments were started. The patient, whose TST was performed twice before, was anergic, and had a normal chest X-ray, and had no TB contact. After 7 months, during the routine control, an increase in density in the bilateral middle-upper zone (Figure 2a) was observed in the chest X-ray, a nodule in the right upper lobe, and a cavitary nodule in the left upper lobe, and consolidation (Figure 2b) was observed in the thorax CT. Sputum was ARB negative and M. tuberculosis reproduction was detected in mycobacteria culture. The patient was given anti-tuberculosis (HRZE) treatment. Sulfasalazine and prednisolone treatments were also continued. After the completion of TB treatment, nodules developed in the lung, rituximab treatment was started, and the nodular lesions regressed completely (Figure 2c).

Case 3, HB

A 69-year-old female patient had been followed up with the diagnosis of psoriatic arthritis for 3 years and also had HT and dementia. The patient was treated with prednisolone and methotrexate, and leflunomide was started 6 months ago. As the patient did not tolerate leflunomide treatment, she was switched to certolizumab treatment. It was observed that the patient, who was anergic to the TST before, was again anergic when the TST was repeated with the booster reaction. INH prophylaxis was not given to the patient who had no pathology in the chest X-ray and had no TB contact. Since the patient who did not follow the treatment regularly complained

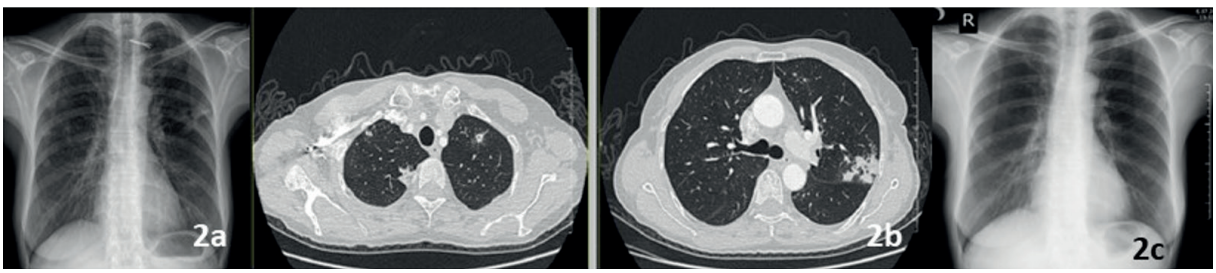

Figure 2. a: Density increase in bilateral mid-upper zone on chest X-ray, b: Nodule in the right upper lobe, cavitary nodule in the left upper lobe, and consolidation in thorax CT, c: Nodules are observed to regress in chest X-ray control.

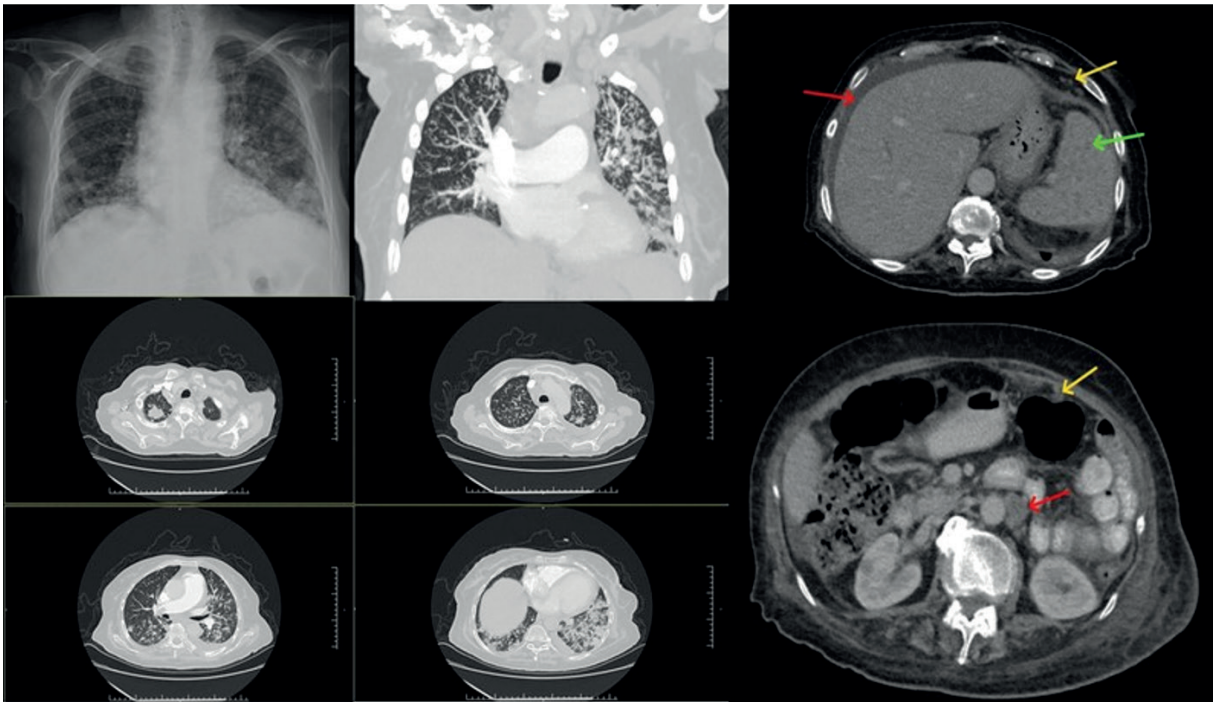

Figure 3. Diffuse nodular and infiltrative lesions on the thorax CT, paraaortic LAP, ascites, pulmonary embolism, and multiple lesions in the spleen.

of weakness and dyspnea, newly developed widespread nodular and infiltrative lesions, paraaortic lymphadenopathy (LAP), ascites, pulmonary embolism, and multiple lesions in the spleen were observed in the thorax CT taken (Figure 3). ARB was negative in the gastric lavage taken from the patient, who did not produce sputum. When the biopsy was taken from the supraclavicular lymph node, granuloma structure, including caseification necrosis, was observed in the pathology. Anti-tuberculosis (HRZE) treatment was started due to the reproduction of M. tuberculosis in the mycobacteria culture. The patient with involvement in the peritoneum, spleen, lung, and lymph nodes was evaluated as having multisystemic TB. The patient, who was intubated in the intensive care unit due to the development of respiratory failure during his follow-up, died.

Case 4, MO

A 33-year-old female patient was being followed up with the diagnosis of adult-onset Still's disease, and her comorbidities were HT and end-stage chronic renal failure (CRF). She had used glucocorticoids and anakinra for a year. Two years ago, endobronchial ultrasound (EBUS) was performed with the preliminary diagnosis of intermittent fever, some calcified lymphadenomegaly on a thorax CT, and a right hilar mass. The patient, who developed a complication of hemopneumothorax during the procedure and had an arrest, responded to cardiopulmonary resuscitation. TST was performed on the patient in an external center whose lymph node biopsy result was reported as benign: TST was recorded as 15 mm, but INH usage information could not be obtained. Latent TB screening is also not recommended for anakinra use by the local health committee of our country. Right supraclavicular lymphadenomegaly was detected in thorax CT, which was requested due to right supraclavicular fullness during routine control in the 1st year of

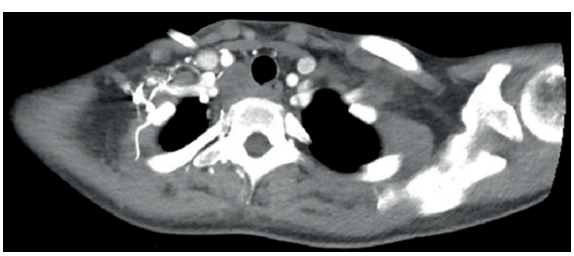

Figure 4. Right supraclavicular lymphadenomegaly on the thorax CT.

anakinra treatment (Figure 4). A fine-needle aspiration biopsy performed on the lymph node was reported as a granulomatous infection with caseification. The patient was started on anti-tuberculosis treatment, and anti-rheumatic drugs were discontinued. During this period, no major problems were encountered, except for mild adult Still's disease attacks.

Case 5, GU

A 36-year-old female patient, who has been followed up with the diagnosis of Behcet's disease for 15 years, had no comorbidities other than bipolar personality disorder. The patient was followed up with azathioprine and cyclosporine, and because of the development of macular edema and ischemic optic neuropathy in the right eye, a pulse steroid was administered. However, due to the inability to control her complaints, she was started on infliximab treatment. The TST before the treatment was 2 mm, and the chest X-ray was normal. Due to the development of toxic hepatitis 15 days after the treatment, adalimumab treatment was started. A max diameter of 14 mm mediastinal LAP was detected in the thorax CT taken after the right hilar fullness was observed in the chest X-ray in the routine control 1 year later (Figure 5a). PET-CT was requested, but the patient did not come to the control visits. In PET-CT taken 1 year later, lymphanetopaties in the anterior mediastinum, prevascular area, and subcarinal area (SUV max 11.2) and supraclavicular 2.5 cm LAP (SUV max 19.2) were observed (Figure 5b). The patient, who had cough and sputum complaints for 1 month, underwent a biopsy of the supraclavicular lymph node. As a result, granuloma with caseification formed by epithelioid histiocytes and Langerhans-type giant multinuclear cells was detected. Renal dose anti-TB treatment was started. The patient, who completed the anti-TB treatment, is being followed up in our rheumatology clinic.

DISCUSSION

In patients with rheumatic disease using anti-TNF therapy, the average TB incidence is 9.62 cases per 1000 patients in all countries (6). Similar to this result, in our study, the overall TB incidence was 0.9%. TB development was observed with anakinra (10%), infliximab (2.4%), certolizumab (1.4%), etanercept (1.2%), and adalimumab (0.9%) of bDMARDs. The patient using infliximab had used tofacitinib, and the patient using adalimumab had previously used infliximab. Bongartz et al.[7] analyzed randomized controlled trials of infliximab and adalimumab and reported a significant increase in the risk of infection. On the contrary, meta-analyses evaluating patients treated with adalimumab, etanercept, infliximab, rituximab, abatacept, and anakinra concluded that the risk of severe infection did not increase (8-10). In the study by Alaşan et al.[11] conducted in Türkiye, it was reported that TB developed in 2 cases (1.8%) due to the use of etanercept and infliximab among 110 patients who were under anti-TNF therapy. Since mycobacterial infections have been reported very rarely in patients receiving rituximab, there is no recommendation to screen for latent TB before using rituximab

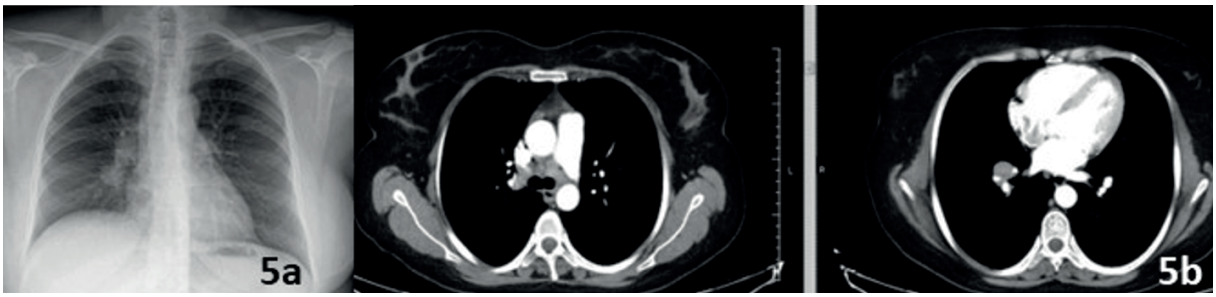

Figure 5. a: Newly formed right hilar fullness on chest X-ray, b: In the PET-CT, In the anterior mediastinum, prevascular area, subcarinal, and supraclavicular LAP is observed.

treatment (12). In our country, screening for latent TB is not recommended before the use of Anakinra. In our study, it was observed that TB developed in one patient after the use of anakinra. This case was investigated in a different institution for the investigation of the etiology of the LAP, but TB could not be completely excluded.

Among the immunosuppressive agents, glucocorticoids increase the risk of infection the most (13). Delayed addition of bDMARDs to treatment leads to longer duration and higher dose use of glucocorticoids, and secondary to this, an increase in severe infection rates may occur (2,3). In this paper, 4 of our 5 cases had glucocorticoid use. Pulse steroid was used in one of these cases. Anakinra and TNF inhibitors are associated with an increased risk of infection compared to conventional DMARDs, especially in the early stages of treatment. The most common sites of infection are the respiratory tract, skin, soft tissue, and urinary tract. The risk of TB has been reported to be higher with TNF inhibitors (especially infliximab) than with traditional DMARDs (14).

Since the effects of immunosuppressive therapy and autoimmunity may cause false negative TST results, a negative TST result should be considered suspicious, and these patients should be followed for an atypical TB presentation closely (15). Since isoniazid is a hepatotoxic drug, a preventive treatment can be avoided in countries with low TB prevalence. However, in countries with a high prevalence of latent TB, such as our country, if we do not treat latent TB, disseminated disease may develop that may be resistant to treatment due to TNF blockers (5). TST was anergic or negative, except for case number 4. No positivity was achieved with the booster reaction either. Interferon-gamma release assay (IGRA) tests were not performed in any of the patients. All of our cases had BCG vaccination scars, and there was no previous TB history or TB contact. However, case number 4 had hilar LAP; therefore, EBUS was performed and no TB was detected. Although respiratory symptoms suggest the diagnosis of TB presence in most of our cases, we also had a case that was detected only by chest X-ray in the routine control. This result draws attention to the importance of routine check-ups every six months and good questioning of pulmonary symptoms.

TB tends to be extrapulmonary and systemic in immunosuppressive patients. However, there is also data showing that the pulmonary form is dominant (6). The disease progressed with pulmonary involvement in 2 of our 5 cases, lymph nodes in two, and multisystemic involvement in one patient. It is recommended to carefully evaluate especially newly formed nodules, cavitation, and hilar enlargement in the chest X-rays of patients who are using bDMARDs and to palpate accessible lymph nodes, especially cervical-supraclavicular LAP, keeping in mind extrapulmonary TB. As in our case with multisystemic TB, other organ involvements should be evaluated with a prediagnosis of TB. The sensitivity of ARB microscopy is low (50-60%), and it decreases distinctly in patients who are co-infected with human immunodeficiency virus (HIV), in children, and in patients with non-pulmonary TB (16). The method accepted as the gold standard in the diagnosis of TB is mycobacterial culture, which requires an incubation period of 6-8 weeks. In 3 of our cases, growth was detected in mycobacterial cultures despite ARB negativity. Therefore, although ARB negativity is detected in patients using bDMARD therapy, the result of the mycobacterial culture should be expected in cases of suspected TB.

It is known that additional diseases such as chronic obstructive pulmonary disease, chronic kidney diseases, and DM increase the risk of infection in patients with rheumatic diseases (3). In our study, there were comorbidities such as DM, asthma, and CRF. In general, it is known that patients with psoriatic arthritis, ankylosing spondylitis, and primary Sjögren's syndrome are relatively younger, have fewer comorbidities, and are generally treated with fewer immunosuppressive treatments than RA patients (17). For these reasons, TB development

can be expected to be less common in this group of patients. However, data show that there is no difference in the incidence of TB between different rheumatic diseases in which patients receive anti-TNF agents (6). Two of our cases also had RA. The mean duration of rheumatologic disease was 6 years. The duration of bDMARD use until the development of TB is 28 months, and it has been reported in the literature that TB develops in the first 20th month in most cases (6).

Our limitations include the lack of information about the comorbidities and other immunosuppressive treatments of patients using bDMARDs and the unequal distribution of patients using bDMARDs. However, our study on cases highlights what should be considered regarding TB development in bDMARD use.

CONCLUSION

TB development was observed with bDMARDs infliximab, certolizumab, etanercept, anakinra, and adalimumab. Since the duration of bDMARD use until the development of TB is 28 months, routine chest X-rays, cervical-supraclavicular LAP examinations, annual TST follow-up, and symptom examinations should not be avoided, especially in TST-negative or anergic cases.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Clinical Research Ethics Committee Ethics Committee (21.02.2023 / 2023/28).

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Original Article

Factors predicting pathological complete response to neoadjuvant chemotherapy in patients diagnosed with non-metastatic muscle invasive urothelial bladder cancer

Non-metastatik kasa invaze ürotelyal mesane kanseri tanılı hastalarda neoadjuvan kemoterapiye patolojik tam yanıtı predikte eden faktörler

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ABSTRACT

Aim: In this study, we aimed to investigate the factors that may have the potential to predict pathological complete response (pCR) with platinum-based neoadjuvant chemotherapy (NAC) in non-metastatic muscle-invasive bladder cancer (MIBC).
Methods: Our study included 46 patients diagnosed with non-metastatic MIBC, who applied to Dicle University Medical Oncology Clinic between 2016-2019 years and received NAC. Age, gender, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node (cN) status, localization of the primary tumor in the bladder, presence of comorbid diseases, renal failure status, hydronephrosis, and NAC regimens were analyzed.
Results: Of the total 46 patients included in the study, 42 (81.3%) were male and 4 (8.7%) were female. The median age at diagnosis was 61.5 (34-77) years. In the group of patients aged <65 years, pCR was achieved in 9 patients (33.3%) and pCR was not achieved in 18 patients. The rate of pCR after NAC in the patient group aged <65 years was higher than in the age ≥65 group, which was statistically significant (p: 0.03). While the median disease-free survival (DFS) was not reached in the pCR arm, the median DFS was calculated as 26 months (95% CI: 4.6-47.3) in the non-pCR arm (Log Rank p=0.23). The mean overall survival (OS) value in the pCR arm was 126 months (95% CI: 106.5-145.4) and the mean OS value in the non-pCR arm was 53.5 months (95% CI: 44.2-62.9) (Log Rank p=0.05).
Conclusion: In our study, age <65 years was found to be an independent prognostic factor for pCR in the neoadjuvant treatment of non-metastatic MIBC. Mean OS was better in patients who achieved pCR.

Keywords: Bladder cancer, neoadjuvant chemotherapy, pathological complete response

ÖZ

Amaç: Bu çalışmada, metastatik olmayan kasa invaze mesane kanserinde (KİMK) platin bazlı neoadjuvan kemoterapi (NAK) ile patolojik tam yanıtı (pTY) predikte etme potansiyeli olabilecek faktörleri incelemeyi amaçladık.
Yöntem: Çalışmamıza 2016-2019 yılları arasında Dicle Üniversitesi Tıbbi Onkoloji Kliniği'ne başvuran metastatik olmayan KİMK tanılı ve NAK alan 46 hasta dahil edildi. Hastaların yaş, cinsiyet, ECOG performans skoru, tümör gradı, patolojik tümör (pT) evresi, klinik lenf nodu (kN) durumu, primer tümörün mesanedeki lokalizasyonu, komorbid hastalık varlığı, böbrek yetmezliği durumu, hidronefroz olup olmaması ve hastaların aldıkları neoadjuvan kemoterapi rejimleri incelendi.
Bulgular: Çalışmaya alınan toplam 46 hastanın 42'si (%81.3) erkek ve 4'ü (%8.7) kadındı. Medyan tanı yaşı 61.5 (34-77) yıl idi. Yaş <65 olan hasta grubunda 9 hastada (%33.3)

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pTY sağlanırken 18 hastada ise pTY sağlanamamıştı. Yaş <65 olan hasta grubunda NAK sonrası pTY sağlanma oranı; yaş ≥65 olan hasta grubuna göre daha yüksek olup bu istatiksel olarak anlamlıydı (p: 0.03). pTY kolunda medyan hastalıksız sağkalıma (HSK) ulaşılamamışken, pTY sağlanamayan kolda medyan HSK 26 ay (95% CI: 4.6-47.3) olarak hesaplandı (Log Rank p=0.23). pTY kolunda ortalama genel sağkalım (GSK) değeri 126 ay (95% CI: 106.5-145.4), pTY sağlanamayan kolda ortalama GSK değeri 53.5 ay (95% CI: 44.2-62.9) olarak hesaplandı (Log Rank p=0.05).
Sonuç: Çalışmamızda metastatik olmayan KİMK'nin neoadjuvan tedavisinde yaşın <65 yıl olması pTY için bağımsız bir prognostik faktör olarak tespit edildi. Ortalama GSK, pTY sağlanan hastalarda daha iyiydi.

Anahtar kelimeler: Mesane kanseri, neoadjuvan kemoterapi, patolojik tam yanıt

INTRODUCTION

Bladder cancer is the second most common urological cancer. At the time of diagnosis, approximately 30% of patients have muscle-invasive bladder cancer (MIBC) (1). Currently, the standard treatment of MIBC is radical cystectomy (RC) and pelvic lymph node dissection after neoadjuvant chemotherapy (NAC). Although local control of the disease is achieved with only RC and pelvic lymphadenectomy, the disease recurs in approximately 40% of patients within 5 years after surgery (2). The most common cause of recurrence is the presence of clinically undetectable micrometastases. Randomized clinical trials have shown that the use of NAC in MIBC provides tumor downstage, eradicates micrometastases, and increases survival (3,4). In a meta-analysis of these clinical trials, it was reported that platinum-based NAC contributed an additional 5% to 5-year survival (5). This survival benefit was especially higher in the group of patients who achieved pathologic complete response (pCR) with NAC and, the pCR rate in cystectomy material after platinum-based NAC was reported to be around 38% (3). In addition, since RC is a morbid surgery, the bladder-sparing approach can be offered in selected patient groups in whom pCR can be reached with NAC. For these reasons, platinum-based NAC is recommended as a standard treatment for MIBC in platinum-eligible patients (6). However, in case of chemotherapy resistance, NAC may predispose patients to side effects and may also increase the risk of disease progression. Therefore, clinically useful predictive markers that can predict NAC response in patients with MIBC are needed. Although many studies have focused on various factors such as demographic characteristics, disease stage, tumor-related molecular factors, and tumor microenvironment that may predict NAC response, factors that may accurately predict NAC response have not been identified to date (7). In this study, we aimed to investigate the factors that could potentially predict pCR to platinum-based NAC in muscle-invaded urothelial bladder cancer.

MATERIALS AND METHODS

In our study, the files of 244 patients who were admitted to Dicle University Medical Oncology Clinic between 2016 and 2019 years and diagnosed with urothelial bladder cancer were analyzed. The study included 46 patients who were diagnosed with non-metastatic MIBC and received NAC. Patient files were retrospectively analyzed through the hospital's data processing system. All participants were evaluated before NAC and selected from patients who could undergo curative cystectomy. Urothelial bladder cancer was diagnosed by histopathologic examination of the tissue obtained by transurethral resection of bladder tumor (TURBT). Age, gender, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node status (cN), localization of the primary tumor in the bladder, presence of comorbid diseases, renal failure status, hydronephrosis, and NAC regimens were analyzed. Clinical staging at diagnosis and response evaluation after NAC was performed by Positron Emission Tomography/Computed Tomography (PET/CT) or computed tomography (CT) and bone scintigraphy in cases with suspected bone metastases. All patients included in the study were ≥pT2 and/or ≥cN1 and M0. Patients with no residual tumor in the cystectomy material or lymph nodes after NAC were considered pCR (ypT0N0). Tumor grade and pathological staging were determined according to the American Joint Committee on Cancer (AJCC) 8th version of TNM

staging. Patients who received chemotherapy for less than 2 cycles, had metastatic disease at the end of chemotherapy, or received radiotherapy for other reasons were excluded. As NAC, cisplatin/gemcitabine (cisplatin 75 mg/m^2 on day 1 and gemcitabine 1,000 mg/m^2 on days 1 and 8) or carboplatin/gemcitabine [carboplatin AUC(4-6) on day 1 and gemcitabine 1,000 mg/m^2 on days 1 and 8] regimens were administered at 21-day intervals. Patients with a solitary kidney, chronic renal insufficiency (creatinine clearance <50 mL/min), or cardiac ejection fraction (EF) of 50% or less received carboplatin instead of cisplatin. In the case of grade 3-4 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, dose adjustment was made or chemotherapy was postponed. Radiological response evaluation was performed after three cycles of chemotherapy.

Statistical analysis

PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, USA) program was used for statistical evaluation of the data. Complementary statistics were used to evaluate patient characteristics and parameter frequencies, and Kaplan-Meier survival analysis was employed for survival analysis. The log-rank P value was used as the basis. Cox regression analysis was utilized for univariate analysis in survival analysis. The confidence interval of 95% and p-significance value <0.05 were accepted.

RESULTS

Of the 46 patients included in the study, 42 (81.3%) were male and 4 (8.7%) were female. The median age at diagnosis was 61.5 (34-77) years. Twenty-seven patients (58.7%) were <65 years old and 19 (41.3%) were ≥65 years old. The baseline characteristics of the patients are shown in Table 1. Patients with and without pCR with NAC were analyzed in terms of gender, age (<65; ≥65), ECOG performance status (PS) (<1; ≥1), tumor T stage (T2; >T2), lymph node status (N0; N+), presence or absence of comorbid diseases, renal failure, hydronephrosis, tumor localization (localized; diffuse), and tumor grade (low; high). In the patient group aged <65 years, pCR was achieved in 9 patients (33.3%), while pCR was not achieved in 18 patients. In contrast, in the patient group aged ≥65 years, pCR was achieved in 1 patient (5.3%) and was not achieved in 18 patients (94.7%). The rate of pCR after NAC was higher in patients aged <65 years than in patients aged ≥65 years, and this was statistically significant (p:0.03) (The relationship between pathological complete response and clinical characteristics is shown in Table 2). As

Table 1. Basal characteristics of the patients.

	All patients, n=46 (%)
Age (median, range) years	61.5 (34-77)
ECOG PS	
0	12 (26.1)
1	30 (65.2)
2	4 (8.7)
T stage	
T2	30 (65.2)
T3	12 (26.1)
T4	4 (8.7)
N stage	
N0	20 (43.5)
N1	9 (19.6)
N2	15 (32.6)
N3	2 (4.3)
Comorbid disease	
No	18 (39.1)
Yes	28 (60.9)
Renal failure	
No	29 (63)
Yes	17 (37)
Hydronephrosis	
No	30 (65.2)
Yes	16 (34.8)
Neoadjuvant regimens	
Gem+cisplatin	39 (84.8)
Gem+carboplatin	7 (15.2)
Tumor localization	
Lateral wall	16 (34.7)
Front wall	11 (23.9)
Back wall	7 (15.2)
Trigon zone	2 (4.3)
Diffuse	10 (21.7)
Tumor grade	
Low	6 (13)
High	40 (87)

ECOG: Eastern Cooperative Oncology Group, PS: performance status, Gem: gemcitabine

Table 2. Relationship of pathological complete response with clinical features.

	All patients, n=46(%)	Complete response received, n(%)	No complete response received,n(%)	P value
Gender				1.00*
Female	4 (8.7)	1 (25)	3 (75)	
Male	42 (81.3)	9 (21.4)	33 (78.6)	
Age				**0.03***
<65	27 (58.7)	9 (33.3)	18 (66.7)	
≥65	19 (41.3)	1 (5.3)	18 (94.7)	
ECOG PS				0.98*
<1	12 (26.1)	5 (41.7)	7 (58.3)	
≥1	34 (73.9)	5 (14.7)	29 (85.3)	
T stage				0.074*
T2	30 (65.2)	4 (13.3)	26 (86.7)	
>T2	16 (34.8)	6 (37.5)	10 (62.5)	
N stage				0.71*
N0	18 (39.1)	3 (16.7)	15 (83.3)	
N+	28 (60.9)	7 (25)	21 (75)	
Comorbid disease				0.48*
No	18 (39.1)	5 (27.8)	13 (72.2)	
Yes	28 (60.9)	5 (17.9)	23 (82.1)	
Renal failure				0.28*
No	29 (63)	8 (27.6)	21 (72.4)	
Yes	17 (37)	2 (11.8)	15 (88.2)	
Hydronephrosis				0.45*
No	30 (65.2)	8 (26.7)	22 (73.3)	
Yes	16 (34.8)	2 (12.5)	14 (87.5)	
Neoadjuvant regimens				0.31*
Gem+cisplatin	39 (84.8)	10 (25.6)	29 (74.4)	
Gem+carboplatin	7 (15.2)	0 (0)	7 (100)	
Tumor localization				1.00*
Local	36 (78.3)	8 (22.2)	28 (77.8)	
Diffuse	10 (21.7)	2 (20)	8 (80)	
Tumor grade				0.10
Low	6 (13)	3 (50)	3 (50)	
High	40 (87)	7 (17.5)	33 (82.5)	

ECOG: Eastern Cooperative Oncology Group, PS: performance status, Gem: gemcitabine, (*): Fisher's exact test

Table 3. Univariate and multivariate analysis results of the relationship between pCR and clinicopathological parameters.

Parameters	Reference/risk	Univariate analysis			Multivariate analysis		
		OR	95% CI	P	OR	95% CI	P
Age	<65/≥65	**9.00**	**1.03-78.5**	**0.04**	**9.00**	**1.03-78.6**	**0.04**
Gender	Female/Male	1.22	0.11-13.20	0.86			
T stage	T2/>T2	0.25	0.60-1.10	0.68			
N stage	N0/N+	0.60	0.13-2.70	0.50			
Renal failure	No/Yes	3.00	0.33-27.05	0.32			
Comorbidity	No/Yes	1.76	0.43-7.27	0.42			
Neoadjuvant regimen	Gem-Cis/Gem-Carbo	5.57	0.00 - ---	0.99			

Gem; gemcitabine, Cis;cisplatin, Carbo;carboplatin, OR; odds ratio, CI: confidence interval

a neoadjuvant treatment regimen, 2/27 (7.4%) of patients aged <65 years and 5/19 (26.3%) of patients aged ≥65 years received gemcitabine + carboplatin. The remaining patients received gemcitabine + cisplatin therapy. Although the two groups were numerically different in terms of the treatment regimens they received, they were statistically similar (p=0.079). In the multivariate

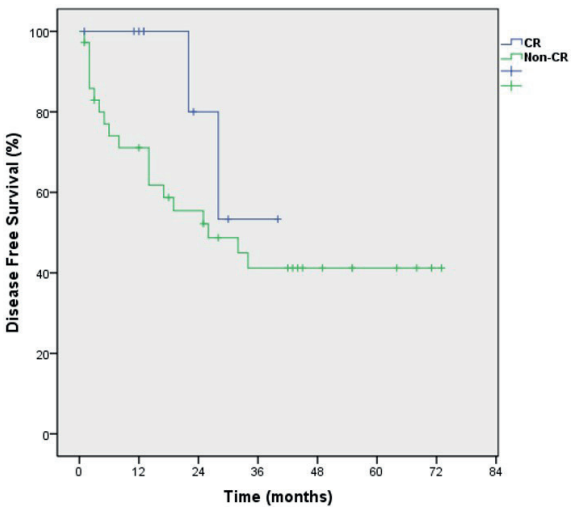

Figure 1. Association between pCR and DFS - Kaplan Meier survival plot.

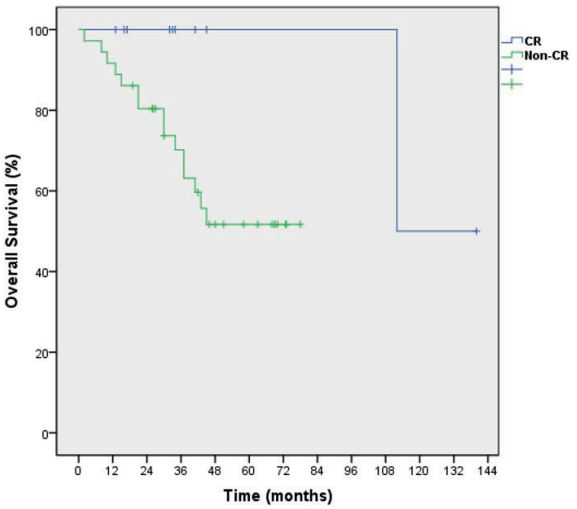

Figure 2. Relationship between pCR and OS – Kaplan Meier survival plot.

and univariate analysis, no statistically significant difference was found between the pCR and non-pCR groups in terms of other parameters except for age (univariate and multivariate analysis results are shown in Table 3). While the median disease-free survival (DFS) was not reached in the pCR arm, the median DFS in the non-pCR arm was calculated as 26 months (95% CI: 4.6-47.3) (Log Rank p=0.23). For all patients, the median DFS was 32 months (95% CI: 21-42.9) (Figure 1). The median overall survival (OS) was not reached in either group. The mean OS was 126 months (95% CI: 106.5-145.4) in the pCR arm and 53.5 months (95% CI: 44.2-62.9) in the non-pCR arm (Log Rank p=0.05) (Figure 2).

DISCUSSION

Muscle-invasive bladder cancer is an aggressive cancer with a poor prognosis. The treatment for MIBC is RC and pelvic lymph node dissection after NAC. In patients who underwent only RC and pelvic lymphadenectomy, 5-year OS rates vary between 25-77% (8). Studies have shown that platinum-based combined NAC given before RC contributes 5-7% to 5-year survival compared to cystectomy alone. This survival advantage was attributed to the eradication of micrometastases by chemotherapy (9). In randomized controlled trials, 5-year survival rates were reported to be approximately 80-90% in patients with no residual muscle-invasive disease after platinum-based combined NAC, while this rate was reported to be between 30-40% in patients with residual disease (10). Current cancer guidelines recommend the use of NAC before cystectomy with a strong level of evidence due to its survival advantage (6). Despite the advantages of NAC, there are concerns that curative surgery may be delayed and surgical complications may increase due to side effects of chemotherapy (11).

Urothelial bladder cancer is one of the most sensitive tumors to cisplatin-based combination chemotherapy. Ineligibility for cisplatin is a negative prognostic factor for NAC outcomes (12). Although there have been studies on the use of carboplatin in the neoadjuvant treatment of urothelial bladder cancer, data on this subject are limited (13). Carboplatin is not recommended for neoadjuvant use except in cases where cisplatin cannot be used because it is less efficient than cisplatin. In cases where NAC is indicated, if cisplatin-based NAC cannot be given, it is recommended to perform surgery first and then give adjuvant chemotherapy (14). One of the neoadjuvant chemotherapy regimens is the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), which has significantly more activity than single-agent chemotherapy. The combination of gemcitabine and cisplatin has similar efficacy

to the MVAC regimen, and both regimens are currently accepted as appropriate options for the neoadjuvant treatment of MIBC (15). In the study by Galsky et al.[16], the pCR rates with MVAC and cisplatin/gemcitabine were 29% and 31%, respectively, and no significant difference was found between the two regimens. Yuh et al.[17] found a pCR rate of 25.6% with neoadjuvant cisplatin/gemcitabine. Peyton et al.[18] found a pCR rate of 41.3% with dose-dense MVAC and 24.5% with cisplatin/gemcitabine. In the study by Schinzari et al.[19], the pCR rates of cisplatin/gemcitabine and carboplatin/gemcitabine regimens were similar. This study stated that carboplatin may be preferred for NAC in patients who are not eligible for cisplatin. In our study, pCR was achieved in 10 of 46 patients (21.7%) who received NAC. As NAC regimens, 39 (84.8%) patients received cisplatin/gemcitabine and 7 (15.2%) patients received carboplatin/gemcitabine. In our study, we did not find a statistical difference between the two chemotherapy regimens in terms of pCR (p=0.31).

In the combined analysis of the Nordic studies evaluating NAC responses, achievement of downstage with NAC was reported as a marker for survival and the 5-year survival rate was 88.2% in patients who achieved pCR with NAC (20). In the SWOG 8710 (Southwest Oncology Group) study, which is one of the pivotal neoadjuvant phase 3 studies, Grossmann et al.[3] reported a pCR rate of 38% and a 5-year overall survival rate of 85% in the patient group who received neoadjuvant MVAC chemotherapy. In this study, median survival was 77 months in the pCR group and 46 months in the non-pCR group. Petrelli et al.[21] reported that the mortality rate was 55% lower and the risk of disease recurrence was 81% lower in patients with pCR compared to the group without pCR. In our study, median DFS was similar in the group with and without pCR (p=0.23). Mean OS was longer in patients with pCR and was statistically borderline significant (p=0.05).

There are several clinical and pathological factors that may determine the NAC response in urothelial bladder cancer. Evidence on the benefit of NAC in histologic variants other than urothelial bladder cancer is limited. While NAC is recommended in small-cell histology, the benefit of NAC in the micropapillary variant is unclear. Surgery is primarily recommended for the subtypes of squamous cell carcinoma, adenocarcinoma, and sarcomatoid bladder cancer (22). Pokuri et al.[23] evaluated factors such as age, tumor histology, clinical T stage (T3-T4), hydronephrosis, and type of chemotherapy in terms of pCR response in bladder cancer patients receiving NAC. Among these factors, only the histological subtype of the tumor was found to be a predictive factor for pCR. In this study, a higher pCR rate was found in pure urothelial histological subtypes compared to mixed histological subtypes. In another study evaluating pCR response to NAC in MIBC, higher pCR rates were found in patients with hemoglobin ≥ 13 (g/dl), absence of hydronephrosis, age ≤ 75 years, absence of lymphovascular invasion (LVI) at TURBT, pT2 versus ≥ pT3 and cN0 versus cN+. However, no statistically significant correlation was found between smoking history, gender, race, alkaline phosphatase, Charlson comorbidity score, weight loss percentage, chemotherapy type, split dose chemotherapy, cumulative dose of cisplatin, and pCR (24).

Studies have indicated that advanced age is an indicator of both a low pathologic response and the inability of patients to tolerate NAC. It has also been shown that advanced age is associated with a higher pathological stage, worse survival, and higher recurrence rates in RC (25). In our study, we evaluated age, gender, ECOG performance score, tumor grade, pathological tumor (pT) stage, clinical lymph node status (cN), localization of the primary tumor in the bladder, presence of comorbid diseases, renal failure status, presence of hydronephrosis, and NAC regimens, which have the potential to predict NAC response in non-metastatic MIBC and have been previously examined in the literature. In our study, we found that age <65 years was an independent prognostic factor in predicting pCR with NAC. We think that this may be due to the fact that patients in the younger age group have better renal function and treatment tolerance, and

therefore experience fewer dose reductions and treatment interruptions. In addition, this suggests that effective treatment in non-metastatic bladder cancer may be closely related to pCR. In our study, we did not find any statistically significant difference between the pCR and non-pCR patient groups in terms of other clinical and pathological factors except for age.

The main limitations of our study are its retrospective design, single-center data, heterogeneity of the groups, and the small number of patients.

CONCLUSION

In our study, age <65 years was found to be an independent prognostic factor for pCR in the neoadjuvant treatment of non-metastatic MIBC. Mean OS was better in patients who achieved pCR.

Ethics Committee Approval: The study protocol was approved by Dicle University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (12.05.2022/130).

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Original Article

A comparative evaluation of dentinal defects after root canal preparation with different rotary and reciprocal systems

Farklı rotary ve resiprokal sistemlerle kök kanal preparasyonu sonrasında dentinal defektlerin karşılaştırmalı değerlendirilmesi

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ABSTRACT

Aim: This study aimed to compare dentinal defects after root canal preparation with various reciprocating and continuous rotary files.
Methods: 90 extracted human mandibular incisor teeth were used. 15 teeth left unprepared and the remaning teeth were randomly divided into 5 experimental groups (n=15). Root canals were prepared with WaveOne (Dentsply Maillefer, Ballaigues, Switzerland), WaveOne Gold (Dentsply Maillefer, Ballaigues, Switzerland), Hyflex EDM OneFile (Coltene/Whaledent, Altstätten, Switzerland), ProTaper Next (Dentsply Maillefer, Ballaigues, Switzerland), and ProTaper Universal (Dentsply Maillefer, Ballaigues, Switzerland) rotary files. Then roots were sectioned at 3, 6 and 9 mm from the apex and evaluated with a stereomicroscope. Statistical analysis was performed with chi-square and Fischer's Exact test. The significance level was set at 5%.
Results: No defects were observed in the unprepared control group. Dentin defect were observed in all the experimental groups, especially in the apical region (3 mm). WaveOne and Hyflex EDM showed more dentinal defects than the control group ($p<0.05$); however, no significant difference was found between them ($p>0.05$). WaveOne caused significantly more dentinal defects than the ProTaper Universal, ProTaper Next, and WaveOne Gold groups ($p<0.05$). Hyflex EDM caused more defects than ProTaper Next ($p<0.05$). There was no difference between the other experimental groups ($p>0.05$).
Conclusion: All the rotary file systems used in this study caused dentinal defects regardless of the motion kinematics.

Keywords: Dentinal defect, rotary instrumentation, stereomicroscope

ÖZ

Giriş: Bu çalışmanın amacı resiprokasyon ve sürekli rotasyonla kullanılan çeşitli eğelerle kök kanal preparasyonu sonrası oluşan dentin defektlerini karşılaştırmaktır.
Yöntem: 90 adet çekilmiş insan alt kesici diş kullanıldı. 15 diş prepare edilmeden bırakıldı ve kalan dişler rastgele 5 deney grubuna (n=15) ayrıldı. Kök kanalları WaveOne (Dentsply Maillefer, Ballaigues, Switzerland), WaveOne Gold (Dentsply Maillefer, Ballaigues, Switzerland), Hyflex EDM OneFile (Coltene/Whaledent, Altstätten, Switzerland), ProTaper Next (Dentsply Maillefer, Ballaigues, Switzerland) ve ProTaper Universal (Dentsply Maillefer, Ballaigues, Switzerland) döner eğeleri ile prepare edildi. Daha sonra köklerden apeksten itibaren 3, 6 ve 9 mm'de kesit alındı ve stereomikroskopla değerlendirildi. İstatistiksel analiz ki-kare ve Fischer's Exact testi ile gerçekleştirildi. Anlamlılık düzeyi %5 olarak belirlendi.
Bulgular: Preparasyon yapılmayan kontrol grubunda defekt gözlenmedi. Tüm deney gruplarında özellikle apikal bölgede (3 mm) dentinal defekt gözlendi. WaveOne ve Hyflex EDM, kontrol grubuna göre daha fazla dentin defekti gösterdi ($p<0.05$); ancak aralarında anlamlı bir fark bulunmadı ($p>0.05$). WaveOne; ProTaper Universal, ProTaper Next ve WaveOne Gold gruplarından daha fazla dentin defektine neden oldu ($p<0.05$). Hyflex EDM, ProTaper Next'den daha fazla defekte neden oldu ($p<0.05$). Diğer deney grupları arasında fark yoktu ($p>0.05$).
Sonuç: Bu çalışmada kullanılan tüm döner eğe sistemleri, hareket kinematiklerinden bağımsız olarak dentin defektine neden oldu.

Anahtar kelimeler: Döner enstrümantasyon, dentin defekti, stereomikroskop

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INTRODUCTION

Disinfection, shaping and filling of the root canal system are essential factors in the success of root canal treatment. Root canal preparation provides both the cleaning of the root canal system by removing the infected tissue from the root canal and the necessary space for an ideal root canal filling (1). However, the root canal preparation may also cause some dentinal defects such as micro-cracks in the root canal wall (2). Premature occlusal contact, chewing forces, and dental treatments may lead to the progression of these micro-cracks and even the formation of vertical root fractures (VRF) (3), which are one of the most undesirable complications of endodontic treatment and often require tooth extraction (4).

The use of nickel-titanium (NiTi) instruments may cause defects in the root canal dentin (5-7). The incidence of dentin defects after root canal preparation with rotary instruments varies depending on the amount of dentin removed from the root canal and the dimensions of the canal enlargement (8,9). Increasing the sizes of preparation poses a risk for VRFs (10). In the root dentin, the crack development increases with the increase in stress. It has been reported that the canal shaping procedure weakens the root and the alloy used in the instrument, the cross-section shape, taper diameter, and operator's usage style have an effect on the incidence of dentin defects (11).

There are conflicting results that the use of NiTi instruments causes defects in dentin. Also, there is no consensus on whether rotation or reciprocation movements make a difference in the incidence of defects in root canal dentin (12-14). The aim of our study is to compare the incidences of dentin defects detected by stereomicroscope following the completion of root canal preparation using the ProTaper Universal (PTU, Dentsply-Maillefer, Ballaigues, Switzerland), ProTaper Next (PTN, Dentsply Maillefer, Ballaigues, Switzerland), Hyflex EDM (HEDM, Coltene/Whaledent, Altstätten, Switzerland), WaveOne (WO, Dentsply-Maillefer, Ballaigues, Switzerland), and WaveOne Gold (WOG, Dentsply-Maillefer, Ballaigues, Switzerland) rotary systems. The null hypothesis of this study was that there would be no difference between the instrument systems, the type of instrument movement, and the third of the root canals in terms of creating dentinal defect.

MATERIALS AND METHODS

Sample size calculation

To evaluate the incidence of dentin defects between any two groups, a difference of at least 8.5% is required in order to test the statistical significance at 85% power and 5% error level. The sample size calculated to be at least 12, and it was decided to have 15 samples in each group to increase the reliability of the data (n=15). The sample size calculated using the G * Power 3.0.10. (Franz Faul, Universität Kiel, Germany) package program.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki, with the approval of the ethics committee of Ankara University Faculty of Dentistry (numbered 36290600/51).

Selection and Preparation of Teeth

Human mandibular incisors extracted for periodontal reasons were used in this study. The teeth were kept in 0.5% sodium hypochlorite (NaOCl) solution for 24 hours after extraction and the attachments on them were removed with a periodontal curette. The presence of any cracks or defects in the roots was examined with a stereomicroscope (Carl Zeiss Microscopy GmbH, Munich, Germany) at x12 magnification.

Teeth without restoration, abrasion, crack, root fracture, calcification, resorption, open apices, and with an inclination angle <5°, apical opening accessible with a #10 K-file were used in the study. Radiographs of each tooth were taken from the buccolingual and mesiodistal aspects. Then, the teeth with more than one root canal and internal resorption were excluded. In order to ensure standardization between the groups,

the diameters of the canals at a distance of 9 mm from the apex on the radiographs taken from the teeth were measured in the buccolingual and mesiodistal directions. The measurements obtained were evaluated by analysis of variance (p=1.000). 90 mandibular incisors meeting these criteria were selected. The teeth were kept in distilled water until the experiment began.

To ensure root length standardization, the teeth were cut with a diamond fissure bur (ISO 806314, 014, Meisinger, Germany) at a distance of 13 mm of the apex under water coolant. The working length was determined 1 mm away from the apical foramen with a #15 K-file (Dentsply Maillefer, Ballaigues, Switzerland). The roots were wrapped in a single layer of aluminum foil and embedded perpendicularly in acrylic resin (Meliodent, Bayer Dental, Leverkusen, Germany) using plastic moulds. After polymerization, the samples were taken out and the aluminum foils were removed. After the silicone-based impression material was applied to the acrylic resin mold, the samples were placed again and randomly divided into 6 groups according to the file system to be used (n=15).

Group 1: Negative Control No root canal preparation was performed.

Group 2: ProTaper Universal PTU files were used at 250 rpm and torque values specified by the manufacturer for each file. First, the coronal part of the root was prepared using the SX file at 250 rpm and 3.0 Ncm torque setting. Subsequently, 2/3 of the root was prepared using the S1 file at 3.0 Ncm and the S2 file at 1.0 Ncm torque setting, respectively. The preparation was then completed using F1 (20 / .07) and F2 (25 / .08) files at 1.5 and 2.0 Ncm torque settings, respectively.

Group 3: ProTaper Next First, the coronal part of the root was prepared using the SX file at 250 rpm and 3.0 Ncm torque setting. Then, the root canal system was prepared using X1 (17 / .04) and X2 (25 / .06) PTN files at 300 rpm speed and 2.0 Ncm torque setting, respectively.

Group 4: Hyflex EDM The HEDM (25 / .08) single file system is used with continuous rotation movement at 500 rpm and 2.5 Ncm torque setting with a forward-backward movement.

Group 5: WaveOne Primary The WO (25 / .08) single file system was used by selecting the WO mode of the endodontic motor.

Group 6: WaveOne Gold The WOG (25 / .07) single file system was used in the WOG mode of the endodontic motor.

In each group, the rotary instrument system was used with the endodontic motor (X-Smart Plus, Dentsply-Maillefer, Ballaigues, Switzerland) in accordance with the manufacturer's instructions. Each file was discarded after 5 uses. Irrigation was applied after every 3 back and forth movements in single file systems and after every file change in multiple file systems. 2 mL 2.5% NaOCl (Werax; İzmir, Turkey) and a 30-gauge irrigation needle (Cerkamed, Poland) were used for irrigation. When resistance was felt while using the file, the file was removed from the canal and re-irrigated with NaOCl. A total of 10 mL NaOCl was used to irrigate each root. Preparation was completed when the working length was reached. All roots were kept in distilled water during the experiment. All stages were carried out by a single operator.

Sectioning from roots

The distances of 3, 6 and 9 mm from the apex of all roots were measured with an electronic caliper and marked with a permanent marker. From the marked points, sections were taken perpendicular to the long axis of the teeth on the Micracut device (Mikracut 201; Metkon, Bursa, Türkiye), under water cooling, with a diamond-coated disc (Exakt 300 CL; Norderstad, Germany).

Examination of Sections by Stereomicroscope

Photographs of all sections were taken at x16 and x25 magnification with a digital camera (Olympus, Tokyo, Japan) connected to a stereomicroscope. A total of 270 digital images, 45 in each group, were examined by two independent endodontists. The sections that were interpreted differently were re-

evaluated and a consensus was reached. If there was no line in relation to the internal/external surface of the root in the sections, it was evaluated as "no defect", if found it was evaluated as "there is a defect". Incomplete cracks, complete cracks, or crazy lines were considered microcracks (6).

Statistical analysis

The SPSS program (Statistical Package for Social Sciences) Windows 17.0 version was used for the statistical analysis of the data. Chi-square and Fischer's exact tests were used to compare the obtained parameters. Significance was set at the $p<0.05$ level.

RESULTS

Representative stereomicroscope images of samples after root canal preparation according to the experimental groups are shown in Figures 1, 2, and 3. No defects were observed in the control group. The incidence of defects was highest at 3, 6, and 9 mm, respectively. The difference between the control and experimental groups was significant in sections of 3 and 6 mm ($p<0.05$). While the WO and HEDM groups at 3 mm showed a higher incidence of defects than the control group ($p=0.0005$), there is no difference between them ($p>0.05$). WO created more defects than PTN, WOG, and control groups ($p<0.001$). However there was no difference between the other groups ($p>0.05$) (Table 1). While there were significantly more cracks at the 3 mm level in the WO group ($p=0.027$), there was no difference between the sections in the other groups (Table 2).

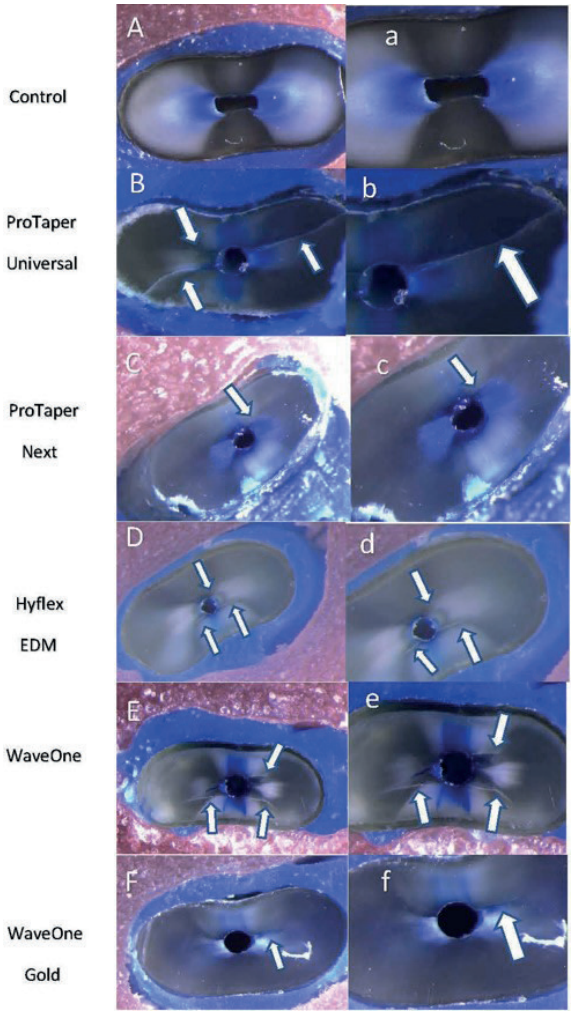

Figure 1. Images of horizontal sections taken at 3 mm from the apex at x16 (A, B, C, D, E, F) and x25 (a, b, c, d, e, f) magnifications according to the experimental groups. No cracks or defects were observed in the control group (A and a). Arrows indicate cracks and defects observed in the samples.

Table 1. Total number and percentage of sections with defects in different groups. Values with identical lowercase superscript letters indicate no significant difference ($p < 0.05$).

Groups	Number and percentage of cracked sections (%)			Total
	3 mm (χ^2:21,950)	6 mm (χ^2:17,504)	9 mm (χ^2:6,141)	
Control	0^{a} (0)	0^{a} (0)	0 (0)	0^{a} (0)
ProTaper Universal	$2^{a,b}$(13,3)	$1^{a,b}$ (6,7)	1 (6,7)	$4^{a,b}$ (8,8)
ProTaper Next	$1^{a,b}$ (6,7)	0^{a} (0)	0 (0)	1^{a} (2,2)
Hyflex EDM	$5^{b,c}$ (33,3)	$1^{a,b}$ (0)	2 (13,3)	$8^{b,c}$ (17,7)
WaveOne	9^{c} (60)	5^{b} (33,3)	2 (13,3)	16^{c} (35,5)
WaveOne Gold	$2^{a,b}$ (13,3)	0^{a} (0)	0 (0)	$2^{a,b}$ (4,4)
p value	0.0005	0.0036	0.2927	0.000013

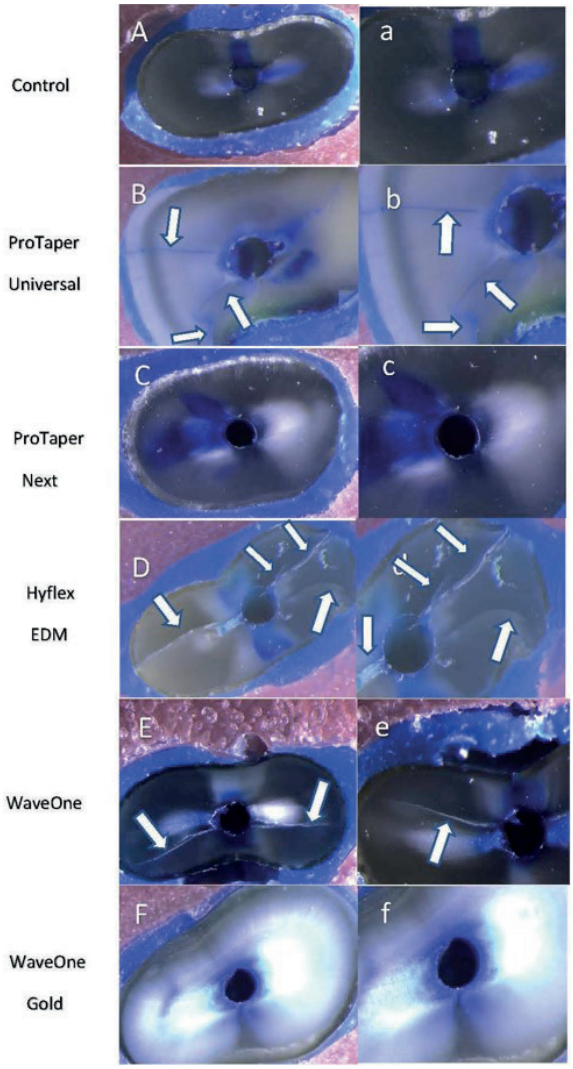

Figure 2. Images of horizontal sections taken at 6 mm from the apex at x16 (A, B, C, D, E, F) and x25 (a, b, c, d, e, f) magnifications according to the experimental groups. No cracks or defects were observed in the control group (A and a), ProTaper Next group (C and c), and WaveOne Gold group (F and f). Arrows indicate cracks and defects observed in the samples.

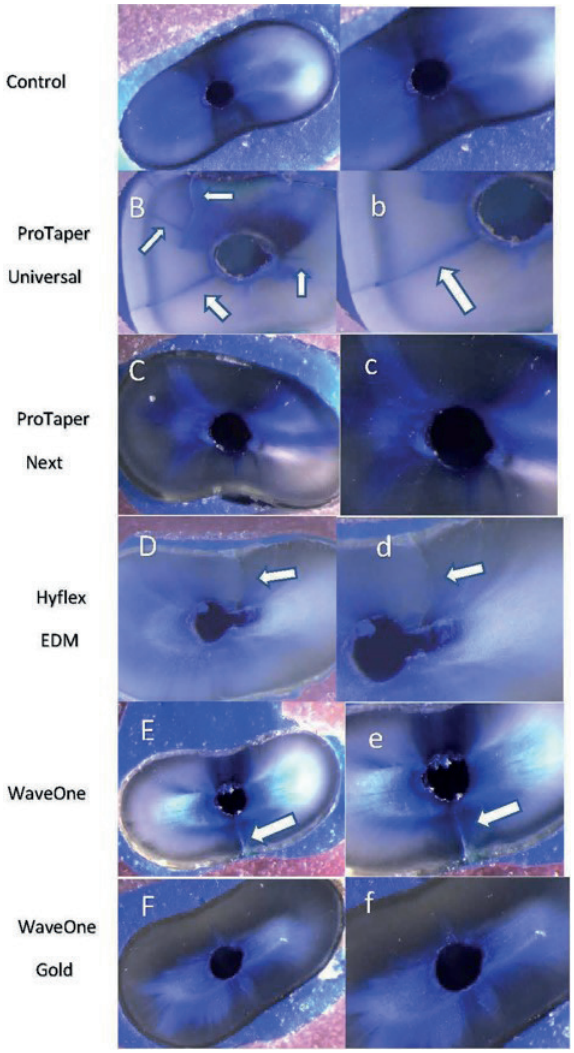

Figure 3. Images of horizontal sections taken at 9 mm from the apex at x16 (A, B, C, D, E, F) and x25 (a, b, c, d, e, f) magnifications according to the experimental groups. No cracks or defects were observed in the control group (A and a), ProTaper Next group (C and c), and WaveOne Gold group (F and f). Arrows indicate cracks and defects observed in the samples.

Table 2. The number and percentage (%) of sections with defects according to groups and levels. Within each group values with identical lowercase superscript letters indicate no significant difference ($p < 0.05$).

	Control	ProTaper Universal	ProTaper Next	Hyflex EDM	WaveOne	WaveOne Gold
3 mm	0	2 (13,3)	1 (6,7)	5 (33,3)	9[a] (60)	2 (13,3)
6 mm	0	1 (6,7)	0 (0)	1 (6,7)	5[b] (33,3)	0 (0)
9 mm	0	1 (6,7)	0 (0)	2 (13,3)	2[b] (13,3)	0 (0)
p value		0.760		0.138	0.0276	

DISCUSSION

Mechanical preparation of root canals allows removal of infected dentin tissue, creation of a suitable form for hermetic canal filling, and prevention of reinfection (1). However, the rotary instrument systems used in mechanical preparation may cause micro-cracks in the dentin (2). Micro-cracks progress and often result in VRF which may require tooth extraction (4). In this study, we aimed to compare the incidence of defect formation in the root canal dentin after the use of PTU, PTN, HEDM, WO, and WOG NiTi instruments. The null hypothesis of this study was partially rejected. While a difference was observed between NiTi instruments and the third of the roots in terms of dentinal defects, motion kinematics did not cause a difference.

Mandibular incisors, which are more prone to microcrack development due to their narrow mesiodistal dimensions, were preferred in this study (5). In our study, dentin defects were formed in all samples except for the control group. Most defects were observed in 3 mm sections. The WO group showed statistically significantly higher incidence of defects in 3 and 6 mm sections, and no difference was observed among the groups at 9 mm. The incidence of defects decreased towards the coronal. In NiTi rotary files, stress is usually concentrated at the tip of the file and the apical region (11). Therefore, the files cause less stress in the coronal region compared to the apical region. The taper angle of the file is effective in the formation of defects in the root canal dentin (5). The taper angle at the apical end of the files is .08, .06, and .07 for WO, PTN X2, and WOG, respectively. This information may explain why more defects were observed in the WO group. Also, the total number of defects observed in all samples was significantly higher in the WO group compared to the PTU, PTN, and WOG groups.

The file design is also effective in increasing compressive and tensile forces in the apical region of the root (15). PTU and WO have a triangular and modified triangular cross-sectional geometry, while PTN has a rectangular cross sectional geometry. The different cross-sectional geometry of PTN may be accountable for less dentin defects in the apical region. In single file systems, more stress occurs after canal preparation. This may be the reason for more defects in the WO group compared to the PTU and PTN groups (1). At the same time, there were more defects in the single file system HEDM group than in the PTU and PTN groups in sections taken from 3 mm and 6 mm, but the difference was not significant. However, the single file system WOG produced significantly less dentin defects compared to the WO group. This may be because WOG is produced with a special heat-treated technology.

There is no consensus on the effect of motion kinematics on the formation of dentinal defects. It has been reported that rotary systems produce more [7] or less [1] dentin defects than reciprocal systems. On the other hand, some studies have not found any difference between motion kinematics (9) or claimed that reciprocal motion does not cause cracks regardless of the working length (16). In our study, there were significantly more defects in HEDM than in PTN in all sections. The higher conical angle of HEDM (.08) compared to PTN X2 (.06), using it at higher speed, and its crater-like surface feature due to the production method may have caused this result (17). Significantly less defects occurred in the WOG group compared to the WO group. This result was attributed to WOG (.07) having a lower taper and higher torsional tensile strength than the WO (.08) system. In the WO group, the most significant defect was observed in 3 mm sections, which is consistent with the study of Bürklein et al. (6). Cicek et al.[18] reported that there was no difference between the dentinal defects caused by PTU, PTN, WO and K-type hand files. The use of mandibular molar mesial roots and evaluating with scanning electron microscopy in this study may have caused the inconsistency in the results. Priya et al.[1] examined dentin defects occurring in both rotational and reciprocal motion kinematics of the PTU, PTN, OneShape, and Reciproc systems

and found that PTN created less dentin defects in both movements compared to PTU. Similarly, in our study, PTN created less dentin defects than PTU group, but there was no difference. This may be due to the completion of root canal preparation with smaller size files in their study. Priya et al.[1] also reported that the rotational movement created more defects than the reciprocating movement. In our study, significantly more defects occurred in the WO group compared to PTU and PTN. Comparing WO and WOG both of which were used with reciprocal motion, more defects were observed in the WO group.

Karataş et al.[19] observed fewer defects in the PTN group in the apical regions compared to the PTU and WO groups. Üstün et al.[20] found no difference between the PTU and PTN groups. Ashraf et al.[21] reported that PTN produced fewer defects than the PTU group, but there was no difference between them. These results are consistent with our study. In line with our findings, Pedulla et al.[22] found no difference between the WOG and HEDM groups in their study, and they observed the most defects in the apical region. It was also observed that these two groups created less defects compared to the WO group. This may be due to the increased flexibility of the WOG and HEDM systems as a result of the heat treatments they are subjected to (2,19). Das et al.[23] reported in their study that there was no difference between PTN and HEDM groups. In our study, significantly more defects occurred in the HEDM group compared to the PTN group. In this study, methodological differences such as the use of mandibular premolar teeth, the creation of a glide path with a #15 K-type hand file, and coronal flaring with the Orifice Shaper before preparation may have caused inconsistencies in the results.

It has been reported that microcomputed tomography (micro-CT), which is a non-destructive method, is more reliable than stereomicroscopy because the sectioning procedure causes the dentinal microcrack development that did not present before the instrumentation (12). However, different results have been obtained in studies conducted with micro-CT. While no cracks were observed after the instrumentation (24-27), in some studies, on the contrary, cracks were observed (8,28-30). Recently, Chen et al.[31] reported that rotating NiTi systems cause dentinal microcracks in their study conducted with optical coherence tomography, which does not require sectioning procedure. Pradeep et al.[25] observed no microcracks in their in vivo study. These findings may be due to the use of young premolar teeth. However, in the current study we do not have any information about the age of the teeth used. This is also one of the limitations of our study. Another limitation of the current study is that microcracks may develop in the samples before instrumentation due to factors such as the force applied when extracting the teeth, the storage conditions(14,32), and the inability to control external factors while simulating clinical conditions(6), and the standardization of the force applied by the operator during preparation (2). De-Deus et al.[33] reported that the microcracks in the root dentin were caused by the extracted teeth, so the results of the studies reporting the presence of microcracks were flawed. Although it is not possible to exclude the possibility that these factors may also cause microcracks in root dentin(34), it is a strong evidence that no cracks were observed in the non-instrumented but sectioned control groups in several stereomicroscope studies (5-7,11,19,22,35-37). Hereby, the aforementioned factors are unlikely to affect the findings (34). In order to better evaluate the findings obtained from the stereomicroscope and micro-CT studies, future experiments are needed in which both methods are tested on the same samples (38).

CONCLUSION

All file systems used in this study created defects in dentin. HEDM used with rotational motion and WO used with reciprocal motion created more defects in dentin than the PTN, PTU and WOG groups. In the light of these findings obtained from this in vitro study, it is not possible to draw a definite conclusion about the effect of motion

kinematics on the formation of dentinal defects, which is a multifactorial situation that depends not only on the type of movement but also on many different features such as the cross-section designs of the files, taper angles, and the structure of the alloy.

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Dentistry Clinical Research Ethics Committee (18.04.2018 / 07/04).

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Original Article

Evaluation of the hygiene habits and awareness of the removable denture wearer geriatric population: A cross-sectional survey study

Hareketli protez kullanan geriatrik popülasyonun hijyen alışkanlıkları ve farkındalıklarının değerlendirilmesi: Bir kesitsel anket çalışması

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ABSTRACT

Aim: Appropriate denture hygiene promotes the oral health of removable denture wearer elderly patients. This study was conducted to evaluate denture hygiene habits and awareness of the removable denture wearer geriatric population.
Methods: A cross-sectional study was carried out by questionnaires which were conducted on 202 volunteered geriatric removable denture wearers at prosthodontics and periodontology clinics. The questionnaires included demographic and denture hygiene habits and awareness information. The collected data were imported to Statistical Package for Social Sciences and the chi-square and Fisher's exact tests were used to evaluate categorical variables represented as a percentage of study participants.
Results: The results of the study reveal that most geriatric patients are aware of effective denture hygiene, but lack correct information. Brushing with soap was the most frequent cleaning method (47.5%). Cleaning only with water and a toothbrush was mostly seen in male participants, while the use of brush and soap, brush and toothpaste and effervescent tablet was mostly seen in female participants ($p<0.05$). Where information about denture cleaning obtained from, differed statistically significantly according to age groups, while the 65-74 age group received more information from the internet and TV, while the 85+ age group received more information from the family and pharmacy ($p<0.05$). 104 (51.5%) patients did not take off their dentures at night. The frequency of cleaning dentures and using cleansing tablet was significantly higher in females than in males ($p<0.05$).
Conclusion: Dentists must pay attention to removable denture wearer geriatric patients' oral hygiene motivations. Geriatricians, pharmacists, and other related health workers, who are frequently and directly related to the geriatric population, and those who care for these patients (family members, nurses) should also play an active role in guiding patients to care about prosthesis cleaning and oral hygiene.

Keywords: Dental habits, geriatrics, oral hygiene, removable dentures

ÖZ

Amaç: Uygun protez hijyeni hareketli protez kullanan yaşlı hastaların ağız sağlığını destekler. Bu çalışma hareketli protez kullanan geriatrik popülasyonun protez hijyen alışkanlıkları ve farkındalığını değerlendirmek amacıyla yapılmıştır.
Yöntem: Bu çalışma, protez ve periodontoloji kliniklerinde çıkarılabilir protez kullanan 202 gönüllü yaşlı üzerinde anketler yoluyla yapılan kesitsel bir çalışmadır. Anketler demografik ve protez hijyeni alışkanlıkları ve farkındalığı bilgilerini içermektedir. Toplanan veriler Sosyal Bilimler İçin İstatistik Paketine aktarılmış ve kategorik değişkenler çalışmaya katılanların yüzdesi olarak gösterilmek üzere ki-kare ve Fisher'in kesin testleri kullanılarak değerlendirilmiştir.

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Bulgular: Çalışmanın sonuçları, çoğu geriatrik hastanın etkili protez hijyeninin farkında olduğunu ancak doğru bilgiye sahip olmadığını ortaya koymaktadır. Sabunla fırçalama en sık yapılan temizleme yöntemidir (%47,5). Sadece su ve diş fırçası ile temizlik en fazla erkek katılımcılarda görülürken, fırça ve sabun, fırça, diş macunu ve efervesan tablet kullanımı en fazla kadın katılımcılarda görüldü ($p<0.05$). Protez temizliği ile ilgili bilgilerin yaş gruplarına göre istatistiksel olarak anlamlı farklılık gösterdiği, 65-74 yaş grubu internet ve TV'den daha fazla bilgi alırken, 85+ yaş grubu aile ve eczaneden daha fazla bilgi almıştır ($p<0.05$). 104 (%51,5) hasta geceleri protezlerini çıkarmamıştır. Protez temizleme ve temizleme tableti kullanma sıklığı kadınlarda erkeklere göre anlamlı olarak yüksekti ($p<0.05$).
Sonuç: Diş hekimleri hareketli protez kullanan geriatrik hastaların ağız hijyeni motivasyonlarına dikkat etmelidir. Geriatrik popülasyonla sıklıkla ve doğrudan ilişkili olan geriatristler, eczacılar ve diğer ilgili sağlık çalışanları ile bu hastaların bakımını üstlenenler (aile üyeleri, hemşireler) de protez temizliği ve ağız bakımı konusunda hastaların yönlendirilmesinde aktif rol almalıdır.

Anahtar kelimeler: Dental alışkanlıklar, geriatri, oral hijyen, hareketli protezler

INTRODUCTION

As a natural consequence of the increased life expectancy, the geriatric population is growing rapidly in Turkey and in the rest of the world (1). The number of people with severe tooth loss who require removable prostheses is increasing proportionately (2). Correct use and maintenance of removable partial, total or implant-supported dentures used in edentulous rehabilitation not only ensures proper aesthetics and function, but also supports the healthy maintenance of supporting mucosal tissues, teeth, implants and the oral cavity (3-5).

Aging, a physiological process, causes changes in the overall health of the patient as well as the oral tissues. Depending on the changes in the calcified tissue and collagen structure in the jaws, decrease in bone density, narrowing and calcification in the dental pulp, changes in oral sensory function and sense of taste may occur. In addition, a decrease in salivary secretion and changes in its composition are observed. Thinning of the oral mucosa also negatively affects local mucosal immunity and antimicrobial capacity (5). It was stated that denture stomatitis, which is one of the problems faced by removable denture users, is seen at a rate of 11% to 67% and it develops due to poor oral hygiene and Candida albicans involvement (6). In addition to all these changes that appear in oral tissues with age, many studies emphasize the importance of oral examination in geriatric patients (7-9). However, the number of studies in the literature analyzing the hygiene habits and awareness of these patients using removable prostheses is limited (2,4,10-14). Our study aimed to evaluate the habits and awareness of geriatric patients about the hygiene of their removable dentures applying to periodontology and prosthodontics clinics.

MATERIALS AND METHODS

Ethical approval

The study was approved by the University of Health Sciences/Gulhane Scientific Research Ethics Committee with the registration number 2022/342. It was conducted following the principles of the Declaration of Helsinki. The aims of the research, warrant of confidentiality, use of findings only for scientific research, and voluntary participation were declared to the participants. Written and verbal informed consent were obtained from the patients.

Study design and participants

This cross-sectional study was conducted with 202 geriatric patients who were referred to the Departments of Prosthodontics or Periodontology, University of Health Sciences Turkey, Gülhane Faculty of Dentistry for dental check-ups, denture renewal, or other treatments between December 2022 and January 2023. The subjects were examined by experienced single prosthodontists to determine the denture type. The inclusion criteria for the present study were: (1) patients aged 65 years or older, (2) patients wearing dentures (complete denture, removable partial denture, or implant-supported removable denture) at least for 6 months, (3) patients with the ability to read and understand. The exclusion criteria for the present study were: (1) the presence of any physical and mental disabilities that might make it difficult to maintain adequate oral and denture hygiene independently, (2)

patients who had just started to wear dentures. The sample size calculation was performed using G Power statistical software (ver.3.1.9.7)* with an alpha risk of 0.05 and a power of 95% for each variable.

Evaluation of demographic characteristics, denture hygiene habits, and awareness

After a brief explanation of the questionnaires, in the first part, a basic data sheet regarding demographics including age, gender, level of education, income, smoking status, and living arrangements was recorded for each patient. In the second part, the questionnaire was based on a similar one used in another study (2,4). It was designed to determine the subjects' general dental evaluation, denture hygiene habits, and awareness.

Statistical analysis

Statistical analysis was performed using IBM-SPSS for Windows version 26 (SPSS Inc., Chicago, IL). Descriptive statistics were expressed as number (n) and frequency (%). Chi-square and Fisher's exact tests were used to determine the relationship between categorical variables. The level of significance for all tests was set at $p<0,05$.

RESULTS

Socio-demographic characteristics

The socio-demographic variables of the subjects are shown in Table 1. The questionnaires were administered to the 220 participants, and 202 completed questionnaires (response rate of 94.6%) were collected. The vast majority of the participants were aged between 65-74 years (64.4%), female (55.4%), high school graduates (38.1%), middle income earners (78.7%), non-smokers (89.6%), and living with their family (74.8%).

Denture hygiene habits and awareness

General descriptive statistics of the dental status and hygiene habits of the participants are presented in Table 2 as numbers and percentages. When the relationships between categorical variables are examined, a statistically significant relationship was found between age and duration of removable denture usage (p=0.001), frequency of going to the dentist (p=0.001), whether the used prosthesis was repaired or fed (p=0.001), from where information about denture cleaning was obtained other than the dentist (p=0.001), how the prosthesis was cleaned (p=0.002) and where the prosthesis was stored when not in use (p=0.001) (Table2). While 75.9% of those who obtained information about denture cleaning from the Internet were between the ages of 65-74, 87.5% of those who obtained information from the pharmacy and 80% of those who obtained information from their family were 85+ individuals.

While the majority of all responses to the question of how the dentures are cleaned were given by those aged 65-74, the use of effervescent tablets was found to be equal in the 65-74 and 85+ age groups.

When asked where the dentures are stored when they are not in use, soaking in water, storing in a dry environment, or soaking in a cleaning solution were the most common responses for individuals

Table 1. The socio-demographic variables of participants.

		n	%
Age	65-74 ages	130	64.4%
	75-84 ages	47	23.3%
	85+ ages	25	12.4%
Gender	Women	112	55.4%
	Men	90	44.6%
Education	Primary School	26	12.9%
	High School	77	38.1%
	University	58	28.7%
	Master	41	20,3%
Income	Low income	21	10,4%
	Middle income	159	78.7%
	Uppermiddle income	22	10.9%
Do you smoke?	Yes	21	10.4%
	No	181	89,6%
Who do you live with?	Alone	37	18.3%
	With my family	151	74.8%
	Residential care	10	5.0%
	With caregiver	4	2.0%

Table 2. General descriptive statistics of participans'dental hygiene attitudes.

		N	%
Which one is your denture type?	Complete denture (CD)	44	21.8
	Removable partial denture (RPD)	154	76.2
	Implant supported removable denture (ISRD)	4	2.0
How long have you been wearing a removable denture?	0-5 years	31	15.3
	6-10 years	158	78.2
	11+years	13	6.4
How many denture have you been wear?	First	123	60.9
	Second	74	36.6
	Third and more	5	2.5
How often do you visit dentist/dental hygienist?	2 in a year	81	40.1
	1 in a year	62	30.7
	Rarely	59	29.2
Did your denture relined or repaired?	Yes	124	61.4
	No	78	38.6
Have you ever had stomatitis due to wearing denture?	Yes	66	32.7
	No	136	67.3
Did your dentist inform you about cleaning your denture?	Yes	184	91.1
	No	18	8.9
Do you use other information sources about denture clening?	Internet	83	41.1
	TV	10	50.0
	Pharmacy	8	4.0
	Family	10	5.5
	Friends	0	0.0
Have you ever visited the dentist for denture care and cleaning the dentures?	Yes	162	80.2
	No	40	19.8
How often do you clean your dentures in a day?	1 in a day	40	19.8
	2 in a day	129	63.9
	3 in a day	28	13.9
	4 and up in a day	5	2.5
Do you wear dentures during the night?	Yes	98	48.5
	No	104	51.5
How do you clean your dentures?	With only tooth brush	33	16.3
	With tooth brush and paste	48	23.8
	With tooth brush and soap	96	47.5
	Washing under tap water	4	2.0
	With solution or effevescent tablet	21	10.4
Where do you store your dentures when you don't wear?	Storage in water	166	82.2
	Storage in dry conditions	9	4.5
	Storage in cleaning solution or efervescent tablets	16	7.9
	Storage in diluted vinegar solution	3	1.5
	Storage in soap or bleach	4	2.0
	Others	4	2.0

between the ages of 65-74, while soaking in diluted vinegar and diluted bleach were the most commonly used methods for 85+ individuals.

A statistically significant relationship was observed between gender and the duration removable denture usage (p=0.048), where information was obtained from other than the dentist (0.008), and how the prosthesis was cleaned (p=0.037). Males constitute 76.9% of those who have been using prostheses for 11 years or more. How the dentures were cleaned differed by gender: 57.8% of those who obtained information about denture cleaning from the internet were men, 64.4% of those who

Table 3. Distribution and relationship between age groups and dental hygiene habits of participants.

		Age groups						
		Age 65-74		Age 75-84		Age 85+		*p.
		N	%	N	%	N	%	
Which one is your denture type?	Complete denture (CD)	24	54.5	16	36.4	4	9.1	
	Removable partial denture (RPD)	102	66.2	31	20.1	21	13.6	.115
	Implant supported removable denture (ISRD)	4	100	0	0.0	0	0.0	
How long have you been wearing a removable denture?	0-5 years	16	51.6	11	35.5	4	12.9	
	6-10 years	110	69.6	34	21.5	14	8.9	**.001**
	11+years	4	30.8	2	15.4	7	53.8	
How many denture have you been wear?	First	81	65.9	25	20.3	17	13.8	
	Second	47	63.5	22	29.7	5	6.8	**.005**
	Third and more	2	40.0	0	0.0	3	60.0	
How often do you visit dentist/dental hygienist?	2 in a year	69	85.2	11	13.6	1	1.2	
	1 in a year	31	50.0	24	38.7	7	11.3	**.001**
	Rarely	30	50.8	12	20.3	17	28.8	
Did your denture relined or repaired?	Yes	93	75.0	21	16.9	10	8.1	**.001**
	No	37	47.4	26	33.3	15	19.2	
Have you ever had stomatitis due to wearing denture?	Yes	46	69.7	14	21.2	6	9.1	.480
	No	84	61.8	33	24.3	19	14.0	
Did your dentist inform you about cleaning your denture?	Yes	121	65.8	40	21.7	23	12.5	.255
	No	9	50.0	7	38.9	2	11.1	
Do you use other information sources about denture clening?	Internet	63	75.9	18	21.7	2	2.4	
	TV	66	65.3	27	26.7	8	7.9	
	Pharmacy	1	12.5	0	0.0	7	87.5	**.001**
	Family	0	0.0	2	20.0	8	80.0	
	Friends	0	0.0	0	0.0	0	0.0	
Have you ever visited the dentist for denture care and cleaning the dentures?	Yes	102	63.0	38	23.5	22	13.6	.554
	No	28	70.0	9	22.5	3	7.5	
How often do you clean your dentures in a day?	1 in a day	23	57.5	12	30.0	5	12.5	
	2 in a day	81	62.8	29	22.5	19	14.7	.303
	3 in a day	23	82.1	5	17.9	0	0.0	
	4 and up in a day	3	60.0	1	20.0	1	20.0	
Do you wear dentures during the night?	Yes	65	66.3	20	20.4	13	13.3	.636
	No	65	62.5	27	26.0	12	11.5	
How do you clean your dentures?	With only tooth brush	29	87.9	3	9.1	1	3.0	
	With tooth brush and paste	27	56.3	14	29.2	7	14.6	
	With tooth brush and soap	64	66,7	24	25,0	8	8.3	**.002**
	Washing under tap water	2	50.0	1	25.0	1	25.0	
	With solution or effevescent tablet	3	38.1	5	23.8	8	38.1	
Where do you store your dentures when you don't wear?	Storage in water	110	66.3	44	26.5	12	7.2	
	Storage in dry conditions	6	66.7	1	11.1	2	22.2	
	Storage in cleaning solution or efervescent tablets	9	66.7	1	11.1	2	22.2	**.001**
	Storage in diluted vinegar solution	1	33.3	0	0.0	2	66.7	
	Storage in soap or bleach	1	25.0	0	0.0	3	75.0	
	Others	3	75.0	0	0.0	1	25.0	

obtained information from TV were women, and 80% of those who obtained information from their families were women.

There was a statistically significant difference between gender and denture cleaning methods. Cleaning only with water and a toothbrush was

more common in male participants, while the use of a brush and soap, brush and toothpaste, and effervescent tablet was more common in female participants (Figure1).

The frequency of going to the dentist has increased with the level of education (p=0.001). Other parameters did not show a statistically significant difference with the level of education. Those who go to the dentist twice a year or more were mostly individuals with an undergraduate degree (35.8%) and a postgraduate degree (32.1%). There was a statistically significant correlation between level of education and how the prosthesis was cleaned (p=0.001).

Those who use only toothbrushes were mostly university graduates (45.5%), those who used toothbrush and paste were mostly high school graduates (45.8%), those who used toothbrush and soap were mostly high school graduates (39.6%), those who cleaned their dentures under running water were mostly university graduates (% 75) and those who cleaned their dentures with effervescent or solution were mostly high school graduates (34.4%).

No statistically significant differences were observed between monthly income and smoking and dental hygiene behaviors (p>0.05).

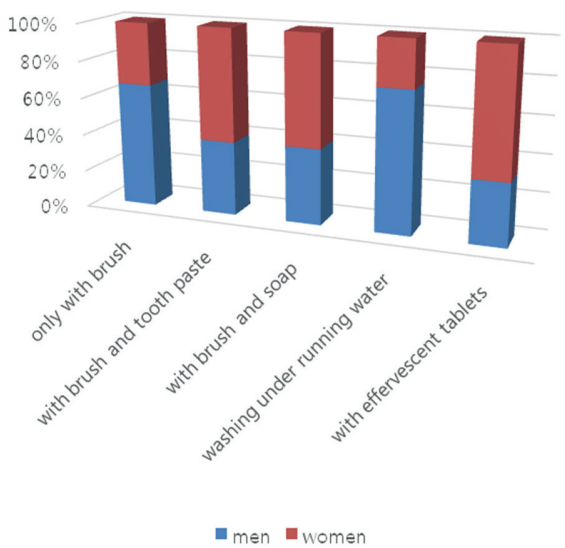

Figure 1. Study participants distributed according to gender and denture cleaning method.

There was a statistically significant relationship between living arrangements and who they received information from other than the dentist for denture cleaning (p=0.019).

It is the participants living with their families who get the most information from all channels, except the dentist, for denture cleaning.

DISCUSSION

Prosthesis-associated plaque can lead to the proliferation of Candida species in the mouth and the development of stomatitis, and is a risk factor for systemic conditions such as bacterial endocarditis, aspiration pneumonia, and generalized infection of the respiratory tract (10). Therefore, effective implementation of hygiene procedures for removable dental prostheses is critical for the protection of the patient's oral and systemic health (10). This study evaluated the habits and awareness of dental hygiene procedures in the geriatric population using removable dental prostheses.

In our study, 91.1% of the participants answered yes to the question of whether they were informed by their dentist about denture cleaning. It was observed that after the dentist, the most common sources of information on denture cleaning were TV (50%) and the internet (41.1%). Access to the right content on TV and the internet about denture cleaning is important in terms of informing the patients (13). However, it has been reported that online information sources, especially YouTube, are a poor source of information on denture cleaning for patients (15).

A study with pharmacists found that the majority of pharmacists (93%) believed it was their role to provide oral health advice in the community (16). We, on the other hand, observed in our study that only 4% of the patients received information about denture cleaning from pharmacists after the dentists.

48.5% of the patients reported that they did not remove their prostheses at night. It is recommended to remove dentures for 6-8 hours at night to reduce prosthesis-related stomatitis and restore mucosal vascularization (17,18). Martori et al. also stated that wearing dentures at night is one of the causes of denture stomatitis (10). Failure to remove removable dentures at night significantly increases the prevalence of Candida-associated stomatitis. Linuma et al. found more plaque on the tongue and denture surfaces, gingival inflammation, positive Candida albicans culture, and increased circulating interleukin-6 levels in patients who did not remove their dentures at night (18). However, in our study, 32.7% of the patients stated having a wound in the mouth due to the use of prostheses.

When participants were asked about how they cleaned their dentures, the participants responded that they cleaned mostly with a toothbrush and soap (47.5%). This was followed by toothbrush and paste (23.8%) and cleaning with a toothbrush (16.3%). There are two types cleaning: mechanical and chemical. Cinquanta et al. reported that 1/3 of the participants cleaned their dentures with paste and toothbrush in the same way as natural teeth, which is preferred because of its low cost (2). Mechanical cleaning involves the removal of plaque with a brush or ultrasonic cleaning and it has been stated that it is the most common cleaning method of cleaning removable denture (19). Chemical cleaning products include sodium hypochlorite, peroxides, various enzymes, and acids. Studies have shown that the combination of mechanical and chemical cleaning has a positive effect on denture cleaning (2,19). In our study, we observed that the majority of patients prefer mechanical cleaning with a toothbrush (87.6%), but only 10.4% of patients used effervescent tablets or solutions for chemical cleaning. The lower rate of cleansing tablet use in this study may be due to the relatively higher cost and lack of consumer awareness of the product. The data collected here showed that soaking in chemical solutions was a less frequently used method of cleaning than the manual brushing method, which is consistent with the studies by Marchini et al.[20] and Cakan et al.[21]. When asked where they soak their dentures when do not wear them, 82.2% said they soak them in water, 7.9% soak them in the cleaning solution, and 4.5% store them in a dry environment. In addition, 3.5% of patients reported soaking their dentures in chemicals such as diluted vinegar, bleach, or soap. These parameters showed statistically significant differences with age (p=0.002), gender (0.037), and level of education (p=0.001). It was observed that 85+ patients mostly preferred effervescent tablets for cleaning the prosthesis, and they preferred diluted vinegar (66.7%), and diluted bleach (75%) for storing the prosthesis, unlike other age groups. It was stated that homemade products could be preferred because they are easy to use, cheap, and effective (6). These chemicals are said to be an effective cleaning technique, particularly for elderly people with impaired motor function (4). We think that the importance of chemical and mechanical cleaning of dentures should be better explained to patients by dentists and related health professionals. While female participants were more concerned about the use of soap, toothpaste, and effervescent, it is more common for male participants to use only water or only brushes (Figure 1). Although the level of education and how the denture cleaning is performed were statistically different, it was observed that effective denture cleaning methods were independent of the education levels of the individuals. Consistent with our study, there are many studies stating that patients do not have sufficient knowledge about prosthesis cleaning and care (1,2,4,5).

This study has limitations. One of the limitations is that the data were self-reported information obtained from geriatric volunteers, which has an impact on the reliability of the responses. Oral hygiene assessment can be confirmed with more concrete data. Another limitation is that the sample size was small. Two departments of a dentistry faculty were selected for convenience and may not be representative of the overall population.

As a result of our study, it was concluded that the patients were knowledgeable about denture cleaning, but this level of knowledge was not sufficient. Geriatric dentistry must be reorganized, moving away from its historical emphasis on prostheses and toward a more holistic approach that actively incorporates geriatric and gerontologic factors. The medical and dentistry communities must collaborate to create home-based programs for senior citizens in order to raise awareness among geriatricians and primary care doctors who treat the homebound.

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Original Article

The efficacy and safety of carotid stenting under dual antiplatelet therapy with ticagrelor and acetylsalicylic acid*

Tikagrelor ve asetilsalisilik asit ikili antiplatelet tedavisi altında karotis stentlemenin etkinliği ve güvenliği

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ABSTRACT

Aim: To prevent thrombotic complications in carotid artery stenting (CAS), it is recommended to use acetylsalicylic acid (ASA) and clopidogrel for at least one month, followed by single antiplatelet therapy. The number of studies on the use of ticagrelor in CAS is very few. We aimed to evaluate the efficacy and safety of ticagrelor in CAS in this study.

Methods: The records of the patients who underwent CAS between January 2020 and January 2022 were scanned and the patients who were treated with the ASA and ticagrelor therapy were included in this study. Demographic data of the patients, vascular risk factors, ipsilateral-contralateral stenosis rates, balloon angioplasty application status, residual stenosis rates, periprocedural ischemic and hemorrhagic events, and vascular events developed during three-month follow-up were noted.

Results: Thirteen patients were included in the present study. Their mean age was 69.38±7.1 years. The mean carotid stenosis rate was 82.07±10.44%, and contralateral stenosis rate was 65.07±32.98%. Stent thrombosis was not observed in any patient. After the procedure, minor ischemic stroke that did not cause disability developed in one patient and puncture site bleeding that did not require transfusion in one patient. One patient had >50% restenosis at three months.

Conclusion: The findings suggest that dual antiplatelet therapy with ticagrelor + ASA appears to be a safe and effective treatment for CAS. Given that clopidogrel resistance cannot be evaluated in many centers, it may be more accurate to prefer ticagrelor, especially in high-risk patients with bilateral stenosis.

Keywords: Carotid artery, clopidogrel, stent, stroke, ticagrelor

ÖZ

Amaç: Karotis arter stentleme (KAS) sonrası trombotik komplikasyonları önlemek amacıyla asetilsalisilik asit (ASA) ve klopidogrel tedavisine en az bir ay devam edilmesi sonrasında tekli antiagregan kullanımı önerilmektedir. KAS'de tikagrelor kullanımı ile ilgili ise az sayıda çalışma bulunmaktadır. Bu çalışmada KAS'de ikili antiagregan tedavi olarak ASA ve tikagrelor kullanımının etkinliği ve güvenilirliğini değerlendirmeyi amaçladık.

Yöntem: Ocak 2020 ile Ocak 2022 tarihleri arasında kliniğimizde KAS uygulanmış olan hastaların dosyaları tarandı. ASA ve tikagrelor tedavisi altında stent uygulananlar çalışmaya alındı. Hastaların demografik verileri, vasküler risk faktörleri, ipsilateral-kontralateral darlık oranları, balon anjiyoplasti oranları, rezidü darlık oranları, periprosedürel ve postoperatif üç aylık takiplerinde gelişen olaylar kaydedildi.

Bulgular: Çalışmaya toplam 13 hasta alındı. Ortalama yaş 69,38±7,1 idi. Karotis arter darlık oranları ortalama %82,07±10,44 idi. Kontralateral darlık oranları ise %65,07±32,98 idi. Hastaların takiplerinde bir hastada transfüzyon gerektirmeyen ponksiyon yeri kanaması, bir hastada minör iskemik inme gelişti. Stent trombozu hiçbir hastada izlenmedi. Üçüncü ayda >%50 restenoz bir hastada saptandı.

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Sonuç: Ticagrelor ve ASA ikili antiagregan tedavisi karotis stentlemede güvenli ve etkin bir tedavi olarak görünmektedir. Klopidogrel direncinin ülkemizde birçok merkezde yapılamadığı da göz önüne alındığında özellikle yüksek riskli ve bilateral darlığı olan hastalarda ticagrelor başlamak doğru bir tercih olabilir.

Anahtar kelimeler: İnme, karotis arter, klopidogrel, stent, tikagrelor

INTRODUCTION

Carotid artery stenting (CAS) is an alternative treatment to endarterectomy for symptomatic and asymptomatic carotid artery stenosis. The frequency of minor ischemic stroke in CAS procedures is still higher than in endarterectomy despite all technical developments in current studies (1). It is recommended that CAS be performed under dual antiplatelet therapy (DAPT). The acetylsalicylic acid (ASA) + clopidogrel combination is frequently used in clinical practice (2). Clopidogrel is an irreversible inhibitor of P2Y12. Approximately 85% of clopidogrel absorbed from the intestines is converted into an inactive metabolite, while the remaining 15% is metabolized by cytochrome P450 enzymes in the liver to become active. Inter-individual variability in liver metabolism may result in decreased efficacy. Efficiency decreases, especially in genotypes carrying the CYP2C19 loss-of-function allele (3). Studies have reported that patients with cerebrovascular diseases have a decreased resistance or response to clopidogrel up to 66% (3,4). However, a study conducted in 26 countries has shown that platelet function tests can only be performed in 16% of centers (4). It is obvious that an effective antithrombotic treatment is required to prevent thrombotic complications that may develop after stenting, and an alternative treatment is needed because of the inadequate response to clopidogrel in approximately one-third of the patients (5).

Ticagrelor is a metabolite that noncompetitively and reversibly inhibits P2Y12 receptors. The most important difference from other P2Y12 antagonists is that it is an active drug and does not need to be metabolized. It has linear pharmacokinetics due to its high protein binding rate (6). The advantage of its pharmacokinetic property reduces individual differences in efficacy, and the antiplatelet activity begins rapidly. In case of any bleeding or side effects, the efficacy disappears quickly after the discontinuation of the drug (7). In studies, the probability of high platelet activity during the procedure was reported to be between 1.5% and 4% in those receiving ticagrelor (8,9). This rate is quite low compared to clopidogrel.

As data on the use of ticagrelor in cerebrovascular diseases increased, it has begun to be recommended in the guidelines. The AHA/ASA guideline recommends the use of ticagrelor in addition to aspirin for 30 days in patients with new minor ischemic stroke and high-risk transient ischemic attack (TIA) patients with >30% stenosis of major intracranial vessels as the level of evidence IIb (10). To our knowledge, there are no randomized controlled studies and recommendations for its use in CAS other than observational studies. In our country, ticagrelor is not reimbursed by the Social Security Institution in the neurology branch. Therefore, we wanted to evaluate the efficacy and safety of this treatment by sharing the data of patients who underwent CAS under ticagrelor + ASA dual antiplatelet therapy in this study.

MATERIALS AND METHODS

After obtaining the approval for the study from Bolu Abant İzzet Baysal University Ethics Committee (date: 03/01/2023, number: 2022-292), the data of patients who underwent CAS under ASA and ticagrelor antiplatelet therapy between January 2020 and January 2022 were evaluated. Patients' age, symptomatic or asymptomatic stenosis status, ipsilateral, contralateral and residual stenosis rates, periprocedural ischemic and hemorrhagic complications, and neurological and cardiac events developed in the three-month follow-up were recorded. It was noted whether silent ischemic lesions developed in patients with diffusion MRI control before and after the procedure.

Statistics

Data were analyzed using the SPSS 22.0 (IBM Corp.; Armonk, NY, USA) program. Categorical variables were expressed as numbers and percentages, and countable variables as means ±SD.

RESULTS

A total of 13 patients (eight male [61%] and five female [39%]) who underwent CAS under ticagrelor and ASA DAPT were included in the present study. The mean age of the patients was 69.38±7.1 (years) (range, 59-83). Vascular risk factors and demographic data of the patients are shown in Table 1. In addition, the demographic, radiological, and clinical data of the cases are given in Table 2 as a patient list. All patients underwent stenting for symptomatic stenosis. The right ICA was stented in six patients (46%) and the left ICA in seven patients (54%). An open-cell stent was used in five patients (39%), and a closed-cell stent was used in eight patients (61%). While distal filters were used in eight patients (61%), no embolic protection device was used in five (39%) patients. The mean ICA stenosis rates were (rate was) 82.07±10.44 (min-max 62-99). The mean contralateral ICA stenosis rate was 65.07±32.98 (10-100). Ten of 13 patients (76%) had more than 50% stenosis in the contralateral ICA. Of these 10 patients, three had contralateral ICA occlusion and two had preocclusive stenosis. None of the patients had residual stenosis greater than 30% after the procedure. A new silent ischemic lesion was detected in five (62%) of eight patients who had diffusion MRI examinations before and after the procedure. A minor ischemic stroke was observed in one patient with the clinic of mild right hemiparesis after the procedure. One patient developed puncture site bleeding that did not require transfusion. No major ischemic event or major hemorrhage was observed three months after the procedure.

DISCUSSION

In this case series, no major ischemic or hemorrhagic events were observed in 13 patients who were treated with CAS under ticagrelor and ASA DAPT and generally had bilateral stenosis. Ticagrelor has started to be used in coronary artery disease after the Dose conflrmation Study assessing antiPlatelets Effects of AZD6140 vs. clopidogRel in non–ST-segment Elevation myocardial infarction (DISPERSE-2) and the Platelet Inhibition and Patient Outcomes (PLATO) studies, which were first published in 2009. The PLATO study reported that almost all patients with clopidogrel resistance had adequate platelet inhibition (11,12).

The first large randomized, controlled study on its use in cerebrovascular diseases is the Acute Stroke or Transient Ischemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes (SOCRATES), published in 2016 (13). In this study, which included high-risk TIA or minor ischemic stroke patients, ischemic stroke was reported to be lower in the ticagrelor group than in the ASA group during the 3-month follow-up. Death and

Table 1. Vascular risk factors, procedural and follow-up data of patients.

Age	69.38±7.13	**Symptomatic n(%)**	13 (100)
M/F n(%)	8(61.5) /5(38.5)	**Stenosis rate (%)**	82.3±10.44
DM n(%)	9(69.2)	**Contralateral stenosis rate (%)**	65.07±32.98
HT n(%)	10(76.9)	**Predilatation n(%)**	8 (61.6)
History of prior stroke n(%)	6 (46.2)	**Postdilatation n(%)**	9 (69.3)
Coronary artery disease n(%)	5 (38.5)	**Residual stenosis rate (%)**	15.3±11.18
Smoker n(%)	6 (46.2)	**Those who had DWI MRI after the procedure**	8/13
Hyperlipidemia n(%)	10 (76.9)	**New ischemic lesion (%)**	5/8 (62.5)
Events in the first 3 months of follow-up	Restenosis>50% 1/13	Puncture site bleeding 1/13	Minor stroke 1/13

M: Male, F: Female, HT: Hypertension, DM: Diabetes mellitus, DWI MRI: Diffusion-weighted magnetic resonance imaging

Table 2. Patient list and demographic and radiological data of patients.

Case	Age	Gender	Stenosis rate	DM	HT	HL	History of prior stroke	CAD	Contralateral stenosis rate	Predilatation	Postdilatation	Distal filter	Residual stenosis rate	Post-procedure DWI MRI control	New ischemic lesion
1	67	M	82	+	+	-	+	+	30	+	+	+	0	-	
2	83	F	95	+	+	+	+	-	53	+	-	-	10	-	
3	63	M	72	+	+	+	+	+	100	-	-	+	27	+	+
4	67	M	84	-	-	+	-	-	50	+	+	+	25	-	
5	65	M	88	+	-	+	-	-	99	+	+	+	23	-	
6	60	M	85	+	+	+	+	-	98	+	+	+	0	+	+
7	74	F	72	-	+	+	-	+	62	-	+	+	16	+	-
8	74	F	62	-	+	+	-	+	10	-	+	-	10	-	
9	74	F	94	+	-	-	+	-	66	+	+	-	28	+	+
10	65	F	99	+	+	+	-	-	15	+	+	-	24	+	+
11	59	M	75	+	+	+	-	-	100	+	-	+	28	+	-
12	75	M	83	-	+	-	+	-	63	-	+	-	8	+	+
13	76	M	79	+	+	+	-	+	100	-	-	+	0	+	-

M: Male, F: Female, HT: Hypertension, DM: Diabetes mellitus, HL: Hyperlipidemia, CAD: Coronary artery disease, DWI-MRI: Diffusion-weighted magnetic resonance imaging

myocardial infarction (MI) were observed less frequently in the ticagrelor group. In the subgroup analysis, it was reported that ticagrelor was more effective in preventing recurrent ischemic events than ASA in patients with ipsilateral large vessel atherosclerosis. There was no difference in the rates of major bleeding and intracranial bleeding between the two groups (13). In the Platelet Reactivity in Acute Nondisabling Cerebrovascular Events (PRINCE) study[14], patients who were administered ASA+clopidogrel and ASA+ticagrelor were compared to patients presenting with TIA or stroke; in the 3-month follow-up, stroke recurrence was less in the ASA+ticagrelor group, especially in those with large vessel atherosclerosis. The fact that only patients from rural China were included in the study prevented the generalizability of the study (15). Patients with mild to moderate acute noncardioembolic ischemic stroke (NIHSS score ≤5) or TIA who did not undergo intravenous or endovascular thrombolysis were enrolled in the Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death (THALES) study. They were randomized to treatment with ASA or ASA+ticagrelor. The total risk of stroke and death within 30 days and the risk of ischemic stroke alone were lower in the ASA+ticagrelor group. Although it did not reach statistical significance, major bleeding was more common in the ASA+ticagrelor group (16). When patients with ipsilateral stenosis were compared in the subgroup analysis of the THALES study, 30-day ischemic stroke and death were less in the ASA and ticagrelor group compared to the ASA group (8.1% vs. 10.9%) (17). In the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events II (CHANCE II) study, 6412 patients with minor ischemic stroke and TIA with the CYP2C19 loss of function allele were randomized 1:1 to clopidogrel+ASA and ticagrelor+ASA treatments. In the 3-month follow-up, the risk of stroke was lower in the ticagrelor group, while dyspnea, arrhythmia, and total bleeding were more common. The main limitation of the study was that it could not be generalized because only Han patients were included in the study (18).

A meta-analysis study reported that the use of ticagrelor had a positive effect on primary and secondary stroke prophylaxis, and there was

a small increase in major and minor bleeding, although this was not statistically significant for major bleeding. It has been reported that dyspnea and hyperuricemia may develop as the most important factors limiting its utilization (19). As studies on its use in ischemic stroke have increased, the use of ticagrelor has started to be included in the guidelines (10).

To our knowledge, there is no large randomized controlled study on the use of ticagrelor in neuroendovascular treatment, but there are case series and cohort studies. Hanel et al.[5] reported that in 18 patients with clopidogrel resistance who underwent neuroendovascular treatment and were switched to ticagrelor treatment, there were no ticagrelor-related side effects or no worsening of clinical outcomes. In the study conducted by Qureshi et al.[20], it was reported that 70 of 106 patients undergoing neuroendovascular intervention had suboptimal platelet inhibition with ASA+clopidogrel treatment, and optimal platelet inhibition developed in 50 of these 70 patients with ticagrelor. Fifi et al.[21] reported that periprocedural thromboembolic complications were more common in patients with clopidogrel resistance in neurovascular stenting applications. In the study by Narata et al.[22], the data of 154 patients who underwent intracranial stenting under ticagrelor and ASA treatment for unruptured aneurysm closure, ticagrelor, and ASA were administered without platelet function testing in all patients, and the patients were followed up for three months after the procedure. In this study, they reported that ischemic complications were lower, and hemorrhage and death were similar to those in the literature in patients treated with both the flow-diverter stent and stent-assisted coils. The study by Karan et al.[23] reported that clopidogrel resistance was detected by a 25% optical light transmission platelet aggregometry (LTA) test in 32 of the patients who were scheduled for neuroendovascular intervention, and the procedure was performed after switching to ticagrelor treatment. None of these patients developed thromboembolic complications .

In the case series reported by Linfante et al.[24], in which patients who received iv (IV) cangrelor for subarachnoid hemorrhage and acute ischemic stroke followed by acute stenting and followed up with ticagrelor treatment, it was reported that this protocol could be an alternative regimen to clopidogrel in acute cases. While all patients who underwent neuroendovascular treatment were included in these studies, we specifically evaluated patients with CAS in our study.

In the study conducted by Kadoglou et al.[25] in rabbits with atherosclerotic carotid stenosis, it was reported that stent thrombosis was less common in rabbits under ASA and ticagrelor DAPT compared to the ASA and clopidogrel group. In the study conducted by Lotan et al.[26], clopidogrel resistance was detected in 110 (34%) of 325 patients who underwent CAS, and ticagrelor treatment was started. While there was no difference between the two groups in terms of cerebrovascular events, and minor and major bleeding, stent restenosis was significantly lower (9 vs. 0) in the ticagrelor group. In a retrospective study by Marcaccio et al.[27] comparing the patients who underwent CAS under ASA + clopidogrel and ASA + ticagrelor treatments, puncture site bleeding was reported to be higher in the ASA + ticagrelor group (5.9% vs. 3%) in patients with transfemoral access. It was reported that there was no difference between the two groups in terms of stroke and death. It was reported that no ischemic stroke, death, or intracranial hemorrhage developed in the 30-day follow-up of 18 patients who had clopidogrel resistance and underwent CAS under ticagrelor + ASA DAPT as reported by Olafson et al (28).

Ghamraoui et al.[8] evaluated 67 patients who underwent CAS with the transcarotid artery revascularization method under ASA+ticagrelor dual antiplatelet therapy and reported that none of the patients developed stroke, MI, or major bleeding during their 30-day follow-up. In this study, it was reported that 8% of the patients developed severe dyspnea and had to change their medication. In the three-month follow-up of

our cases, a minor ischemic stroke was observed in one patient, and bleeding at the puncture site was observed in one patient. The most significant distinguishing feature of our cases was the high prevalence of contralateral ICA stenosis. In 76% of the patients, there was more than 50% stenosis in the contralateral ICA.The most important side effect limiting the use of ticagrelor is dyspnea. Dyspnea due to ticagrelor has been reported in a range of 4.8-14% (8,29). Although it is usually temporary, it may progress and require discontinuation of the drug. Dyspnea was not observed in our cases.

The gold standard test for evaluating platelet inhibition due to P2Y12 inhibitors is the LTA test. Its use in daily practice is limited due to the difficulty of sample preparation, the need for experience and the time-consuming test results (3). More clinically convenient platelet function tests include the VerifyNow assay (Accumetrics, San Diego, Calif), Multiplate Analyzer (F. Hoffmann-La Roche Ltd, Basel, Switzerland), vasodilator-stimulated phosphoprotein phosphorylation assay (Diagnostica Stago, Biocytex, Asnières, France), and A thromboelastography-platelet mapping (TEG-PM). However, these tests cannot be performed in many centers. A multinational study reported that it could only be performed in 16% of the centers (4).

CONCLUSIONS

Ticagrelor and acetylsalicylic acid DAPT appears to be a safe and effective treatment for CAS. Given that clopidogrel resistance is not possible in many centers in Turkey, we think that ticagrelor should be preferred over clopidogrel, especially in high-risk patients with bilateral stenosis. There is a need for multicenter, control-group studies on this subject. The results of the ongoing Prevention of Cerebral Ischemia in Stent Treatment of Carotid Artery Stenosis A randomised multi-centre Phase II Trial, comparing ticagrelor versus clopidogrel with outcome assessment on MRI, (PRECISE-MRI) (ClinicalTrials.gov Identifier: NCT02677545) will also shed light on which antiplatelet therapy should be selected for CAS.

Ethics Committee Approval: The study protocol was approved by the Bolu Abant İzzet Baysal University Ethics Committee (03/01/2023 / 2022-292).

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Original Article

Evaluation of Turkish dentists' knowledge and awareness of temporomandibular disorders

Türk diş hekimlerinin temporomandibular eklem rahatsızlıkları hakkındaki bilgi ve tutumlarının değerlendirilmesi

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ABSTRACT

Aim: The aim of this study was to evaluate the awareness and treatment approaches of general dentists about temporomandibular disorders (TMD).
Methods: A cross-sectional 21-item questionnaire study was performed and was sent to general practitioner dentists in Turkey. The demographics, length of professional experience, and their level of knowledge about TMD management were evaluated.
Results: Eighty general practitioner dentists responded to the questionnaire. In the first part of the questionnaire, a statistically significant difference was found for the statement 'One of the symptoms of TMD is headache.' between the responses of dentists with more than 5 years of professional experience and those with less than 5 years of professional experience ($p=0.012$). No statistically significant difference was found in the responses to the other questions about TMD in other part of the questionnaire ($p>0.05$).
Conclusions: The knowledge and awareness about the diagnosis and treatment of TMD is low among general practitioner dentists. Informative seminars or courses should be organized to increase the knowledge of TMD among general practitioner dentists.

Keywords: Dentist, etiology, temporomandibular disorders, temporomandibular joint

ÖZ

Amaç: Bu çalışmanın amacı, pratisyen diş hekimlerinin temporomandibular bozukluklar (TMD) konusundaki farkındalıklarını ve tedavi yaklaşımlarını değerlendirmektir.
Yöntem: 21 maddelik kesitsel bir anket çalışması yapılmış ve Türkiye'deki pratisyen diş hekimlerine gönderilmiştir. Demografik özellikler, mesleki deneyim süreleri ve TMD yönetimi hakkındaki bilgi düzeyleri değerlendirilmiştir.
Bulgular: Seksen pratisyen diş hekimi anketi yanıtlamıştır. Anketin ilk bölümünde mesleki deneyimi 5 yıldan az olan diş hekimlerinin yanıtları arasında 5 yıldan fazla mesleki deneyime sahip 'TMD belirtilerinden biri baş ağrısıdır.' ifadesinde istatistiksel olarak anlamlı bir fark bulunmuştur. ($p=0,012$). Anketin diğer bölümünde TMD ile ilgili diğer sorulara verilen yanıtlarda istatistiksel olarak anlamlı fark bulunmamıştır ($p>0,05$).
Sonuçlar: Pratisyen diş hekimleri arasında TMD'nin tanı ve tedavisine ilişkin bilgi ve farkındalık düşüktür. Pratisyen diş hekimlerinin TMD hakkındaki bilgilerini artırmak için bilgilendirici seminerler veya kurslar düzenlenmelidir.

Anahtar kelimeler: Diş hekimleri, etiyoloji, temporomandibular eklem, temporomandibular eklem rahatsızlığı

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INTRODUCTION

The temporomandibular joint (TMJ) is a joint that connects the skull to the mandible and is located between the glenoid fossa of the temporal bone and the condylar process of the mandible (1-3). Temporomandibular disorder (TMD) is a general term describing the signs and symptoms of all associated dysfunctions or disorders of the TMJ and its joint components, such as the associated muscles and ligaments (4).

The management of TMD involves the work of dentists with different expertise. The diagnosis of TMD is multifactorial in nature and requires appropriate examination and planning for treatment. Detection and diagnosis of the problem requires the cooperation of maxillofacial radiologists, orthodontists, prosthodontists, or maxillofacial surgeons (4,5). The pain in the affected area, discomfort in the masticatory muscles, reduced movement of the mandible, accompanying noise during the movement of the jaw are some of the symptoms of TMD (6,7).

TMD is estimated to have a prevalence of 5-12% in the population, including adults and children. Therefore, TMD has been recognized as an important public health problem (8). The Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) are used to classify the different categories of TMD. According to the DC/TMD, these disorders can be classified as "acute or chronic" and "complex or simple" (9,10). The lack of knowledge about orofacial pain, especially in children and adolescents, can be a serious limitation in the management of TMD pain (11). Orofacial pain not only affects quality of life but can also be associated with poor general health, depression, and other mental deficiencies (12). Faculties of dentistry use multiple educational strategies, including theoretical, non-clinical, and clinical training to prepare students to become dentists. Dental schools must provide dentists with the necessary skills to face the challenges of daily practice to ensure a high quality of dental care (13). The aim of this was to evaluate the awareness and attitudes of Turkish general dentists toward TMD in order to evaluate the quality of treatment received by patients and the need for TMD continuing education programs.

MATERIALS AND METHODS

A link to the questionnaire created with Google Forms were e-mailed to dentists working in Turkey for this study. Twenty-one participants were excluded from the study because they were specialist dentists, 5 were research assistants and 2 were excluded because of incomplete responses. The G*Power 3.1 program, alpha error probability = 0.05, power value 0.95, effect size 0.50, the total number of participants required was found to be 80 participants.

The questionnaire consists of 21 questions in total. The first part of the questionnaire includes information on gender, institution of employment (public institution / private practice) and length of professional experience (less than 5 years / more than 5 years ≥). The second part of the questionnaire included questions about the etiology and prevalence of TMD and consisted of 10 questions. The last part of the questionnaire evaluated the dentists' knowledge and attitudes toward the treatment of TMD. The inclusion criterion was to be a general practitioner dentist. The exclusion criteria were having a specialty or doctorate in one of the specialties of dentistry or being a practicing dentist.

Statistical method

The data were analyzed using IBM SPSS (version 26, IBM SPSS Statistics, Armonk, USA). The Pearson, chi-square test and Fischer's exact test were used to compare categorical variables. The significance level was set at $p<0.05$.

RESULTS

The total number of general practitioner dentists who answered the questionnaire was 80. When the demographic data of the participants are analyzed, it is seen that 43 of them were female

and 37 of them were male (Table 1). When the institutional information of the participants is examined, it is seen that 33 participant dentists work in public institutions and 47 participant dentists work in private clinics. The average length of professional experience of the participants was 5.9 years.

When the answers given by the participants to the question 'Have you received any training other than your undergraduate / graduate education related to TMJ and / or TMD?' were examined, it is seen that 87.5% of the participants have not received any training and 12.5% has received training (Table 2). When the answers to the question 'What do you think is the most important factor in the etiology of TMD?' are analyzed, it is seen that 32.5% of the participants referred to the occlusal factors, followed by the parafunctional habits with 30%. A statistically significant

Table 1. Demographic data of the participants.

		Experience less than 5 years	Experience more than 5 years	P*
Gender	Female	21	22	0.823
	Male	19	18	
Organization	Public organization	9	24	0.001
	Private practice	31	16	

Table 2. Participants' answers to the second part of the survey (categorical).

		Total	Percentage (%)
Have you received any training other than your graduate education related to TME and/ or TMD?	Yes	10	12.5
	No	70	87.5
What is the most important factor in TMD etiology?	Occlusal factors	26	32.5
	Trauma	5	6.25
	Emotional Stress	24	30
	Deep pain input	1	1.25
	Parafunction	24	30
One of TMD symptoms is headache.	Yes	73	91.25
	No	5	6.25
	No idea	2	2.5
TMD can come as an ear symptom.	Yes	74	92.5
	No	4	5
	No idea	2	2.5
TMD may be the cause of unexplained orofacial pain.	Yes	72	90
	No	2	2.5
	No idea	6	7.5
Mouth opening measurement is a safe way for TMD diagnosis.	Yes	43	53.75
	No	29	36.25
	No idea	8	10
The examination of chewing muscles plays an important role in TMD diagnosis.	Yes	76	95
	No	4	5
TME imaging methods are useful for TMD diagnosis.	Yes	74	92.5
	No	1	1.25
	No idea	5	6.25
What is the incidence of TMD in the general population?	Less than 20 %	5	6.25
	Between 20-40 %	29	36.25
	Between 40-60 %	31	38.75
	Between 60-80 %	15	18.75
How old is the incidence of TMD in the general population?	0-20 years	1	1.25
	20-40 years	63	78.75
	40-60 years	13	16.25
	More than 60 years	3	3.75

Table 3. Participants' answers to the section of the survey according to their experience period.

		Experience less than 5 years	Experience more than 5 years	P
Have you received any training other than your graduate education related to TMD?	Yes	4	6	0.499[a]
	No	36	34	
What is the most important factor in TMD etiology?	Occlusal factors	11	15	0.685[b]
	Trauma	3	2	
	Emotional Stress	14	10	
	Deep pain input	1	0	
	Parafunction	11	13	
One of TMD symptoms is headache.	Yes	33	40	0.012[b]
	No	5	0	
	No idea	2	0	
TMD can come as an ear symptom.	Yes	35	39	**0.232[b]**
	No	3	1	
	No idea	2	0	
TMD may be the cause of unexplained orofacial pain.	Yes	35	37	0.835[b]
	No	1	1	
	No idea	4	2	
Mouth opening measurement is a safe way for TMD diagnosis.	Yes	20	23	0.409[b]
	No	14	15	
	No idea	6	2	
The examination of chewing muscles plays an important role in TMD diagnosis.	Yes	38	38	1.000[b]
	No	2	2	
TME imaging methods are useful for TMD diagnosis.	Yes	35	39	0.201[b]
	No	1	0	
	No idea	4	1	
What is the incidence of TMD in the general population?	Less than 20 %	1	4	0.598[b]
	Between 20-40 %	15	14	
	Between 40-60 %	17	14	
	Between 60-80 %	7	8	
How old is the incidence of TMD in the general population?	0-20 years	1	0	1.000[b]
	20-40 years	31	32	
	40-60 years	7	6	
	More than 60 years	1	2	

[a] *Pearson Chi-Square test,* [b] *Fischer's Exact test.*

difference was found between the responses of dentists with less than 5 years of professional experience and dentists with more than 5 years of professional experience to the statement 'One of the symptoms of TMD is headache.' (p=0,012) (Table 3). 38.75% of the participating dentists answered that TMD is seen in 40-60% of the population, 36.25% in 20-40% of the population, 18.75% in 60-80% of the population and 6.25% in less than 20% of the population. 78.75% of the participating dentists answered that TMD is seen in the population between the ages of 20-40 years, 16.25% between the ages of 40-60 years, 3.75% in patients older than 60 years, and 1.25% between the ages of 0-20 years. No statistically significant difference was found in the responses to the other questions in the second part of the questionnaire (p>0.05).

When the answers given in the last part of the questionnaire were analyzed, it is seen that 67.5% of the participating dentists did not routinely perform TMR treatment, while 32.5% routinely performed TMD treatment (Table 4). 72.5% of the participating dentists reported that not every diagnosed clicking sound should be treated, 65% reported that occlusal splints had a place in the treatment of TMD, 97.5% reported that they referred patients with TMD to specialists, and 65% reported that they could only diagnose

Table 4. Participants' answers to the last part of the survey (categorical).

		Total	Percentage (%)
Do you routinely treat patients with TMD?	Yes	26	32.5
	No	54	67.5
Any diagnosed click should be treated.	Yes	13	16.25
	No	58	72.5
	No idea	9	1.125
Non-steroidal anti-inflammatory drugs are useful in TMD treatment.	Yes	55	68.75
	No	11	13.75
	No idea	14	17.5
Occlusal splints are required for TMD treatment.	Yes	52	65
	No	12	15
	No idea	16	20
Do you refer patients with TMD to specialist dentists?	Yes	78	97.5
	No	2	2.5
How often do you notice TMD in your patients?	Usually	27	33.75
	When the patient has a primary complaint	52	65
	Never	1	1.25
What is the most common TMD finding you have encountered?	Ankylose	1	1.25
	Myofascial pain dysfunction syndrome	8	10
	Subluxation	1	1.25
	Clicking	30	37.5
	Deviation in Mandibula	3	3.75
	Clicking and deviation in Mandibula	25	31.25
	Pain	12	22.5

TMD if the patient's primary complaint was TMJ-related. When the answers to the question "What is the most common TMD finding you have encountered?" are analyzed, the most common TMD findings encountered by the participating dentists are listed as follows: 37.5% clicking sound, 31.25% clicking sound with mandibular deviation, 22.5% pain, 10% myofascial pain dysfunction syndrome, 3.25% mandibular deviation, 1.25% ankylosis, and 1.25% subluxation. When analyzing the answers to the questions in this section, there was no statistically significant difference between the dentists with less than 5 years of professional experience and dentists with more than 5 years of professional experience ($p>0.05$) (Table 5).

DISCUSSION

TMD is one of the most common causes of pain and discomfort in the mouth, jaw, and face, including the ears and forehead. This multifactorial disorder can be caused by many factors such as genetics, stress, and malocclusion (14). There is a general lack of knowledge about TMD among general practitioner dentists in Turkey. 87.5% of dentists did not receive any training for the diagnosis and treatment of TMD after graduating from the faculty. This is particularly critical as specialization or postgraduate study has been shown to increase the ability of healthcare professionals to treat complex diseases (10).

This study also found that health professionals with more years of experience were more aware of TMD. Even if their experience is not directly related to the diagnosis and treatment of TMD, indirect encounters with patients can help health professionals develop good clinical reasoning skills (10).

Çebi et al.[15] conducted a study on oral and dental health students in 2018, the rate of bruxism awareness was found to be 24.2%, while the presence of bruxism was found to be 52.5%. It is seen that bruxism is common among students. However, the awareness of bruxism among students was found to be low.

Table 5. Answers to the last part of the survey according to the time of professional experience.

		Experience less than 5 years	Experience more than 5 years	P
Do you routinely treat patients with TMD?	Yes	9	17	0.056[a]
	No	31	23	
Any diagnosed click should be treated.	Yes	8	5	0.674[b]
	No	27	31	
	No idea	5	4	
NSAIDs are useful in TMD treatment.	Yes	26	29	0.169[a]
	No	4	7	
	No idea	10	4	
Occlusal splints are required for TMD treatment.	Yes	23	29	0.230[a]
	No	6	6	
	No idea	11	5	
Do you refer patients with TMD to specialist dentists?	Yes	39	39	1.000[b]
	No	1	1	
How often do you notice TMD in your patients?	Usually	13	14	1.000[b]
	When the patient has a primary complaint	26	26	
	Never	1	0	
What is the most common TMD finding you have encountered?	Ankylose	1	0	0.197[b]
	Myofascial pain dysfunction syndrome	5	3	
	Subluxation	0	1	
	Clicking	13	17	
	Deviation in Mandibula	3	0	
	Clicking and deviation in Mandibula	10	15	
	Pain	8	4	

[a] Pearson Chi-Square test, [b] Fischer's Exact test.

In a study conducted in Saudi Arabia, the level of public knowledge about TMD was assessed and it was found that 22.7% of the participants chose dentists and 74.5% chose medical doctors as the qualified specialists for TMD treatment. In their study, the available survey data revealed that there was insufficient knowledge about TMD, and they emphasized the need for educational seminars to increase public awareness of TMD (16).

In a study conducted in India, 71% of 148 dentists reported referring their patients with temporomandibular disorders to other health professionals, while 28% did not. Of the dentists surveyed, 92% reported that they would refer their cases to a physiotherapist, if necessary, 8% that they would not, and 1% said that they would collaborate with physiotherapists for definitive treatment plans (17).

In our study, physicians with more than 5 years of experience were found to be statistically significant in some parameters compared to patients with less than 5 years of experience. Although experienced physicians were more successful and willing to diagnose and treat TMD than physicians with less than 5 years of experience, both showed similar statistical results for referral to a specialist. The level of experience of a health professional can influence the clinical decisions they make (18).

López-Frías et al.[19] conducted a study on 130 general dentists in 2019, 96.32% of the participants believe that parafunctional habits, trauma, and psychosocial factors are involved in the etiology of TMD. In our study, the opinion of general dentists on the most important factors playing a role in the etiology of TMD was occlusal factors with a rate of 32.5% and parafunctional habits with a rate of 30%. In addition, 67.5% of

the participating dentists did not routinely treat TMD, while 32.5% did routinely treated TMD, and 65% of them stated that occlusion splints are beneficial for the TMD treatment in the present study.

Prodoehl et al.[20] also found that the number of hours devoted to TMD education in the United States was insufficient. They also suggested that additional postgraduate courses are needed. The results of our study indicate that general practitioner dentists do not have sufficient awareness of TMD. It is important to increase the awareness and knowledge of general practitioner dentists about treatment alternatives for TMD patients through various seminars and courses during their postgraduate education period.

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Original Article

Serum procalcitonin levels in open heart surgery patients and its relationship with mortality and morbidity

Açık kalp cerrahisi yapılan hastalarda serum prokalsitonin düzeyleri ve bunun mortalite ve morbidite ile ilişkisi

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ABSTRACT

Aim: The release of procalcitonin (PCT) has been suggested to be related to the type of surgery and cardiopulmonary bypass (CPB). We aimed to investigate the associations of PCT with hemodynamic stability, type of cardiac surgery, and complications.
Methods: Our study was conducted in 2015 on 76 adult patients divided into three groups according to types of surgery: group I consisted of coronary artery bypass grafting with CPB, group II consisted of cardiac valve replacement, and group III included left ventricle assist device implantation. The patients' serum PCT values were measured preoperatively before induction, 24 and 48 hours postoperatively, and when a complication occurred.
Results: Preoperative PCT levels of the groups were similar. The PCT level in group I was lowest preoperatively, highest in postoperative 24 hours, and showed a decline postoperatively from 24 hours to 48 hours. In group II, the PCT level was increased in postoperative 24 and 48 hours compared to the preoperative level, and there was no difference between postoperative 24- and 48-hour values. In group III, the PCT level was lowest preoperatively and highest in postoperative 24 hours, while the postoperative 48-hour value was lower than the 24-hour value. Intensive care unit (ICU) stay with a higher P1PCTlevel correlated with longer ICU stay. There were no differences between patients with PCT levels ≥ 0.5 and <0.5 regarding the duration of postoperative mechanical ventilation (MV), inotropic agents, and hospitalization. Patients with higher P2PCThad a longer duration of ICU stay, postoperative MV, and hospitalization. There was a correlation between the P2PCT level and the risk of complications.
Conclusion: Increased postoperative PCT levels were associated with complications, longer durations of of hospitalization, ICU stay, and postoperative MV. We suggest that PCT might be a marker for early diagnosis of complications and follow-up of the clinical course.

Keywords: Open-heart surgery, procalcitonin, mortality, left ventricular assist device

ÖZ

Amaç: Prokalsitonin salınımının cerrahinin tipi ve karmaşıklığı ve kardiyopulmoner bypass ile ilişkili olduğu öne sürülmüştür. Bu çalışmada prokalsitoninin (PCT) hemodinamik stabilite, kalp cerrahisi tipi ve komplikasyonlar ile ilişkisini araştırmayı amaçladık.
Yöntem: Çalışmamız 2015 yılında cerrahi tiplerine göre grup I koroner arter bypass greftleme, grup II KPB ile kalp kapak replasmanı ve grup III sol ventrikül destek cihazı implantasyonu olmak üzere üç gruba ayrılan 76 erişkin hasta üzerinde yapılmıştır. Hastaların serum C-reaktif protein (CRP) ve PCT değerleri ameliyat öncesi, indüksiyon öncesi, ameliyat sonrası 24 saat (P1PCT) ve 48 saat (P2PCT) ve komplikasyon oluştuğunda ölçüldü.
Bulgular: Grupların preoperatif PCT düzeyleri benzerdi. Grup I'de PCT düzeyi ameliyat öncesi en düşük, ameliyat sonrası 24 saat en yüksek ve ameliyat sonrası 24'den 48 saate kadar düşüş gösterdi. Grup II'de PCT düzeyi postoperatif 24 (P1PCT), 48 saatte preoperatif düzeye göre artmıştı ve postoperatif 24 ile 48 saat (P2PCT) arasında fark yoktu. Grup III'te

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PCT düzeyi ameliyat öncesi en düşük ve ameliyat sonrası 24 saat en yüksek iken, ameliyat sonrası 48 değeri 24 değerinden daha düşüktü. P1PCT düzeyleri ≥0.5 ve <0.5 olan hastalar arasındaki tek anlamlı fark, daha uzun yoğun bakım ünitesinde (YBÜ) kalış süresi ile ilişkili olarak daha yüksek PCT düzeyi ile YBÜ'de kalış içindi. PCT düzeyleri ≥ 0,5 ve <0,5 olan hastalar arasında postoperatif mekanik ventilasyon, inotropik ajanlar ve hastanede yatış süreleri açısından fark yoktu. P2PCT>0.5 olan hastaların yoğun bakımda kalış süreleri, postoperatif mekanik ventilasyon ve hastanede yatış süreleri daha uzundu. Grup II'nin P1PCT seviyeleri ile VFT, CPBT ve AT ölçümleri arasında ve Grup II'nin P2PCT ve AT ölçümleri arasında pozitif korelasyonlar vardı. Spesifik komplikasyonlar ile PCT seviyeleri arasında herhangi bir korelasyon mevcut değildi. Tek korelasyon, P2PCT seviyesi ile genel olarak komplikasyon riski arasındaydı.
Sonuç: Artmış postoperatif PCT seviyeleri genel olarak komplikasyon gelişimi, hastanede ve YBÜ'de daha uzun kalış süreleri ve postoperatif MV ile ilişkili olduğundan, prokalsitoninin komplikasyonların erken teşhisinde ve klinik seyrin takibinde bir belirteç olabileceğini düşünüyoruz.

Anahtar kelimeler: Açık kalp cerrahisi, prokalsitonin, mortalite, sol ventriküler destek cihazı

INTRODUCTION

Preoperative evaluation, perioperative follow-up, postoperative complications, and their management are of utmost importance in preventing perioperative mortality and morbidity in open-heart surgery. Patient age, comorbidities, functional capacity, and type and duration of surgery are also essential. Perioperative monitoring and postoperative management play a significant role in preventing early complications. Electrocardiography, hemodynamic monitoring, CK-MB, troponins, and brain natriuretic peptide (BNP) are commonly used to diagnose perioperative myocardial infarction and cardiac failure in open-heart surgery. These indicators provide an advantage in determining the prolongation of early postoperative cardiovascular support, intensive care, and hospital stay, and in predicting mortality and morbidity.

Procalcitonin (PCT) is released from the parafollicular thyroid cells as a precursor of calcitonin and is a 16-amino acid peptide (1). The normal serum PCT level is below 0.05 ng/mL.PCT levels above 0.5 ng/mL have diagnostic value in various inflammatory processes, primarily those caused by bacterial endotoxins. The type and complexity of the surgery and the duration of CPB have been claimed to be proportional to serum PCT levels.

Procalcitonin is a valuable indicator for predicting outcomes in patients with acute mesenteric ischemia of venous or arterial origin (2). Moreover, it helps diagnose mesenteric ischemia in patients admitted due to intestinal obstruction (3). Various studies have reported higher complication rates in patients with elevated PCT levels after cardiac surgery (4,5).

Although numerous indicators and classification systems have been used to predict postsurgical complications, determining specific indicators of postoperative complications is of utmost importance for early diagnosis and treatment. Procalcitonin is a marker known to increase in both infectious and septic conditions. The origin of PCT in the inflammatory response is not yet fully understood; however, Procalcitonin has been suggested to be modulated by cytokines and lipopolysaccharides (6).

Increases in cytokine levels are more significant after cardiac surgery and CPB than after other surgical procedures (7). This cytokine "burst" has a progression similar to the systemic inflammatory response syndrome and creates difficulties in diagnosing infections, which are postoperative complications. Therefore, markers that would provide information on the development of postoperative complications are of great importance.

In our literature review, while there were numerous studies on coronary artery bypass grafting (CABG), heart valve surgery (HVS), and pediatric cardiac surgery, we encountered only one study investigating the relationship between left ventricular assist device (LVAD)implantation and serum PCT levels. In our study, we aimed to investigate the PCT trends in cardiac surgeries, including LVAD implantation, on serum PCT levels. In addition, we aimed to investigate whether

hemodynamic stability was associated with PCT levels by using close intraoperative hemodynamic monitoring and to determine the association of C-reactive protein (CRP), another commonly used indicator of PCT levels.

MATERIALS AND METHODS

This was a prospective, observational clinical trial. After approval from the Ethical Committee for Medical Research, Faculty of Medicine, Akdeniz University (code:2012-KAEK-20/No:287, date:10.06.2015),76 patients older than 18 years were included in the study and were divided into three groups, according to the type of surgery as follows: group I, n=37 (49%) CABG; group II, n=18 (24%) heart valve surgery (HVS); and group III, n=21 (27%) LVAD implantation. Descriptive statistics were presented as frequency, percentage, mean, standard deviation, median, minimum, and maximum. The Shapiro–Wilk test was used to test the normality assumption. The Mann–Whitney U test was used to analyze the differences between the measurements of the two groups when the data were not normally distributed, and the independent samples t-test was used when the data were normally distributed. The Kruskal–Wallis test was used for nonparametric comparison of the three groups and the Bonferroni–Dunn procedure was used as a post hoc test for significant results. For analysis of temporal changes in PCT levels in all groups, the Friedman test was used when the data did not comply with a normal distribution, and the Bonferroni–Dunn procedure was used as a posthoc test for significant results. The associations between continuous variables that were not normally distributed were analyzed using the Spearman's correlation test. The statistical significance was set at $p < 0.05$. The Statistical Package for the Social Sciences software package (version 22.0) was used for statistical analysis.

RESULTS

We studied 76 patients; 4 patients died, 6 patients had renal replacement therapy, and 9 patients had stayed in the hospital for more than 28 days. There was no significant difference between mortality and morbidity in terms of PCT level.

The ejection fraction (EF) measurements of the groups are presented in Table 1 as means and medians. The mean EF measurements in groups I and II were significantly higher than those in group III (p=0.001).

The differences among the preoperative, postoperative 24-h (P1PCT), and postoperative 48-h (P2PCT) PCT values are presented in Table 2. In group I, the PCT level was the lowest in the preoperative levels and highest in the P1PCT measurement, whereas the PCT value decreased in the P2PCT levels compared to the P1PCT measurement. In group II, the P1PCT and P2PCTlevels were increased compared to the

Table 1. Patient characteristics of study, Body Mass Index (BMI), Diabete Mellitus (DM), Hypertension (HT). Ejection Fraction (EF), CPB time (CPBT), CCT (cross-clamp time), and AT (anesthesia time).

		Group I	Group II	Group III	p
Gender n(%)	**female**	13 (35.1)	12 (66.7)	4 (19)	0.008
	male	24 (64,9)	6 (33,3)	17 (81)	
Age(years)		61,9±8,9	61,6±7,6	51,5±8,4	<0,05
BMI (kg/m²)		26,1±7,1	25,7±6,2	25,3±5,9	>0,05
Smoking n(%)		17(62,9)	11(64,7)	1(4,7)	<0,001
DM		8(29,6)	5 (27,7)	1 (4,7)	<0,001
HT		16 (59,2)	10 (55,5)	4 (19)	<0,001
EF(%)		55,14±9,7	59,88±3,76	18,45±3,62	<0,001
CPBT(min)		135,1±28,9	152,8±83,1	90,2±35,1	<0,05
CCT(min)		85,4±18,9	97,1±24,6	-	>0,05
AT(min)		301,8±27,8	303,1±99,3	270±57,5	>0,05

Table 2. The differences among the prPCT, P1PCT, and P2PCT procalcitonin values in each group.

	Group I		Group II		Group III		p
	n	Mean±SD	n	Mean±SD	n	Mean±SD	
prPCT	36	0,18 ±0,38	17	0,16±0,38	21	0,48±1,59	<**0,001**
P1PCT	33	1,72±2,18	17	8,25±23,99	21	8±13,11	<**0,001**
P2PCT	33	0,74±1,15	17	13,09±32,76	21	6,97±15,89	<**0,001**

Table 3. The relationships of the PCT value with with intraoperative mechanical ventilation-free time (IOMVF), CPB time (CPBT), CCT (cross clamp time), and AT (anesthesia time). Positive correlation between P1PCT levels in group II and, IOMVF, CPBT, and AT.

Group	PCT		IOMVF (minutes)	CPBT (minutes)	CKT (minutes)	AT (minutes)
		r	0,06	0,191	0,11	0,025
	prPCT (ng/ml)	p	0,728	0,264	0,523	0,884
		n	36	36	36	36
		r	-0,281	-0,156	-0,149	-0,104
Group I	P1PCT (ng/ml)	p	0,113	0,385	0,409	0,563
		n	33	33	33	33
		r	-0,281	-0,084	-0,173	-0,021
	P2PCT (ng/ml)	p	0,114	0,644	0,336	0,908
		n	33	33	33	33
		r	-0,07	-0,07	0,025	0,14
	prPCT (ng/ml)	p	0,784	0,784	0,922	0,579
		n	18	18	18	18
		r	0,485*	0,486*	0,414	0,727**
Group II	P1PCT (ng/ml)	p	0,048	0,048	0,098	0,001
		n	17	17	17	17
		r	0,447	0,472	0,18	,511*
	P2PCT (ng/ml)	p	0,072	0,056	0,488	0,04
		n	17	17	17	17
		r	0,005	0,031		0,039
	prPCT (ng/ml)	p	0,983	0,893		0,866
		n	21	21		21
		r	0,229	0,216		0,075
Group III	P1PCT (ng/ml)	p	0,317	0,347		0,747
		n	21	21		21
		r	0,213	0,212		0,098
	P2PCT (ng/ml)	p	0,354	0,356		0,673
		n	21	21		21

Table 4. The relationships between PCT and the development of postoperative complications in general.

		Prpct			p1pct			p2pct		
		<**0,5 %**	≥**0,5 %**	**p**	<**0,5 %**	≥**0,5 %**	**p**	<**0,5 %**	≥**0,5 %**	**p**
Complication	**Absent**	83,1%	75,0%	0,541	93,8%	78,2%	0,272	93,5%	72,5%	**0,023**
	Present	16,9%	25,0%		6,3%	21,8%		6,5%	27,5%	

preoperative PCT value, whereas no difference was found between the P1PCT and P2PCT levels. Similar to the group I, the PCT level was the lowest in the preoperative levels and highest in the P1PCT levels, whereas the PCT value decreased in the P2PCT measurement compared to the P1PCT measurement in group III.

The differences between the patients with P1PCT measurements <0.5 and ≥0.5 ng/mL in terms of the postoperative mechanical ventilation duration (PMVD), inotrope requirements (PIRD), and durations of intensive care (ICSD) and hospital stays(HSD) are presented in Figure 1. The only difference between the two groups was the

duration of ICU stay; patients with a P1PCT value of ≥0.5 ng/mL had a longer duration of ICU stay than those with a P1PCT value of <0.5ng/mL. No significant differences were observed in the duration of postoperative mechanical ventilation, postoperative inotrope requirement, or hospital stay between the two groups.

The differences between the patients with P2PCT measurements <0.5 ng/mL and ≥0.5 ng/mL regarding the PMVD, PIRD, ICSD, and HSD are presented in Figure 2. Patients with a P2PCT value ≥0.5 ng/mL had more prolonged mechanical ventilation, intensive care, and HSD than those with a P2PCT value <0.5 ng/mL. No significant difference was observed in the duration of postoperative PIRD between the groups.

The relationships between PCT measurements (intraoperative mechanical ventilation-free time [IOMVFT]), CPB duration, CCT, and AT measurements were investigated. According to the correlation tests, positive correlations between group II's P1PCT measurement and the duration of mechanical ventilation (r=0,485; p=0,048), CPBT (r=0,486; p=0,048), and AT (r=0,727; p=0,001) were determined. In addition, the P2PCT value in group II was positively correlated with AT (r=0,511; p=0,036). The results are presented in Table 3. There was no relationship between CRP level and IOMVFT, and CPB duration, CCT, and AT measurements were investigated.

The relationships between PCT levels and postoperative complications are presented in Table 4. According to the correlation tests, there was no significant relationship between PCT level and any complication. The only positive correlation was between the P2PCT value and the development of complications in general (p=0.023), which signifies that if PCT levels do not normalize, complications will occur.

DISCUSSION

Studies have shown that bacterial endotoxins are the most important factor affecting PCT levels (8). Although not as much as infection, surgical trauma may also affect PCT levels. A significant elevation of PCT levels was observed, particularly following esophagectomy. Such an elevation was suggested to be because of the bacterial translocation that developed due to transient bacterial contamination during surgery. Following surgical trauma, another possible cause of PCT elevation is the release of cytokines during wound healing (9).

Few studies have been conducted on PCT kinetics following surgery. One of the most significant studies on this subject was the study conducted by Meisner et al., which investigated PCT kinetics following various types of surgery. In that study, PCT kinetics were investigated in 130 patients who had undergone various surgical procedures. It was reported that minor and aseptic surgeries did not affect PCT, whereas high PCT levels were determined after abdominothoracic and major procedures (9). Procalcitonin levels can spontaneously reach 1 ng/mL after minor and aseptic procedures and 2 ng/mL after cardiac surgery.

In contrast, a patient in whom PCT concentration reaches 10 ng/mL after uncomplicated surgery should be carefully investigated for infection. In their study on the effect of cardiopulmonary bypass surgery on PCT levels, Aouifi et al. divided their patients into three groups as follows: group I, patients who underwent CABG and cardiopulmonary bypass; group II,patients who underwent CABG only; and group III, patients who underwent HVS. The authors investigated the PCT levels in the preoperative period and for 5days in the postoperative period and reported that the PCT level increased in all three groups, not exceeding 5 ng/mL, reached its peak value on the 1st postoperative day, and returned to its normal level on the 5th postoperative day. Very high PCT levels were determined in 10patients who developed complications (7 patients, circulatory failure; 2patients, active endocarditis; and1patient, septic shock). In these patients, the serum PCT levels ranged between 6.2–230 ng/mL.

In conclusion, the development of postoperative complications should be suspected when PCT concentrations > 5 ng/mL are measured. Additionally, PCT is a marker superior to CRP for monitoring postoperative complications (10). In the study conducted by Kallel et al., PCT levels were measured preoperatively and at 4-h, 24-h, 48-h, 72-h, and 96-h serum samples of 40 patients who underwent CABG and HVS under CPB. The PCT level peaked on the 1st postoperative day (0.96±1.00 ng/mL) and progressively decreased on the following postoperative days. When the two groups were compared, it was found that the PCT level did not correlate with the type of surgery (11).

Serum PCT levels were correlated with organ dysfunction in sepsis and APACHE II scores (12,13). Moreover, PCT levels were well correlated with the severity of organ dysfunction, as evaluated by the SOFA score. Meisner et al. reported that PCT levels were well correlated with the maximal SOFA scores in the first two postoperative days in 208 patients who underwent CPB.

Meisner et al. determined the correlation between postoperative PCT levels and the development of SIRS, respiratory failure, and requirement for inotropic support (13). Similarly, Dörge et al. reported that patients who developed postoperative organ failure had higher PCT levels than those with a complication-free postoperative period (4). Adamik et al.[14] showed that PCT levels did not change in patients responding to treatment following CPB and with complications, mainly when renal and hepatic dysfunction developed in addition to respiratory and circulatory failure.

Hennig et al.[15] investigated markers that could predict the development of post-LVAD right ventricular failure and determined statistically significantly high PCT levels in the failure group (PCT levels 0.322 vs. 0.106 mg/dL; p=0.048). They also found statistically significant increases in endothelin-1 and neopterin levels, in addition to increased PCT levels.

Kettner et al.[16] investigated the dynamics of post-LVAD PCT and reported that even though it was an inflammatory marker, its level did not explicitly increase due to infection after the LVAD procedure. On the contrary, they reported that in patients with increased PCT levels, the overall risk of postoperative complication development increased.

In our study, the PCT levels were investigated preoperatively and, on the 1st, and 2nd postoperative days in the three groups of patients undergoing CABG, HVS, and LVAD. In all groups, PCT levels increased and peaked on the 1st postoperative day. In group I patients in whom CABG was performed under CBP, the mean PCT value was 1.72 ng/mL($p<0.001$) on the 1st postoperative day, and the maximal value was 9.3 ng/dL. In group II patients who underwent HVS, the mean value was 8.25 ng/mL ($p<0.001$) and the maximal value was 100 ng/mL. In group III patients who underwent LVAD implantation, the mean PCT level was 8 ng/mL ($p<0.001$), and the maximal value was 55.9 ng/mL. The PCT levels tended to decrease on the 2nd postoperative day in all three groups. Fifteen patients developed postoperative complications. We determined elevated PCT levels in these patients during the complications. When the present complications caused new complications, PCT levels were also high. The serum PCT levels varied within the range of 1.07–100 ng/mL in these patients. In their extensive study, Loebe et al. investigated the preoperative PCT levels of 691 patients in whom CABG, heart valve replacement, aortic surgery, and CABG+ heart valve replacement were performed with CBP. The serum PCT levels of survivors were measured daily until they were transferred from the intensive care unit to the surgical ward, and the serum PCT levels of the deceased patients were measured daily until their death. They found a significant correlation between CBP duration and serum PCT levels ($p<0.01$). They determined significant relationships with the type of surgery, requirement for vasopressor support, and requirement for intra-aortic balloon pump support (17). We determined positive correlations

and significant relationships between serum PCT levels and MVF (r=0.485; p=0,048), CBP (r=0.486; p=.048), and durations of anesthesia (r=0.727; p=0.001) in group II patients who underwent HVS. In group II, we determined a positive correlation and significant relationship between the serum PCT level on the 2nd postoperative day and the duration of anesthesia (r=0,511; p=0,036). This is a warning sign for us to be careful about the potential development of complications when the expected decrease in serum PCT level does not occur.

In terms of predicting mortality, for a cut-off value of 34.2 ng/mL, PCT had a sensitivity of 100% and specificity of 90%, whereas its sensitivity was 100% and specificity was 65% for a cut-off value of 5 ng/mL. In addition, PCT levels were associated with the development of postoperative complications. Lecharny et al.[18] reported a higher mean PCT level in the patient group who experienced postoperative myocardial infarction than in the patient group with a postoperative period. In their study on 52 pediatric patients undergoing cardiac surgery, Minami et al.[19] determined that postoperative calcitonin levels were associated with the duration of postoperative mechanical ventilation and intensive care stay. Ina study of 25 pediatric patients undergoing cardiac surgery, Beghetti et al.[20] determined significant relationships between postoperative serum PCT level, duration of intensive care stay, and inotrope requirement in the postoperative period.

In our study, the only difference between the patient groups with serum PCT levels ≥0.5 ng/mL and <0.5 ng/mL on the 1st postoperative day was the duration of intensive care stay; the patient group with higher PCT levels had a more prolonged intensive care stay (p=0.046). No differences were found in the duration of postoperative mechanical ventilation, inotropic support, or hospitalization between the patient groups with serum PCT levels ≥ 0.5 ng/mL and<0.5 ng/mL on the 1st postoperative day.

The patient group with serum PCT levels ≥0.5 ng/mL on the 2nd postoperative day was determined to have a more prolonged duration of postoperative mechanical ventilation (p=0.041), intensive care stay (p=0.001), and hospitalization (p=0.012) than the patient group with a PCT value <0.5 ng/mL; there was no difference regarding the duration of the postoperative inotropic support requirement between the two groups.

We investigated the relationship between serum PCT levels and prognosis. As the results of correlation tests, no significant relationships were determined between complications, such as sepsis, ARDS, acute renal failure, local infection, and low-output state, and the serum PCT levels on the 1st and 2nd postoperative days. When we questioned whether a complication had developed without specifying the type of complication, we determined a significant relationship between the serum PCT levels on the 2nd postoperative day and the development of complications (p=0.023), indicating that when the expected decrease in serum PCT level is not observed in patients undergoing open-heart surgery, a complication may develop. Such patients need to be closely followed up, and detailed investigations are required.

In our study, three patients completed the surgical procedure with an extracorporeal membrane oxygenator (ECMO) due to cardiac failure. In both patients in whom surgery was accomplished with ECMO implantation, serum PCT levels were 100 ng/mL starting from the 1st and 2nd days, and these values did not change with the development of complications. Both patients died on the 7th postoperative day with PCT levels of 100ng/mL.

We determined that postoperative serum PCT levels varied according to the type of surgery. Postoperative serum procalcitonin levels were higher in those who underwent heart valve replacement and LVAD implantation than in those who underwent CABG with CPB. We concluded that when the expected decrease in serum PCT

does not occur in the postoperative period, it may indicate the potential development of complications, such as infections. These results of high PCT levels give us hints about intensive care costs and new complications, such as intensive care infections. If PCT levels do not normalize, the possibility of complications increases. The limitations of our study were that this was a single-center study and had a small number of cases and complications. In light of these results, we believe that PCT maybe a good early biomarker to follow the clinical course.

Ethics Committee Approval: The study protocol was approved by the Medical Research, Faculty of Medicine, Akdeniz University Ethics Committee (10.06.2015 / 2012-KAEK-20/No:287).

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Original Article

Quantitative analysis of muscle volumes in COVID-19 pneumonia with an automated segmentation system

COVID-19 pnömonisinde kas morfolojisinin otomatik segmentasyon sistemi ile kantitatif analizi

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ABSTRACT

Aim: The aim of this study was to quantitatively analyze volume of the erector spinae muscle in COVID-19 pneumonia using an artificial intelligence-based automated segmentation program, and to investigate the relationship between pulmonary infiltration ratio and volume of the erector spinae muscle.
Methods: In this retrospective study, thoracic CT images of patients who tested positive for SARS-CoV-2 on RT-PCR and had COVID-19 pneumonia were analyzed. Based on the percentage of pulmonary involvement, the study cohort was divided into two groups (Group I: less than 25% involvement and Group II: more than %25 involvement). Volume of the erector spinae muscle and severity of lung involvement were quantitatively analyzed using an artificial intelligence-based automated segmentation program. The data of group I and group II were compared.
Results: The study population consisted of 74 subjects; 35 in Group I and 39 in Group II. Significant negative correlations were observed between the total pulmonary infiltration ratio and the volume of the erector spinae muscle. Furthermore, the analysis demonstrated that lung density, total lung infiltration volume, serum C-reactive protein (CRP) level, serum ESR level, and total erector spinae muscle volume can serve as valuable indicators for assessing the severity of lung involvement in patients with COVID-19 pneumonia.
Conclusion: Measurement of erector spinae muscle volume may be useful for assessment of pulmonary infiltration in patients with COVID-19 pneumonia.

Keywords: Erector spinae muscle volume, COVID-19 pneumonia, pulmonary infiltration, automated segmentation, artificial intelligence

ÖZ

Amaç: Bu çalışmanın amacı, yapay zeka tabanlı otomatik bir segmentasyon programı kullanarak COVID-19 pnömonisindeki erektör spina kas hacmini kantitatif olarak analiz etmek ve pulmoner infiltrasyon oranı ile erektör spina kas hacmi arasındaki ilişkiyi araştırmaktır.
Yöntem: Bu retrospektif çalışmada, RT-PCR'de SARS-CoV-2 testi pozitif çıkan ve COVID-19 pnömonisi olan hastaların toraks BT görüntüleri analiz edildi. Akciğer tutulum yüzdesine göre çalışma kohortu iki gruba ayrıldı (grup I: %25'in altında tutulum ve grup II: %25'in üzerinde tutulum). Erektör spina kas hacmi ve akciğer tutulumunun ciddiyeti, yapay zeka tabanlı bir otomatik segmentasyon programı kullanılarak kantitatif olarak analiz edildi. Grup I ve grup II verileri karşılaştırıldı.
Bulgular: Çalışmaya; I. grupta 35, II. grupta 39 olmak üzere 74 kişi dahil edildi. Toplam pulmoner infiltrasyon oranı ile erektör spina kasının hacmi arasında anlamlı negatif korelasyonlar gözlendi. Ayrıca analiz, akciğer yoğunluğunun, toplam akciğer infiltrasyon hacminin, serum CRP seviyesinin, serum ESR seviyesinin ve toplam erektör spina kas hacminin, COVID-19 pnömonisi olan hastalarda akciğer tutulumunun ciddiyetini değerlendirmek için değerli göstergeler olarak hizmet edebileceğini göstermiştir.
Sonuç: Erektör spina kas hacminin ölçülmesi, COVID-19 pnömonisi olan hastalarda pulmoner infiltrasyonların değerlendirilmesinde fayda sağlayacaktır.

Anahtar kelimeler: Erektör spina kas hacmi, COVID-19 pnömonisi, pulmoner infiltrasyon, otomatik segmentasyon, yapay zeka

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INTRODUCTION

The outbreak of COVID-19, which is caused by the SARS-CoV-2 virus belonging to the Coronaviridae family, emerged in late 2019 in Wuhan, China, and rapidly escalated into a global pandemic, prompting the World Health Organization (WHO) to declare it a major global health crisis (1,2). Until June 7, 2023, the COVID-19 pandemic has been officially documented across nearly all nations worldwide, affecting close to 767 million individuals and resulting in approximately 6.94 million reported fatalities on a global scale (3).

The gold standard method for confirming SARS-CoV-2 infection is the reverse-transcription polymerase chain reaction (RT-PCR) test, commonly employing samples from the upper respiratory tract. Nevertheless, earlier research indicates that certain RT-PCR tests exhibit reduced sensitivity (4). Chest computed tomography (CT) has demonstrated higher sensitivity in detecting infection when compared to the reverse-transcription polymerase chain reaction (RT-PCR) (5). Among adults, the utilization of thorax CT plays a crucial role as a diagnostic tool for identifying COVID-19 pneumonia (6). The clinical presentation of COVID-19 encompasses a wide range of symptoms, varying from individuals who show no symptoms to those experiencing mild to severe respiratory illness, and in some cases, respiratory failure resulting in death. Several factors and underlying medical conditions have been recognized as influential in determining the prognosis (7).

Research has demonstrated a positive association between overall patient well-being and muscle quality, indicating that quantitative assessments of muscle can serve as a valuable prognostic indicator across various health conditions such as pulmonary disorders (8,9), cirrhosis (10), different types of malignancies (11-13), and surgical outcomes (14,15). Moreover, the presence of low muscle mass has been linked to decreased immune resilience and heightened susceptibility to infectious diseases, including pneumonia (16). Several noninvasive techniques can estimate muscle quantity; among them, magnetic resonance imaging and computed tomography (CT) are considered to be optimal (17). While there are studies in the literature that assess the relationship between muscle mass and COVID-19 pneumonia using different methods in various muscle groups, there is currently no standardized evaluation method available (18,19).

However, to our knowledge, the relationship between the total volume of the erector spinae muscle, measured using an automated segmentation program between the T1-T12 vertebrae, and the lung infiltration ratio in COVID-19 pneumonia has not been investigated. Therefore, our study aimed to perform a quantitative analysis of volume of the erector spinae muscle in COVID-19 pneumonia using an artificial intelligence-based automated segmentation program. Additionally, we aimed to assess the relationship between lung infiltration and volume of the erector spinae muscle.

METHODS

In this retrospective study, thorax CT images of patients with COVID-19 pneumonia were analyzed. The study protocol was approved by the Institutional Ethics Committee (approval number: 2023/21). Patients with incomplete or insufficient data, inadequate CT images, negative results on SARS-CoV-2 RT-PCR testing, a history of surgical procedures, or a cancer diagnosis were excluded from the study (n=37). Between January 2021 and June 2021, a total of 74 symptomatic patients who tested positive for SARS-CoV-2 on RT-PCR underwent standard protocol chest CT scans to evaluate COVID-19 pneumonia. Age, gender, type of medical care (either as inpatient or outpatient), comorbidities, RT-PCR results, laboratory characteristics, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), aspartate and alanine transaminases (AST and ALT), creatine kinase (CK), D-dimer were recorded from patients' files and institutional database. Thorax CT examinations were performed using

a 64-slice CT device (General Electric Revolution EVO, 64x2 slices). The scanning range extended from the apex to the base of the lung. Scans were acquired during deep inspiration and breath-hold without contrast administration. The CT scanning protocol included the following parameters: tube voltage of 120 kVp, tube current ranging from 70 to 400 mA, rotation time of 0.5 s, pitch of 1.375, and slice thickness of 5 mm. The Digital Imaging and Communication in Medicine (DICOM) standard images of patients with COVID-19 pneumonia findings on CT were retrospectively obtained from our hospital's Picture Archiving and Communication System (PACS) database. The CT images were imported into the 3D Slicer software using the DICOM standard. The 3D reconstruction module called Editor and Models (version 5.2.2) in 3D Slicer was utilized for calculating the volumes of the erector spinae muscle (between T1-T12 vertebrae), lung volume, lung density, and pulmonary infiltration volume. The lung infiltration ratio was determined by dividing the pulmonary infiltration volume by the lung volume. Figure 1 displays the evaluation of lung infiltration and erector spinae muscle using 3D Slicer. Based on the percentage of pulmonary involvement, the study cohort was divided into two groups. Based on the percentage of pulmonary involvement, the study cohort was divided into two groups. Group I included subjects with a pulmonary infiltration ratio (PIR) less than or equal to 25%, while Group II comprised subjects with a pulmonary infiltration ratio (PIR) of 26% or greater.

Statistical analyses

Statistical analyses were performed using SPSS 18 software (IBM Co, Chicago, Il, USA). Normality analysis of the study variables was conducted using the Kolmogorov-Smirnov test. Variables that followed a normal distribution were analyzed using independent samples t-test and presented as mean and standard deviation. Non-normally distributed variables were presented as median (min-max) and compared using the Mann-Whitney U test. Categorical variables were compared between study groups using the chi-square test and reported as numbers and percentages. ROC analysis was conducted to assess the specificity and sensitivity of the study parameters in detecting pulmonary infiltrations greater than 25%. A p-value less than 0.05 was considered statistically significant.

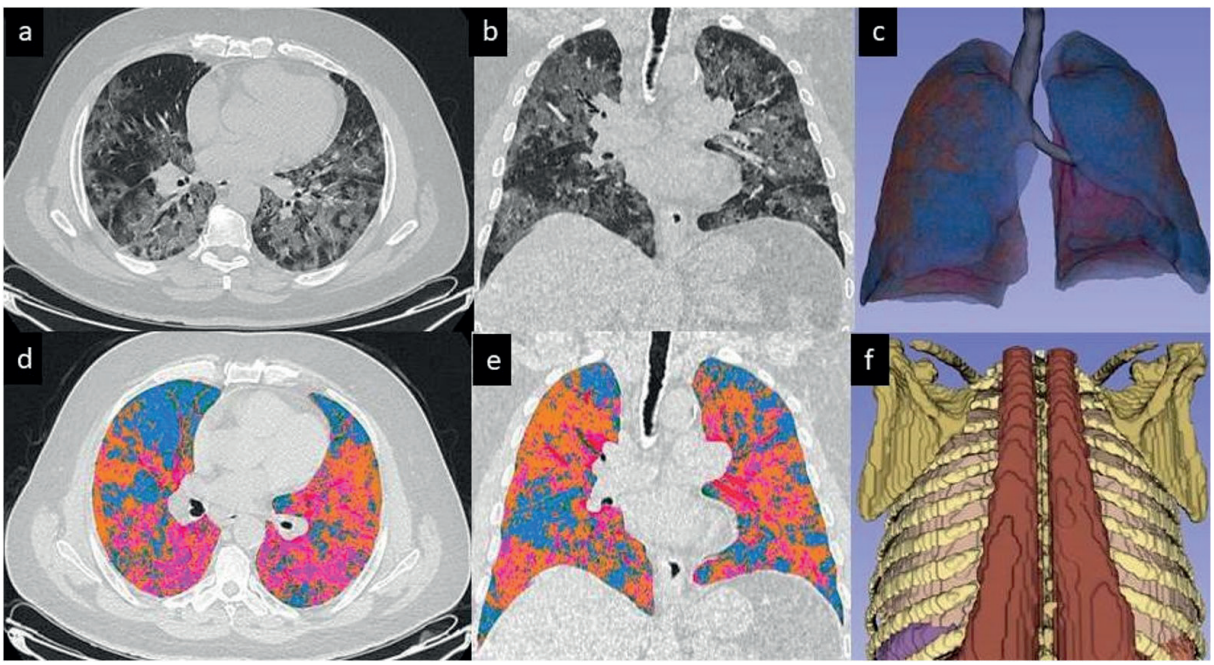

Figure 1. Images of a patient with COVID-19 pneumonia; axial (a), coronal (b) Chest CT images, three-dimensional volumetric (c), axial (d), coronal (e) lung, and erector spinae muscle (f) images obtained using 3D Slicer.

RESULTS

The study population consisted of 74 subjects: 35 in Group I (pulmonary infiltration ratio ≤ 25%) and 39 in Group II (pulmonary infiltration ratio > 25%). The mean ages of Group I and Group II were 56.5 ± 2.3 years and 59.9 ± 2.5 years, respectively (p=0.25). 18 (51%) of Group I and 17 (44%) of Group II were women. Gender of the study and control groups was not statistically different (p=0.50). Table 1 shows the demographic characteristics of the study population.

There were no statistically significant differences between group I and group II in terms of AST (p=0.51), ALT (p=0.18), D-dimer (p=0.09), and CK (p=0.67) levels.

There were no statistically significant differences in comorbidities between the two groups (p=0.13).

The rate of inpatient medical care was significantly higher in Group 2 patients (p=0.02).

Serum ESR (p=0.03) and CRP (p<0.001) levels of Group I and Group II were significantly different.

The mean lung density of subjects in Group I and Group II was (-855 ± 9.5) HU and (-834 ± 6) HU, respectively (p < 0.001).

The mean volumes of right lung infiltration (p < 0.001), total lung infiltration (p < 0.001), left lung dorsal infiltration (p < 0.001), right lung ventral infiltration (p < 0.001), volume of the right erector spinae muscle (p < 0.001), volume of the left erector spinae muscle (p < 0.001), and volume of the total erector spinae muscle (p < 0.001) were found to be significantly different between subjects in Group I and Group II.

Table 1. Demographic characteristics of the study population.

		Group I (n=35)	Group II (n=39)	p
Gender (n,%)	Women	18 (51%)	17 (44%)	0.25
	Men	17 (49%)	22 (56%)	0.25
Age (years)		56.5 ± 2.3	59.9 ± 2.5	0.50

The median volumes of the right lung (p < 0.001), left lung (p < 0.001), total lung (p < 0.001), left lung infiltration (p < 0.001), right lung dorsal infiltration (p < 0.001), left lung ventral infiltration (p < 0.001), and total pulmonary infiltration ratio (p < 0.001) were found to be significantly different between patients in Group I and Group II. Table 2 summarizes the data of group I and group II.

Serum CRP level was significantly and positively correlated with lung density (r: 0.4, p<0.001) and total lung infiltration volume (r: 0.34, p= 0.003). On the other hand, lung density was positively correlated with total lung infiltration volume (r: 0.62, p<0.001). Furthermore, a negative correlation was observed between the total pulmonary infiltration ratio and the volumes of the right erector spinae muscle (r: 0.57, p<0.001), left erector spinae muscle (r: 0.59, p<0.001), and total erector spinae muscle (r: 0.58, p<0.001). Additionally, the analysis revealed a negative association between age and erector spinae muscle volume (r: 0.38, p=0.001).

In ROC analysis, a lung density higher than -845 HU demonstrated 100% sensitivity and 91% specificity in detecting a pulmonary infiltration ratio of 26% or greater (AUC: 0.98, p < 0.001, 95% CI: 0.96-1). A total lung infiltration volume higher than 848 cm3 exhibited 85% sensitivity and 74% specificity in detecting a pulmonary infiltration ratio of 26% or greater (AUC: 0.88, p < 0.001, 95% CI: 0.80- .96). A serum CRP level higher than 75 mg/L showed 72% sensitivity and 74% specificity in detecting a pulmonary infiltration ratio of 26% or greater (AUC: 0.74, p < 0.001, 95% CI: 0.63-0.85). A serum ESR level higher than 69 mm/h demonstrated 69% sensitivity and 63% specificity in detecting a pulmonary infiltration ratio of 26% or greater (AUC: 0.65, p = 0.031, 95% CI: 0.51-0.78). A total erector spinae muscle volume lower than 488 cm3 exhibited 80% sensitivity and 72% specificity in detecting a pulmonary infiltration ratio of 26% or greater (AUC: 0.82, p < 0.001, 95% CI: 0.72-0.92) (Figure 2).

Table 2. Comparative overview of data of group I and group II.

	Group I (n=35)	Group II (n=39)	
	Mean ± Std	**Mean ± Std**	**p**
Lung density (HU)	-855 ± 9.5	-834 ± 6	< **0.001**
Right lung infiltration volume (cm^3)	400 ± 82	597 ± 158	< **0.001**
Total lung infiltration volume (cm^3)	752 ± 158	1113 ± 306	< **0.001**
Left lung dorsal infiltration volume (cm^3)	221 ± 66	318 ± 101	< **0.001**
Right lung ventral infiltration volume (cm^3)	140 ± 29	221 ± 67	< **0.001**
Right erector spinae muscle volume (cm^3)	287 ± 62	221 ± 41	< **0.001**
Left erector spinae muscle volume (cm^3)	284 ± 60	218 ± 40	< **0.001**
Total erector spinae muscle volume (cm^3)	571 ± 121	439 ± 79	< **0.001**
	Median (min-max)	**Median (min-max)**	**p**
Right lung volume (cm^3)	2060 (1461-3611)	1727 (1078-2736)	< **0.001**
Left lung volume (cm^3)	1898 (1226-2994)	1403 (1011-2345)	< **0.001**
Total lung volume (cm^3)	4178 (2687-6235)	3263 (2240-4919)	< **0.001**
Left lung infiltration volume (cm^3)	332 (208-613)	507 (301-912)	< **0.001**
Right lung dorsal infiltration volume (cm^3)	399 (226-580)	572 (379-993)	< **0.001**
Left lung ventral infiltration volume (cm^3)	121 (86-238)	185 (102-353)	< **0.001**
Total pulmonary infiltration ratio (%)	20 (8-25)	33 (28-51)	< **0.001**
AST (U/L)	36 (16-514)	38 (18-140)	p=0.51
ALT (U/L)	34 (9-119)	28 (6-81)	p=0.18
D- dimer (µ/mL)	0,66 (0,1-10)	0,90 (0,1-3)	p=0.09
CK (U/L)	106 (7-1402)	108 (8-2038)	p=0.67
ESR (mm/h)	37 (7-140)	52 (13-140)	**p=0.03**
CRP (mg/L)	39 (0.1-234)	123 (0.1-350)	< **0.001**

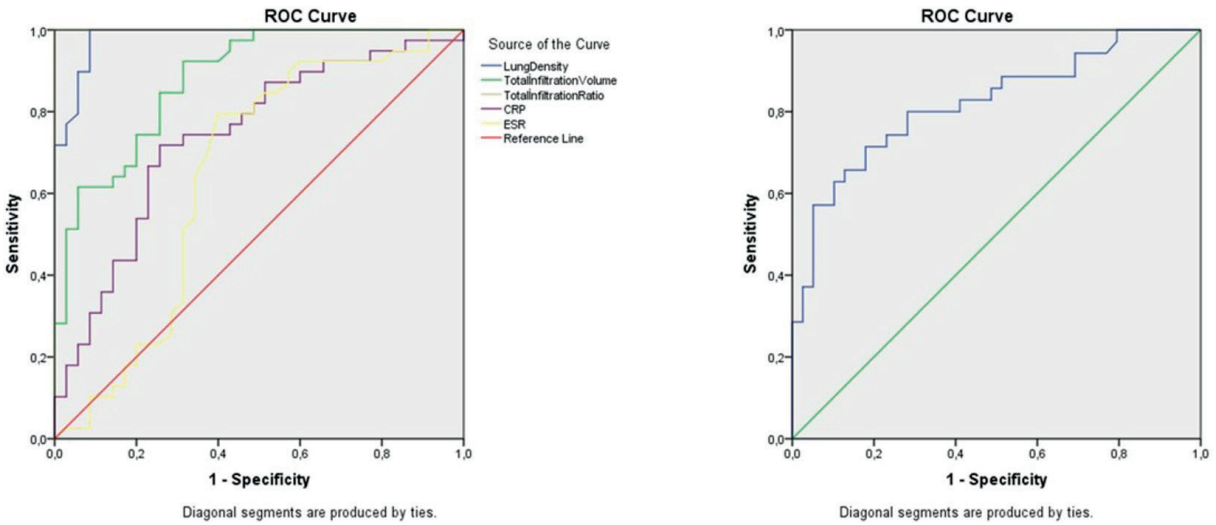

Figure 2. ROC curves of the variables in detecting higher pulmonary infiltration.

DISCUSSION

In our study, we utilized an artificial intelligence-based automated segmentation program to quantitatively analyze the volume of the erector spinae muscle in COVID-19 pneumonia. The findings of our study revealed significant differences in the volumes of the erector spinae muscle and lung infiltrations among patients with varying degrees of pulmonary involvement. Furthermore, significant associations were observed among different variables.

Serum CRP exhibited significant positive correlations with lung density and total lung infiltration volume. Lung density showed a

positive correlation with total lung infiltration volume. Conversely, lung density displayed a negative correlation with the volume of the erector spinae muscle. The ROC analysis indicated that lung density, total lung infiltration volume, serum CRP level, serum ESR level, and total erector spinae muscle volume could potentially serve as indicators for detecting a higher pulmonary infiltration ratio. These results emphasize the importance of assessing the volume of the erector spinae muscle and its association with lung infiltration in providing valuable insights into the severity and prognosis of COVID-19 pneumonia.

The relationship between low muscle volumes and mortality has been reported in different populations with various lung diseases, such as chronic obstructive pulmonary disease (COPD) (8), cancer (11), and idiopathic pulmonary fibrosis (20). Moreover, it is associated with surgical outcome in subject with pancreas cancer (12). Computed tomography-based measurements of muscle primarily demonstrate a correlation with the degree of health condition severity. Similarly, there are studies that report the correlation between muscle volume and density and the severity of COVID-19 pneumonia. Hocaoglu et al.[21] reported that the use of CT-derived measurements of the pectoralis muscle can serve as a valuable predictor for determining the severity of COVID-19 pneumonia and the mortality rate in adult patients. Similarly, Beltrão et al.[22] have reported that in their investigation conducted on the first slice, which includes the lung bases, low muscle mass and high visceral fat mass are predictive factors for mortality in patients hospitalized with moderate-to-severe COVID-19. In addition, Giraudo et al.[23] have observed that reduced muscle mass can be used as an indicator for predicting the need for intensive care unit (ICU) hospitalization in patients with COVID-19. Furthermore, it has been reported that low muscle mass is associated with mortality in patients with COVID-19, regardless of other demographic risk factors (18). These findings further support the association between muscle mass and disease severity in COVID-19 patients. The results of our study support the existing literature by demonstrating that lower erector spinae muscle volume is associated with higher levels of lung infiltration and a higher rate of hospitalization in patients with COVID-19.

Additionally, it has been noted in the literature that age and accompanying comorbidities can impact muscle volume (24). However, our study revealed no significant differences in age and accompanying comorbidities between the groups. This finding suggests that low muscle mass may independently serve as a marker for increased lung infiltration in COVID-19 patients.

C-reactive protein serves as a systemic marker of acute-phase response, indicating inflammation, infection, and tissue damage, and can be utilized as an indicator of inflammation (25). Previous studies have suggested that CRP levels can aid in the diagnosis of COVID-19 patients and predict the outcomes of COVID-19 infections (26). Wang27 and Chen et al.[28] have documented a positive correlation between CRP levels and the severity of COVID-19. On the other hand, ESR is another inflammatory marker that primarily reflects changes in various plasma proteins. In COVID-19 patients with pneumonia and severe disease, ESR levels were found to be elevated. However, its prognostic value was limited. The sensitivity and specificity values for pneumonia, intensive care needs, and mortality were lower than those of CRP (29). Additionally, CRP and CRP-based indicators were suggested as predictors of mortality in the CLEAR COVID study (30). According to the results of our study, serum ESR and CRP levels are higher in COVID-19 patients with high lung infiltration. Furthermore, a positive correlation has been observed between CRP and lung infiltration rate, with CRP demonstrating higher sensitivity and specificity compared to ESR.

Limitations of the present study include its retrospective design, single-center nature and relatively small study cohort. However, to the best of our knowledge, our present study is the first in the literature to perform a quantitative analysis of

total erector spinae muscle volume in COVID-19 pneumonia using an automated segmentation system.

In conclusion, we found significant differences in muscle volume and lung infiltrations among patients with varying degrees of pulmonary involvement. These results suggest that measuring erector spinae muscle volume may be useful in assessing pulmonary infiltrations in patients with COVID-19 pneumonia.

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee (2023/21).

Conflict of Interest: The authors have declared that they have no conflict of interest.

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Case Report

A case: Rose Bengal test positive Crimean Congo hemorrhagic fever patient

Bir olgu: Rose Bengal testi pozitif Kırım Kongo kanamalı ateşi hastası

Hatice Bozkurt Yavuz

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ABSTRACT

Brucella is one of the most common bacterial zoonosis. Crimean-Congo Hemorrhagic Fever (CCHF) is a potentially life-threatening infection. They have similar epidemiologic and clinical presentations. A 40-year-old male patient, engaged in animal husbandry, presented to the emergency unit with complaints of weakness, headache, and fever. Because of his low platelet count, he was referred to the internal medicine clinic. The patient did not have a history of contact with a tick or a CCHF patient. The Brucella Rose Bengal Test (RBT) was performed and the result was positive. After he was referred to the infectious diseases clinic, the CCHF RT-PCR test was found to be positive and the Brucella Wright agglutination test was negative. The patient, who was diagnosed with CCHF, was discharged in good condition. A positive RBT result does not always make a definitive diagnosis of Brucella infection. In areas where CCHF and Brucella are endemic, CCHF should be considered even if there is no history of ticks.

Keywords: Brucellosis, Crimean-Congo hemorrhagic fever, Rose Bengal, thrombocytopenia

ÖZ

Brusella en yaygın bakteriyel zoonozlardan biridir. Kırım-Kongo kanamalı ateşi (KKKA) potansiyel olarak yaşamı tehdit eden bir enfeksiyondur. İki hastalık benzer epidemiyolojik ve klinik prezentasyona sahiptirler. Hayvancılıkla uğraşan 40 yaşında erkek hasta halsizlik, baş ağrısı ve ateş şikayetleri ile acil servise başvurdu. Trombosit sayısının düşük olması nedeniyle dahiliye kliniğine yönlendirildi. Hastanın kene veya KKKA hastası ile temas öyküsü yoktu. Brucella Rose bengal testi (RBT) yapıldı ve sonuç pozitifti. Enfeksiyon hastalıkları kliniğine sevk edildikten sonra KKKA RT-PCR testi pozitif, Brucella Wright aglütinasyon testi negatif bulundu. KKKA tanısı konulan hasta sağlık durumu iyi olarak taburcu edildi. Pozitif RBT sonucu her zaman Brucella enfeksiyonunun kesin tanısını koymaz. KKKA ve Brusella'nın endemik görüldüğü bölgelerde kene öyküsü olmasa bile KKKA açısından dikkatli olunmalıdır.

Anahtar kelimeler: Bruselloz, Kırım-Kongo kanamalı ateşi, Rose Bengal, trombositopeni

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INTRODUCTION

Brucella, one of the most common bacterial zoonosis, is seen in more than five hundred thousand new cases each year. Brucella melitensis, Brucella abortus, and Brucella suis are the three species generally associated with human disease (1). The main route of transmission of the disease is the consumption of unpasteurized milk and dairy products, the consumption of undercooked meat or skin penetration of those can also be counted as the other routes of transmission (2).

Brucellosis has a lower fatality rate of 2%, however, it can cause severe disability (3). On the other hand, Crimean-Congo hemorrhagic fever (CCHF) is a life-threatening infection, with reported mortality rates of 13%–30%, caused by the CCHF virus which belongs to the genus Nairovirus in the Bunyaviridae family. It may exhibit a severe profile with fatal bleeding or may exhibit a mild clinical course (4). The affected population and the clinical presentation of CCHF and brucellosis are similar, so brucellosis should be considered in the differential diagnosis of CCHF in endemic areas.

CASE REPORT

A 40-year-old male patient, engaged in animal husbandry, applied to the emergency unit of our hospital in April 2020 with complaints of weakness, headache, and fever at night. His fever was 37.8˚C in the hospital. There was no history of COVID-19 contact. Laboratory results of the patient are shown in Table 1, as 1st day. Since our region is endemic area for CCHF and because the season is favorable for tick cases, the history of tick was enquired. It was learned that there was no history of ticks or a family member with a recent CCHF disease. The patient was referred to the internal medicine clinic. Two days later, the patient applied to the internal medicine outpatient clinic, thrombocytopenia deepened and the ALT and AST values, which were normal at the emergency admission, increased. The results of the 3rd day are shown in Table 1.

In the internal medicine clinic, while taking the patient's history, it was learned that he had been treated for Brucella six years ago. The patient had nausea, vomiting, and diarrhea for two days. It was suspected that the patient, who did not have a history of contact with a tick or a CCHF patient, might have had a Brucella infection. Therefore, Brucella Rose Bengal agglutination test was performed in the clinical biochemistry laboratory and the result was positive. The patient was referred to the infectious diseases clinic in a tertiary care hospital.

The CCHF RT-PCR (Reverse-Transcription-Polymerase Chain Reaction) test was found to be positive upon his admission to the tertiary infectious diseases clinic. The result of the Brucella Wright agglutination test (with Coombs antiserum) was negative with <1/20. The patient was diagnosed with CCHF. After hospitalization, the patient's blood counts were closely monitored (Table 1, days 3-9). Due to the decrease in platelet count, 5 units of platelet suspension and 2 units of fresh frozen plasma were given to the patient. The patient was discharged on the 7th day of his admission. The written informed consent was obtained from the patient for the publication of this case report.

Table 1. Laboratory results of the patient.

	1.day	3.day	4.day	5.day	6.day	7.day	8.day	9.day	10.day
PLT (10^9/L)	125	43	34	32	32	20	72	91	209
WBC (10^9/L)	3,2	1,3	1,5	1,9	2,6	3,2	4,1	5,0	5,7
aPTT (s)	29	28	28	32	28	23	21	-	-
ALT (U/L)	44	125	145	224	271	228	208	125	102
AST (U/L)	32	51	60	118	164	160	202	156	154
CK (U/L)	-	-	450	488	263	188	102	179	50
LDH (U/L)	288	221	625	596	579	548	458	483	549

PLT: Platelets; WBC: White Blood Cells; aPTT: Activated partial thromboplastin time; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CK: Creatine Kinase; LDH: Lactate Dehydrogenase

DISCUSSION

Symptoms that are non-specific and easily confused with many diseases are common in brucellosis. Since it can present with hematological findings, it is possible to be confused with any disease that can cause hematological involvement (5). Hematological findings can be seen as a result of bone marrow suppression in brucellosis. Similar laboratory findings such as leukopenia, thrombocytopenia, and anemia can be seen in CCHF. ALT, AST, LDH, and CK elevation can also be seen in both diseases (6,7).

In our case, Brucella infection was primarily considered due to the absence of tick history, but CCHF could not be excluded due to the rapid deepening of thrombocytopenia. The main route of transmission of CCHF is tick bite, but humans are also infected by crushing infected ticks, and contact with a CCHF patient, or body secretions of viraemic animals (4). Therefore, it should be kept in mind that CCHF can be transmitted without a history of ticks. CCHF should be considered in deteriorating blood counts, especially in people engaged in animal husbandry.

The Rose Bengal test detects smooth lipopolysaccharide-specific immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) (8). The Rose Bengal test has high sensitivity and relatively low specificity. However, it may give false positive results in people who have had Brucella previously. A study showed that the positive predictive value is 0.89 and the specificity is 76.9% in people who had Brucella infection before (9). It is also known that Vibrio cholerae, Francisella tularensis, and Yersinia enterocolitica 0:9 show cross-reactivity in this test (8). Vaccination, antibody residues, and laboratory errors can be considered for cross-reactivity (10). Moreover, a recent study found that the Rose Bengal test may cause false positive results in patients with Coronavirus disease (COVID-19) (11).

People who come into contact with livestock in endemic areas, such as shepherds, veterinarians, farmers, and butchers, are at high risk for CCHF. In addition, laboratory workers are at risk of disease transmission (12). Both diseases are common in those living in rural areas and involve animal husbandry.

In conclusion, in areas where CCHF and Brucella are endemic, CCHF should beconsidered in cases of rapid progression of thrombocytopenia, even if there is no history of ticks. Thrombocytopenic patients should be evaluated for CCHF, especially in the epidemic season. A positive Rose Bengal test does not always make a definitive diagnosis of Brucella.

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