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İÇİNDEKİLER/CONTENTS
Araştırma Makaleleri /Research Articles

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Araştırma Makaleleri /Research Articles

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Is Serum C- Reactive Protein to Albumin Ratio Be A New Biomarker for Assessing Disease Activity and Quality of Life in Rheumatoid Arthritis?

Serum C- Reaktif Protein/Albumin Oranı, Romatoid Artritte Hastalık Aktivitesini ve Yaşam Kalitesini Değerlendirmek için Yeni Bir Belirteç Olabilir Mi?

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Abstract

The C-reactive protein (CRP)/albumin ratio is a biomarker that has gained importance in recent years in demonstrating systemic inflammation. The aim of this study was to evaluate the relationship of CRP/albumin ratio with disease activity and quality of life in patients with rheumatoid arthritis (RA). Fifty RA patients were included in this cross-sectional study. The CRP/albumin ratio was calculated from the blood of the individuals included in the study. The disease activity score-28 (DAS-28) measurement scale was used to determine disease activity. The Health Assessment Questionnaire (HAQ) was used to assess functional status, and the Short-form health survey 36 (SF-36) was used to assess the quality of life. When the patients were evaluated according to the disease activity level, the CRP/albumin ratio was statistically significantly higher in patients with moderate-high disease activity compared to those in remission in post-hoc analyses (p=0.006). In correlation analyzes, moderate and positive correlation (p=0.002, rs= 0.426; p<0.001, rs= 0.536, respectively) was observed between CRP/albumin ratio and erythrocyte sedimentation rate (ESR) and DAS 28-ESR scores. When the patients were evaluated according to the drug treatments they received, no significant difference was observed between conventional DMARD and biological DMARD users in terms of CRP/albumin ratio, SF-36, and HAQ scores (p>0.05). Our results suggest that CAR may be used in clinics to determine inflammation and disease activity as an inexpensive and easily applicable biomarker.

Keywords: C-reactive protein, albumin, rheumatoid arthritis, disease activity

Özet

Serum C- reaktif protein /albumin oranı Romatoid Artritte sistemik inflamasyonu göstermede son yıllarda önem kazanan bir biyobelirteçtir. Bu çalışmanın amacı Romatoid artritli (RA) hastalarda CRP/ albumin oranının hastalık aktivitesi ve hayat kalitesi ile olan ilişkisini değerlendirmektir. Bu kesitsel çalışmaya 50 RA hastası dahil edilmiştir. Çalışmaya alınan bireylerin kanlarından CRP/ albumin oranı hesaplandı. Hastalık aktivitesini tayin etmek amacıyla hastalık aktivite skoru (DAS-28) ölçüm skalası kullanıldı. Fonksiyonel durum değerlendirmedi için Sağlık değerlendirme anketi (HAQ) anketi, yaşam kalitesini değerlendirmek için de Kısa-form 36 (SF-36) anketi kullanıldı. Hastalar, post-hoc analizlerde hastalık aktivite düzeyine göre değerlendirildiğinde hastalık aktivitesi orta-yüksek olanlarda CRP/albumin oranının remisyondakilere oranla istatistiksel olarak anlamlı oranda yüksek olduğu gözlendi (p=0.006). Korelasyon analizlerinde CRP/ albumin oranı ile eritrosit sedimentasyon hızı (ESR) ve DAS 28-ESR skorları arasında ılımlı ve pozitif yönde korelasyon (p=0.002, rs= 0.426; p<0.001, rs= 0.536, sırasıyla) izlendi. Hastalar aldıkları ilaç tedavilerine göre değerlendirildiğinde konvansiyonel hastalık modifiye edici anti-romatizmal ilaç (DMARD) ve biyolojik DMARD alanlar arasında CRP/albumin oranı, SF-36 ve HAQ skorları açısından anlamlı fark izlenmedi (p>0.05). Çalışmamızın sonuçları, ucuz ve kolay uygulanabilir bir biyobelirteç olarak CRP/ albumin oranının kliniklerde inflamasyon ve hastalık aktivitesini belirlemek için kullanılabileceğini düşündürmektedir.

Anahtar Kelimeler: C- reaktif protein, albumin, romatoid artrit, hastalık aktivitesi

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1. Introduction

Rheumatoid arthritis (RA) is an autoinflammatory chronic disease characterized by synovial inflammation that severely leads to joint deformities. Although the etiology of RA is not known precisely, it is thought to be related to genetic and environmental factors (1). The disease is characterized by synovitis, which occurs due to immunological and inflammatory responses in the joints involved in the acute stages of the disease. Ultimately cartilage-destroying enzymes, prostaglandins, leukotrienes, free radicals, and acute phase reactants lead to progressive destruction of articular cartilage and bone (2). Early diagnosis and treatment of the disease prevent irreversible joint deformations (3). It usually presents with polyarticular involvement in the hands and feet. RA is also associated with an increased risk of cardiovascular disease as an extraarticular involvement. Early diagnosis of the underlying inflammation is essential for effective treatment in rheumatoid arthritis. Furthermore, measurement of disease activity is essential to target treatment and improve outcomes (4).

Disease activity level and duration of remission play an essential role in the progression of the disease (5). Acute phase reactants are important in the diagnosis and follow-up of the disease. Laboratory parameters such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and disease activity score-28 (DAS-28) are used to evaluate disease activity in RA patients (6). Although ESR and CRP are the most commonly used acute phase reactants, they are non-specific, show short-term inflammation, and can be affected by many factors (7). In this sense, other biomarkers indicating inflammation are needed. Several studies suggested that CRP/albumin ratio (CAR) is a new laboratory indicator and CAR concentration increased in cancer and cardiovascular disease, and is associated with the inflammation .They revealed that high CRP levels and low albumin levels were concerned with the inflammatory process and as a new predictive biomarker, CAR might be used to assess disease activity in RA patients (8, 9). Yang et al (8) found that CAR has a correlation with DAS-28 in RA patients, and can be used as an indicator to assess the activity of RA. However, studies investigating CAR in systemic autoinflammatory diseases such as RA are scarce in the literature. Therefore, in this study we aimed to investigate the relationship between CAR and disease activity and quality of life in RA patients.

2. Patients and Methods

This cross-sectional study included subjects among the 50 RA patients admitted to our clinic for regular follow-up visits. The inclusion criteria were as follows; being above 18 years and diagnosed according to the American College of Rheumatology/ European League Against Rheumatism 2010 RA classification criteria (10). The exclusion criteria were an active infectious disease, pregnancy, a history of any drug modification, hematological malignancies, other chronic inflammatory diseases, liver disease, and kidney failure. Participants were fully informed about the experimental procedures and gave their informed consent. The study protocol was approved by the Selcuk University Ethics Committee (decision number: 2021/360, date: 07.07.2021) was obtained.

Patients' clinical assessments were performed by the same physician. The DAS 28 score was calculated using the number of painful joints or swollen joints, a visual analog scale (VAS), the levels of ESR according to the formula $0.56 * \sqrt{(TJC28)} + 0.28 * \sqrt{(SJC28)} + 0.70 * \ln(ESR) + 0.014 * VAS$ (General Health) (11). High disease activity related to DAS28 >5.1, score between 3.2 to 5.1 means moderate disease activity, and score for the low disease activity is defined in the range of 2.6 to 3.2. A cutoff point for "remission" is defined as <2.6 (12).

Blood samples were analyzed from the antecubital peripheral vein of patients after after a 10-hour fast. Serum ESR was measured by Westergren's method. Serum CRP was measured using an immunoturbidimetric method with Beckman Coulter AU5800 device (IDS Co Ltd., Japan)

with a standard range of 0-5 mg/L. Albumin level was measured by the bromocresol green method (Siemens). RF was measured using the immunoturbidometric method with Beckman Coulter AU5800 device (IDS Co Ltd., Japan), and levels above 20 IU/mL were defined as positive. Anti-CCP was measured by Enzyme-linked immunosorbent assays (Euroimmunag), and levels above 5U/ml were defined as positive.

The functional status was assessed with Health Assessment Questionnaire (HAQ). It is developed for patients with arthritis. It is a scale consisting of 20 questions. A high score indicates impaired functionality (13, 14).

The Quality of life (QOL) was assessed with the Short-form health survey 36 (SF-36) questionnaire. SF-36 consists of 36 items and eight domains that indicate physical functioning, physical role limitation, pain, general health, vitality, social functioning, emotional role limitation, and mental health. The score of each domain ranges from 0 (worst QOL) to 100 (the best QOL) (15). Turkish validity and reliability were proven by Kaya et al (16).

Sample size

The sample size estimation was performed using the GPower V3.1.7 (University of Kiel, Kiel, Germany). It was determined that minimum 42 participants must be recruited to detect a difference at 5% type1 error, 0.8 effect size (effect size, d=0.8, Cohen large effect size) and 95% power.

Statistical analysis

All statistical analyses were performed with IBM SPSS Version 22. The normality of the distribution was checked with the Shapiro-Wilk test. Descriptive statistics for numerical variables are presented as mean ± standard deviation, median (min-max), and interquartile range (IQR). Statistics for categorical variables are presented as frequency (n) and percentage (%). Kruskal-Wallis test was used to assess the relationship between remission, low, moderate, high disease activity groups according to DAS28-ESR. The differences between albumin, CAR, DAS 28-ESR, HAQ and SF-36 scores between the groups receiving conventional disease-modifying antirheumatic drug (DMARD) and biological DMARD were evaluated with the Mann Whitney-U test. Spearman's correlation coefficient (rs) was used to determine the nonparametric correlation between variables. $P<0.05$ was considered the level of significance.

3. Results

The details regarding the demographic and clinical characteristics of patients are given in Table 1. The patients included 12 males (24%) and 38 females (76%), with a mean age of 46.8 ± 11.28 years. Of the patients, 2% were illiterate, 64% were primary and secondary school graduates, 22% were high school, and 12% were university graduates. Sixty-two percent of patients were housewives, while 26% were employed and 12% were retired. The median (min-max) ESR was 18 mm/hour (12-38) and median CRP was 5.18 (3.38-10.72) mg/L, median CAR was 1.26 (0.81-2.55), median albumin was 4.2 (2.9- 4.8) g/dL, and median DAS28-ESR was 2.99 (2.37-3.77). Patients doing regular aerobic exercise were 20%.

Table 1. Demographic and clinical characteristics of patients (n=50)

Age (years)(mean± SD)	**46.8 (±11.28)**
Gender (n)(%)	
Male	12 (24%)
Female	38 (76%)
BMI (mean± SD)	28.5 (±4.28)

Duration of symptoms (year) (median min-max)	8.5 (1-34)
Drug (n)(%)	
Conventional DMARD	24 (48%)
Biological DMARD	26 (52%)
Morning stiffness duration (n)(%)	
30 minutes	35 (70%)
30-60 minutes	5 (10%)
>60 minutes	10 (20%)
Regular exercise (aerobic /30 min/3 times a week) (n)(%)	
Yes	10 (20%)
No	40 (40%)
RF (n)(%)	
Positive	29 (58%)
Negative	21 (42%)
Anti CCP (n)(%)	
Positive	36 (72%)
Negative	14 (28%)
ESR (mm/h)(Median) (25-75%)	18 (12-38)
CRP (mg/dl)(Median) (25-75%)	5.18 (3.38-10.72)
CAR (Median)((25-75%)	1.26 (0.81-2.55)
Albumin (g/dl) (Median) (25-75%)	4.2 (2.9- 4.8)
DAS28-ESR(Median) (25-75%)	2.99 (2.37-3.77)

SD Standard deviation, BMI Body mass index, DMARD disease-modifying antirheumatic drug, RF Rheumatoid factor, Anti-CCP anti- Cyclic citrullinated peptid, ESR Eritrocyte sedimentation rate, CRP C reactive protein, CAR C reactive protein to albumin ratio, DAS-28-ESR disease activity score-28- Eritrocyte sedimentation rate

In post-hoc analysis, CAR values were significantly higher in the patients with high-moderate disease activity than patients in remission (p=0.006). There was a significant difference in CRP between low disease and moderate-high disease activity groups (p=0.002) (Table-2).

Table 2. Comparison of laboratory data according to DAS 28 ESR groups

	(Remission) (n=9)	disease activity) (n=22)	(Moderate-high disease activity) (n=19)	value
CRP (median min-max)	3.3 (1.1-19.3)	**6.6 (1.2-25)**	**8.9 (1.6-47.5)**	**0.002***
Albumin (g/dl) (median min-max)	4.2 (3-4.8)	4.2 (2.9-4.6)	4.1 (3.2-4.5)	0.756[a]
CAR (median min-max)	**0.758 (0.23-5.03)**	1.546 (0.3-8.5)	**2.21 (0.4-14.8)**	**0.006***

*a One-way Anova test, * Kruskal-Wallis Test, CRP C-reactive protein, CAR C- reactive protein to albumin ratio*

When the patients were divided into two groups regarding receiving conventional DMARD and biological DMARD, there was no difference between the groups in terms of albumin, CAR, DAS 28-ESR, HAQ scores, and SF-36 subscales (p>0.05) (Table-3).

Table 3. Comparison of clinical and laboratory data according to the treatment

Parameters	Conventional DMARD (n=24))	Biological DMARD (n=26)	p value
HAQ score (median min-max)	0.35 (0-1.9)	0.22 (0-3)	0.921[a]
SF -36 subscale			
Physical Function (median min-max)	65 (0-100)	80 (5-100)	0.270[a]
Physical Role Limitation (median min-max)	50 (0-100)	100 (0-100)	0.208[a]
Emotional Role Limitation (median min-max)	100 (0-100)	100 (0-100)	0.588[a]
Energy (mean± SD)	43.54 (±24.06)	47.50 (±23.4)	0.558[b]
Emotional Well-being (mean± SD)	62.83 (±21.4)	63.53 (±22.1)	0.910[b]
Social Functions (median min-max)	69 (0-100)	81.5 (13-100)	0.201[a]
Pain (median min-max)	46.5 (0-100)	63 (0-100)	0.502[a]
General Health (median min-max)	47.91 (±20.3)	50.38 (±22.8)	0.689[b]
DAS 28-ESR (mean± SD)	2.93 (±0.85)	3.30 (±1.1)	0.211[b]
Albumin (median min-max)	4.2 (3-4.8)	4.19 (2.9-4.6)	0.359[a]
CAR (median min-max)	1.10 (0.23-4.6)	2.23 (0.3-14.8)	0.132[a]

a Mann-Whitney U test, b Student T-test, HAQ Health Assessment Questionnaire, SF-36 Short-form 36, DAS28-ESR Disease activity score 28- Erythrocyte sedimentation rate, SD Standard deviation, CAR C-reactive protein to albumin ratio

Correlation analysis showed that there was a significant and moderate positive correlation between CAR, ESR and DAS 28-ESR (p=0.002, rs= 0.426; p<0.001, rs= 0.536, respectively). Furthermore, there was a significant and strong positive correlation between CAR and CRP (p<0.001, rs= 0.994) (Table 4).

Table 4. C-reactive protein/albumin ratio (CAR) and its correlation with other clinical parameters

Parameters	CAR	
	p value	rs
DAS 28- ESR	**0.002**	0.426
HAQ score	0.301	0.149
	0.001	0.536
	0.001	0.994
	0.757	0.045
ESR (mm/h)	0.766	0.043
CRP (mg/dl		
RF positive	0.779	-0.041
Anti-CCP positive		

SF -36 subscale	0.428	-0.115
Physical Function	0.607	0.074
Physical Role Limitation	0.564	0.084
Emotional Role Limitation	0.896	0.019
Energy	0.689	-0.058
Emotional Well-being	0.909	0.017
Social Functions	0.893	0.019
Pain		
General Health		

rs Spearman correlation coefficient, CAR; C- reactive protein to albumin ratio, DAS28-ESR Disease activity score 28- Erythrocyte sedimentation rate, HAQ Health Assessment Questionnaire, ESRErythrocyte sedimentation rate, RF Rheumatoid factor, Anti-CCP anti-citrullinated peptide, SF-36 Short-form 36

4. Discussion

The main finding of this study was the higher level of the CAR in the patients with high-moderate disease activity. There was a moderate positive correlation between ESR, CRP, and DAS 28-ESR scores. These results might support the role of CAR in inflammatory conditions such as RA. Some of the studies in the literature suggested that CAR value was superior to CRP in predicting mortality alone (17, 18). A study done by Yang et al.(8) showed that the positive correlation between CAR and CRP, ESR, and DAS 28 scores is similar to our findings. Therefore, CAR might be use in terms of disease activity in the patients with RA. Another study, comparing 32 Takayasu arteritis patients and 32 healthy controls, revealed that CAR was significantly correlated with disease activity, CRP, and ESR levels (19). Unlike the results of our study, Sunar et al (20) found a weak correlation between the CAR and DAS 28-ESR in the RA patients. They stated that the CAR might be an additional marker in disease activity, among other markers. On the other hand, several previous studies have shown that CAR was increased in cancer and cardiovascular diseases, which may suggest that there is a relationship between inflammation and CAR (21, 22). Some studies suggested that CAR was a long term biomarker and it would give more precise results in mortality compared to CRP alone (17, 18).

The CRP divided into albumin levels is known as CAR. Albumin is not only related to nutritional status but also related to inflammation. In systemic inflammation, albumin levels decrease, and acute phase reactants increase. Therefore, there is an association between hypoalbuminemia and CRP levels (23). In our study, we did not have any patients with hypoalbuminemia. However, there was no difference in terms of albumin levels between groups, in intragroup comparison showed that patients with moderate-high disease activity had decreased albumin levels. Although many studies showed the relationship between CAR and other inflammatory conditions, few studies in the literature report its relationship with autoimmune diseases (8, 9, 20). To the best of our knowledge, this is the second cross-sectional study investigating the relationship between CAR and disease activity and quality of life in RA patients. We found that CAR was significantly higher in the high disease activity group than patients in remission and moderate to strongly associated with ESR, CRP, and DAS28-ESR scores. This result may be used as a positive indicator for the literature in terms of disease activity assessment in RA. However, we did not observe any correlation between CAR and quality of life and HAQ scores which may be related to the most patients have low disease activity in our study. Similar to our study, a recent study did not find any relationship between CAR and quality of life (20).

In our study, there were no differences in CAR levels, DAS 28-ESR, SF-36, and HAQ scores between conventional and biological DMARD groups regarding the drug treatment options. This may be arised from the

suppressive effect of the given treatments on inflammation. Similar to our results, a recent study revealed no relationship in CAR and DAS28-ESR levels between biological and conventional DMARD therapy (20). Another study investigating the predictive factors for drug treatment in RA also reported that, among other factors, CRP was the most associated marker with the clinical outcomes of RA (24).

The DAS-28 scale is the most commonly used scale to determine disease activity for RA in clinics. However, applying this scale is time-consuming in busy clinics. Since the CAR is an easily calculated laboratory data, it may be beneficial in time-saving in the evaluation of disease activity.

Serum RF and anti-CCP values are known as essential indicators in disease activity and progression (25). However, we did not detect a correlation between CAR and RF and anti-CCP values in this study which may be related to the small sample size of our study.

This study had some limitations. First, our study was a cross-sectional study, and there were no control patients. The second limitation is the small sample size which may weaken the generalizing of the results. More precise results can be obtained with further randomized-controlled clinical studies in which the sample size is increased.

5. Conclusion

This study provided evidence of the relationship between CAR and disease activity. Our results suggest that CAR may be used in clinics to determine inflammation and disease activity as an inexpensive and easily applicable biomarker.

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Research Article / Araştırma Makalesi

A Qualitative Evaluation of the Health-Care Workers Infected with COVID-19

COVID-19 ile Enfekte Olan Sağlık Çalışanlarının Kalitatif Değerlendirilmesi

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Abstract

This study aims to determine the thoughts and opinions of healthcare professionals working in a pandemic hospital and infected with COVID-19 regarding the reasons for taking the agent, the disease process, and the risks in the environment in which they work. This study was designed as a qualitative descriptive study. The study, which is working in a pandemic hospital in Turkey and 14 health workers who were infected with COVID-19 was carried out between June-July 2020. The researcher collected the data through face-to-face interviews with a semi-structured, in-depth interview form created in line with the aims of the study. In the study, three main themes were determined under the heading of; the negative effects on health of COVID-19 as a healthcare worker during the pandemic process, thoughts about the cause of becoming COVID-19, and experiences and effects during the COVID-19 disease process. During the interviews, healthcare professionals stated that they were caught COVID-19 because of their work and workplace, they were stigmatized due to their illnesses, they lost their health due to COVID-19, and they had concerns that some health problems would not pass. However, they stated that they had a shortage of personal protective equipment at the beginning, they did not receive training on the subject, and the risk of being infected with COVID-19 was high due to the excessive working hours. Healthcare workers suffering from COVID-19 have experienced the infection physically and mentally in a very severe way.

Keywords: Coronavirus, COVID-19, health-care workers

Özet

Bu çalışmanın amacı, bir pandemi hastanesinde çalışan ve COVID-19 ile enfekte olan sağlık çalışanlarının, etkeni alma nedenleri, hastalık süreci ve çalıştıkları ortamdaki risklere ilişkin düşünce ve görüşlerini belirlemektir. Bu araştırma nitel tanımlayıcı bir araştırma olarak tasarlanmıştır. Türkiye'de bir pandemi hastanesinde çalışmakta olan ve COVID-19 ile enfekte olan 14 sağlık çalışanı ile Haziran-Temmuz 2020 tarihleri arasında yürütülmüş olan kalitatif bir çalışmadır. Veriler, araştırmacı tarafından, çalışmanın amaçları doğrultusunda oluşturulan yarı yapılandırılmış, derinlemesine görüşme formu ile yüz yüze görüşülerek toplanmıştır. Araştırmada pandemi sürecinde sağlık çalışanı olarak COVID-19 un sağlık üzerine negatif etkileri, COVID-19'a yakalanma nedeni ile ilgili düşünceler ve COVID-19 hastalık sürecinde yaşananlar ve etkileri başlığı altında üç ana tema belirlenmiştir. Yapılan görüşmelerde sağlık çalışanları yaptıkları iş ve işyerinden dolayı COVID-19'a yakalandıkları, hastalıkları nedeniyle damgalandıklarını, COVID-19'a bağlı olarak sağlıklarını kaybettiklerini ve bazı sağlık sorunlarının geçmeyeceğine ilişkin kaygılarının olduğunu belirtmişlerdir. Bununla birlikte başlangıçta kişisel koruyucu malzeme sıkıntısı yaşadıklarını, konu ile ilgili eğitim almadıklarını ve çalışma saatlerinin fazla olması nedeniyle COVID-19 ile enfekte olma risklerinin fazla olduğunu ifade etmişlerdir. COVID-19 hastalığına yakalanmış olan sağlık çalışanları, enfeksiyonunu bedensel ve ruhsal olarak ağır bir şekilde yaşamışlardır.

Anahtar Kelimeler: Koronavirus, COVID-19, sağlık çalışanları

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1. Introduction

In the COVID-19 pandemic, frontline health-care workers (HCW) who provide treatment and care to patients around the world play the most important role. The risk of contamination is very high for the physician, nurse, paramedic, transport personnel and laboratory staff due to their profession, who are in close contact with patients infected with COVID-19 (1). Due to the rapid spread of the disease to many parts of the world, HCW are inadequate in return for the increased patient and workload (2,3). In this pandemic, where societies and the governance systems of countries were caught unprepared, thousands of HCW all over the world were infected with COVID-19 and even died.

Since there is no systematic reporting system for HCW infected with COVID-19, it is difficult to obtain and track up-to-date and accurate data. For this reason, the real number of HCW infected with COVID-19 has not been determined. World Health Organization (WHO) President Dr. Ghebreyesus has stated that the at least 10% of COVID-19 infections in the world is constituted by health care workers and "Physical and psychological fatigue experienced by many health care workers, after working for several months in extremely stressful situations" (4). There are no reports that have been published in Turkey about how many health workers infected with COVID-19, according to their profession, age the group, treatment processes. It has been reported that the number of HCW who are diagnosed with COVID-19 is more than 40 thousand now, and who died is 107 (5). In the press release issued by the Health Minister of the Republic of Turkey on October 14, 2020. According to these data, in Turkey at that time, the ratio of total COVID-19 diagnosis of HCW is 11.8% in the total number of diagnoses, the proportion of total deaths is 1.2% in the total number of deaths. It has been reported that 3.8% of cases in China (1716-44672) and 14% of cases in Italy are HCW (6). In fact, in January 2020, the rate of infected HCW in some hospitals was increased by up to 13%, and in Wuhan, this number was determined as 29%.[6] In the statement made by the International Council Nursing (ICN) on October 28, 2020, it was reported that more than 20.000 HCW died due to COVID-19 (7).

Due to the COVID-19 pandemic, the number of patients and deaths continues to increase day by day all over the world. It is predicted that HCW will be more affected, work under severe and adverse conditions, become infected, and even die in the fight against the epidemic, which has not yet an effective vaccine and treatment. This study was planned to identify the causes of COVID-19, the disease process, working environment, and protective practices of HCW who work in a pandemic hospital and infected with COVID-19 during the COVID-19 pandemic process in a university hospital and determine its opinions and recommendations.

2. Materials and Methods

This study is a study in which the phenomenological (case science) method is used as a qualitative study on the HCW working in a pandemic hospital in Turkey, and diagnosed COVID-19 are included in the study. The study population consists of 18 HCW diagnosed with COVID-19 working at XX University Health Research and Application Center. Sampling selection was not made in the study, and although the whole population was planned to be included in the study, the study was conducted with 14 HCW (77.77% of the population) who agreed to participate in the study.

Collection of data

A semi-structured interview form, developed by researchers to collect data, consists of open-ended questions that include the causes of the disease during the COVID-19 pandemic process, the problems they experience as a COVID-19 patient, their working environment and conditions, their feelings and thoughts, and the questions about their experiences with COVID-19 is used.

An in-depth interview method was used for data collection. Verbal consents were obtained to interview health-care professionals who participated in the study. The interview was held in a quiet and calm room whenever the

participant was available. The researcher interviewed by manual recording, considering that the voice recording during the interview may be uncomfortable with recording the information to be provided by the health-care professionals, which may affect the study data. Each individual was interviewed for 30-60 minutes.

Data analysis

After the interview with the participants, the researchers encoded the data, and the themes related to the subject were obtained by the content analysis method. The prepared themes and sub-themes were then concluded with the researchers by gathering together, re-evaluating, and reaching a common view (8).

Ethical consideration

Before starting the study, a study permit was obtained from the Ministry of Health, and ethics committee approval was obtained from the Non-Invasive Clinical Research Ethics Committee of XX University (Date: 22.05.2020, TÜTF-BAEK / 09/16).

3. Results

The average age of the HCW participating in the study is 35.64 ± 7.29, 78.5%, and (n = 11) of them are women and 64.28% are nurses. A total of 14 health-care workers, nine nurses, three doctors, one radiology technician, and one cleaning staff participated in the study. Their working time is an average of 10.71 ± 6.96 years; all of them stated that they received COVID-19 from the hospital/patient, and their family members did not have COVID-19.

The statements analyzed are organized under three main themes: The negative effects of COVID-19 on health as a healthcare worker during the pandemic process, thoughts about the cause of being COVID-19, and experiences and effects of COVID-19 disease processes (Table 1).

Table 1. Themes

Themes
- The negative effects on health of COVID-19 as a healthcare worker during the pandemic process
- Thoughts on the reason for being infected with COVID-19
- Experiences and effects of COVID-19 disease processes

1- Being a health-care worker during the COVID-19 pandemic process

The health-care professionals participating in the study reported that they caught COVID-19 during the pandemic process, as they were obliged to take care of patients infected with COVID-19 due to their profession. It has been determined that some employees still have health problems due to this disease and are worried about their health.

"While I was caring for a patient with COVID-19, I also got sick. I had lived very bad days. My recovery process took about three weeks, but I still have trouble breathing. I think I will always continue like this, and I will not be able to regain my old health (nurse,7)"

"We always worked when everyone was afraid of getting sick during the "stay at home" campaigns. It is really difficult to be a health-care professional in this process. I finally got sick. I was so scared and stressed (radiology technician)"

It has been determined that employees cannot go home due to the high contagiousness of COVID-19, and health-care professionals are in the riskiest occupation group, they have to stay separate from their parents, spouses, and children a feeling of death is generally felt during the disease process.

"As I work in the pandemic service, we stayed in separate places to protect my loved ones. Later, "When I became COVID-19, I was in the hospital for a long time, and I was terrified. I thought very much that I would

never see my children again and leave them alone; I mean death. I could not support them in this process (nurse, 1)"

"Since I work in the pandemic service, I stayed in a specified dormitory in order not to infect my children and my wife. Then when I got COVID-19, I felt so alone and helpless. "I thought a lot that I would die and never see my loved ones again. My husband had a hard time taking care of the children; my children were very upset that they couldn't see me. We missed each other in the same city (nurse, 2)"

Almost all health-care professionals participating in the study stated that they were seen as potential virus carriers by society as they were involved in the care and treatment of patients infected with COVID-19 during the pandemic process. In other words, they were stigmatized, and they were negatively affected during this process.

"Everyone in the apartment where I lived knew that I was a health-care worker. And when I was infected with COVID-19, everyone marginalized my family and me. Of course, there would be social distance, but it was very painful for those around us to escape/behave like we have the plague (nurse,3)"

"My family and friends were the most supportive in the process of becoming infected with COVID-19. However, local newspapers shared my illness, and everyone around me was talking about me. The attitude of my neighbors in the apartment made me very sad. Patient privacy was not taken seriously. What I went through at that time was a nightmare (nurse,4)"

2- Thoughts on the reason for being infected with COVID-19

The health-care professionals participating in the interview think that; the treatment and care practices with a high risk of contamination due to being a health-care worker, lacking personal protective equipment at the beginning, and not having sufficient training on the subject are the reasons for being COVID-19 infected

Health-care workers participating in the interview have the opinion that they have Covid-19 disease due to their treatment and care practices with a high risk of transmission due to being a health-care worker.

"Any intervention made on a patient with COVID-19 is very risky. Especially respiratory system practices increase the risk. Moreover, since the patients are alone, we even feed their meals. No matter how much I tried to pay attention to our contact with the patient, I eventually became COVID-19 (nurse,4)"

The participants reported that their personal protective equipment was insufficient. At the beginning of the pandemic process, and therefore they caught COVID-19. This situation was thought to cause anxiety in employees.

"It is very important to use protective equipment in protection from COVID-19. There was a shortage of protective equipment for a while at the beginning. There were no masks, gloves, aprons, and visors. There were times which I bought protective equipment with money. But I think I got COVID-19 because I used the same protective materials for a long time (doctor,2)"

Participants stated that in-hospital training on COVID-19 could not be done face-to-face due to the risk of transmission, and therefore there is a lack of knowledge on how to protect themselves.

"Face-to-face training about COVID-19 was attempted at the hospital but did not happen due to the risk of contamination. The training was provided with videos. I think these training did not reach their exact purpose; we had a lack of knowledge (personnel)"

Participants reported that there were practices such as lockdowns and flexible working for society during the pandemic process, but they continued to work because they were health-care workers, and they always carried a risk. For this reason, they recommended that working hours should be regulated and necessary protective and safety practices should be implemented in order to reduce the risk in working environments.

"During the pandemic process, we employees should have been tested without any symptoms, but they were not done. We could not get the complete necessary training. While other institutions worked flexibly, we worked full time. Material shortages at the beginning were too much. Unless all these problems are fixed, it is not possible for us to stay healthy in such a working environment (doctor 3)"

"I think it is a big deficiency that there is a lack of protective equipment in the working environment, and our health controls are not carried out. In this process, weekly working hours should be arranged by flexible working (nurse,9)"

3- Experiences and effects of the COVID-19 disease process

Employees reported that they were both physically and mentally affected during the disease and that some health problems still persisted.

"The disease started with a fever and cough. When I found out that I had COVID-19, I first couldn't believe it. I thought about how I got infected, and then I wondered if I had infected my children, my wife, my friends. Everyone should do their part to protect themselves and each other. Otherwise, this disease will never end (radiology technician)"

"First of all, my complaints were started with a fever and joint pain. When my test was positive, I was very scared because I am 52 years old. I had very serious respiratory problems, but "Thank God" I was treated without going to intensive care. But I still don't think I'm getting better, I have fatigue, I have breathing problems as I move, and I have psychological stress and sleep problems (personnel)"

Approximately half of the participants stated that the problem is universal and that it can be overcome with less harm if we stay cool in this process, while the other half stated that they were very lonely in this process, and they were psychologically affected by the problems of exclusion from the society.

"Since I already knew the process as a health-care professional, I was able to act calmly by trying to think positively. I think I managed this process well; it even allowed me to understand the patients and the hospital environment better, it gave me empathy (doctor,2)"

"As a reanimation nurse, I had the hardest time in my profession. In practices such as providing care and treatment to patients with protective equipment, it becomes difficult to "breathe, hear, communicate, and there are times when you cannot wipe your sweat." Psychologically, the illness affected me very much, we were under constant stress, but I think I did my best as it is the duty of health-care professionals (nurse,6)"

4. Discussion

It is admirable for health-care professionals to work devotedly at the risk of death during the COVID-19 pandemic process. However, as reported in both this study and other studies, HCW have been "stigmatized" that they are seen as potential virus carriers by society (9.10). Stigma is a public health problem that needs to be tackled as an external stressor that can potentially harm at least as much as depression and other mental symptoms (11). In particular, it has been stated that fear arising from discrimination, prejudice, and lack of knowledge has a negative effect on the efforts of health authorities and health-care professionals in China and other countries and triggers chaos (10). In addition, a group of nurses in China were not allowed to enter even the neighborhoods where they were live by their neighbors for fear of spreading disease (10). This process deeply affected health-care professionals psychologically, and some unethical and immoral behaviors observed in this situation created a very serious problem.

As with all infections, the first precaution to be taken in COVID-19 infection is health-care workers' protection.[11] Both Centers for Disease Control and Prevention and WHO reports that N95 or higher respirators should be used during aerosol-generating procedures. But as identified in both this study and other studies, HCW experienced problems with personal protective equipment access during the pandemic (12,13). and they are infected

with COVID-19 due to insufficient training. In a study conducted in Wuhan, China, health-care workers' first reason to become infected was insufficient personal protective conditions at the beginning of the epidemic, and their awareness about protection was not strong enough. Therefore, it was reported that HCW did not apply effective personal protection to the patient before any procedure (14). The World Health Organization recommends that health-care professionals exercise their right to refrain from working in risky working environments until necessary precautions are taken (15). Considering the high number of infected health-care professionals and lost their lives during the pandemic, this right is not used by HCW.

COVID-19 is a highly contagious respiratory infectious disease that causes respiratory, physical, and psychological dysfunction in patients (16). Since it is known that 95.8% of the confirmed cases have recovered, patient care is very important after the diagnosis of COVID-19 (17). The current study determined that mostly respiratory distress and fatigue symptoms are experienced by the HCW with COVID-19. Respiratory rehabilitation is recommended for patients diagnosed with COVID-19 and receiving treatment (18). Rehabilitation Association experts in China have developed practical and applicable respiratory rehabilitation guidelines for COVID-19 patients. It is recommended to establish an appropriate rehabilitation program for the individual (16). However, in this study, it is thought that such a program was not implemented for employees and that they continue to work despite respiratory complaints, and thus the recovery process of HCW will prolong.

The Occupational Safety and Health Administration (OSHA) emphasizes that it is important to support employees psychosocially against the COVID-19 epidemic in workplaces to feel safe and reduce the anxiety that may develop (19). The process of coping with both the lack of social support due to being separated from loved ones and the health problems that develop and continue due to COVID-19 continue. Statements that indicate that there is a difference according to pre-pandemic well-being are important. In the study, it is gratifying that there were no HCW who died in the hospital where the study was conducted due to the young age of those with COVID-19, but thousands of HCW died all over the world. According to the International Council of Nurses (ICN) statement, the number of nurses who died due to COVID-19 is more than the number of nurses who died in World War I, which lasted four years. According to the statement, 1500 nurses in 44 countries died due to COVID-19 (7). However, we think these numbers do not fully represent the true number of HCW infected with COVID-19.

COVID-19 is the first new occupational disease described in this decade (20). In the hospital where the study was conducted, the work accident / occupational disease notification of HCW with COVID-19 was made from the first day by the employee health unit. But it is not yet accepted as an occupational disease in Turkey. It has been reported that employees with a high risk of being infected with the virus are eligible or compensation as work accident / occupational disease in many countries (Italy, Germany, Belgium, South Africa, Canada, Malaysia, the United States) (21). It is thought that making work accident notifications, protecting the rights of employees, as well as disclosing the epidemic information in a transparent manner will be very beneficial for the subsequent psychological interventions, as well as the positive effect on the social and psychological situation.

In the study, HCW requested the implementation of flexible working models in order to conduct COVID-19 tests for control purposes, to reduce patient contact and the number of employees to reduce in-hospital risk. In this context, to reduce the risk, HCW who take care of probable/definite COVID-19 patients and those who care for other patients should be separated or assigned alternately according to the facilities of the institution (22). Web-based forms can be created to facilitate entry by using personal smartphones. Tests and screenings of HCW with fever or respiratory symptoms should be evaluated, if possible, in a separate clinic reserved for employees (14). Training of all personnel

should be reestablished, and personal protective equipment should be adequate and ensured that they are of appropriate quality.

Limitations

The main limitation of the study is that it does not cover only one pandemic hospital and all healthcare professionals. Another limitation of ours is the recording of the interviews, since the participants did not give their consent.

5. Conclusion

Healthcare workers have been one of the most affected professions in the fight against coronavirus, which has affected the world in a very short time. It is seen how difficult it is to be a HCW in this process. Because HCW are heroes who lost their health so that patients with COVID-19 recover. In the study, it was determined that while working during the epidemic process, HCW had problems, especially in accessing personal protectors, and they were caught coronavirus due to their low awareness and that both their physical and mental health was deeply affected during this process. Broader research should be planned to understand the effects of the COVID-19 pandemic process on health-care workers.

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Research Article / Araştırma Makalesi

Comparison of APACHE II and Modified Charlson Index in Mortality Prediction in Patients at Medical Intensive Care Unit

Dahiliye Yoğun Bakım Hastalarında Mortalite Öngörüsünde APACHE II ve Modifiye Charlson İndeksinin Karşılaştırılması

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Abstract

Acute Physiology and Chronic Health Evaluation II (APACHE II) and Modified Charlson Index (MCI) are used to predict the fatality in intensive care units (ICU). We aimed to investigate the difference between these scores in the prediction of fatality in the medical intensive care unit. Our study is important because in our literature overview, this study is one of the rare studies that compares these scoring systems. 108 ICU patients included. In all subjects APACHE II and MCI performed. Procalcitonin, C-reactive protein(CRP) levels of patients were recorded. Patients were then grouped according to mechanically ventilated or not; mortality happened or not. Statistically significance found in age($p<0.045$), mechanical ventilation, procalcitonin, CRP and MCI ($p<0.001$) about mortality . MCI sensitivity and specifity were higher than APACHE II in %95 confidance interval. Area under curve in ROC analysis was CRP (0.728), Procalcitonin (0.719), MCI (0.686), APACHE II (0.665) respectively. Our study demonstrates that the Modified Charlson Index combined with procalcitonin and CRP can be used for predicting mortality in medical ICU as well as APACHE II

Keywords: APACHE II, Modified Charlson indeksi, Dahili yoğun bakım ünitesi, Prokalsitonin, C-reaktif protein

Özet

Acute Physiology and Chronic Health Evaluation II (APACHE II) ve Modifiye Charlson indeksi (MCI) yoğun bakımlarda mortalite öngörüsünde kullanılmaktadır. Biz bu skorlama sistemlerinin dahili yoğun bakımda yatan hastalardaki mortalite öngörüsünde aralarında fark olup olmadığını araştırdık. Çalışmamız dahili yoğun bakımda mortalite öngörüsünde bu iki skorlama sistemini karşılaştıran ilk çalışma olması açısından önemlidir. Çalışmaya 108 yoğun bakım hastası dahil edildi. Hastaların hepsine yatışlarının ardından APACHE II ve MCI hesaplandı. Hastaların prokalsitonin ve C-reaktif protein(CRP)seviyeleri kaydedildi. Hastalar mekanik ventilasyon uygulanıp uygulanmaması ve mortalite oluşup oluşmaması açısından gruplandırıldı. Mortalite açısından yaş($p<0,045$), mekanik ventilasyon, prokalsitonin, CRP ve MCI istatiksel olarak anlamlı bulundu($p<0,001$). MCI 'nin % 95 güven aralığında sensitivitesi ve spesifitesi APACHE II ye göre daha yüksekti. ROC analizinde eğri altındaki alan (Area under curve) sırasıyla CRP için 0.728, Prokalsitonin için 0.719, MCI için 0.686, APACHE II için 0.665 di. Çalışmamız Modifiye Charlson indeksinin, procalcitonin ve CRP ile birlikte dahili yoğun bakımda mortaliteyi öngörmede APACHE II gibi kullanılabileceğini göstermiştir.

Anahtar Kelimeler: APACHE II, Modified Charlson indeksi, Dahili yoğun bakım ünitesi, Prokalsitonin, C-reaktif protein

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1. Introduction

Predicting mortality and morbidity risks of hospitalised patients is important for plannig a sufficient treatment and patient care. For this purpose several scoring systems constituded for diseases using the features of related ilness as vital signs or laboratory and clinical findings.

Disease severity, age, nutrition, comorbidities, inflammation biomarkers, artificial ventilation support and infection status are the important factors determining intensive care unit (ICU) survival.

Various scoring systems are used to predicting mortality in ICU. Among them Acute Physiology and Chronic Health Evaluation II (APACHE II), mortality prediction model (MPM) and Simplified acute physiology score (SAPS) are the most used scoring systems (1, 2).

Modified Charlson index (MCI) is also used for mortality prediction. MCI assesses patients according to 17 co-morbidities (3). Beside predicting the mortality and morbidity in ICU patients, MCI also used for assesing the mortality estimation in patients with sarcoma, orthotopic liver transplantation and pulmonary diseases (4-6). There is limited data about the prediction and risk assessment of the MCI for ICU patients (7). Furthermore there are only a few studies that compare MCI and APACHE II and have controversial results. Additionally a number of studies suggested interpreting MCİ together with APACHE II could improve prognostic prediction (8) (9). Therefore, we tried to show the difference between MCI and APACHE II scoring systems for predicting hospital mortality among medical intensive care unit patients.

2. Methods

We evaluated patients hospitalised to Kecioren Research and Training Hospital intensive care unit between 01.01.2018 and 31.12.2018 after approval of local ethical committee. Patients older than 18, and diagnosed with diseases related to internal medicine were included in the study. Coronary care patients, surgery and postoperative patients, neurological disease, and gynecology and obstetrics patients were excluded. The demographic data, procalcitonin, CRP, APACHE II, and MCI scores and supportive therapies were retrospectively collected from the hospital database.

Statistical analysis

Patients were grouped according to mortality and both groups were analysed for several demographic and clinical features . APACHE II scores were considered high risk if >8, and MCI scores were considered high risk if > 3.

For statistical analysis, version 22.0 of SPSS was used. The normality of the distribution of continuous variables was tested by the Kolmogorov-Smirnov test. Variables shown as mean±SD if continuous and if discrete as median and IQR (Inter Quartile Ranges) 25-75.AUC (area under curve) values calculated with ROC (Receiver Operating Characteristic) analysis. Chi-square test was applied to investigate the relationship between 2 categorical variables. Comparison of continous variables done by using Mann Whitney U test. P value < 0.05 was accepted as statistically significant.

Ethical Approval

Health Sciences University Keçiören Education and Research Hospital Ethics Committee Permission was obtained with the letter dated 12.08.2020 and numbered 2156. Our research design was compatible with the Declaration of Helsinki, and was accepted by the Institutional Review Board (December 18, 2018; 43278876-929)

3. Results

108 cases were involved (n: 64 (53%) female; 44 (47%) male). Median age was 77(IQR: 67 –82). Forty five (41.7%) patients died and 63 patients were discharged. Fifty seven (52,8 %) patients were mechanically ventilated. Demographic data, laboratory findings and scoring points of patients were demonstrated in table 1.

Table-1. General characteristics of patients

Sex *n (%)*	
• **Female**	**64(53)**
• **Male**	**44(47)**
Age *median (IQR%25-75)*	77 (67 –82)
Comorbidities *n (%)*	
• **Chronic Hypertension**	44(40.7)
• **Diabetes Mellitus**	44(40.7)
• **Chronic Kidney Disease**	49(45.4)
Mortality *n(%)*	
• **Presence**	45(41.7)
• **Absence**	63(58.3)
Mechanical Ventilation *(%)*	
• **Presence**	57(52.8)
• **Absence**	51(47.2)
Procalcitonin median (*IQR%25-75)*	0,67(0,11-5,4)
CRP median (*IQR%25-75)*	5,54(1,65-10-57)
APACHE II median (*IQR%25-75)*	29(22-36)
Modified Charlson index median (*IQR%25-75)*	7(5-9)
APACHE II	
• **0-8 *n(%)***	4(3)
• **8< *n(%)***	104(96,3)
Modified Charlson index	
• ***0-3 n(%)***	10(9,3)
• ***3<n(%)***	98(90,7)

As shown in table 2; when both groups were compared for several parameters, it was found that there are statistically significance in age (p<0,045); mechanical ventilation, procalcitonin,crp, and modified charlson score.(p<0,001)

When comparing the diagnostic performance of each scoring system and several markers for mortality, it was found that MCI was as useful as APACHE II. Sensitivity, specifity, positive predictive value and negative predictive value of MCI and APACHE II were displayed in table 3.

Table-2. Characteristics and laboratory data of patients according to Mortalitiy

	Mortalitiy(+)	Mortalitiy(-)	PValue
Sex *n (%)*			
• **Female**	28(62,2)	36(57,1)	**0,5**
• **Male**	17(37.8)	27(42.9)	
Age *(IQR%25-75)*	78(74,5-85,5)	76(64-81)	**0.045**
Comorbidities *n (%)*			
• **Chronic Hypertension**	25(55,6)	32(50,8)	0,6
• **Diabetes Mellitus**	19(42,2)	25(39,7)	0,7

• **Chronic Kidney Disease**	25(55,6)	24(38,1)	0,07
Mechanical Ventilation *(%)*			
• **Presence**	43(95,6)	14(22,2)	**<0.001**
• **Absence**	2(4,4)	49(77,8)	
Procalcitonin (*IQR%25-75)*	3,24(0,35-12,83)	0,33(0,01-1,50)	**<0.001**
CRP (*IQR%25-75)*	*8,68(5,03-14,9)*	*4,16(1,3-8,53)*	**<0.001**
APACHE II			
• **0-8 *n(%)***	2(4,4)	2(3,2)	0.55
• **8< *n(%)***	43(95,6)	61(96,8)	
Modified Charlson index			
• ***0-3 n(%)***	1(2,2)	9(14,3)	**0.03**
• ***3<n(%)***	44(97,8)	54(85,7)	

Table-3. Comparison of Apache 2 and Modified Charlson scores findings % (95%CI)

	APACHE 2	M.CHARLSON
Sensitivity	95,56 (84,85-99,46)	97,78 (88,23-99,94)
Specificity	3,17 (0,39-11)	14,29 (6,75-25,39)
Accuracy	41,67 (32,25-51,55)	49,07 (39,33-58,87)
PLR	0,99 (0,91-1.07)	1,14 (1,02-1,27)
NLR	1,4 (0,2-9,57)	0,16 (0,02-1,18)
PPV	41,35 (39,49-43,23)	44,9 (42,19-47,6)
NPV	50(12,76-87,24)	90 (54,16-98,56)

PLR: Positive likelihood ratio, NLR: Negative likelihood ratio, PPV: positive predictive value, NPV: Negative predictive value

4. Discussion

Scoring systems predict the risk of mortality by using symptoms, physical examination findings and the results of the laboratory tests . Therefore our aim was to establish a scoring system that is valid and reliable. The objective of our research was to compare the performance of MCI and APACHE II systems for predicting the mortality of ICU patients. Our study's importance and difference from previous studies is that it was one of the few studies carried out in a medical intensive care unit. According to our knowledge, most of these studies in the literature were done in surgical and anesthesia intensive care units.

In our study, age, and mechanical ventilation were associated with mortality as expected. Procalcitonin, CRP, and MCI were associated significantly with mortality, however APACHE II was not associated with mortality. MCI was more sensitive and specific than APACHE II, the accuracy was superior in MCI compared to APACHE II (%95 confidence interval) .Table 3

There are conflicting results regarding the comparison of scoring systems in the literature. Evran et al. reported that age was significantly linked with higher mortality rates (10). One study determined APACHE II had a more correct evaluation system for fatality contrast to ODIN(organ dysfunction and infection system), SAPS2 and MCI in geriatric patients undergoing emergency abdominal surgery (11). Quach et al.found that the MCI had not enough accuracy as APACHE II for prognosticating hospital mortality in an intensive care unit (12). APACHE II was found a better option for betokening to sepsis related deaths (13).However Dosset et al. did not suggest APACHE II for the trauma associated

mortality prediction in the first 24 hours (14). In another study APACHE III was found more sensitive and specific than APACHE II in predicting mortality(15). PIRO (predisposition, insult, response, organ dysfunction) score, APACHE II and MEDS(mortality in emergency department sepsis) were similar in forecasting mortality in sepsis cases (16). Another study that analysed the association between mortality and procalcitonin, CRP, and SOFA(sequential organ failure assessment) score in ICU, showed that both procalcitonin and CRP were associated with mortality(17).In sepsis patients Chien-Chang Lee et al showed MEDS score was the most specific and procalcitonin was the most sensitive in predicting mortality(18). Similar to our results some studies showed MCI can be useful in mortality prediction. A study comparing MCI and APACHE II found that these scoring systems are similar in short and prolonged-term mortality for ICU patients (19). Violante Di Donato et al. concluded that MCI could be used as a prognostic factor for surgery needed vulvar cancers(20). Sampada B.Desai et al found that MCI can predict postsurgical adverse events. Like our results there was a high negative predictive value for adverse events(21). Another study in patients undergoing prostatectomy MCI was an effective prognostic factor(22). A study in kidney transplant recipients suggested MCI in clinical practice to stratify the mortality hazard in patients who undergo renal transplantation(23).However another study showed no association between MCI and mortality (24)

In decision we demonstrated that MCI combined with procalcitonin and CRP can be used reliably for predicting mortality instead of APACHE II in medical ICU cases.

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Çocukluk Çağı Behçet Hastalığında Mukoza ve Cilt Tutulumu

Mucosal and Cutaneous Involvement of Behcet's Disease in Children

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Özet

Behçet hastalığı, her tip ve boyuttaki damarları etkileyerek çoklu organ tutulumu ile seyreden kronik, otoinflamatuar bir vaskülittir. Her sistemi etkileyebilse de hastalık için tanı koydurucu ve karakteristik olan tutulum mukoza ve cilttir.Bu çalışma ile çocukluk çağı Behçet hastalığı tanısı ile merkezimizde takip edilen hastaların mukokutonöz tutulum oranlarının, tutulum şiddetlerinin, tedavi yanıtlarının bildirilmesi ve diğer organ tutulumları arasındaki ilişkinin ortaya konulması hedeflenmiştir. Retrospektif olarak düzenlenen bu çalışma Ocak 2007 ile Haziran 2021 tarihleri arasında 16 yaşından önce Behçet hastalığı tanısı almış olguları içermektedir. Hastaların elektronik dosyalarından demografik, klinik özellik ve tedavileri not edildi. Mukokutanöz tutulumları detaylı şekilde gruplandırıldı. Çalışmaya dahil edilen 79 hastanın %57'si kızdı. Tekrarlayan oral aft tüm hastalarda (%100), genital ülser 57 hastada (%72,7) ve kutanöz tutulum 37 hastada (%46,8) tespit edildi. Diğer organlarda etkilenme olmadan izole mukokutanöz tutulum 22 hastada (%27,8) gözlendi. Kutanöz tutulum, 30 hastada (%38) papülopüstüler lezyon, 8 hastada (%10,1) eritema nodozum benzeri lezyon, 4 hastada (%5,1) folikülit ve 2 hastada (%2,5) yüzeyel tromboflebit şeklindeydi. Paterji testi uygulanan 73 hastanın (%92,4) 22'sinde (%27,8) pozitifti. Çalışmamızda majör ROA ve majör GÜ sıklığı kızlarda daha fazla görüldü (p=0,059, p=0,046). Mukokutanöz tutulum için lokal tedavilere ek olarak tüm hastalara kolşisin başlandı. Çocukluk çağı Behçet hastalığı mukokutanöz bulguları ile ilgili olan çalışmamızda tekrarlayan oral aft, genital ülser ve cilt bulguları en sık görülen 3 bulgudur. Majör tekrarlayan oral aft ve genital ülser kız hastalarda daha sık gözlemlendi. Mukokutanöz bulgular Behçet hastalığında tanıya giden yolda ilk basamak olup dikkatle değerlendirilmelidir.

Anahtar Kelimeler: Çocukluk çağı Behçet hastalığı; deri; genital ülser; oral aft; tedavi

Abstract

Behçet's disease is a chronic, autoinflammatory vasculitis with multi-organ involvement affecting vessels of all types and sizes. Although it can affect any system, the diagnostic and characteristic involvement of the disease is mucosa and skin.In this study, it was aimed to show the rate, severity and treatment response of mucocutaneous involvement of children who were diagnosed Behçet's disease in our center. This retrospective study included cases diagnosed with Behçet disease before the age of 16 between January 2007 and June 2021. Demographic, clinical features and treatments were noted from the electronic files of the patients. Mucocutaneous involvements patients were evaluated in detail. Of the 79 patients included in the study 57% were girls. Recurrent oral aphthae were detected in all patients (100%), genital ulcers in 57 patients (72.7%), and cutaneous involvement in 37 patients (46.8%). Isolated mucocutaneous involvement was observed in 22 patients (27.8%) without other organ involvement. Cutaneous involvements were papulopustular lesion in 30 patients (38%), erythema nodosum-like lesion in 8 patients (10.1%), folliculitis in 4 patients (5.1%), and superficial thrombophlebitis in 2 patients (2.5%). Pathergy test was positive in 22 (27.8%) of 73 patients (92.4%). In present study, the frequency of major recurrent oral aphthae and major genitale ulceration was higher in girls (p=0.059, p=0.046). Colchicine was started in all patients in addition to local treatments for mucocutaneous involvement. In our study, recurrent oral aphthae, genital ulcer and skin lesions were the most common involvements respectively. Major recurrent oral aphtha and genital ulcer were observed more frequently in female patients. As a conclution, mucocutaneous lesions are the early step of diagnosing Behçet's disease and should be evaluated carefully.

Keywords: Skin; childhood Behçet's disease; genital ulcer; oral aphthae; treatment

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1. Giriş

Behçet hastalığı (BH), her tip ve boyuttaki damarları etkileyerek çoklu organ tutulumu ile seyreden kronik, otoinflamatuar bir vaskülittir (1). Her sistemi etkileyebilse de hastalık için tanı koydurucu ve karakteristik olan tutulum mukoza ve cilttir. Klinisyeni erken evrede tanıya götürebilen mukoza ve cilt etkilenmeleri sıklıkla; rekürren oral aft (ROA), genital ülser (GÜ), eritema nodozum benzeri lezyon (ENL), papülopüstüler lezyon (PPL) ve pozitif paterji testi (PT) şeklindedir. Ancak hastalığın şiddetini, seyrini ve tedavi şeklini belirleyen diğer organ (oküler, gastrointestinal, nörolojik ya da vasküler) etkilenmeleridir (2). BH sıklıkla İpek yolu güzergâhındaki ülkelerde görülmekte olup Türkiye en sık görüldüğü ülkedir (80-370 olgu: 100.000). Diğer ülkelerde hastalık prevalansı 5-35:100.000 aralığındadır. BH tipik olarak 20-40 yaşlar arasında bulgu vermekle birlikte %4-26 oranındaki hastanın şikayetleri çocuklukta başlamaktadır (3,4). Atipik ya da inkomplet bulgulardan dolayı çocukluk çağı Behçet hastalığını (çBH) tanımak zor olabilmekte hastalar geç tanı alabilmektedir. ÇBH'nı tanılamak için son dönemde erişkin tanı kriterlerine ek olarak pediatrik tanı kriteri de geliştirilmiştir (5-7). Tüm tanı kriterleri, mukokutanöz bulguların sık ve hastalık için karakteristik olmasından dolayı ağırlıklı olarak içermektedir (Tablo 1). Mukokutanöz bulguların zamanında doğru şekilde değerlendirilmesi hastaların ağır organ tutulumları açısından sağlıklı takibini ve gerekli tedavilerin yerinde yapılmasını sağlayacaktır.

Bu çalışma ile çBH tanısı ile merkezimizde takip edilen hastaların mukokutonöz tutulum oranlarını, tutulum şiddetlerini ve tedavi yanıtlarını bildirmeyi hedefledik.

Tablo 1. Behçet hastalığı tanı kriterleri

Behçet Hastalığı Tanı Kriterleri		
ISG (Erişkin)* (5)	**ICBD (Erişkin)** (6)**	**PEDBD (Çocuk)*** (7)**
ROA (zorunlu) en az 3 adet/yıl	*ROA (2 puan) en az 3 adet/yıl*	***ROA (1) en az 3 adet/yıl***
GÜ	*GÜ (2 puan)*	***GÜ (1)***
Cilt bulguları	*Cilt bulguları (1 puan)*	***Cilt bulguları (1)***
Okuler tutulum	Okuler tutulum (2 puan)	**Okuler tutulum (1)**
PPT	Vasküler tutulum (1 puan)	**Vasküler tutulum (1)**
	Nörolojik tutulum (1 puan)	**Nörolojik tutulum (1)**

ISG-International Study Group, ICBD-International Criteria for Behçet's disease, PEDBD- Pediatric Behçet's Disease, BH-Behçet Hastalığı, ROA-Rekürren oral aft, GÜ-Genital ülser, PPT-Pozitif paterji testi
** Zorunlu kriter ve diğerlerinden en az 2 tanesi, ** 4 ve üzeri puan, *** 3 ve üzeri puan*

2. Gereç ve Yöntemler

Retrospektif olarak tasarlanan bu çalışma Ocak 2007 ile Haziran 2021 tarihleri arasında 16 yaşından önce BH tanısı almış olguları içermektedir. BH tanısı 2016 sonrasında pediatrik tanı kriterleri ile önceki dönemlerde erişkin tanı kriterleri ışığında uzman çocuk romatologları tarafından konmuştur (5-7). Çalışmaya 16 yaşından sonra tanı almış, düzenli kontrole gelmeyen hastalar dahil edilmemiştir. Helsinki deklerasyonuna uygun şekilde yürütülen çalışmamıza Ankara Şehir Hastanesi Klinik Araştırmalar Etik Kurulunca onay verilmiştir.

Hastaların elektronik dosyalarından demografik, klinik özellik ve tedavileri not edildi. Mukokutanöz tutulumları detaylı şekilde gruplandırıldı. Büyüklüğü 10 mm'den fazla olan OA ve GÜ lezyonları major, diğerleri minor olarak sınıflandırıldı (2). Yıllık ROA sayısına göre hastalar ROA≥ 12 ve ROA<12 adet olacak şekilde gruplandırıldı. Uygun doz kolşisin ve lokal tedaviye rağmen ROA ve GÜ'de sıklık, büyüklük, iyileşme zamanında düzelme olmadığı için beslenme, hareket etme ve günlük hayatı olumsuz etkileyerek, doz artırmayı ya da ek tedaviyi gerektiren lezyonlar dirençli olarak kabul edildi. GÜ tanı anında aktif ya da skar olmasına göre tanımlandı. Hastalar izole mukokutanöz tutulumu olanlar ve diğerleri diye

gruplandırıldı. Tüm hastalar oftalmolog ve bazı hastalar BH'nın sistemik tutulumu açısından pediatrik nörolog ve gastroenterolog tarafından değerlendirildi.

Paterji, HLA B51 sonuçları not alındı. Tanı anındaki ve son vizitteki hastalık aktiviteleri Behçet Hastalığı Güncel Aktivite Formu (BDCAF) ile değerlendirildi (8).

İstatiksel değerlendirme

Hasta verileri SPSS 22. versiyon kullanılarak değerlendirildi. Kategorik veriler sayı ve yüzde olarak tanımlandı. Sayısal verilerin normal dağılıma uyup uymadığı Shapiro-Wilk test ile değerlendirildi. Normal dağılıma uymayan sayısal veriler medyan, minimum ve maksimum olarak tanımlandı. Kategorik veriler arasındaki fark ki-kare testi, sayısal değerler arası fark non-parametrik Mann Whitney-U testi ile değerlendirildi. Sayısal bağımlı değişkenler için non-parametrik Wilcoxon Signed Rank test uygulandı.

3. Bulgular ve Analizler

Demografik veriler

Çalışmaya dahil edilen 79 hastanın %57'si kızdı. Hastaların medyan yaşı 17 yıl (6-24), şikayetlerin başlama yaşı 11 yıl (2-15) ve tanı alma yaşı 14 yıl (2-17) olarak tespit edildi. Tanı için medyan geçen süre 1 yıl (0-12) ve hastaların medyan takip süresi 1 yıl (1-13) olarak belirlendi. Hastaların 18'inde (%22,9) 1. derece akrabada, 10'unda (%12,5) 2. derece akrabada BH öyküsü mevcuttu. Ailede BH olan hastalar anlamlı olarak daha erken tanı aldı (p=0,031).

Mukokutanöz tutulum

Çalışmamızda ROA tüm hastalarda (%100), GÜ 57 hastada (%72,7) ve kutanöz tutulum 37 hastada (%46,8) tespit edildi. Diğer organlarda etkilenme olmadan izole mukokutanöz tutulum 22 hastada (%27,8) gözlendi.

Rekürren oral aft 20 hastada (%25,3) majör karakterde, 17 hastada (%21,5) tedaviye dirençli ve 40 hastada (%50,6) yılda 12 ve üzerinde geliştiği görüldü.

Genital ülser 16 hastada (%20,3) majör, 41 hastada (%51,9) minör ve 13 hastada (%16,5) tedaviye dirençli olduğu belirlendi. Tanı anında 20 hastada (25,3) aktif, 17 hastada (%21,5) skar ve 19 hastada (%24) her ikisi beraber görüldü.

Kutanöz tutulum, 30 hastada (%38) PPL, 8 hastada (%10,1) ENL, 4 hastada (%5,1) folikülit ve 2 hastada (%2,5) yüzeyel tromboflebit şeklindeydi.

Paterji testi uygulanan 73 hastanın (%92,4) 22'de (%27,8) test pozitifti.

Mukokutanöz dışı organ tutulumu

Çalışmada 57 hastada (%72,2) mukokutanöz dışı etkilenme ve hastaların 35'inde (%44,3) ciddi organ (oküler, vasküler ve nörolojik) tutulumu mevcuttu. Ciddi organ tutulumları %19 oranında üveit, %15,2 oranında tromboz, %8,9 oranında ekstraparankimal ve %5,1 oranında parankimal nörolojik tutulum olarak gözlendi.

Hastaların %36,7'sinde kas iskelet, %22,8'inde gastrointestinal, %19'unda göz, %19'unda nörolojik, %16,5'inde vasküler etkilenme, %11,4'ünde ateş, %6,3'ünde epididimit ve %55,7'sinde HLA B51 pozitifliği mevcuttu.

Mukokutanöz bulguların sıklığını ve şiddetini etkileyen faktörler

Çalışmamızda majör ROA ve majör GÜ sıklığı kızlarda daha fazla görüldü (p=0,059, p=0,046). Cinsiyetin, BH pozitif aile öyküsünün ve HLA B51 varlığının ÇBH'nın mukokutanöz bulgularına etkileri Tablo 2'de özetlendi. Majör ROA, ailede BH olanlarda anlamlı olarak daha fazla görüldü (p=0,034). Kutanöz bulgular ise, ailede BH olanlarda anlamlı olarak daha azdı (p=0,001).

Çocukluk çağı Behçet hastalığının izole mukokutanöz formunun kız hastalarda anlamlı şekilde daha sık olduğu fakat diğer parametrelerde anlamlı fark olmadığı tespit edildi (p=0,005) (Tablo 3).

Tablo 2. Çocukluk çağı Behçet hastalığı mukokutanöz bulgularını etkileyen faktörler

	Cinsiyet N (%)			Ailede BH (N, %)			HLA B51 (N, %)			İzole Mukokutanöz tutulum N (%)		
	Kız 45 (%57)	Erkek 34 (%43)	P değeri	Var 28 (%35,4)	Yok 51 (%64,6)	P değeri	Pozitif 44 (%55,7)	Negatif 35 (%44,3)	P değeri	Var 22 (%27,8)	Yok 57 (%72,2)	P değeri
ROA	45 (%57)	34 (%43)	0,367*	28 (%35,4)	(%64,6)	0,440 *	44 (%55,7)	35 (%44,3)	0,218	22 (%27,8)	57 (%72,2)	0,530*
GÜ	36 (%45,6)	21(%26,6)	0,073*	18 (%22,8)	39 (%49,4)	0,298 *	31 (%39,2)	26 (%32,9)	0,706	19 (%24,1)	38 (%48,1)	0,080*
Majör ROA	15 (%19)	5 (%6,3)	0,059*	11 (%13,9)	9 (%11,4)	**0,034** *	12 (%15,2)	8 (%10,1)	0,654	7 (%8,9)	13 (% 16,5)	0,403*
Majör GÜ	13 (%16,5)	3 (%3,8)	**0,046***	4 (%5,1)	12 (%15,2)	0,416 *	9 (%11,4)	7 (%8,9)	0,917	4 (%5,1)	12(%15,2)	0,147*
Dirençli OA	11 (%13,9)	6 (%7,6)	0,584*	6 (%7,6)	11 (%13,9)	0,988 *	13 (%16,5)	4 (%5,1)	0,052*	3 (%3,8)	14 (%17,7)	0,230*
Dirençli GÜ	9 (%11,4)	4 (%5,1)	0,375*	4 (%5,1)	9 (%11,4)	0,763 *	9 (%11,4)	4 (%5,1)	0,282	2 (%2,5)	11 (%13,9)	0,273*
Cilt tutulumu (PPT hariç)	19 (%24,1)	18 (%22,8)	0,371*	6 (% 7,6)	31 (% 39,2)	**0,001** *	20 (%25,3)	17 (%21,5)	0,783	5 (%6,3)	32 (%40,5)	0,080*
PPT	11 (%13,9)	11 (%13,9)	0,459*	6 (%7,6)	16 (%20,3)	0,346 *	11 (%13,9)	11 (%13,9)	0,527	6 (%7,6)	16 (%20,3)	0,943*

BH-Behçet Hastalığı, ROA-Rekürren oral aft, GÜ-Genital ülser, PPT-Pozitif paterji testi
**Ki-kare test*

Tablo 3. İzole mukokutanöz tutulumlu hastalar ile diğer organ tutulumu olan hastaların kıyaslanması

		İzole Mukokutanöz Tutulum Var 22 (%27,8)	İzole Mukokutanöz Tutulum Yok 57 (%72,2)	P değeri
Cinsiyet	Kız 45 (%57)	18 (%22,8)	27 (%34,2)	**0,005***
	Erkek 34 (%43)	4 (%5,1)	30 (%38)	
Ailede BH	Var 28 (%35,4)	10 (%12,7)	18 (%22,8)	0,248*
	Yok 51 (% 64,6)	12 (%15,2)	39 (%49,4)	
HLA B51	Pozitif	12 (%15,2)	32 (%40,5)	0,898*
	Negatif	10 (%12,7)	25 (%31,6)	
Şikayetlerin başlama yaşı (yıl)		10,45±2,59	9,86±3,63	0,672**
Tanı yaşı (yıl)		13,09±2,45	12,23±3,36	0,446**
Tanı alma süresi (yıl)		2,64±2,32	2,37±2,99	0,260**

*BH-Behçet Hastalığı, *Ki-kare test, **Mann Whitney U test*

Tanıda gecikme ile izole mukokutanöz ve mukokutanöz dışı organ tutulumu arasında anlamlı ilişki gözlenmedi (p=0,263, p=0,08).

Mukokutanöz bulguların varlığı diğer organ tutulumlarını işaret edebilir mi?

Genital ülser varlığı ve GÜ'in majör karakterde olması ile oküler tutulum arasında zayıf ama istatistiksel olarak anlam negatif ilişki tespit edildi (r= -0,419, p= 0,001). Rekürren oral aft, GÜ ve kutanöz bulgular ile ÇBH'nın diğer organ tutulumları arasında anlamlı herhangi bir ilişki belirlenmedi.

Genital ülser ve kutanöz bulguların varlığına göre gruplanan hastalar; oküler, vasküler, nörolojik, kas iskelet ve gastrointestinal tutulum sıklığı açısından kıyaslandı. GÜ'i olan hastalarda oküler tutulum görülme oranı, olmayanlara göre anlamlı olarak az bulundu (p=0,001). Ancak diğer parametrelerde gruplar arasında anlamlı fark görülmedi.

Tedavi

Mukokutanöz tutulum için lokal tedavilere ek olarak tüm hastalara kolşisin (0,03 mg/kg/g) başlandı. Kolşisin tedavisi ile ROA'ı ve/veya GÜ'i tamamen düzelmeyen 12 (%15,2) hastada kolşisin dozu 0,06 mg/kg/g'e kadar çıkıldı. Şikayetleri düzelmeyen 5 (%6,3) hastaya azathioprin (1-2 mg/kg/g) ve 1 (%1,26) hastaya kısa süreli sistemik steroid (0,5 mg/kg/g) tedaviye eklendi.

Hastaların ilk ve son vizitteki durumları için yapılan BDCAF skorlaması arasında anlamlı fark mevcuttu. Tedavi ile hastalık aktivitesinin kontrol edildiği ve BDCAF skorunun azaldığı görüldü (p=0,001).

Tedavi sonrası BDCAF skorundaki azalma oranı ile hastaların klinik tutulumları arasında ilişki araştırıldığında, izole mukokutanöz ve ekstrakutanöz organ tutulumu olan iki grupta pozitif yönde anlamlı ilişki tespit edildi (sırası ile r=0,319, p=0,004 ve r=0,276, p=0,014).

4. Tartışma ve Sonuç

Çocukluk çağı Behçet hastalığının mukoza ve cilt tutulumuna dikkat çekmeyi hedefleyen çalışmamızda ROA, GÜ ve cilt lezyonları sırası ile en sık ilk 3 bulgudur. Behçet hastalığının en erken ve en sık bulgusu olan mukokutanöz tutulumunun zamanında farkına varılması hastaların ağır organ etkilenmesi olmadan tanı almasına ve gerekli önlemlerin alınmasına olanak sağlamaktadır. Mukokutanöz bulgular ağır organ hasarı riski taşımasa da, hastaların gündelik hayatını etkilemekte, yaşam kalitesini oldukça düşürmektedir (9). Bu nedenle izole mukokutanöz tutulumlu hastalarda da lokal tedavilerin yanı sıra sistemik tedavi ihtiyaçları da dikkate alınmalıdır.

Ülkemizden yapılan ÇBH çalışmalarında mukokutanöz tutulum oldukça sık bildirilmiştir (10-13). Çalışmalarda %100 oranında ROA, %55-82,7 oranında GÜ ve %32,3-76 oranında cilt bulguları gözlendi. Başlıca cilt bulguları %32,3-38 oranında PPL, %10,1-37,3 oranında ENL olarak tespit edildi. Pozitif PT %19-46 oranındaydı. Diğer ülkelerden yapılan çalışmalarda da mukokutanöz bulguların sıklığı benzerdi (14-17). ROA sıklığı %91,7-100, GÜ sıklığı %33,6-76,5, cilt lezyon sıklığı %23,9-88,9 ve PPT sıklığı %6,5-57 oranındaydı.

Behçet hastalığının en sık ve en erken bulgusu olan ROA hastalığın klinik tablosu oturmadan yıllar önce görülmeye başlayabilmektedir. Prospektif olarak takip edilen ROA'lı 67 hastanın %52,2'sinde ortalama 7,7 yıl sonra BH semptomlarının geliştiği tespit edilmiştir (18). Çalışmamızda medyan tanıda gecikme üresini 1 yıl bulundu ama sürenin 1 olguda 12 yıla kadar uzadığı görüldü. Ülkemizde Behçet hastalığına olan farkındalık yüksek olduğu için diğer yayınlarda da tanı gecikme süresi 1-3 yıl bildirilmiştir (11-13). İzole ROA ile başvuran hastalarda kötü ağız hijyeni, vitamin eksiklikleri gibi diğer nedenler dışlandıktan ya da tedavi edildikten sonra; aft sıklığı, kaç tane çıktığı, büyüklüğü, derinliği ve iyileşme süresi klinisyene riskli grup için bilgi verecektir. BH'da ROA'ın tek başına tanı değeri kısıtlı olsa da ailesinde BH olan olgularda ROA'nın sık, çoklu ve majör karakterde olması takip ve tedaviyi planlamada yol gösterebilir. Çalışmamızda da gösterildiği gibi çocukta majör ROA'nın olması ailevi BH olanlarda klinisyeni BH'na daha fazla yaklaştırmaktadır.

Bununla birlikte çalışmamamızda ROA sıklığını, büyüklüğünü ya da tedavi yanıtını olumlu ya da olumsuz etkileyen başka bir faktör gözlemlenmemiştir.

Behçet hastalığının bir diğer karakteristik bulgusu olan tekrarlayan GÜ erken dönem bulgularındandır ve ROA ile beraber başlayabilir. Ancak, ROA ile kıyaslandığında GÜ'in tanı için daha spesifik olduğu gösterilmiştir (5). Genital ülser daha büyük ve derin olup daha yavaş ve iz bırakarak iyileşir. Bu nedenle steroid ve immunsupresif tedavi gerektirir. Erkeklerde en sık skrotumda, kızlarda labiumda gelişir. Çalışmamızda 2. en sık bulgu olan GÜ'in tanı anında %25,3 aktif, %21,5 skar, %24,1 aktif ve skar lezyon olduğu tespit edilmiştir. Genital ülser oranı diğer Türkiye çalışmalarında %55-82,7 aralığındadır (10-13). Bunlara ek olarak çalışmamızda majör GÜ'in kız cinsiyette daha sık olduğunu gözlemledik. GÜ ile oküler tutulum arasındaki negatif yöndeki ilişkinin, erken dönemde GÜ için başlanan steroid ve immunsupresif tedavinin koruyucu etkisi ile açıklayabiliriz. GÜ oranları çalışmamıza benzeyen yine biri Türkiye'den (%82,7), diğerleri Tunus (%76,5) ve İngiltereden (%74) olan 3 çalışmanın oküler tutulum oranları sırası ile %30,9, %44,4 ve %8,7 olarak tespit edildi (12,14,15).

Kutanöz bulgular çalışmamızda 3. en sık (%46,8) tutulum olmuştur. Behçet hastalığı ciltte en sık papülopüstüler ve eritema nodozum benzeri lezyon olarak kendini göstermektedir (19). PPL akneiform karakterdedir ve bazen akne vulgaris tanısı bile alabilmektedir. Hastalarımızda PPL %38, ENL %10,1 oranında görüldü. Daha nadir olarak %5,1 oranında folikülit ve %2,5 oranında yüzeyel tromboflebit gözlemlendi. Türkiyeden yapılan diğer çalışmalarda PPL oranları çok benzer olmakla birlikte, çalışmamızın ENL oranı diğer çalışmalara göre düşüktür (10-13). Çalışmamızda ailede BH olan hastalarda kutanöz bulguların daha az olduğu gözlemlendi. Ailede BH varlığı ebeveynlerin BH farkındalığını artırdığı için bu hastalara daha erken tanı konulup tedaviye daha erken başlanmaktadır. Bu hastalar uygun tedavi altında oldukları için kutanöz bulguları daha az geliştirmektedir. BH'nın kutanöz tutulumu ile ilgili güncel çalışmalar; non-foliküler PPL örneklerinde gösterilen lökoklastik vaskülit ya da nötrofilik vasküler lezyonun diagnostik kriter olması gerektiği yönündedir (19).

Pozitif paterji testi, steril iğne ile yapılan mikro travma sonrasında 24-48 saat sonra o bölgede oluşan non-spesifik deri lezyonudur. Eritemli endurasyon ve ortasında papül ya da püstül oluşur. PPT erişkin tanı kriterleri arasındadır ancak pediatrik tanı kriteri paterji testini içermemektedir. Hastalarımıza yüksek oranda (%92,4) paterji testi uygulandı ve %27,8 oranında pozitif görüldü. PPT en yüksek İran ve Tunus (%55-57) çalışmalarında görülürken en düşük İngiltere ve İtalya (%6,5-14,5) çalışmalarında tespit edildi. Türkiye çalışmalarında PPT değerleri çok değişken olup %19-46,8 aralığındaydı (10-13). PT gerek invaziv olması, toplumlar arasında pozitiflik oranının değişkenlik göstermesi, uygulayıcı ve kullanılan materyalin özelliklerine bağımlı olması nedeni ile çocuk BH kriterleri içinde yer almamıştır. Ayrıca işlem sonrası doğru sonuç için uygulama bölgesinin korunması çocuk hastalarda oldukça zordur. Bunlara ek olarak çalışmamızda PT oldukça yüksek oranda uygulandı ancak ciddi organ tutulumunu işaret eden bir ilişkili bulunmadı.

Çocukluk çağı Behçet hastalığında mukokutanöz bulgular öncelikle lokal steroid, bakım ürünleri ve uygun dozda kolşisin ile tedavi edilmektedir. Bazen dirençli olgularda ve akut atak sırasında kısa süreli sistemik steroid kullanmak gerekebilir. Dirençli olgularda mümkünse kolşisin dozu artırıla bilinir ya da tedaviye azathioprin eklenebilir (2,20). Tüm hastalarımız lokal sterid ve kolşisin tedavilerini aldılar. Dirençli olan 12 hastaya kolşisin doz artırımına gidildi. Doz artırımına yanıt vermeyen 5 hastaya azathioprin ve 1 hastaya sistemik steroid başlandı.

Hastalarımızın izleminde BDCAF ile yaptığımız değerlendirme hastalık aktivitesini kontrol edebildiğimizi gösterdi. BDCAF çocuklara yönelik olmasa da çocuk hastaların tedavi yanıtı ve prognozunu değerlendirmede kullanılmaktadır (11).

Çalışmanın retrospektif yöntem ile tek merkezde ve az sayıda hasta ile yapılması temel kısıtlılığıdır.

Sonuç olarak çocukluk çağı Behçet hastalığında ROA, GÜ ve cilt bulguları en sık görülen bulgulardır. Ailesinde BH olan çocuklarda majör ROA olduğu takdirde BH dikkatle araştırılmalıdır. Etkin tedavi ile BDCAF skoru izole mukokutanöz tutulumu olan çocuk hastaklarda da gerilemektedir.

Mukokutanöz bulgular BH'nın kalıcı hasar bırakan ya da hayatı tehdit eden unsurlarından olmasa da tanıya giden yolda ilk basamak olup dikkatle değerlendirilmelidir ve mukokutanöz bulgulara farkındalığı artıracak olan bu çalışma gerçek hastalar ile çocuk romatologlarının buluşmasını kolaylaştıracaktır.

Erken evrede ROA olan hastaların prospektif olarak takip edildiği çalışmalar zamanında doğru tanı koymada bize yardımcı olacaktır.

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Research Article / Araştırma Makalesi

Determination of the Risk Factors in Patients Admitted with Bleeding Due to Warfarin use and Evaluation of the Current Bleeding Risk Scores

Varfarin Kullanımına Bağlı Kanama ile Başvuran Hastalarda Risk Faktörlerinin Belirlenmesi ve Mevcut Kanama Risk Skorlarının Değerlendirilmesi

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Abstract

Warfarin is the most common drug used in oral anticoagulation. The most serious side effect is bleeding. The aim of this study is to determine the risk factors that increase bleeding. In this retrospective study, we evaluated 283 patients with the diagnosis of bleeding due to warfarin use. The patients were divided into two groups as major and minor bleeding according to the need for blood transfusion. Age, gender, international normalized ratio (INR) level, drug use history, presence of additional disease, duration of treatment, warfarin dosage and laboratory data were obtained from patient files. Bleeding risk scores of 197 patients for whom laboratory data could be obtained before the bleeding event were calculated. The mean age of the patients was 69.16 ± 12.90 years. 51.9% were female and 48.1% were male. The major bleeding group was older (p=0,007). The rate of drug use that interacts with warfarin was 53.3%. Acetylsalicylic acid (ASA) usage rate was 31.4%. ASA use was more common in the major bleeding group (p=0,000). Concomitant disease was detected in 86.9% of the patients. The most common concomitant diseases were heart disease 59%, hypertension 56.5% and diabetes 21.2%, respectively. Heart disease was more common in the major bleeding group (p=0,001). The hemoglobin value measured at least one month before the bleeding was found to be significantly lower in the major bleeding group (p=0,001). Only the ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) median score was significantly higher in patients experiencing major bleeding than minor bleeding (p = 0.002). In our study, it was found that major bleeding due to warfarin was associated with advanced age, ASA use, concomitant heart disease and anemia development before bleeding. Therefore, close monitoring of the bleeding profile is very important. Patients and their care providers should be well informed about the side effects of the drug.

Keywords: Warfarin; oral anticoagulation; risk of bleeding; bleeding risk scores

Özet

Varfarin oral antikoagülasyonda kullanılan en yaygın ilaçtır. En ciddi yan etkisi kanamadır. Bu çalışmanın amacı kanamayı artıran risk faktörlerini belirlemektir. Bu retrospektif çalışmada varfarin kullanımına bağlı kanama tanısı alan 283 hastayı değerlendirdik. Hastalar kan transfüzyonu ihtiyacına göre majör ve minör kanama olarak iki gruba ayrıldı. Hasta dosyalarından yaş, cinsiyet, uluslararası normalleştirilmiş oran (INR) düzeyi, ilaç kullanım öyküsü, ek hastalık varlığı, tedavi süresi, varfarin dozu ve laboratuvar verileri elde edildi. Kanama olayı öncesi laboratuvar verilerine ulaşılabilen 197 hastanın kanama risk skorları hesaplandı. Hastaların ortalama yaşı 69,16±12,90 yıldı. Majör kanama grubu daha yaşlıydı (p=0,007). %51,9 kadın, %48,1 erkek idi. Varfarinle etkileşen ilâç kullanım oranı %53,3 idi. Asetilsalisilik asit (ASA) kullanım oranı %31,4'tü. ASA kullanımı majör kanama grubunda daha yaygındı (p=0,000). Hastaların %86,9'unda eşlik eden hastalık varlığı tespit edildi. En sık eşlik eden hastalıklar sırasıyla kalp hastalığı %59, hipertansiyon %56,5 ve diyabet %21,2 olarak görüldü. Kalp hastalığı major kanama grubunda daha sıktı (p=0,001). Kanamadan en az bir ay önce bakılan hemoglobin değeri majör kanama grubunda anlamlı olarak daha düşük bulundu (p=0,001). Majör kanaması olan hastalarda minör kanamaya göre sadece ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) medyan skoru anlamlı olarak daha yüksekti (p = 0.002). Çalışmamızda varfarine bağlı majör kanamanın ileri yaş, aspirin kullanımı, eşlik eden kalp hastalığı ve kanama öncesi anemi gelişimi ile ilişkili olduğu bulundu. Bu nedenle kanama profilinin yakın takibi çok önemlidir. Hastalar ve bakım sağlayıcıları ilacın yan etkileri hakkında iyi bilgilendirilmelidir.

Anahtar Kelimeler: Varfarin; oral antikoagulasyon; kanama riski, kanama risk skorları

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1. Introduction

Arterial and venous thrombosis is major causes of morbidity and mortality rates. Arterial thrombosis is the most common cause of acute myocardial infarction, ischemic stroke and leg gangrene, while deep vein thrombosis can lead to fatal pulmonary embolism (PE) and postphlebitic syndrome (1). Currently, there are oral (warfarin and other vitamin K antagonists) and parenteral (heparin, low molecular weight heparins, fondaparinux, hirudin, bivalirudin, lepirudin and argatroban) anticoagulant drugs that are licensed for use in the prophylaxis or treatment of these diseases. New agents have also been added to these agents in recent years. Warfarin is the most widely used oral anticoagulant in the world and blocks vitamin K dependent coagulation factors (II, VII, IX, X) and vitamin K dependent coagulation inhibitors.

Since it has a very narrow therapeutic window, it is not possible to adjust the sufficient therapeutic dose in every patient (2). The effectiveness of warfarin is demonstrated by the international normalized ratio (INR) value, rather than measuring the drug level. For most indications, an INR of 2.5 (2.0-3.0) is targeted, but 3.0 (2.5-3.5) is predicted for patients with mechanical prosthetic heart valves (3).The most important complication of warfarin is bleeding. At values above INR 5.0, the risk of bleeding increases exponentially, but it is difficult to determine the exact risk in patients (4,5). There are many factors that affect the occurrence of bleeding. In our study, we wanted to investigate the risk factors in cases with bleeding due to warfarin seen in our region by retrospectively examining the patients' files.

2. Material and Methods

In this study, a total of 283 patients diagnosed with bleeding due to warfarin use in the Internal Medicine Clinic of the Ministry of Health Konya Training and Research Hospital between September 1, 2010 and August 31, 2014 were retrospectively evaluated. By examining the patient files, the patient's age, gender, INR value, treatment duration, warfarin dosage, medication history, presence of additional disease, mortality rate and laboratory data were obtained. The patients were divided into two groups as major and minor bleeding according to the need for blood transfusion. The patient's need for 2 or more units of erythrocyte suspension for therapeutic purposes was defined as major bleeding, and the need for 1 unit of erythrocyte suspension or no need at all was defined as minor bleeding. The effects of the obtained data on major and minor bleeding were investigated. Bleeding risk scores of 197 patients, whose laboratory data could be obtained at least one month before the bleeding event, were calculated. The OBRI (Outpatient Bleeding Risk Index), HEMORR2HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol) and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) bleeding risk scores were computed according to original definitions (6-10).

OBRI includes four risk factors (age ≥65 years, history of stroke, history of gastrointestinal bleeding, and comorbid disease). Patients were defined as “low risk” for 0 points, “intermediate risk” for 1-2 points, and “high risk” for 3-4 points (6).

The HEMORR2HAGES score assigned a score for: liver or kidney disease, ethanol abuse, malignancy, advanced age (≥75 years), decreased platelet count or function, uncontrolled hypertension, anemia, genetic factors, risk of extreme falls, history of stroke. Patients were defined as “low risk” for 0-1 points, “moderate risk” for 2-3 points, and “high risk” for ≥4 points. (7,10).

In the HAS-BLED risk score, one point was assigned for the presence of uncontrolled hypertension (systolic blood pressure [BP] >160 mmHg), impaired kidney or liver function, history of stroke, history of bleeding (or bleeding predisposition). , unstable INR,

elderly (age > 65 years), concomitant use of acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol consumption (more than 20 units per week). A HAS-BLED score of ≤2 was classified as “low risk”, and a HAS-BLED score of ≥3 was classified as “high risk”(8,10).

The ATRIA score was assigned three points for the presence of anemia or a concomitant diagnosis of severe kidney disease (creatinine clearance <30 ml/min), 2 points for age ≥75 years, and one point for a positive history of clinical bleeding or hypertension (9,10).

Statistical analyses

While evaluating the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, frequency) were used while evaluating the study data. For the comparison of parameters not showing normal distribution between more than two groups, the Kruskal Wallis test was used and the Mann Whitney U test was used to identify the group that caused the difference. Two-group Student's t-test was used for parameters showing normal distribution, and Mann Whitney U test was used for two-group comparisons of parameters not showing normal distribution. Chi-square test was used to compare qualitative data. The results were evaluated at a 95% confidence interval, and the significance level was $p < 0.05$.

Ethical approval

Local Ethical Committee of Necmettin Erbakan University (Ethical approval license: Reference Number: 2014/45 Date: 05/12/2014) approved the study protocol. We conducted the study according to the principles of the Declaration of Helsinki.

3. Results

A total of 283 patients retrospectively evaluated. Major bleeding was observed in 148 (52.2%) patients. Clinical characteristics of patients according to major bleeding occurrence are summarized in in a table (Table 1).

Table 1. Descriptive and clinical characteristics of groups

	Major bleeding (n=148)	Minor bleeding (n=135)	p value
Age, (years)	71,05±12,16	67,10±13,41	p=0,007
Age ≥ 65 years (n), %	107 (72,3%)	83 (61,4%)	p=0,053
Age ≥ 70 years (n), %	97 (65,5%)	67 (49,6%)	P=0,007
Sex (male), %	81 (54,7%)	55 (45,3%)	p=0,513
INR > 5	90 (60.8%)	98 (72.6%)	p<0,001
Treatment duration > 1 year	83 (62,4%)	74 (59,2%)	p=0,684
Dosage ≥ 35mg/week	91 (61,5%)	95 (70,3%)	p=0,062
ASA	61 (%41,2)	28 (%20,7)	p=0,000
NSAIDs	15 (%10,1)	22 (%16,2)	p=0,125
Clopidogrel	5 (%3,3)	6 (%4,4)	P=0,644
Heart disease	97 (%65,5)	70 (%51,8)	p=0,001
Hypertension	80 (%54,0)	80 (%59,2)	p=0,378
DM	30 (%20,2)	30 (%22,2)	p=0,794
History of Stroke	33 (%22,2)	22 (%16,2)	p=0,193
History of MI	28 (%18,9)	17 (%12,5)	p=0,139
History of GI bleeding	13 (%8,7)	5 (%3,7)	p=0,078
Anemia	50 (53,2%)	26 (25,2%)	p=0,000
Labil INR	20 (%21,3)	28 (%27,2)	p=0,337

** INR: International Normalized Ratio, ASA: Acetylsalicylic acid, NSAIDs: Non-steroidal anti-inflammatory drug, DM: Diabetes mellitus, MI: Myocardial infarction, GI: Gastrointestinal*

Table 2. Bleeding risk score categories

	Major bleeding	Minor bleeding	Overall	p value
OBRI, median (IQR)	1 (0-4)	1(0-3)	1(0-4)	p=0,063
OBRI				
Low (0)	15 (16%)	24 (23,3%)	39 (19,8%)	
Intermediate (1-2)	67(71,3%)	75 (72,8%)	142(72,1%)	
High (3-4)	12(12,8%)	4 (3,9%)	16 (8,1%)	
HEMORR$_2$HAGES, median(IQR)	2(0-5)	1 (0-5)	2 (0-5)	p=0,094
HEMORR$_2$HAGES				
Low (0-1)	40 (42,5%)	53 (51,4%)	73 (47,2%)	
Intermediate (2-3)	40 (42,5%)	45 (43,7%)	85 (43,1%)	
High (>3)	14 (14,9%)	5 (4,9%)	19 (9,6%)	
HAS-BLED, median (IQR)	2 (0-5)	2 (0-5)	2 (0-5)	p=0,349
HAS-BLED				
Low (0-2)	61 (64,9%)	76 (73.8%)	137(69,5%)	
High (>2)	33 (35,2%)	27 (26,2 %)	60 (30,4%)	
ATRIA, median (IQR)	3 (0-8)	1 (0-5)	2 (0-8)	p=0,002
ATRIA				
Low (0-3)	54 (57,5%)	82 (%79,6)	136(69,1%)	
İntermediate/high (≥4)	40 (42,5%)	21 (%20,4)	61 (30,9%)	

OBRI (Outpatient Bleeding Risk Index), IQR (Inter Quantile Range), HEMORR$_2$HAGES (Hepatic or Renal Disease, Ethanol Abuse, Malignancy, Older Age, Reduced Platelet Count or Function, Re-Bleeding, Hypertension, Anemia, Genetic Factors, Excessive Fall Risk and Stroke), HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile International Normalized Ratio, Elderly, Drugs/Alcohol) and ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation)

136 (51.9%) of the patients were men and 147 (48.1%) were women, and the mean age of the patients was 69,16±12,90 years. There was no significant difference in terms of gender between the groups (p=0,513). Patients in the major bleeding group were older, and the mean age 71,05 vs 67,10 years (p=0,007).

60.8% of the patients in the major bleeding group and 72.6% of the patients in the minor bleeding group had an INR level of 5 and above (p<0.001).. When the patient groups were compared in terms of warfarin dose, the difference was not statistically significant (p=0.062). Warfarin was mostly used at a dose of 35-50 mg/week in both groups.

49.8% (n = 141) of patients had no history of drug use that interacted with warfarin. The rate of using drugs interacting with warfarin in the major bleeding group was 53.4% (n = 79), and 46.7% (n = 72) in the minor bleeding group. ASA was the most commonly used drug in both groups. The use of ASA was statistically significantly higher in the major bleeding group (p = 0.000).

Except for the warfarin indication, 86.9% (n= 246) of the patients had at least one concomitant disease. The most common indications for warfarin use were atrial fibrillation (32.9%) and heart valve disease(36.7%). Concomitant disease was found in 87.8% (n = 130) in the major bleeding group and 85.9% (n = 116) in the minor bleeding group. Of all patients, 59% (n=167) heart disease, 56.5% (n=160) hypertension, 32.7% (n=60) diabetes, 19% (n=54) chronic obstructive pulmonary disease, 6.3% (n=18) chronic renal failure, 2.4% (n=7) malignancy and 0.3% (n=1) chronic liver disease were seen. While no statistically significant difference was found in patients with hypertension (p = 0.378) and diabetes (p = 0.794), a significant statistical difference was found in patients with heart disease (p = 0.001).

When the laboratory data of the patients at least one month before the bleeding event were examined, anemia was significantly more common in the major bleeding group (54.3% vs 25.2%, p=0,001). Labile INR was detected in 21.3% (n = 20) in the major bleeding group and 27.2% (n = 28) in the minor bleeding group (0.037).

Bleeding risk scores of 197 patients from 283 patients, whose laboratory data before bleeding were obtained from the hospital information system, were evaluated in terms of major and minor bleeding (Table 2). There was no statistically significant difference in

median scores of HAS-BLED (p = 0.349), HEMORR2HAGES (p = 0.094) and OBRI (p = 0.063) between major and minor bleeding groups. Only the ATRIA median score was significantly higher in patients experiencing major bleeding than minor bleeding (p = 0.002).

Mortality was observed in only two (0.007%) of our patients included in the study, and both were in the major bleeding group. One of the reasons for the low mortality was that patients presenting with intracranial bleeding complication were not included in the study.

4. Discussion

The most important complication that restricts the use of warfarin is bleeding. Bleeding due to warfarin use is more common in the elderly. In a study, it was found that patients with atrial fibrillation (AF) aged 70 years and older are at high risk. It was found that being 70 years or older carries a 1.63 times higher risk of bleeding (11). In the study conducted by Wallvik et al., an increased risk of bleeding was found 1.6 times less than 60 years old, 2.9 times in patients between 60 and 69 years old, 4.8 times in patients between 70 and 79 years old, and 6.6 times in patients aged 80 and over (12). In our study, the mean age of the patient group was found to be 69.16 ± 12.90 years. It was determined that the major bleeding group was older. The incidence of major bleeding was higher in patients aged 70 years and over (p = 0.007). When the data of the World Health Organization (WHO) is examined, it is seen that the elderly population is increasing in developed countries (13). Also, considering the prevalence of atherosclerotic diseases (such as strokes, ischemic heart diseases) in this age period, it is understood that age is an important parameter. Therefore, we think that before starting warfarin treatment, physicians should take this situation into consideration and provide better follow-up and information in the elderly group.

Gender is very important in the pharmacokinetic and pharmacodynamic effects of drugs. The place of gender is controversial regarding the bleeding complication of warfarin. Studies emphasizing that there is no male or female superiority or gender have been reported. In our study, we could not detect the effect of gender on major and minor bleeding. Male gender was observed more in the major bleeding group and females in the minor bleeding group.

Bleeding due to warfarin therapy correlates with the degree of anticoagulant therapy. But elderly patients are more sensitive to warfarin, a lower dose is sufficient to achieve therapeutic value and they are more prone to bleeding, including intracranial hemorrhage, even if their INR is in the therapeutic range. In addition, elderly patients are more likely to use one or more drugs that interact with warfarin (3). In the study, the rate of patients with INR>5 was found to be higher in the minor bleeding group and the weekly warfarin dose was also found to be higher. We think that this difference is due to the older age of the main bleeding group, the presence of more co-morbidities, and the higher use of drugs that interact with warfarin, such as ASA.

Drugs that affect warfarin metabolism produce different effects on INR levels depending on the inhibition or activation of the CYP2C9 enzyme (14). Therefore, we investigated the use of drugs (ASA, NSAIDs, heparin, clopidogrel, antiepileptics, antibiotics, antidepressants, antihyperlipidemics, thyroid drugs, amiodarone, allopurinol, and metformin) among patient groups. In our study, a significant difference was observed between the groups in terms of using only ASA. In a study by Kathleen M. Galatro et al. comparing patients who took warfarin alone with patients who received a combination of warfarin and low-dose ASA, they found that the frequency of both minor and major bleeding was higher in the group of patients receiving the combination treatment (15). Dentali F et al. and James D. Douketis reported that the risk of bleeding was 1.5–2 times higher in patients using ASA and warfarin combination, similarly (5,16). Especially NSAIDs and randomly used ASA are drugs that are frequently prescribed and increase the risk of bleeding with warfarin. We recommend that these drugs should not be used together with warfarin as much as possible, if it is necessary to apply to the patient, the frequency of INR

follow-up should be increased and the patient should be informed about this issue.

When the rates of comorbidities in both groups were compared, it was found that the rates of comorbidities were higher in the major bleeding group. Several studies emphasize that the presence of an accompanying disease is a risk factor for bleeding. The most common accompanying diseases in the study of Shireman et al. were hypertension and heart disease (11). In our study, the most common accompanying diseases were heart disease and hypertension, respectively. A significant statistical difference was found between groups in patients with heart disease ($p = 0.001$). One of the reasons why the patient group with concomitant diseases is more risky in terms of major bleeding is the use of multiple drugs in these patients.

Anemia before the bleeding event was more common in the major bleeding group. Although we have not been able to determine the mechanism of association, the anemia may reflect bleeding susceptibility or recent subclinical bleeding.

Although it is not widely used today, scoring systems such as OBRI, HEMORR2HAGES, HAS-BLED and ATRIA are available for patients who will start warfarin (6-9). When the bleeding risk scores were examined in terms of major and minor bleeding in this study, ATRIA was found to be statistically significant. We think that giving more than 1 point to advanced age and anemia parameters in ATRIA risk scoring reveals this difference.

5. Conclusion

In patients using warfarin, the INR target value range should be determined according to the risk status of each patient, and close INR controls should be performed until the target INR value is reached. Major bleeding is the most important cause of morbidity and mortality in the event of a possible overdose. In our study, it was found that major bleeding due to warfarin was associated with advanced age, aspirin use, concomittant heart disease and anemia development before bleeding. Therefore, regular use of warfarin and close monitoring of the bleeding profile are very important. Patients and their care providers should be well informed about the side effects of the drug.

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Research Article / Araştırma Makalesi

Eskisehir Osmangazi University Faculty of Medicine Students' Knowledge Levels about Botulinum Toxin: Survey Study

Eskişehir Osmangazi Üniversitesi Tıp Fakültesi Öğrencilerinin Botulinum Toksini Hakkında Bilgi Düzeyleri: Anket Çalışması

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Abstract

The aim of the study is to evaluate the knowledge and awareness level of medical students through a questionnaire about botulinum toxin, which is widely used in medicine. The correct answer(s) of each question is explained at the end of the questionnaire thus it is aimed to encourage students to learn more about the subject by providing necessary information. The study is a cross-sectional descriptive study conducted by Google survey method to Osmangazi Medical Faculty students in the 2020-2021 academic year. Of the 404 students who responded the survey, 53 were 1st grade, 103 were 2nd grade, 50 were 3rd grade, 64 were 4th grade, 68 were 5th grade and 68 were 6th grade students. The questionnarie contains eight questions and the correct answer to each question is ten points. In questions with more than one correct answer, the weighted average score of each correct answer is calculated by division of ten to the number of correct answers. The total score of the questionnarie is eighty points. The average scores of the first to sixth grades were 38.87, 41.21, 56.75, 56.59, 60.66 and 62.95 respectively. According to the results of our study the level of knowledge of medical students about Botulinum toxin increases with the grade and both the level of knowledge and awareness about Botulinum toxin are at an acceptable level.

Keywords: Botulinum toxin; medical school; student; knowledge level; survey

Özet

Tıpta kullanımı çok yaygın olan Botulinum toksininin tıp fakültesi öğrencileri arasında bilinirlik ve farkındalık düzeyinin bir anket çalışması üzerinden değerlendirilmesi planlanmıştır. Anket sonunda her sorunun doğru yanıtı/yanıtları açıklanmış olup, öğrencilere gerekli bilgiler verilerek bu konuda daha fazlasını öğrenmeye teşvik etmek amaçlanmıştır. Çalışma 2020-2021 öğretim yılı içinde Osmangazi Tıp Fakültesi öğrencilerine Google anket yöntemi uygulanarak gerçekleştirilmiş kesitsel tanımlayıcı bir çalışmadır. Ankete yanıt veren 404 öğrencinin 53'ü 1. sınıf, 103'ü 2. sınıf, 50'si 3. sınıf, 64'ü 4. sınıf, 68'i 5. sınıf ve 68'i de 6. sınıf öğrencisidir. Sekiz soruluk bu anket çalışmasında her sorunun doğru yanıtı 10 puan olarak belirlenmiş; anket, toplamda 80 puan üzerinden değerlendirilmiştir. Birden fazla doğru yanıtı olan sorularda sorunun değeri doğru yanıt sayısına bölünerek; her bir doğru şıkkın ağırlık puanı hesaplanmıştır. Puan ortalamaları birinci sınıf öğrencilerinden başlayarak sırasıyla 38,87; 41,21; 56,75; 56,59; 60,66 ve 62,95 olarak hesaplanmıştır. Sınıfla beraber Botulinum toksini bilgi düzeyinin de arttığı gözlenmektedir. Çalışmamızın sonucuna göre tıp fakültesi öğrencilerinin Botulinum toksini hakkındaki bilgi düzeyleri ve farkındalıkları kabul edilebilir seviyededir.

Anahtar Kelimeler: Botulinum toksini; tıp fakültesi; öğrenci; bilgi düzeyi; anket

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1. Introduction

Botulinum toxin (BT) is a neurotoxic protein produced by Clostridium botulinum, a gram-positive anerobic spore bacterium, and is also one of the most toxic biological substances known.

Although BT stands out as a cosmetic application today, its use in medicine is becoming widespread. It is also used in the treatment of hyperactive nerve disorders, including excessive sweating, chronic pain and some allergy symptoms, treatment of muscle spasticity and some other muscle diseases1. Its first use in medicine was described by Alan Scott as an alternative to surgery in the treatment of strabismus and blepharospasm2.

Although BT is generally considered safe, complications may occur; they are usually mild and temporary. The most common complications are ecchymosis, injection into the wrong muscle group or spreading from the injection site causing temporary paralysis of unwanted muscles. Other complications include asymmetry, muscle weakness, eyelid/eyebrow ptosis and difficulty in swallowing3,4 and they can be prevented largely by the practitioner's mastery of anatomy.

Medical students should learn all aspects of the medicine to practice along the evidences, guidelines, and ethics after their graduation. Besides they have an unnamed responsibility to inform and guide their environment in medical matters. Therefore, in this study we aimed to determine the knowledge and awareness levels of medical students about BT and its scope of application and to evaluate the differences according to the grades.

2. Material and method

The study was approved by Eskisehir Osmangazi University (ESOGÜ) non-interventional clinical research ethics committee (decision # 18.02.2020/19). The study is a cross-sectional and descriptive study. BT information questionnaire prepared with "Google surveys" were mailed to Osmangazi Medical Faculty students of 2020-2021 academic year. A total of 1582 students received the questionnaire.

The survey consists of 8 questions of 10 points each. The questions # 2 and 7 have multiple correct answers. For questions with multiple correct answers, 10 points is divided by the number of the correct answers thus the weight score of each correct option is calculated. The survey is evaluated on a total of 80 points.

Statistical Analysis

The distribution of each continuous variable was tested for normality using the Shapiro-Wilk test and is expressed as median value (%25_%75). Non-normally distributed variables were performed using the Kruskal Wallis test. A p-value <0.05 was considered significant. All analyses were performed using the SPSS version 22.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

Of the 1582 students, 407 answered the survey. The grade levels and the number of responding students are presented in Table 1.

Table 1. Distribution of total number of students in ESOGÜ Faculty of Medicine and number of students who answered the survey to the classrooms.

Grade level	Number of students	Number of students who answered the survey	Participation rate
1	306	53	%17,32
2	290	103	%35,51
3	278	52	%18,7
4	235	64	%27,23
5	239	67	%28,03
6	234	68	%29,05
Total	1582	407	%25,72

Table 2. TIP FAKÜLTESİ ÖĞRENCİLERİNİN BOTULİNUM TOKSİNİ İLGİLİ BİLGİ DÜZEYLERİNİ ÖLÇME ANKETİNE VERDİKLERİ CEVAPLARIN DAĞILIMI

STUDENTS' ANSWERS TO THE SURVEY

		1.SINIF (1st grade)	2.SINIF (2nd grade)	3.SINIF (3rd grade)	4.SINIF (4th grade)	5.SINIF (5th grade	6.SINIF (6th grade)
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Botulinum toksini nedir? **What is botulinum toxin?**	Bir tür dolgudur. It is a kind of filler.	31 (%58,5)	50 (%48,5)	9 (%18)	15 (%23,4)	12 (%18,2)	7 (%10,3)
	Bir tür zehirdir* It is a kind of poison.	25 (%47,2)	59 (%57,3)	44 (%88)	56 (%87,5)	60 (%90,9)	65 (%95,6)
	Bilmiyorum I don't know	2 (%3,8)	3 (%2,9)	1 (%2)	0 (%0)	1 (%1,5)	0 (%0)
	Yüzün bazı bölgelerindeki istenmeyen kırışıklardan kurtulmak* Treatment of facial rhytids	51 (%96,2)	98 (%95,1)	50 (%100)	62 (%96,9)	65 (%98,5)	67 (%96,5)
	Şaşılık* Strabismus	19 (%35,8)	15 (%14,6)	12 (%24)	32 (%50)	38 (%57,6)	46 (%67,6)
	Servikal distoni* Cervical dystonia	9 (%17)	14 (%13,6)	14 (%28)	25 (%39,2)	40 (%60,6)	47 (%69,1)

BT hangi endikasyonlarda kullanılabilir? **Which are the indications of BT?**	Migren* Migraine	13 (%24,5)	20 (%19,4)	12 (%24)	27 (%42,2)	27 (%40,9)	34 (%50)
	Blefarospazm* Blepharospasm	5 (%9,4)	9 (%8,7)	6 (%12)	16 (%25)	44 (%66,7)	48 (%70,6)
	İdrar kaçırma* Urinary incontinance	16 (%30,2)	17 (%16,5)	14 (%28)	28 (%43,8)	28 (%42,4)	42 (%61,8)
	Hemifasial spazm* Hemifacial spasm	9 (%17)	13 (%12,6)	14 (%28)	29 (%45,3)	39 (%59,1)	49 (%72,1)
	Aşırı terleme* Hyperhydrosis	21 (%39,6)	29 (%28,2)	26 (%52)	39 (%60,6)	42 (%63,6)	49 (%72,1)
	Cerebral palsili çocuklarda* Children with cerebral palsy	6 (%11,3)	9 (%8,7)	8 (%16)	14 (%21,9)	31 (%47)	51 (%75)
	Geceleri diş sıkma/gıcırdatma* Bruxism	21 (%39,6)	34 (%33)	18 (%36)	43 (67,1)	36 (%54,5)	47 (%69,1)
	Bilmiyorum I don't know	5 (%9,4)	8 (%7,8)	1 (%2)	1 (%1,6)	3 (%4,5)	4 (%5,9)
Botulinum toksini vücutta nereye etki eder? **Where does botulinum toxin**	Tüm vücuttaki kas ve sinirlere To all muscles and nerves all over the body	1 (%1,9)	5 (%4,9)	1 (%2)	1 (%1,6)	4 (%6,1)	5 (%7,4)
	Uygulandığı bölgedeki kas ve sinirlere* To the muscles and nerves in the	50 (%94,3)	96 (%93,2)	50 (%100)	64 (%100)	66 (%100)	66 (%97,1)

affect in the body?	injection area						
	I don't know	4 (%7,5)	6 (%5,8)	0 (%0)	0 (%0)	0 (%0)	0 (%0)
Botulinum toksininin moleküler yapısı nedir? **What is the molecular structure of botulinum toxin?**	Protein* Protein	13 (%24,5)	52 (%50,5)	29 (%58)	43 (%67,2)	42 (%63,6)	48 (%70,6)
	Lipit Lipid	9 (%17)	12 (%11,7)	1 (%1)	1 (%1,6)	1 (%1,5)	2 (%2,9)
	Karbonhidrat Carbohydrate	1 (%1,9)	4 (%3,9)	0 (%0)	0 (%0)	1 (%1,5)	0 (%0)
	Mineral Mineral	2 (%3,8)	4 (%3,9)	1 (%2)	0 (%0)	0 (%0)	0 (%0)
	Bilmiyorum I don't know	33 (%62,3)	44 (%42,7)	19 (%38)	23 (%35,9)	22 (%33,3)	19 (%27)
Botulinum toksininin etki mekanizması nedir? **What is the mechanism of action of botulinum toxin?**	Sinaptik aralıktaki nörotransmitterleri parçalar. Breaks down neurotransmitters in the synaptic range.	11 (%20,8)	13 (%12,6)	6 (%12)	6 (%)	2 (%3)	2 (%2,9)
	Nöronları zehirleyerek sinirsel iletimi engeller. Inhibits neuronal transmission	10 (%18,9)	15 (%14,6)	0 (%0)	3 (%)	2 (%3)	1 (%1,5)
	Nöronların mitokondrilerini baskılayarak enerjisiz bırakır Suppresses the mitochondria of	2 (%3,8)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	0 (%0)

	neuronal cells						
	Sinir uçlarından asetil kolin salınımını engeller* inhibits the release of acetylcholine from nerve endings	26 (%49,1)	54 (%52,4)	42 (%84)	50 (%78,1)	61 (%92,4)	64 (%94,1)
	Bilmiyorum I don't know	12 (%22,6)	26 (%25,2)	4 (%8)	10 (%15,6)	4 (%6,1)	2 (%2,9)
Botulizm nedir? **What is botulismus?**	Yiyecekler ile Clostridum botulinum bakteri toksinin alınmasıyla oluşan enfeksiyon hastalığı* An infectious disease caused by ingestion of Clostridum botulinum bacterial toxin with food	16 (%30,2)	23 (%22,3)	36 (%72)	44 (%68,8)	55 (%83,3)	56 (%82,4)
	Kasların spastik kasılı kalmasıyla oluşan durum Condition caused by spastic contraction of the muscles	7 (%13,2)	20 (%19,4)	7 (%14)	17 (%26,6)	18 (%27,3)	11 (%16,2)
	Çok soğuk havalarda yüz kaslarının felciyle karakterize durum Condition characterized by paralysis of facial muscles in very cold weather	5 (%9,4)	7 (%6,6)	1 (%2)	3 (%4,7)	0 (%0)	0 (%0)
	Bilmiyorum I don't know	32 (%60,4)	57 (%55,3)	6 (%12)	6 (%9,4)	2 (%3)	3 (%4,4)

Tıbbi ve kozmetik Botulinum toksini uygulaması kimlere yapılamaz? **To whom cannot be applied medical and cosmetic Botulinum toxin?**	18-65 arası herkese Anyone aged between 18-65	1 (%1,9)	2 (%1,9)	0 (%0)	1 (%1,6)	1 (%1,5)	2 (%2,9)
	Hamilelik-Emzirme dönemi yaşayanlara* During pregnancy and breastfeeding*	27 (%50,9)	64 (%62,1)	36 (%72)	38 (%59,4)	35 (%53)	42 (%61,8)
	Çocuklara Children	19 (%35,8)	52 (%50,5)	20 (%40)	19 (%29,7)	24 (%36,4)	12 (%17,6)
	Kas hastalığı olanlara* For those with muscle diseases*	26 (%49,1)	64 (%62,1)	28 (%56)	29 (%45,3)	33 (%50)	24 (%35,3)
	Bilmiyorum I don't know	15 (%28,3)	17 (%16,5)	7 (%14)	15 (%23,4)	13 (%19,7)	10 (%14,7)
Kozmetik Botulinum toksini uygulamasını kimler yapabilir? **Can it be used in cosmetic Botulinum toxin use?**	Plastik, Rekonstrüktif ve Estetik cerrahi uzmanı, Dermatoloji uzmanı* Plastic, Reconstructive and Aesthetic surgery specialist, Dermatology specialist	49 (%92,5)	92 (%89,3)	50 (%100)	61 (%95,3)	65 (%98,5)	60 (%88,2)
	Bütün sağlık çalışanları All healthcare workers	1 (%1,9)	0 (%0)	0 (%0)	0 (%0)	0 (%0)	1 (%1,5)
	Herhangi bir branştan bir hekim A physician of any specialty	1 (%1,9)	0 (%0)	1 (%2)	5 (%7,8)	5 (%7,6)	15 (%22,1)
	Güzellik salonunda çalışan estetisyenler Estheticians working in beauty centers	5 (%9,4)	13 (%12,6)	9 (%18)	8 (%12,5)	2 (%3)	0 (%0)

	Bilmiyorum I don't know	5 (%9,4)	8 (%7,8)	0 (%0)	1 (%1,6)	0 (%0)	0 (%0)
	Ortalama puan **Average score**	38,87	41,21	56,75	56,59	60,66	62,95

Table 2 shows the percentage of correct answers for each question according to the grade level. The average scores of the students for each question and for total according to their grades are shown in Table 3.

Table 3. Students' averages of points in each question according to their grade

	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Total
1st grade	4,24	3,11	9,33	2,16	4,15	2,92	4,19	8,77	38,87
2nd grade	5,29	2,42	9,12	4,46	5,04	1,74	4,8	8,34	41,21
3rd grade	8,26	3,38	9,9	5,76	8,07	7,11	5,33	8,94	56,75
4th grade	8,2	4,92	9,92	6,48	7,58	6,41	4,41	8,67	56,59
5th grade	8,58	5,96	9,7	6,27	9,03	7,54	4,25	9,33	60,66
6th grade	9,26	7,06	9,56	6,99	9,34	8,16	4,49	8,09	62,95

Each question is evaluated on 10 points and the maximum score that can be obtained is 80.

According to the statistical analysis results, there is a significant difference between the scores of the students from different grades in questions 1 and 2 ($P<0.001$). There is no statistical difference between graders for question # 3. In the 4th, 5th, 6th questions, graders 1 and 2 differed significantly from other grades ($P<0.001$). There is no statistical difference between the grades in questions #7 and 8. The 1st and 2nd graders differed significantly from other classes in total scores ($P<0.001$).

4. Discussion

Botulinum toxin is a neurotoxic protein produced by Clostridium botulinum, a gram-positive anaerobic spored bacterium, and is one of the most toxic biological substances known5.. Of the seven serotypes, only species A and B are medically used6,7,8. Other species are much rarer and often cause animal diseases. Botulinum neurotoxin causes flaccid neuroparalysis by preventing the release of acetylcholine neurotransmitter from the axon ends at the neuromuscular junction9.. The toxin shows its effect by breaking down key proteins necessary for nerve activation. First, it binds to the neuronal cells then it is taken into a vesicle through receptor-mediated endocytosis9. The vesicle becomes acidic as it moves through the cell membrane into the cell, and pushes of the toxin along the vesicle membrane towards cell cytoplasm5. Once toxin enters the cell cytoplasm, it divides the SNARE proteins (proteins that mediate vesicle fusion) and leads to paralysis by interfering nerve signals4. The disease caused by this toxin has been called botulism.

BT, which stands out with its cosmetic facial rejuvenation usage in written and social media, and it is usually confused with fillers. In the first question of the survey, students were asked whether BT was toxin (poison) or filler. The lowest average score in this question belonged to 1st graders with 4.24 (correct answer rate 47.2%). The average score increased to 5.29 in 2nd graders (correct response rate 57.3%), without a statistical difference between these two grades. The correct response rate and average score of the first question showed a raise from the 3rd graders to the 6th graders. Most of the 6th students knowed BT is a toxin. The average scores of 3rd to 6th graders differed significantly from 1st and 2nd graders. As the result of the question is in the basic curriculum of 2nd and 3rd years of medical school, 3rd graders and superiors are expected to be familiar with the subject. Depending to the timing of the survey, some of the 2nd graders may not have had the opportunity to process this issue yet.

The second question in the survey covers the areas of clinical use of BT rather than the mechanism of action or structural properties of the toxin. 96% of 1st grade students know that BT is used for cosmetic purposes, but their information about other clinical usage areas were low. This question was answered more accurately by 4th graders and above because they are more familiar with the various clinical usage of BT based on the compulsory clinical courses and internships from the 4th grade. The largest proportional increase of a subject under this question was the blepharospasm treatment (from 9.4% to 70.6%) which is a very common treatment method extensively discussed Ophthalmology internship. This subject had a higher marking rate in the 5th and 6th graders than in previous classes. The least known application of BT was in migraine treatment (50%). The average scores of this question were not different between 1st, 2nd, and 3rd graders, but they differed significantly from 4th, 5th, and 6th graders. The proportional increase in the right answers of this option with the class level, show that students use the information they gained from previous classes and make healthier assessments. In another BT awareness level survey applied on a hundred dental college students in Chennai, India, only 50% of students knew that toxin injection was effective in reducing facial rhytids; in our study, this rate (97.2%) was higher11.

In the third question, independent from the grade level, all students stated that the toxin have the paralytic effect solely in the area of injection; there was no statistical difference between classes.

In the fourth, fifth and sixth questions, the molecular structure of BT, mechanism of action and botulismus disease were asked as an academic knowledge. In the fourth question, the average score of the 1st and 2nd graders were lower than in other classes and statistically not different from each other. There was a significant difference between 3rd, 4th, 5th and 6th graders from 1st and 2nd graders. This subject is in the curriculum of physiology and pharmacology which are thought in the second and third years of medical school therefore 3rd graders and above are expected to had the physiologic and

pharmacologic properties of BT. Again, depending to the timing of the survey, some of the 2nd graders may not have learned this subject yet. The 3rd graders and above replied the fourth, fifth and sixth questions with high scores without a statistical difference between them. More comprehensive information and increasing awareness about BT is an not a surprising finding for upper grades of medical school students.

In the seventh question, the students were asked to whom BT can be applied. Unlike many drugs BT can be used even in the pediatric age group especially in spasticity and has been approved for use by the American Health and Food Organization in several indications 12. In contrast, the pregnancy category of BT is C and its use in pregnancy is not recommended if the potential benefit to the pregnant woman is greater than the potential harm to the fetus13. BT injections are contraindicated in patients with progressive muscle diseases, such as Myasthenia-Gravis and Eaton-Lambert syndromes, as it can aggravate the symptoms of the disease14,15 Although many students replied correctly, this question had the lowest average scores in all grades and there was no statistical difference between classes. The reason may depend on the content of the basic curriculum; it usually covers the general aspects of mechanisms, indications and contraindications. In a similar survey study, Imam et al showed that only 2/3 of the students thought that BT injections may not be safe during pregnancy or breastfeeding.

The eighth question is related to the legislation and is not included in the curriculum. In this question the students were asked who could administer BT injections. Cosmetic filler and Botox injections are often identified with youth and beauty. When there is not enough supervision by the lawmakers, these kinds of applications are prone to abused by several occupational groups other than physicians. Everyday we witness various news in the media about a BT/filler disaster performed in beauty centers or even in hairdressers. In 03.08.2015 of the Ministry of Health of the Republic of Turkey released an article - numbered 23590821/180/1423- about BT injections. The article states that “The training of facial cosmetic procedures are given in plastic, reconstructive and aesthetic surgery and dermatology departments in our country therefore only these specialists are allowed to perform of cosmetic injection procedures in the facial area. In other words, to perform botulinum toxin injections for facial cosmetic procedures, it is an obligation to have been trained in these specialties as well as having the title of Doctor of Medicine. Without these conditions, it is not possible for non-physicians to engage in professional activities in the field of medicine based on the knowledge or documents obtained from various courses... " 17.. It is also stated that BT injections can be performed by the relevant branch physicians for various clinical indications such as cervical dystonia and spasticity. In this question of the survey, some of the students answered that beauticians may also perform this medical practice. Despite the recent reports of complications or even deaths because of the under the counter cosmetic practices which are carried out in beauty centers; it is interesting and worrisome that a physician candidate can accept a medical practice performed by non-physicians. To overcome this erroneous disbelief, it should be emphasized more frequently in the clinical courses that all kinds of medical procedures should be performed by health personnel who are specialized in the relevant specialty and who can cope with the possible complications. A similar misconception was highlighted in the publication of Imam et al. In his survey, although 66% of the 386 female medical students emphasized that the toxin may have significant side effects and/or complications, 32.4% stated that BT can be sold and applied without a prescription16.

5. Conclusion

Compared to the 1st and 2nd grade students, which are the basic classes of the faculty, the knowledge and awareness levels of the other classes are higher. Botulinum toxin has been included in the curricula of various basic and clinical branches especially in the physiology and pharmacology courses in the 2nd and 3rd grades general surgery, neurology, plastic surgery, and ophthalmology in the upper grades. Besides, the intense interest of media

to noninvasive procedures such as BT may draw attention and accentuate the awareness levels of medical students. However, the variety of complications and contraindications should be underlined, and it should be emphasized that any medical procedure whether it is cosmetic or not, should be performed by physicians not by other professions.

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Research Article / Araştırma Makalesi

Long-Term Effects of COVID-19 on Adolescents

COVID-19'un Adölesanlar Üzerindeki Uzun Dönem Etkileri

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Abstract

Long-term effects are increasingly reported in adult patients with coronavirus disease-2019 (COVID-19) but there are not enough studies in adolescents. This study aimed to evaluate the long-term effects of COVID-19 in the adolescent population. Adolescent patients diagnosed with non-severe COVID-19 between October 2020 and January 2021 in our center were questioned in terms of long-term effects by telephone call. A total of 109 adolescent patients with non-severe COVID-19 were evaluated. In five of them at least of one myalgia/fatigue, cough, chest pain, palpitation, sleep disorderand psychiatric problems are seen as long- term effects of COVID-19. These five patients had a median age of 16.4 years (range 11.5-17) and three of them are boys. The mean time that we evaluate these patients after diagnosis is 121.6±13.1 days. All of them categorized as 'mild' COVID-19 infection and none of them were hospitalized. Only one patient has the underlying disease 'asthma'. Long-term COVID-19 symptoms can also be seen in otherwise healthy children after mild disease. Especially psychiatric complaints should not be ignored and pediatricians should be more careful in terms of these effects.

Keywords: adolescent, coronavirus, long COVID-19, pandemic, Turkey

Özet

Yeni koronavirüs hastalığı-2019 (COVID-19) geçiren yetişkin hastalarda uzun dönem etkiler, giderek daha fazla bildirilmekte ancak adölesanlarda konuyla ilgili yeterli çalışma bulunmamaktadır. Bu çalışma, COVID-19'un adölesan hasta grubunda uzun vadeli etkilerini değerlendirmeyi amaçlamıştır. Merkezimizde Ekim 2020-Ocak 2021 tarihleri arasında ağır olmayan COVID-19 tanısı alan adölesan hastalar telefonla aranarak uzun dönem etkiler açısından sorgulandı. Ağır olmayan COVID-19 tanısı alan 109 adölesan hasta çalışmaya dahil edildi. Bu hastaların beşinde miyalji/yorgunluk, öksürük, göğüs ağrısı, çarpıntı, uyku bozukluğu ve psikiyatrik sorunların en az biri COVID-19'un uzun dönem etkileri olarak görüldü. Bu beş hastanın medyan yaşı 197 ay (138-204) olup üçü erkekti. Tanı konulduktan sonra hastaların değerlendirildiği ortalama süre 121,6±13,1 gündü. Tümü 'hafif' COVID-19 enfeksiyonu tanısı almış olup hiçbirinin hastane yatış öyküsü yoktu. Sadece bir hastada altta yatan hastalık 'astım' vardı. Uzun dönem COVID-19 semptomları, öncesinde sağlıklı olan adölesanlarda hafif hastalık kliniğinden sonra görülebilir. Özellikle psikiyatrik şikayetler göz ardı edilmemeli ve çocuk doktorları bu etkiler konusunda daha dikkatli olmalıdır.

Anahtar Kelimeler: koronavirüs, uzun COVID-19, adölesan, pandemi

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1. Introduction

Since December 2019, the world has been dealing intensively with a newly identified infectious disease named COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).1,2 Although the knowledge on the clinical course of the disease increases day by day, there are still many unknowns.

The clinical course of the disease varies from asymptomatic to severe respiratory failure.3,4It seems to have less severe course in children than adults with good prognosis but recently, complications related to COVID-19 were reported.3-5One of these is multisystem inflammatory syndrome in children (MIS-C) and the other one is long-term COVID-19 associated signs and symtoms.5-7Although MIS-C criteria and treatment method are increasingly included in the literature, the data examining the long-term effects of COVID-19 in the pediatric patient group are very limited.7-9 Adolescence is a special period, COVID-19 pandemic and the measures taken in this direction has negative effects on adolescent health but it is a question of how these effects will be who have had COVID 19.10In this study, we aimed to investigate the presence and duration of long term symptoms related to COVID-19 in adolescents.

2. Material and Methods

Adolescent patients diagnosed with non-severe COVID 19 infection between October 2020 and January 2021 in the University of Health Sciences, Zeynep Kamil Maternity and Children's Hospital were included in this cross-sectional retrospective study. The definition of adolescent was defined according to WHO and patients between the ages of 10-18 were included.11Patients with negative PCR results or severe COVID-19 were excluded from the study.

In our study, only the patients that the diagnosis was confirmed by positive real-time reverse transcriptase-polymerase chain reaction from nasopharyngeal swabs were included. Real-time PCR diagnostic kits authorized by the General Directorate of Public Health (GDPH) Microbiology Reference Laboratory were used for the diagnosis.12In addition, only patients classified as asymptomatic, mild or moderate were included in the study. Patients were categorized according to the features defined by Dong et al. such as, the patients with no signs or symptoms were defined as 'asymptomatic', patients with symptoms of acute upper respiratory tract infection but without pneumonia as 'mild', presence of pneumonia but with no obvious hypoxemia as 'moderate'.13

Post COVID-19 patients were called by phone and a questionnaire was applied to their parents. In the questionnaire, the presence of symptoms throughout illness and whether any complaints are still present were asked. If the patient has an ongoing complaint, whether it affects his/her daily activities and school life, or whether there is a clinic visit for this is questioned. Also, whether there was a change in sleep patterns that did not exist before COVID 19 infection was questioned with the following three questions: Is he/she having trouble with falling asleep? Does he/she wake up often? Has there been a change in total sleep time?

A review of data on the demographics, clinical, laboratory, radiological, treatment, and outcomes was recorded. Clinical data were extracted from medical records, which included age, sex, underlying disease, presenting symptoms, exposure history, leucocyte, lymphocyte and thrombocyte count. The leucocyte and lymphocyte count levels were determined by comparison with our local age-related normal ranges.14Thrombocytopenia was defined as thrombocyte count below 150,000/mm3; while neutropenia was defined as neutrophil count < 1,500/mm3.

All procedures performed in studies involving human participants were in accordance with the Helsinki Declaration. Approval for the study was obtained from the local ethics committee of University of Health Sciences, Zeynep Kamil Maternity and Children's Hospital (March 2021–78).

Statistical analysis

The statistical package SPSS version 15.0 (IBM SPSS Statistics, Chicago, IL) was used for data analysis. Quantitative variables were expressed as mean (±standard deviation) or median values, while qualitative variables were expressed as percentages.

3. Results

There were 124 adolescents diagnosed with COVID-19 during the study period. All the patients were called by phone, 109 of them were contacted and their families were interviewed. Fifty six (51.4 %) of the patients were male and 53 (48.6 %) were female. Among patients, the mean age (±SD) was 14.4 (±2) years. There was no history of chronic disease in 95.4% (104) of the patients. Comorbidities such as congenital hypothyroidism, asthma, dyslexia, ulcerative colitis, and atrial septal defect were present in five patients.

Of the 109 patients, 75.2% had an exposure history with an infected family member, 17.5% had contact with a friend with COVID-19, while 7.3% of patient had no history of contact.

Seven (6.4%) patients were asymtomatic. Among the complaints on admission fever was present in 27.5% of cases. The most common symptoms were fatigue/myalgia (46.8%) and cough (33.9%) followed by headache (20.2%), sore throat (18.3%), ageusia (11.9%), anosmia (7.3%),rhinorrhea (4.6%), diarrhea (2.8%), dyspnea (2.8%), chest pain (1.8%), conjunctivitis (1.8%) abdominal pain (0.9%), vomiting (0.9%), and rash (0.9 %).

Analysis of blood tests was available for 19 (17.5%) children at the time of diagnosis. The median WBC was 5730 (3690−16300) cells/mm3, neutrophil was 3590 (2060-13500) cells/mm3, lymphocytewas 1610 (880-2680) cells/mm3. Lymphopenia, leukopenia, and leukocytosis were identified in 9.2%, 2.8% and 0.9% of patients, respectively. Increased levels of C-reactive protein (CRP) were detected in five patients.

Seven (6.4%) of the patients were classified as ‘asymptomatic’, 101 (92.7%) as mild, one (0.9%) as ‘moderate’. Only one patient were admitted to the hospital with diagnosis of pneumonia and length of stay in the hospital was 3 days.

We found ongoing symptoms or complaints in five patients. When these 5 patients and asymptomatic patients were excluded from the group, the average duration of symptoms related to COVID-19 was 3.6±2.3 days.

In patients with ongoing symptoms, the mean of time that we evaluate patients after diagnosis is 121.6±13.1 days. The median age of these patients was 16.4 (11.5-17) years while two of them were girls. All of them categorized as ‘mild’ COVID-19 infection and none of them were hospitalized. Only one patient has underlying disease ‘asthma’.

One patient after 132 days from the diagnosis described cough, chest pain, palpitation, myalgia/fatigue. For this reason, she has visited pediatric clinics four times and was also evaluated by a pediatric cardiologist. The chest x-ray was normal. Electrocardiography showed a normal sinus rhythm with no abnormalities. In echocardiographic evaluation mitral valve prolapsus and mild mitral regurgitation were seen. She also had fear of not being able to breathe and pessimism. In this respect, the patient, who was evaluated by a child psychiatrist, was included in the psychotherapy program with the diagnosis of anxiety and mild depressive symptoms. All of her current complaints began after she had a COVID-19 infection.

The second patient who has also underlying asthma history has ongoing dyspnea and myalgia/fatigue. She can continue to do daily activities but she was unable to work because she could not stand for a long time while working in a clothing store as part-time work before COVID-19. The patient visited the pediatric outpatient clinic once with these complaints, and her physical examination and laboratory results were normal.

One patient continues to suffer from myalgia/fatigue but he carries out his daily activities and follows all of the school lessons

online. He also has serious concerns about going out that he went out only 4 times in the past five months after the diagnosis. The patient, who plays violin and piano and was very enthusiastic about music education quit lessons after COVID-19 with fear of going out. He is also having trouble with falling asleep and wakes up frequently at night. Although the family thought it was necessary to visit the psychiatry clinic, he did not accept.

The other two patients complained of myalgia/fatigue even they go on to do their daily activities. These two patients similarly stated that they did not want to go out or school with fear of reinfection. One of these patients had a child psychiatry visit. Detailed characteristics of the patients are presented in Table 1.

Table 1. Characteristics of the peditric patients with long term effects of COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender, age at diagnosis	Female, 16.8 years	Female, 17 years	Male, 14.7 years	Male, 16.4 years	Male, 11.5 years
Underlying disease	None	Asthma	None	None	None
Disease classification	Mild	Mild	Mild	Mild	Mild
Initial symptom	Myalgia/fatigue	Dyspnea	Fever	Myalgia/fatigue	Myalgia/fatigue
Treatment	None	None	None	None	None
Current complaint	Cough, chest pain, palpitation, myalgia/fatigue, fear of not being able to breathe and pessimism	Dyspnea, myalgia/fatigue	Myalgia/fatigue, fear of going out, sleep disorder	Myalgia/fatigue, fear of going out and reinfection	Myalgia/fatigue, fear of going out and reinfection
The day of assessment after the diagnosis	130	105	139	118	116

4. Discussion

In this study, the presence of possible long-term findings due to COVID-19 in children was investigated, and findings attributable to this infection were defined in five patients. The most commonly seen complaints were myalgia/fatigue. One remarkable result is that

psychiatric problems were seen in four patients.

Long COVID is increasingly gained importance in the world that many organizations are at the stage of launch clinics and publishing clinical guidelines for it.15There is researches on how COVID-19 may influence children's lives but there is little information about children with long COVID.16,17On the other hand adult studies on long term effects of COVID 19 infection are increasing reported. In an adult study from Italy; 143 adults patients mostly diagnosed with pneumonia and hospitalised were assessed a mean of 60 days after onset of diseaese and only 18 (12.6%) had no findings associated with COVID-19 while more than half of the patients experience three or more symtoms. Most frequently seen symptoms were fatigue, dyspnoea, joint pain, chest pain, cough and anosmia. In nearly half of the patient (44.1 %) described worsened quality of life.18 In the evaluation of 384 hospitalized patients after a median of 2 months after discharge, 53% reported breathlessness, 34% cough and 69% fatigue while 14.6% had depression. In addition, it is reported that radiological abnormalities continue in a significant number of patients.19 Huang reported that at 6 months after symptom onset %76 of patients still had complaints. Fatigue or muscle weakness is the most commonly seen complaint that effected more than half of the patient. Sleep difficulties and anxiety or depression was reported nearly in 25% of patients.20

Ludvigsson8 describes five pediatric patient with fatigue, dyspnoea and heart palpitations or chest pain that lasting for at least six months. In addition to these sypmtoms headaches, difficulties concentrating, depression, sleep disorders, miyalgia, dizziness, abdominal pain, diarrhoea and vomiting and also defined. Four of the five patients were girls and the median age was 12 year. Another important point of the article is that patients diagnosed with COVID-19 by their physician with no microbiological confirmation.

There are predictions that the pandemic will have many psychiatric effects on both people who are infected or not.21,22The reason for this is likely to be multifactorial that might include hospital admissions, drug use, social isolation, and the thought that many people lose their lives with the same diagnosis in the world. In the study, we showed the existence of psychiatric complaints in four children who did not have any before COVID-19, and two of them needed professional help from a child psychiatrist.

There are many uncertainties regarding risk factors for long-term COVID-19. There is a variety of data on which gender the post-covid-19 symptoms are seen more frequently. In the Carfi study mostly male affected (62.9%) but there also studies that showed a higher percentage was observed in women.8,18,20,23 In our study approximately the same number of boys and girls affected (two girls, three boys). The fact that only one of our patients had an underlying disease ‘asthma’and no comorbidity was detected in the other four patients is evidence that long COVID-19 can affect healthy children even in mild cases.

Our study has some limitations. Based on the retrospective study design, laboratory and radiological data was not available for all the patients. We were not able to reach all the parents by phone. Our results are based on the statements of the parents which may include recall bias. Only the findings that families think developed after the child had the COVID-19 infection are included. Our study was not sufficient to give prevalence for long COVID in the adolescent patient group because only asymptomatic, mild, and moderately affected patients were included, as post COVID symptoms may be affected by clinical severity of the disease.

Our exclusion of severe COVID-19 patients limits the generalization of our results. Besides, diagnostic scales were not used for sleep disorders and depression diagnoses.

5. Conclusions

To our knowledge, this study is one of the very few that focused on long term effect of COVID 19 in adolescents. Clinicians have focused much more on the period that the

diagnosis was done but much more studies are needed to identify the prevalence, risk factors, clinical spectrum, and prognosis of long COVID in children to create a protocol on how and at what intervals these patients should be followed up. Also whether these patients will need rehabilitation in the long term is not clear at this time. Therefore, we believe that our data will contribute suggestive information about the long-term problems these patients will face and how they should be followed up.

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Research Article / Araştırma Makalesi

Measuring Fatigue in Rheumatoid Arthritis' Patients with the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and the Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS): A Cross-Sectional Study

Romatoid Artrit Hastalarında Bristol Romatoid Artrit Yorgunluk Çok Boyutlu Anketi (BRAF-MDQ) ve Bristol Romatoid Artrit Yorgunluk Sayısal Derecelendirme Ölçeği (BRAF-NRS) ile Yorgunluğun Ölçülmesi: Kesitsel Bir Çalışma

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Abstract

Fatigue is a common problem in Rheumatoid Arthritis (RA) and many factors are responsible for its etiology. The aim of this cross-sectional study was to investigate the current status of fatigue and to evaluate the factors related to fatigue by using the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS) developed specifically for RA in patients with RA. 64 patients with RA were included in the study. The Disease Activity Score (DAS28-CRP) of 28 joints was used to assess disease activity, and the Health Assessment Questionnaire (HAQ) was used to assess functional status. In addition, BRAF-MDQ and BRAF-NRS scales were used to assess fatigue, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) were used to screen for psychiatric symptoms. All correlations between BRAF-MDQ, BRAF-NRS scales and DAS28-CRP, BAI, BDI were statistically significant ($p<0.05$, each other). BRAF-MDQ, BRAF-NRS scales were found to be unrelated to age, seropositivity, and drugs used. Considering the effect of disease activity, HAQ, anxiety and depressive symptoms on the BRAF-MDQ total, it was associated only with BAI ($p<0.001$, 95% CI 0.593-1.768). In this study, we showed the contribution of anxiety and depressive symptoms to fatigue as well as disease activity. We consider that effective interventions focusing on these symptoms can improve fatigue and reduce the burden of chronic disease.

Keywords: Anxiety; bristol rheumatoid arthritis fatigue multidimensional questionnaire; bristol rheumatoid arthritis fatigue numerical rating scale; depression; rheumatology; rheumatoid arthritis

Özet

Yorgunluk Romatoid Artrit'te (RA) sık görülen bir sorundur ve etiyolojisinden birçok faktör sorumludur. Bu kesitsel çalışmanın amacı, RA'lı hastalarda RA için özel olarak geliştirilen Bristol Romatoid Artrit Yorgunluk Çok Boyutlu Anketi (BRAF-MDQ) ve Bristol Romatoid Artrit Yorgunluk Sayısal Derecelendirme Ölçeği (BRAF-NRS) kullanılarak yorgunluğun mevcut durumunu araştırmak ve yorgunluk ile ilgili faktörleri değerlendirmektir. RA'lı 64 hasta çalışmaya dahil edildi. Hastalık aktivitesini değerlendirmek için 28 eklemin Hastalık Aktivite Skoru (DAS28-CRP), yorgunluğu değerlendirmek için BRAF-MDQ, BRAF-NRS ölçekleri, psikiyatrik semptomları taramak için Beck's Depresyon Envanteri (BDI), Beck's Anksiyete Envanteri (BAI), fonksiyonel durumu Değerlendirmek için Sağlık Değerlendirme Anketi (HAQ) kullanıldı. BRAF-MDQ, BRAF-NRS ölçekleri ile DAS28-CRP, BAI, BDI arasındaki tüm korelasyonlar istatistiksel olarak anlamlıydı ($p<0.05$, birbirİ). BRAF-MDQ, BRAF-NRS ölçeklerinin yaş, seropozitiflik ve kullanılan ilaçlarla ilişkisiz olduğu bulundu. Hastalık aktivitesi, HAQ, anksiyete ve depresif semptomların BRAF-MDQ toplamına etkisi dikkate alındığında sadece BAI ile ilişkili idi ($p<0,001$, %95 CI 0,593-1.768). Bu çalışmada, anksiyete ve depresif belirtilerin hastalık aktivitesinin yanı sıra yorgunluğa katkısını gösterdik. Bu semptomlara odaklanan etkili müdahalelerin yorgunluğu iyileştirebileceğini ve kronik hastalık yükünü azaltabileceğini düşünüyoruz.

Anahtar Kelimeler: Anksiyete; bristol romatoid artrit yorgunluk çok boyutlu anketi; bristol romatoid artrit yorgunluk sayısal derecelendirme ölçeği; depresyon; romatoloji; romatoid artrit

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1. Introduction

Rheumatoid Arthritis (RA) is an autoimmune, chronic inflammatory disease characterized by joint swelling, tenderness and destruction of synovial joints, which can lead to severe disability.

A total of 40-70% of people with rheumatoid arthritis report severe fatigue, a very important symptom of RA, as in other chronic diseases (1,2).

It has been previously stated that RA fatigue is a multifactorial experience likely to differ from that in other chronic conditions (3). It is thought that fatigue may be a result of the systemic effects of the disease, pain and joint symptoms, or the drugs used in the treatment, as well as due to conditions such as sleep disorders and bad mood (4,5).

RA-specific questionnaires have been developed to evaluate several dimensions of fatigue experienced by RA patients (6). The aim of the study was to investigate the current state of fatigue and factors related to it in patients with RA using the Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ) and Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale (BRAF-NRS) developed specifically for RA.

2. Materials and Methods

In this cross-sectional study, 64 patients diagnosed with RA according to the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2010 EULAR/ACR (19) criteria, followed in the rheumatology outpatient clinic between April 2021 and October 2021, were randomly included.

Patients who were pregnant, diagnosed with comorbid diseases such as overlap syndrome, diabetes, congestive heart failure, kidney failure, cancer, fibromyalgia, chronic fatigue syndrome, severe psychological disorder, using antidepressant or anxiolytic group drugs, and could not speak and/or understand Turkish were excluded from the study.

All participants gave written full consent in accordance with the Declaration of Helsinki. The Ethics Committee of the University of Cukurova approved the study (April 2021, approval number = 110).

The demographic data of the patients and the drugs used were recorded. The number of tender and swollen joints was determined by physical examination. C-reactive protein (CRP, mg/L), rheumatoid factor (RF, nephelometric) and anti-cyclic citrulline peptide (anti-CCP, U/ml) values were noted in laboratory findings. Disease activity was calculated with the Disease Activity Score of 28 joints, CRP (DAS28-CRP) (7).

BRAF-MDQ and BRAF-NRS scales were used to evaluate fatigue, Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI) were used to screen for psychiatric symptoms, and Health Assessment Questionnaire (HAQ) was used to evaluate functional status.

The BRAF-MDQ consists of 20 items on the effect of fatigue symptoms in the last 7 days. There are four sub-dimensions: physical fatigue (4 items), living with fatigue (7 items), cognitive fatigue (5 items), and emotional fatigue (4 items). Except for item 1 (0-10 points), 2 (0-7 points), and 3 (0-2 points), the others receive 0-3 points. A total fatigue score is obtained by summing 20 item scores. The BRAF-MDQ total fatigue score ranges from 0 to 70. Physical fatigue, living with fatigue, cognitive fatigue and emotional fatigue scores are obtained by summing the subscale items.

The BRAF-NRS has three subgroups to assess the severity and impact of fatigue and coping with fatigue over the past 7 days. Each item scores between 0 and 10 (2) (Question 1: 0; I did not feel tired - 10; I felt completely exhausted, Question 2: 0; had no effect-10; had a great effect, Question 3: 0; very good–10, not good at all) (8,9,10).

HAQ is a total of 20 questions consisting of 8 subtitles. It consists of dressing, getting up, eating, walking, hygiene, lying, grasping and external activities (11,12).

BAI is used to determine the frequency of anxiety symptoms experienced by individuals. It is a Likert-type self-assessment tool consisting of 21 items, each scored between 0 and 3. Anxiety level is measured according to the total score on this scale (0-7 points = minimum, 8-15 points = mild anxiety, 16-25 points = moderate anxiety, 26-63 points = severe anxiety) (13,14)

BDI: Behaviors and symptoms specific to depression are described in sentences. Each sentence is given a score between 0-3. It consists of twenty-one items, which are listed from mild to severe form. Patients are asked to choose the statement that best describes their current situation, and the result is obtained by summing up the items (15,16)

Statistical Analysis

Statistical analyzes were performed using SPSS 23.0 (SPSS Inc, Chicago, IL, USA). The conformity of the data to the normal distribution was analyzed with the Kolmogorov-Smirnov test. The analysis of normally distributed continuous variables was done with Student's t-test, and the analysis of non-normally distributed continuous variables was done with Mann Whitney U test. Spearman correlation test was used to analyze the relationships between continuous variables. Those with a P value below 0.05 were considered statistically significant. A linear regression model was created to determine the effect of DAS28-CRP, HAQ,BAI, and BDI on BRAF-MDQ total. The impact of each variable was expressed with the regression coefficient of the linear regression model, with 95% confidence intervals. Those with a P value below 0.05 were considered statistically significant.

3. Results

The average age of 64 patients, 38 (59.4%) of whom were women, was 47 and the average disease duration was 45 months. The median DAS28-CRP score was 1.66. 37 (57.8%) of the patients were in remission. 49 (76.9%) were receiving cDMARD and 15 (23.4%) were receiving bDMARD treatment (Table 1). All scores of the instruments used in the study are shown in Table 1.

Table 1. Demographic, clinic characteristics and scores of questionnaires of the study group

		Median(IQR)
Age		47 (6)
Gender, Female/Male, n		38/26
Disease duration (months)		45(84)
Seropositive, n(%)		51(70.9)
Drugs used	cDMARD. n(%)	49(76.6)
	bDMARD. n(%)	15(23.4)
DAS28-CRP		1.66 (1.98)
HAQ		0.825 (0.6)
BRAF-MDQ	Physical	29 ±19.73[a]
	Living	9.5 (11)
	Cognitive	7.5 (11)
	Emotiona	6 (8)
	Physical	4(6)
BRAF-NRS	Fatigue severity	3(2)
	Effect of fatigue	3(2)
	Coping with fatigue	3(2)
BAI		21.66 ±16.50[a]
BDI		16.23± 12.90[a]

BAI; Beck's Anxiety Inventory, BDI; Beck's Depression Inventory, BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, bDMARD; biological disease-modifying antirheumatic drug, cDMARD; conventional disease-modifying antirheumatic drug, CRP; C-reactive protein, DAS28; Disease Activity Score of 28 joints,HAQ; Health Assessment Questionnaire [a]: mean±std şeklinde verilmiştir.

While no statistically significant correlation was found between age and BRAF-MDQ and BRAF-NRS subgroups (p> 0.05), there was a weak correlation with disease duration (r=0.251, p<0.05).

BRAF-MDQ total was significantly higher in females (p<0.05) (Table 2). While HAQ showed weak correlation with BRAF-MDQ total (r=0.25, p<0.05), no statistically significant correlation was observed between BRAF-NRS subgroups (p> 0.05).

Table 2. Relationship between BRAF-MDQ, BRAF-NRS and gender, seropositive and drugs used

		BRAF-MDQ	p	BRAF-NRS-Fatigue severity[b]	p	BRAF-NRS Effect of fatigue[b]	p	BRAF-NRS Coping with fatigue[b]	p
Gender	Female	34.121±17.46	**<0.05**	3(0-10)	**<0.05**	3(0-7)	>0.05	3(0-7)	>0.05
	Male	20.154±20.251		3(0-10)		3(0-8)		3(0-8)	
Seropositive	Negative	24.154±23.00	>0.05	3(0-10)	>0.05	3(0-8)	>0.05	2(0-8)	>0.05
	Positive	29.54±18.91		3(0-10)		3(0-7)		3(0-7)	
Drugs used	cDMARD	26.25±19.52	>0.05	3(0-10)	>0.05	3(0-7)	>0.05	3(0-7)	>0.05
	bDMARD	32.62±19.91		3(0-10)		3(0-8)		3(0-8)	

BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, [b]: given as median (minimum-maximum).

All correlations between BRAF-MDQ, BRAF-NRS scales and DAS28-CRP, BAI, BDI were statistically significant. Relationships between fatigue questionnaires and DAS28-CRP, HAQ, BAI and BDI scores are presented in Table 3. Considering the effect of disease activity, HAQ, anxiety and depressive symptoms on the BRAF-MDQ total, it was associated only with BAI (p<0.001, 95% CI 0.593-1.768). (Table 4).

Table 3.Spearman's (ρ) correlation coefficients between fatigue DAS28-CRP, HAQ. anxiety and depressive symptoms

		DAS28-CRP		HAQ		BAI		BDI	
		r	p	r	p	r	p	r	p
BRAF-MDQ	Total	0.990	< 0.001	0.254	<0.05	0.993	< 0.001	0.993	< 0.001
	Physical	0.972	< 0.001	0.251	<0.05	0.976	< 0.001	0.976	< 0.001
	Living	0.985	< 0.001	0.289	<0.05	0.986	< 0.001	0.978	< 0.001
	Cognitive	0.959	< 0.001	0.195	<0.05	0.964	< 0.001	0.961	< 0.001
	Emotional	0.944	< 0.001	0.172	<0.05	0.949	< 0.001	0.949	< 0.001
BRAF-NRS	Fatigue severity	0.869	< 0.001	0.199	>0.05	0.876	< 0.001	0.995	< 0.001
	Effect of fatigue	0.805	< 0.001	0.128	>0.05	0.813	< 0.001	0.810	< 0.001
	Coping with fatigue fatigue	0.746	< 0.001	0.146	>0.05	0.758	< 0.001	0.760	< 0.001

BAI; Beck's Anxiety Inventory, BDI; Beck's Depression Inventory, BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, CRP; C-reactive protein, DAS28; Disease Activity Score of 28 joints, HAQ; Health Assessment Questionnaire

Table 4. Linear regression analyses with BRAF-MDQ

Variable	β	95% CI	p value
DAS28-CRP	.054	-2.943, 4.836	0.628
HAQ	-.042	-3.318, 0.478	0.140
BAI	**.987**	**0.593, 1.768**	**0.000**
BDI	-.046	-.592, 0.450	0.786

BAI; Beck's Anxiety Inventory, BDI; Beck's Depression Inventory, bDMARD; biological disease-modifying antirheumatic drug, cDMARD; conventional disease-modifying antirheumatic drug, BRAF-MDQ; Bristol Rheumatoid Arthritis Fatigue Multidimensional Questionnaire, BRAF-NRS; Bristol Rheumatoid Arthritis Fatigue Numerical Rating Scale, CRP; C-reactive protein, DAS28; Disease Activity Score of 28 joints, HAQ; Health Assessment Questionnaire

4. Discussion

As a result of this study, it was observed that fatigue in RA patients was correlated with disease activity, anxiety and depression symptoms, while it was not associated with age, seropositivity, and drugs used.

There are few studies in the literature investigating the relationship of fatigue with disease activity and psychiatric symptoms using BRAF-MDQ, BRAF-NRS questionnaires in RA patients. Fatigue, a common and persistent problem in RA, has many adverse effects on patients' ability to perform daily self-care and socially relevant tasks, to the detriment of their physical, mental or emotional well-being (17). Fatigue in RA was found to be responsible for 52-57% of physical and social functioning problems, 64% of mental health symptoms, and 51% of perceived worsening in general health (18). However, unlike pain or disability, fatigue is rarely seen as a therapeutic target in its own right (19).

Colak S. et al., in their study of 180 patients, more than half of whom were in remission, showed that fatigue and disease activity were associated. Olsen CL. et al. showed in their longitudinal, prospective studies that fatigue persisted in patients who achieved remission after 6 months of DMARD therapy (20). Our sample was also predominantly in remission or low disease activity, and a significant correlation was observed between DAS28-CRP and fatigue ($p<0.05$).

Many of the inflammatory biomarkers that are elevated in RA, especially tumor necrosis factor (TNF)-α and interleukin (IL-6) have been associated with fatigue (4). There are studies showing that fatigue continues even though disease activities are in remission (21). This may indicate that fatigue is not only associated with disease activity or systemic inflammation, but also with other factors such as anxiety, depression, and physical disability.

Progressive joint damage can cause increased fatigue. However, thanks to evolving treatment options, the role of disability are complex to interpret, as joint damage and disability that once determined the course of RA are less common (21). While there was a significant but weak correlation between our patients' HAQ scores and BRAF-MDQ total and subgroups, we did not detect a correlation between BRAF-NRS subgroups. In the linear regression analysis, HAQ was not found to be a predictive factor for fatigue ($p>0.05$, 95% CI:-3.318, 0.478). Stebbings S. et al. investigated fatigue-related factors in RA patients using the Multidimensional Assessment of Fatigue-Global Fatigue Index (MAF-GFI). They found that the strongest fatigue correlates in the RA cohort were depression ($P < 0.001$) and anxiety ($P < 0.001$). They found no significant association with HAQ ($P = 0.10$), pain ($P = 0.43$), and DAS-28 ($P = 0.07$) (22).

There are different results in the literature about the relationship between disease duration and fatigue. While there are studies stating that long illness/symptom duration is significantly associated with fatigue, there are also studies that do not support the relationship between fatigue and duration of illness (23,24). In this study, no correlation was found between disease duration and fatigue ($p>0.05$).

Belza et al. showed that female gender was among the variables responsible for fatigue in RA patients (23). Similarly, BRAF-MDQ

total and BRAF-NRS fatigue severity scores were significantly higher in females in our study (p<005). Nikolaus et al. reported that younger women were more susceptible to fatigue than men and older people (25). In our study, no relationship was found between age and fatigue (p>0.05).

The prevalence of psychiatric comorbidity is also high in patients with RA. The reported lifetime prevalence of depression ranges from 16 to 48%, while estimates of the prevalence of anxiety vary between 13 and 70% (26,27,28). The relationship between psychological symptoms and fatigue has been previously evaluated with fatigue scales other than BRAF-MDQ and BRAF-NRS, and it is shown that there is a strong relationship between fatigue and depression and anxiety (23,29,30,31,32).

Patients with RA describe not only physical, but also cognitive fatigue, such as emotional one and lack of motivation and inability to concentrate. In this study, fatigue was evaluated by disease-specific BRAF-MDQ and BRAF-NRS questionnaires, and its relationship with anxiety and depression was examined. A strong correlation was found with physical, living, cognitive and emotional fatigue (P<0.05, each other). When the effect of disease activity, HAQ, anxiety and depressive symptoms on BRAF-MDQ total was examined, it was observed that it could be accounted for only by BAI (p<0.001, 95% CI 0.593-1.768).

There are some limitations in this study. First, the number of patients is small. Therefore, it is not representative of the entire RA population. Secondly, it is not possible to determine from our data whether anxiety and depression affect BRAF-MDQ and BRAF-NRS or whether fatigue causes anxiety and depression. Longitudinal studies with larger samples may provide stronger evidence for the cause/effect relationship between variables. Another is that other factors such as fatigue-related sleep disturbance, social support status were not evaluated, and evaluating them could provide additional information. The patients in this study had a relatively low to moderate HAQ score, so it may not be possible to know whether high disability may contribute differently to fatigue. However, this study may contribute to the literature in terms of demonstrating the level of fatigue and related factors even in patients with little or no functional limitation. In addition, to the best of our knowledge, it is one of the rare studies in the literature evaluating BRAF-MDQ, BRAF-NRS, and psychological symptoms.

5. Conclusion

Many factors are blamed for the etiology of fatigue in RA patients. This study showed the contribution of disease activity, anxiety, and depressive symptoms to fatigue. We think that more extensive studies on related factors are needed to make effective interventions against fatigue in RA patients.

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Research Article / Araştırma Makalesi

Retrospective Evaluation of Patients with Systemic Autoimmune Diseases Admitted to Intensive Care

Yoğun Bakıma Yatan Sistemik Otoimmün Hastalıkları olan Hastaların Geriye Dönük İncelenmesi

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Abstract

Systemic autoimmune diseases can cause life-threatening complications that require admission to the intensive care unit. Early recognition of these complications can improve patient outcomes. The aim of this study is to evaluate patients with systemic autoimmune diseases hospitalized in the intensive care unit and identify the factors affecting the patient outcomes. Patients (aged > 18) with systemic autoimmune diseases who were hospitalized in a tertiary general intensive care unit between 2010 and 2020 were retrospectively analyzed. Demographic data, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, reasons for admission to the intensive care unit, information on treatments for primary diseases and those administered in the intensive care unit, and survival rates were recorded. The study included 67 adult patients. The main reason for hospitalization was infection (n = 35), and 43 patients died in the intensive care unit. The need for mechanical ventilation during intensive care hospitalization and the presence of fungal infection as per fungal cultures performed at hospitalization were found to be associated with mortality. In addition, the presence of high disease severity scores was associated with mortality. The mortality rate of patients with systemic autoimmune diseases requiring intensive care unit admission was found to be high. The majority of deaths occurred as a result of infections associated with immunosuppression. Such deaths can be prevented by implementing specific measures and conducting training targeting these issues.

Keywords: Vasculitis, mortality, intensive care unit, systemic autoimmune diseases

Özet

Sistemik otoimmün hastalıklar, yoğun bakım ünitesine kabul gerektiren hayatı tehdit eden komplikasyonlara neden olabilir. Bu komplikayonların erken tanınması hasta sonuçlarını iyileştirebilir. Bu çalışmanın amacı yoğun bakım ünitesine yatan sistemik otoimmün hastalığıolan hastaları değerlendirimek ve sonuçlara etki eden faktörleri belirlemektir. Yöntem: 2010-2020 yılları arasında 3 basamak genel yoğun bakıma yatırılan sistemik otoimmün hastalıkları olan 18 yaş üstü hastalar geriye dönük olarak incelendi. Demografik bilgileri, APACHE 2 ve SOFA skorları, yoğun bakıma yatış nedenleri, primer hastalıklarına yönelik aldıkları tedaviler, yoğun bakımda uygulanan tedaviler ve sağ kalım oranları kayıt edildi. 67 erişkin hasta çalışmaya dahil edildi. Başlıca yatış nedenlerinin enfeksiyon (n:35), olduğu görüldü. 43 hasta yoğun bakımda kaybedildi. Yoğun bakım yatışı sırasında mekanik ventilasyon ihtiyacı olması ve yatış kültürlerinde mantar üremesi olması mortalite ile ilişkilii bulunmuştur. Ek olarak yüksek hastalık skorlarının varlığı mortalite ile ilişkilli bulunmuştur.
Yoğun bakım ünitesine yatış gerektiren sistemik otoimmün hastalıkların ölüm oranı yüksektir. Ölümlerin büyük çoğunluğu immünsüpresyona bağlı enfeksiyon nedeniyle olmaktadır. Bu yönde uygulanacak tedbirler ve eğitimler ile bu ölümlerin önüne geçilebilir.

Anahtar Kelimeler: Vaskülit, mortalite, yoğun bakım ünitesi, sistemik otoimmün hastalıklar

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1. Introduction

Systemic autoimmune diseases (SADs) are diseases characterized by systemic inflammation caused by the dysfunction of immune system regulatory mechanisms and can affect any organ. They are classified as major rheumatological diseases and systemic vasculitis(1). The use of corticosteroids in the 1950s and the introduction of immunosuppressants for treatment in the 1970s significantly increased the survival of patients with SADs. Nevertheless, SADs are associated with life-threatening complications that require intensive care unit (ICU) admission. The complications associated with organ failure are mainly related to disease activation or infections that develop after immunosuppressive therapy (2). Developments in diagnosis and treatment options for SADs also positively affect patient outcomes in ICU. Therefore, in our study, we aimed to examine patients with SADs hospitalized in our ICU and identify the factors affecting mortality in these patients.

2. Methods

This retrospective study included patients with SADs (age >18) who were treated in Eskişehir Osmangazi University Medical Faculty, Department of Anesthesiology and Reanimation Anesthesiology and Reanimation ICU between January 1, 2010 and January 1, 2020 and admitted to the ICU for >24 hours. Patients' data were collected from the hospital information management system and archived records. Ethics committee approval (Eskişehir Osmangazi University Ethical Committee; E-25403353-050.99-133102, 13.01.2021) was obtained before starting the study. As the study was retrospective, informed consent was not sought from the patients.

The patients were divided into systemic connective tissue disease and systemic vasculitis groups. Age, gender, immunosuppressive therapy data, and reasons for ICU admission were recorded. Disease severity was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores. The need for invasive mechanical ventilation (IMV) or non-invasive mechanical ventilation (NIMV), renal replacement/dialysis therapy, plasmapheresis therapy, vasoactive drugs, and extracorporeal membrane oxygenation during ICU admission were recorded. Furthermore, the length of stay in the ICU and the outcome which led to discharge from the ICU were recorded. Patients were classified according to survival, and predictive factors for survival were identified.

Statistical analysis

All the data were analyzed using the Statistical Package for Social Sciences for Windows 22 on the computer. Descriptive values for quantitative (numerical) variables were expressed as mean±standard deviation, and those for qualitative (categorical) variables were expressed as frequency and percentage. The conformity of quantitative variables to a normal distribution was evaluated using the Shapiro–Wilk test. The relationship between qualitative variables was analyzed using the chi-square and Fisher's exact tests. Values with $p<0.05$ were considered statistically significant.

3. Results

Patient records were analyzed, and 68 patients who met the criteria were included. One patient was excluded from the study due to the lack of data. Finally, a total of 67 patients, 42 females and 25 males, were included in the study. High APACHE II (23±8.22) and SOFA (9.96±4.39) scores indicated a high disease severity in the patients, and there was a statistically significant difference between the patients who survived and those who died ($p<0.05$).

The main category of diseases were systemic connective tissue diseases (n = 42) and systemic vasculitis (n = 25). Reasons for admission to the ICU were infection (n = 35), active disease/exacerbation (n = 24), and other (n = 8). Pneumonia (n = 26) was the leading cause of infectius cause of ICU admission. Pulmonary hemorrhage (n = 11) was the leading cause of disease activation. The following types of vasculitis were identified: granulomatosis with polyangiitis (Wegener's granulomatosis) (n = 10), polyarteritis nodosa

(n = 6), Takayasu arteritis (n = 1), eosinophilic granulomatosis with polyangiitis (Churge–Strauss syndrome) (n = 1), microscopic polyangiitis (n = 3) and Behcet's disease (n = 4). Rheumatic disease types were—systemic lupus erythematosus (SLE) (n = 19), ankylosing spondylitis (n = 1), rheumatoid arthritis (RA) (n = 12), sarcoidosis (n = 4), Sjogren's disease (n = 5), and scleroderma (n = 1).

The mean length of stay in the ICU was 22.11±32.5 days, and 43 patients (64.17%) died during their ICU stay. The causes of death were sepsis (n = 31), refractory hypoxemia (n = 3), subarachnoid hemorrhage (n = 3),and disease exacerbation (n = 6).

Fifty-two patients had a diagnosis of SAD at the time of their admission to the ICU, and 16 patients were treated with corticosteroid therapy alone and 9 patients with only biological agents. Furthermore, 14 patients were diagnosed with SAD after hospitalization, and 1 patient was diagnosed after admission to the ICU.

During their stay in the ICU, the patients received corticosteroid (n = 49), plasmapheresis therapy (n = 11), and intravenous immunoglobulin (n = 1) treatments for their primary disease. Fifty-seven patients received IMV and 10 patients received NIMV support. In addition, 33 patients required renal replacement therapy.

It was found that the need for IMV during hospitalization and presence of fungal infection according to cultures performed at the time of hospitalization were associated with mortality (Table 1).

Table 1. Factors affecting mortality

		Mortality		Total	p
		No	Yes		
Diagnostic status	**New diagnosis**	**6 (50)**	**6 (50)**	**12**	* X^2 :1.27 *p:0.258*
	Chronic disease	18 (32,7)	37 (67,3)	55	
Primary diagnosis	**SRD**	17 (40,5)	25 (59,5)	42	X^2 :1.06 *p:0.303*
	Vasculitis	7 (28)	18 (72)	25	
Reason for admission	**Exacerbation**	**11 (44)**	**14 (56)**	**25**	X^2 :1.84 *p:0.397*
	Infection	11 (34,4)	21 (65,6)	32	
	Other	**2 (20)**	**8 (80)**	**10**	
Growth observed in cultures performed at admission	Fungal	21 (50)	21 (50)	42	* X^2 :9.6 *p:0.027*
	Gram-negative bacteria	1 (9,1)	10 (90,9)	**11**	
	Gram-positive bacteria	2 (20)	8 (80)	10	
	Atypical bacteria	**0 (0)**	**4 (100)**	**3**	
Steroid therapy use	Yes	3 (27,3)	8 (72,7)	11	X^2: 0,79 *p:0.67*
	No	5 (31,3)	11 (68,8)	**16**	
	Pulse steroid	16 (40)	24 (60)	40	
Immunomodulator use	**Yes**	**16 (40)**	**24 (60)**	**40**	X^2: 0.75 *p:0.385*
	No	8 (29,6)	19 (70,4)	27	
Biological agent use	**Yes**	21 (36,2)	37 (63,8)	**58**	* X^2: 0.02 *p:0.87*
	No	3 (33,3)	6 (66,7)	9	
IMV	**No**	17 (29,8)	40 (70,2)	**57**	X^2: 5.97 *p:0.01*
	Yes	7 (70)	3 (30)	10	

Immunosuppression therapy administration in the ICU	**Yes**	4 (22,2)	14 (77,8)	**18**	X^2:1,98 *p:0,159*
	No	20 (40,8)	29 (59,2)	49	
RRT	**Yes**	13 (38,2)	21 (61,8)	**34**	X^2: 0,17 *p:0.67*
	No	11 (33,3)	22 (66,7)	33	
Plasmapheresis	**Yes**	20 (35,7)	36 (64,3)	**56**	X^2: 0.01 *p:0.967*
	No	4 (36,4)	7 (63,6)	11	

SRD: Systemic rheumotologial diseases; IMV: Invasive mechanical ventilation; ICU: Intensive care unit; RRT: Renal replacement therapy

4. Discussion

In our study in which we evaluated 67 patients with SADs who were admitted to the ICU, we found that the mortality rate of this patient group was 64.17% and the most common cause of mortality was sepsis. In various publications, ICU mortality rate of patients with SADs varies between 17% and 33% (3). Another study reported that the mortality rate of patients with SADs was 16%–20% in Colombia and the USA(4).

In general, patients with SADs requiring ICU admission can be grouped as having rheumatic diseases or systemic vasculitis. In a study conducted in the USA in 2020, it was found that the most frequent admission to the ICU was due to SADs such as SLE, RA, and systemic vasculitis, which was similar to our study results (5). Unlike these data, as per previous studies conducted in the 90s, the most common SADs requiring ICU admission were RA and systemic vasculitis. According to Parperis et al., the reason for these differences is the success achieved in the last 20 years with the use of biological agents in the treatment and control of RA, resulting in fewer hospitalizations (6). In our study, the majority of the patients in the rheumatic disease group had SLE and RA. Ina study by Haijnen et al., 86 patients admitted to the internal ICU during a 5-year period were evaluated, and the most common reason for hospitalization was identified to be systemic vasculitis, sarcoidosis, systemic sclerosis, and SLE (1); this difference may be due to the ethnic characteristics of the population of that region. In a study evaluating 51 patients with SADs admitted to the ICU, 23 patients were followed with a diagnosis of small vessel vasculitis, and this group was found to have higher APACHE II and SOFA scores and Simplified Acute Physiology Score (SAPS) II; a greater need for renal replacement, transfusion of blood products, and immunosuppressive therapy; and higher ICU mortality rates (60.9%) compared to the group of patients with other ADs (35.3%) (7). In our study, a total of 25 patients required ICU admission due to systemic vasculitis.

According to some studies, the most common reasons for hospitalization of patients with rheumatic diseases who required ICU admission were sepsis (31%), followed by pneumonia (10%) (8). Although hospitalizations due to infection have been reported with rates of up to 60% in the literature, some publications have reported higher rates for acute exacerbations than those of infections as reasons for ICU admission (9,10). Our study is in line with the literature since the most common reason for ICU admission was infection-related causes followed by exacerbation of the primary disease. Pneumonia and urosepsis are the leading infectious causes of ICU admission. The fact that the infections were treated before the occurrence of sepsis may be because the majority of our patients were hospitalized due to pneumonia.

Assessments regarding ICU admission of patients with SADs have shown that a high APACHE II score, multiple organ failure, and advanced age are associated with mortality (5). In several studies, an APACHE II score of >19 and a mean APACHE II score of 25 were associated with mortality, and the mean APACHE II scores of survivors were found to be 10 and 14.8 (k1-8,23). In our study, we did

not establish threshold APACHE II and SOFA scores for evaluating mortality, but we found that scores at hospitalization of patients who died were significantly higher than those of patients who survived. Polok et al. reported that APACHE II and SOFA scores at hospitalization were found to be associated with mortality in 21 patients with SADs who were followed up in the ICU due to diffuse alveolar hemorrhage, and 85% of the patients needed mechanical ventilation (11). In our study, 11 patients were admitted to the ICU due to diffuse alveolar hemorrhage; they had high mortality rates and greater need for IMV. In addition, our study found that the need for IMV was associated with ICU mortality. We believe that this may be due to severe hypoxia that is secondary to ventilatory associated pneumonia (VAP) or can otherwise be observed in these patients.

In a study conducted in France in which 31 patients with SADs treated in the ICU were evaluated over a 10-year period, APACHE II scores and SAPS II were found to be associated with mortality, whereas the Birmingham Vasculitis Activity Score (BVAS), which assesses the severity of vasculitis, appeared to be clinically related but could not be statistically correlated with mortality. In addition, the need for renal replacement therapy and catecholamines were also associated with mortality. Unlike our study's sex ratio, 21 patients in that study were male and 10 were female. Eighty-one percent of the patients needed mechanical ventilation, and 52% died in the ICU. The most common cause of death was found to be septic shock (2). In our study, APACHE II and SOFA scores were found to be associated with mortality, which was in line with the literature, but BVAS was not assessed as it was not actively used in our clinic; as a result, the correlation between disease activity and mortality could not be evaluated.

As per a review published in 2013 on patients with SADs requiring ICU admission, respiratory failure was the most common reason for ICU admission and, in addition to what was already reported in the literature, multiple organ failure and advanced age were found to be associated with mortality (5). In some studies, in addition to these criteria, infection as the reason for ICU admission, prolonged hospitalization before ICU admission, shock, use of vasopressors, and the need for mechanical ventilation and plasmapheresis were also associated with mortality (12,13). The length of stay in the ICU and presence of renal and cardiovascular comorbidities during stay in the ICU are other risk factors associated with mortality (8).

In a prospective randomized study of 2020 that compared plasma exchange and glucocorticoid treatments in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, it was found that plasmapheresis therapy did not contribute to standard treatment and low-dose glucocorticoid treatment was not inferior to high-dose treatment (14). These findings led us to think that using low-dose steroid treatments or adjusting the dose for patients in the ICU may be beneficial for them since these treatments may predispose them to infections during ICU stay although a direct relationship with mortality could not be established.

In a study that assessed 34 cases of ANCA-associated vasculitis treated for the first time in the internal medicine ICUs of 4 university hospitals of Turkey between 2008 and 2018, 20 patients (58.8%) died during treatment in the ICU, with septic shock being the most common cause of death (60%), followed by hemoptysis and respiratory failure (20%) and hemorrhagic shock (10%). There was no difference between the patients that died and the survivors in terms of the immunosuppressive therapy administered. Acinetobacter baumannii was found to be the most common cause of new-onset infections in patients who survived and those who died during their stay in the ICU. Consistent with the literature, in mentioned study, APACHE II and SOFA scores and SAPS II were found to be associated with mortality, but BVAS was not associated with ICU mortality. Researchers evaluating short-term mortality in this group of patients also concluded that new-onset ICU infections, shock, need for vasopressor, thrombocytopenia, need for platelet transfusion, and liver dysfunction were associated with mortality in this group

(15). In our study, a statistically significant increase was found between mortality and the need for IMV. The mortality rate in patients who needed IMV was 70%. No correlation was found between mortality and steroid treatments used during hospitalization and immunomodulatory treatments. However, it was observed that there was a significant relationship between the use of biological agents during treatment and increased mortality. Nevertheless, since we could not find a study evaluating the correlation between the use of biological agents and mortality, we could not make a comparison on this subject. In order to clarify this, we believe there is a need for evaluating whether the necessity of using biological agents in the treatment algorithm of the patients includes other concomitant factors that increase mortality. In light of these findings, we believe that limiting the use of biological agents or administering alternative treatments to patients admitted to the ICU can be considered.

In our study, the presence of fungal infection as per fungal cultures performed at the time of hospitalization was found to be associated with mortality. In addition, 48.83% (21/43) of the patients had a growth of gram-negative bacteria in the cultures, and 90% of these patients died. Furthermore, 80% patients with the presence of gram-positive bacteria and all patients with atypical bacterial growth died. In their study, Ozdemir et al. (15) found that new-onset ICU infections mostly caused by A. baumannii were associated with mortality. Similarly, our study showed that infections existing at the time of hospitalization were also associated with mortality. Therefore, due to these reasons and owing to the predisposition of this patient group to infections by gram-negative bacteria and fungi, we believe it would be appropriate to maintain the use of empirical broad-spectrum anti-infective agents.

5. Conclusion

In our study, the main limitation of which was its retrospective design, we observed that SADs requiring ICU admission included SLE and systemic vasculitis; this finding was in line with the literature. In addition, we found that bacterial and fungal infections and sepsis caused by immunosuppression due to the drugs used in the treatment of these diseases were the leading reasons for ICU admission. Therefore, we conclude that raising the awareness of such patients regarding infections and sepsis, which are preventable causes, and implementation of specific measures in this area could reduce the cases of ICU admissions in this patient group and may be effective in reducing deaths.

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Research Article / Araştırma Makalesi

The Effect of Astaxanthin on Smoke Inhalation Injury on Rats: Experimental Study

Sıçanlarda Akciğer İnhalasyon Hasarı Üzerine Astaxanthinin Etkisi: Deneysel Çalışma

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Abstract

Smoke inhalation damage defined as mucosal damage in the respiratory system caused by flames, hot air, steam, toxic gas and particulate matter in smoke. Oxidative stress is an important mechanism, as high temperature smoke contains a high concentration of strong oxidants. The resultant inflammatory response, if uncontrolled, causes abundant inflammatory cell accumula-tion in the lungs, producing excessive reactive oxygen species (ROS) and inducing oxidative stress injury. A total of forty adult male Sprague-Dawley albino rats were used. Sham group (n:8) was kept in smoke study room for 28 min without giving any injury and treatment. Control group (n:8); the dorsum of rats was shaved and surgically scrubbed. After receiving 30% burn injury they received four series of smoke and four series of 100% oxygen between smoke inhalations. ASX groups; after receiving 30% burn injury the same inhalation injury protocol was applied to these groups. After exposure to smoke and burn injury, ASX10 (n:8) animals received 10 mg/kg/d astaxanthin, ASX30 (n:8) animals received 30 mg/kg/d astaxanthin, ASX100 (n:8) animals received 100 mg/kg/d astaxanthin dissolved in 5ml of olive oil for 3 days with orogastric route. For histopathologic examination, samples were taken from trachea, and mid-portion of parenchyma. For biochemical analysis, samples taken from the right lower lobes and stored at –80 °C. Histologic assessment of alveolar congestion and neutrophilic infiltration were statistically increased in group control than ASX10, ASX30 and ASX100 groups. Histologic assessment of haemorrhage and alveolar wall thickness was increased in group control than ASX30 and ASX100 groups. 4-HNE and NF-κβ levels in control group was significantly increased than ASX10, ASX30 and ASX100 groups. Proinflammatory cytokines TNF-α, IL-6 and IL-1β levels in lung tissue decreased by astaxanthin treatment at doses of 30mg/kg/d and 100mg/kg/d ($p<0,05$). Oxidative stress marker MDA levels and GR levels in lung tissue decreased by astaxanthin treatment ($p<0,05$). Our results have demonstrated that astaxanthin use have a beneficial role in smoke inhalation injury accompanying 30% tbsa burn of rats. Thus, astaxanthin may represent a potential approach to prevent systemic response due to oxidative stress and inflammatory processes of smoke inhalation injury and >30% burns.

Keywords: Astaxanthin; inhalation burn; smoke inhalation; burns

Özet

Respiratuar sistemde, sıcak hava, alev, toksik gazlar ve partiküllerin yarattığı mukozal hasarı tanımlamak için inhalasyon hasarı terimi kullanılmaktadır. Yüksek sıcaklıktaki duman yüksek konsantrasyonda güçlü oksidanlar içermekte ve oksidatif stres yaratarak oluşan hasarda rol oynamaktadır. Oluşan inflamatuar cevap kontrol edilemezse, akciğerlerde abondan inflamatuar hücre birikimine, reaktif oksijen radikalleri üretimine ve oksidatif stres yaralanmasına yol açmaktadır. 40 adet erişkin erkek Sprague -Dawley albino rat kullanılarak gerçekleştirilen deneyde, Sham grubu (n :8) duman odasında 28 dakika boyunca herhangi bir yaralanma veya tedavi meydana getirmeden tutuldu. Kontrol grubunda (n:8) ratların sırtı tıraşlanarak cerrahi usullere uygun şekilde örtüldü. %30 oranında yanık oluşturulduktan sonra 4 seri halinde duman inhalasyonu ve bunların aralarında %100 oksijen uygulaması yapıldı. ASX uygulanan gruplarda ise, %30 yanık oluşturulduktan sonra aynı inhalasyon hasarı protokolu uygulandı. Yanık ve inhalasyon hasarına uğratıldıktan sonra ise, ASX10 (n:8) rata 10 mg/kg/gün astaxantin, ASX30 (n:8) rata 30 mg/kg/gün astaxantin, ASX100 (n:8) rata 100 mg/kg/ gün astaxantin 5 ml zeytinyağı içinde çözülmüş olarak orogastrik yoldan 3 gün boyunca verildi. Histopatolojik inceleme için trakea ve akciğer parankiminin orta lobundan örnekleme yapıldı. Biyokimyasal analiz için ise sağ alt akciğer loblarından örnek alınarak -80°C 'de muhafaza edildi. Alveoler konjesyon ve nötrofilik infiltrasyonun histopatolojik bulguları ASX10, ASX30 ve ASX100 gruplarıyla kıyaslandığında kontrol grubunda istatistiksel olarak anlamlı ölçüde yüksek görüldü. Hemoraji ve alveoler duvar kalınlaşması kontrol grubunda, ASX30 VE ASX 100 gruplarına kıyasla artmış olarak saptandı. 4-HNE ve NF-κβ değerleri kontrol grubunda, ASX10, ASX30 ve ASX100 gruplarına oranla anlamlı oranda yüksek bulundu. TNF-α, IL-6 ve IL-1β gibi pro-inflamatuar sitokin düzeyleri 30mg/kg/gün ve 100mg/kg/gün astaxantin ile tedavi edilen grupta anlamlı olarak düşük bulundu ($p<0,05$). Akciğer dokusundaki oksidatif stress markerlarından MDA ve GR düzeyleri astaxantin ile tedavi edilen grupta anlamlı ölçüde düşük bulundu ($p<0,05$). Sonuç olarak, vücut yüzey alanının %30'u yanan ve eş zamanlı akciğer inhalasyon hasarı oluşturulan sıçanlarda astaxantin kullanımının tedavide olumlu etkileri olduğu görüldü. Astaksantinin oksitadif stres ve inflamasyona bağlı oluşan sistemik cevabın tedavisinde olumlu yönleri olduğu görülmüştür.

Anahtar Kelimeler: Astaksantin; inhalasyon yanığı; duman inhalasyonu; yanık

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1. Introduction

Smoke inhalation damage defined as mucosal damage in the respiratory system caused by flames, hot air, steam, toxic gas and particulate matter in smoke (1). The major cause of morbidity and mortality in victims of fires are respiratory complications (2). Smoke inhalation injury is mainly caused by three mechanisms. These mechanisms are heat, particles in smoke and pulmonary irritants which cause systemic toxicity (3). The resultant inflammatory response may cause higher fluid resuscitation volumes, progressive pulmonary dysfunction, prolonged ventilator days, increased risk of infections and acute respiratory distress syndrome (ARDS) (4). Smoke inhalation is an independent factor affecting mortality in burn patients and increases it alone by 20% in cases accompanied by burns (5). Even if there is no inhalation injury, patients with severe burns are at high risk of respiratory failure. This may occur as an isolated event or as a component of multiple organ system failure initiated by systemic infection (6).

Oxidative stress is an important mechanism, as high temperature smoke contains a high concentration of strong oxidants. (7). The oxidants leads to cellular DNA damage, ATP deficiency and cell necrosis. Histological features of burn injury include interstitial oedema, hyaline membrane formation and neutrophil sequestration in the lung. Fibrinogens activated by neutrophil sequestration and inflammatory mediators accumulate in airways to form obstruction and cause ventilation / perfusion incompatibility (3, 8). Based on the complex pathogenesis of smoke inhalation injury, drugs with different mechanisms of action such as bronchodilators, anticoagulants, antioxidants, and corticosteroids have been investigated (9). Astaxanthin (ASX), a potent antioxidant, pinkish-red pigment and member of xanthophile family with a ketocarotenoid structure. Carotenoids such as zeoxanthine, lutein and beta-carotene have many common points with ASX in metabolic and physiological aspects. Furthermore, the bioactivity and antioxidant properties of ASX is much higher due to the presence of keto- and hydroxy- groups at both ends of the molecule (10). The use of astaxanthin dose dependently for smoke inhalation injury has been investigated because it has the potential to reduce oxidative stress and anti-inflammatory features (11).

2. Material and Methods

Animals

A total of forty adult male Sprague-Dawley albino rats (mean body weight: 300±30g) were used. The study protocol was approved by the Animal Experiments Local Ethics Committee of Eskisehir Osmangazi University (492-2) and was supported by Eskişehir Osmangazi University Scientific Research Projects Commission with project number 2017-1477. Rats were randomly divided into 5 groups (Sham: 8, Control: 8, ASX10mg: 8, ASX30mg: 8, ASX100mg: 8). The animals were caged separately and environment was maintained at room temperature with a 12-h light/dark cycle. Standard laboratory food for rats and water were provided to the animals.

Experimental Protocol

All surgical procedures were performed by the same surgeon under general anaesthesia with intraperitoneal thiopental (Pental® Sodium 0.5g, I.E. ULAGAY, Istanbul) 50mg / kg injection. Sham group was kept in smoke study room for 28 min without giving any injury and treatment. For control group, the dorsum of rats was shaved and surgically scrubbed. To produce the burn, a hot metal plate was heated with a Bunsen burner for 2 min, and then held in placed on the rats back for 10 s (12). After receiving 30% burn injury they received four series of smoke and four series of 100% oxygen between smoke inhalations. Each smoke exposure was 3 min and each oxygen exposure was 4 min. (13). We determine the ASX oral administration dosages which leads systemic antioxidant effect from previous studies (11). ASX groups after receiving 30% burn injury were kept in smoke room. The same inhalation injury protocol was applied to these groups. After exposure to smoke and burn injury, ASX10 animals received 10 mg/kg/d astaxanthin, ASX30 animals received 30 mg/kg/d astaxanthin, ASX100 animals received 100 mg/kg/d astaxanthin dissolved in 5ml of olive oil for 3 days with orogastric route. Fluid resuscitation during the experiment was carried out using Ringer's lactate solution following the formula: 4 ml/% burned body surface area/kg body weight for the first 24 h, and 2 ml/% burned body surface area/kg body weight/day for the next 48 h (14). One half of the volume for the first day was

infused in the initial 8 h, and the rest was infused over the next 16 h. After the experiment, the rats were returned to their cages at normal room temperature and atmosphere. At the end of 72 h, the rats were sacrificed under deep anaesthesia (thiopental 100 mg / kg i.m.). The abdomen was opened; the diaphragm was incised to allow the lungs to collapse. By a midline sternal incision thorax was opened, and the lungs were rapidly removed en bloc along with the trachea. For histopathologic examination, samples were taken from trachea, and mid-portion of parenchyma. For biochemical analysis, samples taken from the right lower lobes and stored at –80 °C.

Histopathology

Lungs were harvested for observing morphologic alterations. The right middle lobes of the lungs were fixed with 10% formalin, embedded in paraffin, and sectioned to 4 µm thickness. After deparaffinization and rehydration, the sections were stained with hematoxylin and eosin. The pathological sections were observed in a blinded fashion. Pathological injury score was evaluated blindly according to Mikawa's method (15). Pathological scores (lung damage) were evaluated by (a) alveolar congestion; (b) haemorrhage; (c) neutrophilic infiltration and (d) thickness of the alveolar wall / hyaline membrane formation. Each item was graded on a 5-point scale (0, minimal damage; 1, mild damage; 2, moderate damage; 3, severe damage; 4, maximal damage) (16).

Immunohistochemical analysis of NF-κB and 4-hydroxynonenal

Paraffin-embedded sections 4-µm in thickness were stained for nuclear factor κB (NF-κB) and cytoplasmic 4-hydroxynonenal (4-HNE) immunohistochemically. The immunohistochemical experiments were performed according to the manufacturer's recommendations. Briefly, the dewaxed or PBS-washed tissue sections were cultured in 3% hydrogen peroxide to eliminate intrinsic peroxidase and quenched in normal goat serum for 30 min. The sections were then incubated at 4 °C overnight with polyclonal rabbit anti-rat NF-κB or 4-hydroxynonenal antibody, followed by addition of the anti-rabbit immunoglobulin and streptavidin conjugated to horseradish peroxidase. Finally, 3, 3′-diaminobenzidine was used for colour development, and hematoxylin was used for counterstaining. Brown staining in cytoplasm and/or nucleus was taken as a positive indicator for expression. The results were evaluated semi-quantitatively according to percentage of positive cells.

Biochemical Measurements

The right base lobe of lung tissues was harvested and immediately homogenized on ice-surface in 5 volumes of normal saline. The homogenates were centrifuged at 1200 rpm/min for 10 min. The glutathione reductase (GR), malondialdehyde (MDA), interleukin 6 (IL-6), interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) content in the supernatants were respectively measured using GR, MDA, IL_6, IL1β and TNF-α assay kits (Elabscience).

Statistical Analysis

The Shapiro Wilk test was used to investigate the suitability of data to normal distribution. In the comparison of the groups with normal distribution, independent sample t-test analysis was used for the two parameters and the one-way ANOVA was used for the groups with three parameters or more. In comparison of the groups which do not conform to normal distribution, Mann-Whitney U test was used for the two parameters and Kruskal-Wallis H test was used for the three parameters or more. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used in the implementation of the analyses. A p value below 0.05 was considered as a criterion for statistical significance.

3. Results

Histopathologic findings

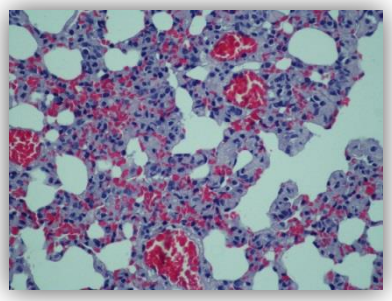
Histologic assessment of alveolar congestion and neutrophilic infiltration were statistically increased in group control than sham, ASX10, ASX30 and ASX100 groups ($p<0,05$) while there were no statistically difference between sham, ASX10, ASX30 and ASX100 groups. Histologic assessment of haemorrhage was increased in group control than sham, ASX30 and ASX100 groups $p(<0,05)$ while there were no difference between sham, ASX10, ASX30 and ASX100 groups. Histologic assessment of thickness of alveolar wall was increased in group control than ASX30 and ASX100 $p(<0,05)$, increased wall

thickness also observed in ASX10 group than ASX30 group p(<0,05), while there were no difference between sham, ASX30 and ASX100 groups (Table 1) (Fig.1).

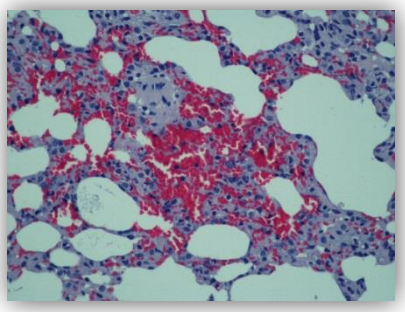
Table 1. Histopathologic and immunohistochemical findings with statistical analyses

		Mean ± Std. Dev.	p	Multiple Comparisons
Alveolar congestion	**Sham (1)**	1.13 ± 0.35	<0,05	1-5: 0.005
	ASX 10 (2)	1.13 ± 0.35		2-5: 0,005
	ASX 30 (3)	1 ± 0		3-5: 0,001
	ASX 100 (4)	1.13 ± 0.35		4-5: 0,005
	Control (5)	1.75 ± 0.71		
Haemorrhage	**Sham (1)**	0.88 ± 0.64	<0,05	1-5: 0,041
	ASX 10 (2)	1.25 ± 1.28		3-5: 0,012
	ASX 30 (3)	0.63 ± 1.06		4-5: 0,006
	ASX 100 (4)	0.5 ± 0.76		
	Control (5)	1.88 ± 0.83		
Neutrophilic infiltration	**Sham (1)**	0.25 ± 0.71	<0.05	1-5: <0,001
	ASX 10 (2)	0 ± 0		2-5: <0,001
	ASX 30 (3)	0 ± 0		3-5: <0,001
	ASX 100 (4)	0 ± 0		4-5: <0,001
	Control (5)	1.25 ± 0.89		
Thickness of the alveolar wall and hyaline membrane formation	**Sham (1)**	1.25 ± 0.89	<0,05	2-3: 0,032
	ASX 10 (2)	1.5 ± 0.53		3-5: 0,002
	ASX 30 (3)	0.75 ± 0.46		4-5: 0,014
	ASX 100 (4)	1 ± 0.53		
	Control (5)	1.88 ± 0.83		
NF-κβ	**Sham (1)**	8.75 ± 3.54	<0.05	1-2: 0,024
	ASX 10 (2)	17.5 ± 9.64		2-4: 0,036
				1-5: <0,001
				2-5: <0,001
				3-5: <0,001
				4-5: <0,001
	ASX 30 (3)	13.5 ± 6.82		
	ASX 100 (4)	9.38 ± 3.2		
	Control (5)	55 ± 10.69		
4-hydroxynonenal	**Sham (1)**	53.75 ± 13.02	<0.05	1-2: 0,003
	ASX 10 (2)	70 ± 8.86		1-3: 0,035
	ASX 30 (3)	65 ± 11.95		1-4: <0,001
	ASX 100 (4)	75 ± 10.69		1-5: <0,001
	Control (5)	86.88 ± 4.58		2-5: 0,002
				3-5: <0,001
				4-5: 0,027

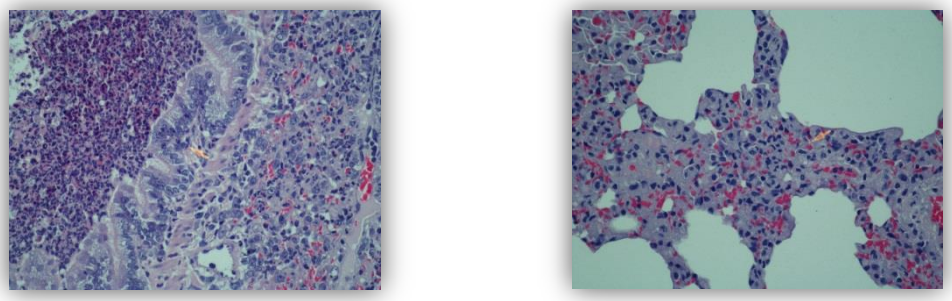
H&E Staining



Alveolar congestion Score 2



Haemorrhage Score 3



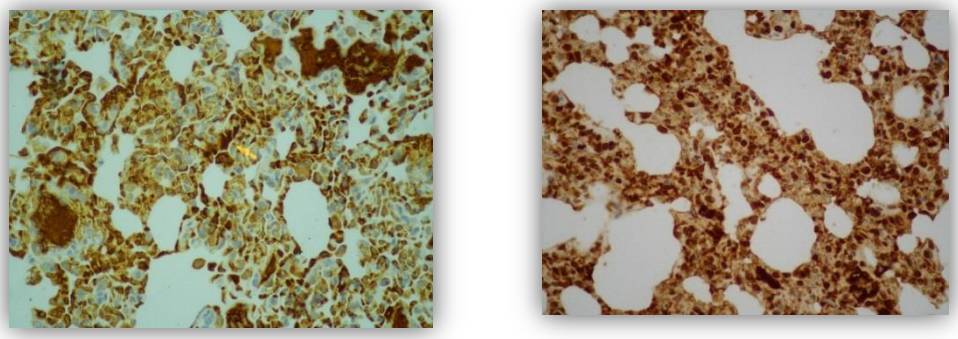
Neutrophilic infiltration Score 3 | **Alveolar wall thickness Score 3**

Figure 1. Upper left: Example with alveolar congestion score 2: Congestion is observed in capillaries and venules in the alveolar wall (HE x 400). Upper right: Sample with bleeding score 3: erythrocytes are heavily involved in the alveolar wall and in the lumen (HE x 400). Lower left: A neutrophilic infiltration score of 3: neutrophilic infiltration is observed in the bronchial lumen (left half), in the alveolar wall and interalveolar area (right half) and in the bronchial epithelium (arrow) (HE x 400). Lower right: Example of alveolar wall thickness 3: pronounced thickening (arrow) in the interalveolar septum (HE x 400)

Immunohistochemical analysis of NF-κβ and 4-hydroxynonenal

4-HNE and NF-κβ was detected in all animal samples. 4-HNE levels in sham group was significantly lower than control, ASX10, ASX30 and ASX100 groups p(<0,05), however 4-HNE levels in control group was significantly increased than sham, ASX10, ASX30 and ASX100 groups p(<0,05). No difference between ASX10, ASX30 and ASX100 groups were found (Table 1) (Fig. 2).

Immunohistochemical staining



NF-κβ | **4-HNE**

Figure 2. Example of NF kappa B staining of 70%, nuclear and cytoplasmic staining is more common in the alveolar epithelium (x400), with 4-HNE staining of 50% nuclear and cytoplasmic positivity is observed in the alveolar epithelium and interalveolar area (x400).

NF-κβ levels in control group was significantly increased than sham, ASX10, ASX30 and ASX100 groups p(<0,05). Levels in ASX 10 group was significantly increased than sham and ASX100 groups p(<0,05). No difference between ASX10 to ASX30 groups were found. There were no statistically difference between sham, ASX30 and ASX100 groups were found (Table 1) (Fig. 2).

Biochemical Findings

Proinflammatory cytokines TNF-α, IL-6 and IL-1β levels in lung tissue decreased by astaxanthin treatment (p<0,05) (Table 2). No difference

detected between sham, ASX10, ASX30 and ASX100 groups. Although no difference detected on only IL-6 levels between ASX30 and control groups (p=0,065). Oxidative stress marker MDA levels in lung tissue decreased by astaxanthin treatment (p<0,05) (Table 2). No difference detected between sham, ASX10, ASX30 and ASX100 groups. Glutathione reductase enzyme levels found significantly increased in control group than sham, ASX10, ASX30 and ASX100 groups (p<0,05) (Table 2). No difference detected between sham, ASX10, ASX30 and ASX100 groups.

Table 2. Biochemical findings with statistical analyses

		Mean ± Std. Dev.	p	Multiple Comparisons
TNF-α	Control (1)	408.78 ± 236.91	<0.05	1-2: 0,001 1-3: 0,002 1-4: 0,018 1-5: 0,002
	Sham (2)	188.68 ± 74.34		
	ASX10 (3)	212.68 ± 41.72		
	ASX30 (4)	262.14 ± 47.74		
	ASX100 (5)	208.61 ± 68.81		
Glutathione Reductase	Control (1)	965.33 ± 175.2	<0,05	1-2: <0,05 1-3: <0,05 1-4: <0,05 1-5: 0,003
	Sham (2)	857.51 ± 127.99		
	ASX10 (3)	849.01 ± 65.68		
	ASX30 (4)	838.8 ± 47.02		
	ASX100 (5)	799.98 ± 39.1		
IL-6	Control (1)	420.28 ± 249.09	<0.05	1-2: 0,002 1-3: <0,05 1-5: 0,001
	Sham (2)	169.34 ± 107.55		
	ASX10 (3)	259.3 ± 121.93		
	ASX30 (4)	275.66 ± 150.45		
	ASX100 (5)	139.36 ± 65.51		
IL-1β	Control (1)	220.77 ± 60.44	<0.05	1-2: <0,001 1-3: <0,001 1-4: <0,001 1-5: <0,001
	Sham (2)	60.98 ± 21.5		
	ASX10 (3)	71.1 ± 28.61		
	ASX30 (4)	80.43 ± 29.98		
	ASX100 (5)	61.94 ± 22.66		
MDA	Control (1)	127.09 ± 73.08	<0,05	1-2: 0,01 1-3: <0,05 1-4: 0,018 1-5: 0,01
	Sham (2)	74.92 ± 13.79		
	ASX10 (3)	85.91 ± 33.93		
	ASX30 (4)	79.18 ± 24.68		
	ASX100 (5)	74.44 ± 11.26		

4. Discussion and Conclusion

Smoke inhalation injury leads to inflammatory process, acute respiratory distress syndrome (ARDS) and systemic inflammatory response syndrome (SIRS) due to proinflammatory cells merged in to the systemic circulation (17). The toxic particulates of smoke produce acute airways inflammation that can lead to oedema, mucosal damage, small airways obstruction, atelectasis, and respiratory failure. In addition, tissue oxygenation is impaired due to increased carboxyhemoglobin level. Development of oxygen hunger in tissues occurs due to hyper metabolic condition and direction of blood flow changes from intestines to muscle and soft tissues. As a result, bowel perforations and multiple organ failures can be seen. Cardiac dysfunction may develop due to impediment in oxygen transport and hypovolemia. Although,

systemic antioxidant levels may decrease significantly. However, it is still a matter of debate as to why antioxidants, which are very important in protecting against oxidative stress injury, have decreased. It is thought that the levels of antioxidants are reduced because of transposition to immune active areas, dilution due to liquid treatment, inadequate intake and increase of disposal by biological fluids (18). It has been shown that vitamin C use in inhaled lung injury reduces the fluid requirement, oedema development and reduce the duration of mechanical ventilation. These results support the use of other antioxidant substances (such as vitamin E, alpha-gamma tocopherol, etc.) as supportive in the treatment of inhalation damage. As a matter of fact, alpha and gamma tocopherol have a positive effect on pulmonary functions and increased PaO2: FiO2 ratio.

Astaxanthin is a xanthophyll carotenoid found in a variety of living organisms, including microalgae, fungi, seafood, and some birds such as flamingos and quails (20). Humans are unable to manufacture carotenoids, including astaxanthin, and therefore need to consume these in their diet. Astaxanthin is a potent quencher of reactive oxygen and nitrogen species, especially singlet oxygen. Many studies have reported using astaxanthin as an antioxidant (21-22).

In our study, morphological and histopathological changes of smoke inhalation injury in control group observed as similar as literature (19). Mortality prevented by performing intermittent smoke and oxygen exposure as described in literature (13). Increased neutrophilic infiltration, alveolar congestion, alveolar wall thickness and haemorrhage was observed in control group with respect to ASX30 and ASX100 groups in histopathologic examination. This difference between control and treatment groups are statistically significant ($p<0,05$). However, there is no difference in alveolar wall thickness and haemorrhage scores between control and ASX10 group.

Tissue 4-HNE levels is an important biomarker of oxidative stress. A small amount of 4-HNE is located in normal tissues but levels are elevated because of oxidative stress induced lipid peroxidation (23). In our study, lower ratio of tissue 4-HNE immunopositive area seen in all of the ASX treated groups than control group ($p<0,001$). These findings indicates lower level of oxidative stress develops in ASX treated groups.

Literature review demonstrates that NF-κB pathway involved in the inflammatory lung injuries and some antioxidants have found positive effects on damage reduction (24, 25). NF-κB is a rapid response nuclei transcrip¬tion factor and two subunits were included in NF-κB. NF-κB is located in the cytoplasm and is combined to the inhibitory unit inhibitory κB (IκB). When IκB is phosphorylated by its kinase IκB kinase, it could translocate into nucleus to adjust gene transcription, including proinflammatory cytokines (26). In our study, lower ratio of nuclear NF-κB are seen in all of the ASX treated groups than control group ($p<0,001$). Thus, the anti-inflammatory and antioxidant effects of astaxanthin through suppression of NF-κB pathway in smoke inhalation injuries has showed by this study.

In our experimental model, TNF-α, IL-1β and IL-6 levels were lower in the ASX treated groups than the control group. ASX 10 and ASX100 groups have significantly lower TNF-α, IL-1β and IL-6 levels compare to control group. ASX30 group have significantly lower TNF-α, IL-1β levels compare to control group. Suzuki et al. (27) showed that in the endotoxin-induced uveitis in mice, ASX suppressed TNF-α at an early stage and had anti-inflammatory effects. It is thought that ASX is the result of regulating the release of reactive oxygen species, although it is not yet established which way to suppress TNF-α (28). Xuefeng et al. (29) studied astaxanthins effects on ischemia/reperfusion induced renal injuries. Astaxanthin has been shown to reduce TNF-α, IL-1β and IL-6 levels and have anti-inflammatory and anti-apoptotic effects.

Glutathione reductase (GR) is an enzyme and catalyses the reduction of glutathione disulphide to the glutathione (GSH). Our study demonstrates that GR levels are significantly increased at control group than ASX treated groups ($p<0,05$). Astaxanthin

performs its antioxidant action by binding both free oxygen radicals and by inducing paroxonase-1 which is an antioxidant enzyme and increases intracellular GSH levels (30). Smoke inhalation injury induced antioxidant depletion results as activation and increase of GR levels in control group. ASX enhances GSH levels via paroxonase-1 activation so decreased GR levels were found on our experimental study. Malondialdehyde (MDA), a peroxide produced in the reaction of free radicals and polyunsaturated fatty acids in the cell membranes, indicates an intensified oxidative stress response, lipid peroxidation and tissue injury. We found MDA levels increased significantly in control group than ASX treated groups ($p<0,05$), it proves astaxanthin has antioxidant effects.

From the histopathologic aspect, haemorrhage and alveolar wall thickness scores of ASX30 and ASX100 groups are lower compared to control group and no significant difference found between ASX10 and control groups. Astaxanthin administration from oral route may be more than 10mg/kg/d for histopathologicly positive results. Our results have demonstrated that astaxanthin use have a beneficial role in smoke inhalation injury accompanying 30% burn of rats. Thus, astaxanthin may represent a potential approach to prevent systemic response due to oxidative stress and inflammatory processes of smoke inhalation injury and >30% burns.

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Research Article / Araştırma Makalesi

The Relationship Between Daily Carbonhydrate and Fat Intake A long with Migraine

Günlük Karbonhidrat ve Yağ Alımı ile Migren Arasındaki İlişki Diyet & Migren

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Abstract

The pathophysiology of migraine is not fully understood. The trigeminovascular pathway activation, cortical spreading depression, vascular dysfunction, pro-inflammatory and oxidative states, and gut microbiota are investigated. In this study, we aimed to evaluate the relationship between diet and migraine disease characteristics of our patients. This study was conducted with episodic migraine without aura (n:30) and chronic migraine patients (n:30). Demographic data, body mass indexes (BMI), migraine characteristics were recorded from headache diaries. Food consumption were noted Daily from diet diaries. Total calorie intake and carbohydrate and fat amounts were calculated with an internet-based calorie calculator program.The mean age was 40.1±7.83 years in chronic migraine group (group 1), and 39.1±6.09 years in group 2. The mean BMI of group 1 was significantly higher (respectively; 28.3±3.14, and 24.9±3.29). The mean duration of migraine was found longer in group 1. The mean headache attack duration was 29.9±21.85 hours in group 1, and 29.6±22.4 was in episodic migraine without aura group (group 2). There was no significant difference between both groups in terms of headache attack duration. Average Daily carbohydrate intake is 178.53±44.86 grams in group 1, and 171.42±50.67 grams in group 2. The mean Daily fat intake was 58.01±13.65 grams in group 1 and 56.62±7.51 grams in group 2. No significant difference was found between the groups in terms of Daily calorie, mean Daily fat and, average carbohydrate intake. In our study, we did not find difference in food intake between groups, but BMI of the chronic migraine group were higher. The role of diet on the migraine pathophysiology is still under investigation. An integrative approach to migraine patients by reviewing their diet will help to understand the pathophysiology of migraine, increase the quality of life of patients and prevent unnecessary drug usage.

Keywords: Episodic migraine; chronicmigraine; body massindex; diet; calorieintake; carbohydrateintake; Fatintake

Özet

Migren patofizyolojisi hala tam anlaşılamamıştır. Trigeminovasküler yolak aktivasyonu, kortikal yayılan depresyon, vasküler disfonksiyon yanında proinflamatuar ve oksidatif durum,ve barsak mikrobiatası incelenmektedir. Bu çalışmada diyet özellikleriyle, migrenin hastalık karakteristikleri arasında bir ilişki olup olmadığını araştırmayı amaçladık. Bu çalışma kronik migren (grup 1) (n:30) ve epizodik aurasız migren (grup 2) (n:30) hastalarıyla yürütüldü. Demografik bilgiler, vücut kitle indeksi (VKİ), migren hastalık özellikleri baş ağrısı günlüklerinden kaydedildi. Hastalar bir ay boyunca tükettikleri gıdaların günlüğünü tuttular. Alınan günlük ortalama kalori, karbonhidrat ve yağ miktarları internet temelli bir kalori hesaplama programıyla hesaplandı. Yaş ortalaması grup 1'de 40.1±7.83 ve grup 2' de 39.1±6.09 yıldı. Ortalama VKİ grup 1'de daha yüksekti (sırasıyla; 28.3±3.14, and 24.9±3.29). Ortalama migren hastalık süresi grup 1' de daha uzundu. Ortalama başağrısı atağının süresi grup 1'de 29.9±21.85, grup 2' de 29.6±22.4 saatti. Başağrısı atağının süresi açısından gruplar arasında anlamlı fark yoktu. Günlük ortalama karbonhidrat alımı grup 1'de 178.53±44.86, grup 2' de 171.42±50.67 gramdı. Günlük ortalama yağ alımı grup 1'de 58.01±13.65, grup 2' de 56.62±7.51 gramdı. Günlük kalori, yağ ve karbonhidrat alımı açısından gruplar arasında anlamlı fark yoktu. Çalışmamızda gıda alımları açısından gruplar arasında fark bulmadık fakat VKİ kronik migren grubunda daha yüksekti. Diyetin migren patofizyolojisindeki rolü hala araştırılmaktadır. Migren hastalarındaki diyetlerinin de gözden geçirilerek bütüncül bir yaklaşım, migren patofizyolojisinin anlaşılmasına, hastaların yaşam kalitesinin arttırılmasına ve gereksiz ilaç kullanılmasının önlenmesine yardımcı olacaktır.

Anahtar Kelimeler: Epizodikmigren; kronikmigren; vücut kitle indeksi; diyet; kalorialımı; karbonhidratalımı; yağalımı

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1. Introduction

Migraine is a chronic neurological disease which genetic and environmental factors have role in it's development. Life time prevalence of migraine is estimated to be 14% of adults (1). The pathophysiology of migraine is still not fully understood. The roles of trigeminovascular pathway activation, cortical spreading depression, vascular dysfunction, pro-inflammatory and oxidative states, and gut microbiota are investigated. Taking into account all these factors that are suggested to play a role in the pathophysiology of migraine and an integrative approach to the treatment of migraine patients increases the quality of life and treatment success of patients (2). Therefore, it is becoming increasingly important to review and adjust the diets of patients.

In order to contribute to the treatment of migraine, approaches such as losing weight, removing foods that trigger migraine attacks from the diet, restricting calories, carbohydrates and fats, or adding supplements such as omega-3 and vitamin D to the diet are suggested (2). The effect of these treatment approaches on treatment investigated in limited number of studies (3,4).

In this study, we planned to monitor the food intake behaviors of patients with episodic and chronic migraine for one month and investigate whether there is a relationship between average daily calorie intake, carbohydrate and fat intake and migraine disease duration, monthly average attack frequency and monthly average duration.

2. Material and Methods

This study was conducted with 30 patients with episodic migraine without aura (EAM) and 30 patients with chronic migraine (CM) who admitted to the Neurology outpatient clinic of University of Health Sciences, Izmir Bozyaka Education and Research Hospital, between February 2021, and July 2021.The patients' age, gender, duration of migraine disease, monthly average headache frequency, average headache duration, medications used in attacks and prophylaxis were obtained from the patients' headache diaries and medical records. The diagnosis of migraine was made according to the International Classification of Headache Disorders-3 criteria (5).

The height and weight of the patients were noted at the beginning of the study. Body mass indexes (BMI) were calculated (6). Neurological and systemic examinations were performed. The patients kept a diary of the foods they consumed for a month. Daily average calorie intake, carbohydrate and fat intake were calculated with an internet-based calorie calculator program.

Inclusion criteria of the patient group were to be between the ages of 18-55, to be diagnosed with episodic migraine without aura, and to be diagnosed with chronic migraine. Those with any chronic neurological or systemic disease other than migraine (diabetes mellitus, chronic kidney failure, thyroid dysfunction, malignancy, etc.), those who smoke, use alcohol, have any disease that may affect the sense of taste and smell, take antineoplastic or corticosteroid treatment, have pregnacy and the patients who could not keep a regular headache and food diary were excluded from the study. Informed constent form was taken from participants and the study was approved by local ethical committee (Reference number 2021/11, Date: 26/01/2021).

Statistical analyses

The obtained data were analyzed using the SPSS version 23 program. The normality of the data distribution was determined by the Shapiro-Wilk test. Mann-Whitney U t set was used because our data did not show normal distribution. Analysis results were presented as mean standard deviation (minimum-maximum). $p< 0.05$ were considered significant.

3. Results

Thirty patients were included in the chronic migraine group (group 1) and 30 patients in the episodic migraine group (group 2). The mean age of group 1 was 40.1±7.83 (18-55), and the mean age of group 2 was 39.1±6.09 (33-54). No statistical difference between the two groups was found (p=0.358). Both patient groups were all females (p=1,000) (Table 1).

The mean BMI of group 1 was 28.3±3.14 (23.52-33.62), mean BMI of group 2 was 24.9±3.29 (20.9-32.0). The mean BMI of group 1 was significantly higher than group 2 (p<0.001). The mean duration of migraine in group 1 was 20.3±7.81 (5-40) years, and the mean duration of migraine in group 2 was 12.7±6.3 (5-30) years, and there was a statistically significant difference between them (p <0.001). The mean monthly attack frequency of group 1 was 19.53±3.54 (15-27) and the monthly mean attack frequency of group 2 was 5.06±3.06 (1-12). There was a statistically significant difference when compared (p<0.001). The mean headache attack duration of group 1 was 29.9±21.85 (6-72) hours, and the mean headache attack duration of group 2 was 29.6±22.4 (6-72) hours. There was no significant difference between both groups (p=0.068) (Table 1).

Average daily calorie intake was 1546.83±169.45 kcal (1350-1987) and, 1542.46±157.47 kcal (1258-1725) in group 2. No significant difference was found between groups with regard to average daily calorie intake (p=0.155). Group 1 average daily carbohydrate intake is 178.53±44.86 grams (75.16-235.39), group 2 average daily carbohydrate intake is 171.42±50.67 grams (48.86-250.0). There was no difference between the two groups iwith regard to daily average carbohydrate intake (p=0.274). The mean daily fat intake was 58.01±13.65 grams (41.55-99.52) in group 1 and 56.62±7.51 grams (42.52-75) in group 2. No significant difference was found between the groups in terms of mean daily fat intake (p=0.918) (Table 1).

Table 1. Descriptive and clinical characteristics of groups

	Group 1 (n:30/Female) (mean±SD)(min-max)	**Group 2 (n:30/Female) (mean±SD)(min-max)**	***p***
Age	40.1±7.83 (18-55)	39.1±6.09 (33-54)	0.358
BMI(kg)	28.3±3.14 (23.52-33.62)	24.9±3.29 (20.9-32.0)	**<0.001**
Duration of migrain (years)	20.3±7.81(5-40)	12.7±6.3 (5-30)	**<0.001**
Attack frequency (n/month)	19.53±3.54(15-27)	5.06±3.06 (1-12)	**<0,001**
Headache attack duration (hours)	29.9±21.85 (6-72)	29.6±22.4 (6-72)	0.068
Calorie intake (kcal/day)	1546.83±169.45 (1350-1987)	1542.46±157.47 (1258-1725)	0.155
Carbohydrate intake (gram/day)	178.53±44.86 (75.16-235.39)	171.42±50.67 (48.86-250.0)	0.274
fat intake (gram/day)	58.01±13.65 (41.55-99.52)	56.62±7.51(42.52-75)	0.918

** Group 1: Chronic migraine, Group 2: Episodic migraine, BMI: Body Mass Index, kcal: kilocalori*

4. Discussion and Conclusion

In our study, the mean BMI of patients with CM was found to be higher than those with EM, in line with the publications reporting that obesity may be a risk factor for the chronicity of migraine. There was no significant difference between the daily calorie, carbohydrate and fat intake of the patients in both groups.

It has been suggested in the early 2000s that there may be a relationship between obesity

and primary headaches. In a population-based prospective study in which obese individuals were followed for nearly one year, it was revealed that obese individuals have a 5-fold higher risk of developing chronic daily headaches compared to individuals with normal weight (7). In addition, there are many studies showing that obesity is a risk factor for the conversion from episodic migraine to chronic migraine (8-10). It was revealed that the frequency of headaches increases as BMI increases in a population-based study examining more than 30,000 migraineurs (11).

The relationship of obesity and migraine can be interpreted by some possible mechanisms. Studies conducted on individuals with obesity have found elevated levels of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (12,13). These pro-inflammatory cytokines also increase in individuals with migraine during a migraine attack (14,15). Persistent low-grade inflammatory status in obese individuals may trigger migraine attacks. It has also been shown that CGRP and substance P, which play a role in triggering migraine attacks, increase in obese individuals and migraine patients (16,17). In the light of these reports, it is suggested that obese individuals tend to have more frequent and severe migraine attacks. From another point of view, studies show that adiponectin levels secreted from adipocytes decrease during migraine attacks (18), and low adiponectin levels play a role in the development of obesity, atherosclerosis, and diabetes (19). In this case, it can be suggested that patients with chronic migraine who have frequent attacks have a predisposition to obesity.

In our study, we did not find a difference in food intake between episodic and chronic migraine groups, but BMI' s of our chronic migraine group were higher. In the studies investigating the relationship of obesity and migraine, recording the weight of the patients in the episodic migraine period and comparing them with their weight in the chronic migraine period, simultaneously following the patients with food diaries may clarify whether the conversion from episodic migraine to chronic migraine is triggered by weight gain, or whether the weight of the patients changes from episodic migraine to chronic migraine.

Studies conducted with fat-restricted diets have reported a decrease in headache severity and frequency (20), and also, a decrease in the need to use attack medication (21). In another study, it was observed that adding omega-3 to the diet decreased the headache frequency (22). In a randomized controlled study on a carbohydrate-restricted diet, 350 migraine patients were divided into low glycemic index diet group (high fiber intake group) and prophylactic drug group. One month after dietary restriction was applied, the frequency of attacks decreased in both two groups (4). However, it has also been found that a low-calorie diet with low carbohydrate and fat consumption has no effect on migraine treatment (23). On the other hand, Evans et al. Reported no difference between the diets of healthy women and women with migraine (24).

In our study, we did not find difference between daily calorie, carbohydrate and fat intake between patient groups. However, the follow-up period of the patients was limited to one month. The one-month follow-up period may not have been long enough to allow us to reveal the difference in food consumption between the two groups. In addition, when we examined the food diaries of our patients, we noticed that they consumed high-calorie foods in the first days, but they turned to low-calorie foods in the following days. The fact that our patients took note of the foods they consumed may have changed their food consumption behavior and led them to prefer foods with less calories. In addition, considering the amount of omega-3 intake and the glycemic index of carbohydrates can also help to show the effects of diet on migraine.

The role of diet on the migraine pathophysiology is still under investigation. Diet has an effect on the colonization, maturation and stabilization of the intestinal flora. Studies in animals and humans have shown that the composition of human intestinal flora changes within 4 days after consuming a specific diet. High-fat diets reduce the amount of bacteria synthesizing short-chain fatty acids (25). Reducing the

amount of short-chain fatty acids increases intestinal permeability. The participation of pro-inflammatory cytokines such as IL-1 beta and TNF alpha released from the intestines into the circulation increases. The release of pro-inflammatory cytokines may trigger migraine pain through stimulation of nociceptive responses in the trigeminal pathway. Gut microbiota changes (dysbiosis) affect the normal breakdown of nutrients (tryptophan metabolism), barrier permeability, and ultimately affect communication pathways by affecting mucosal immune and endocrine cells, resulting in increased gut peptides (↑ CGPR), cytokines (↑ IL-10) produced by some agents, and hormones (↓ 5-HT) are reported to cause abnormal release. It is suggested that increased cytokine and CGRP levels, as well as decreased 5-HT levels, trigger and perpetuate migraine attacks by modulating the vasodilator responses of dural vessels (25, 26)

It is reported that alterations in the gut microbiota according to dietary changes and decrease of possibly inflammation can have a significant effect on migraine. Migraine may be improved by encouraging intake of proper consumption of fiber, carbonhydrates with low glycemic-index, vitamin D, and omega-3 fatty acids, low-fat vegan and gluten-free food, probiotics (27).

Our study was conducted with a limited patient group and a follow-up period of one month. Future studies needed be planned in larger patient groups, with longer follow-up periods, and by noting the weight change dates of the patients, the glycemic index of the foods they consume, and the omega-3 intake.

In conclusion, studies have shown that diet affects the pathophysiology of migraine at many points. An integrative approach to migraine patients by reviewing their diet will help to understand the pathophysiology of migraine, increase the quality of life of patients and prevent unnecessary drug usage. We think that it will be very useful to monitor our patients with headache diaries as well as diet diaries.

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Research Article / Araştırma Makalesi

The Role of Regional Block and Sedation Accompanied Thoracoscopy on the Diagnosis and Treatment of Post-Trauma Patients Chest Tube Inserted

Travma Sonrası Göğüs Tüpü Uygulanan Hastalarda Rejyonel Blok ve Sedasyon Eşliğinde Torakoskopinin Tanı ve Tedavideki Yeri

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Abstract

Traumatic hemothorax/pneumothorax; is a pathological condition seen in blunt and sharp thoracic traumas and can generally be treated by tube thoracostomy. While patients are being followed up with tube thoracotomy, analgesics support, and respiratory exercise support; emergency thoracotomy is usually not required. Early thoracoscopy is a method that has come to the fore in recent years. This thoracoscopy is known to have therapeutic and diagnostic benefits. In our study; the files of 40 patients who underwent tube thoracostomy after traumatic hemothorax/pneumothorax were reviewed retrospectively. Twenty of these patients, whose radiological and clinical improvement could not be achieved after tube thoracostomy, underwent thoracoscopy with sedo-analgesia on the first day after the procedure. The remaining 20 patients were followed up without any additional procedures. Patients' age, gender, trauma type, tube thoracostomy indication, presence of additional trauma, length of chest tube stay, length of hospital stay, WBC, RDW, %Neu, pO2, pCO2, SO2, presence of tube malposition, and complications were recorded from patient files. Demographic data of the two groups were similar. While tube withdrawal time was 4.7±1.5 days in the thoracoscopy group, it was 6.9±1.9 days in the control group. This difference was statistically significant ($p < 0.001$). The mean hospital stay was 7.1±2.0 days in the first group, while it was 9.3±3.3 days in the control group. This difference was statistically significant (p=0.014). In both groups, there was a 1 (5%) patient who developed a need for thoracotomy. Thoracoscopy with sedo-analgesia in early period is a safe method for patients who have undergone tube thoracostomy due to trauma. This method reduces the duration of chest tube removal and hospital stay of patients. The need for thoracotomy after follow-up was similar in both groups.

Keywords: Hemothorax; pneumothorax; regional block; sedation; thoracic trauma; tube thoracostomy.

Özet

Travmatik hemo/pnömotoraks künt ve keskin toraks travmalarında görülen ve genellikle tüp torakostomi uygulanarak tedavi edilebilen patolojik durumdur. Hastalar tüp torakostomi, analjezik ve solunum egzersizi desteği ile izlenirken acil torakotomi genellikle gerekmez. Erken dönem torakoskopi uygulanması son yıllarda gündeme gelen bir yöntemdir ve bu torakoskopinin tedavi edici ve tanısal faydaları olduğu bilinmektedir. Çalışmamızda travmatik hemo/pnömotoraks sonrası tüp torakostomi uygulanmış 40 hastanın dosyası retrospektif olarak incelenmiştir. Tüp torakostomi uygulanması sonrası radyolojik ve klinik iyileşmesi sağlanamamış bu hasta grubunun 20'sine işlem sonrası birinci günde sedo-analjezi eşliğinde torakoskopi uygulanmış, 20'sine ise ek işlem uygulanmadan takibine devam edilmiştir. Hastaların yaşı, cinsiyeti, travma tipi, tüp torakostomi endikasyonu, ek travmasının varlığı, göğüs tüpü kalış süresi, hastanede yatış süresi, WBC, RDW, %Neu, pO2, pCO2, SO2 değerleri, tüp malpozisyonu varlığı ve gelişen komplikasyonlar hasta dosyalarından kaydedilmiştir. Çalışmaya katılan iki grubun da demografik verileri benzerdi. Tüp çekilme süresi torakoskopi uygulanan grupta ortalama 4,7±1,5 gün iken, kontrol grubunda ise ortalama 6,9±1.9 gündü ve bu fark istatistiksel olarak anlamlıydı ($p < 0,001$). Torakoskopi uygulanan grubun hastanede yatış süresi ortalama 7,1±2,0 gün iken, kontrol grubunda ise ortalama 9,3±3,3 gündü ve bu fark istatistiksel olarak anlamlıydı (p=0,014). Her iki grupta da 1'er (%5) hastada torakotomi ihtiyacı gelişti. Travma nedeni ile tüp torakostomi uygulanmış hastalara erken dönem sedoanaljezi ile torakoskopi uygulanması güvenli bir yöntemdir ve hastaların göğüs tüpünün çekilme süreleri ile hastanede kalış sürelerini azalttığı görülmektedir. Takip sonrası torakotomi gereksinimi ise iki grupta da benzer bulunmuştur.

Anahtar Kelimeler: Hemotoraks; pnömotoraks; rejyonel blok; sedasyon; toraks travması; tüp torakostomi

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1. Introduction

Thoracic injuries; affecting other systems due to the impact of vital organs and deterioration of oxygenation, are important causes of trauma-related deaths, especially between the ages of 20 and 40(1). In this age group, 20-25% of trauma-related deaths is caused by thoracic trauma (2). 70% of thoracic traumas are blunt and 30% are penetrating injuries. Chest traumas range from simple soft tissue injuries to life-threatening intrathoracic injuries.

In different studies, although thoracic pathologies in traumas vary; rib fractures are usually in the first place. Rib fracture occurs in 35-40% of patients with thoracic trauma. Treatment varies according to the age of the patient, the number of broken ribs, the accompanying pathologies and the condition of the underlying lung. Pneumothorax and hemothorax in the early period; may cause atelectasis and pneumonia in the late period. Its treatment is a good analgesia and a good control of bronchial secretions. In 5-15% of patients flail chest thorax trauma is seen (3).

The most common intrathoracic pathologies in thoracic traumas are pneumothorax, hemothorax and hemopneumothorax (4). The rate of thoracotomy in thoracic traumas is 10% in blunt traumas and 20-30% in penetrating traumas. Accepted thoracotomy indications: Presence of shock; presence of ongoing bleeding symptoms and signs (bleeding of 1000 ml or more in tube thoracostomy, 200 ml/hour bleeding in 2-4 hours, 100 ml/hour bleeding in 6-8 hours, persistence of hypovolemic shock findings despite blood replacement); completely opaque appearance of one side hemithorax on chest radiograph; signs of hemopericardium or cardiac tamponade; increased or non-drainable hemothorax; tracheal, bronchial, or diffuse parenchyma laceration; and continued (>7 days) massive air leak despite tube thoracostomy (5).

In traumatic hemothorax/pneumothorax the generally accepted first approach is thoracic tube application, and thoracotomy in case of hypoxia due to massive air leak or failure to maintain hemodynamic stability due to active bleeding (6). Although tube thoracostomy is a more easily applicable and inexpensive method, its effectiveness may be insufficient in some cases and therefore additional surgical interventions may be required. This can extend patient length of stay in the hospital for a longer period (7). Especially in cases with early removal of chest tubes, the incidence of retained hemothorax increases (8). This may force physicians to keep the chest tube in the intrapleural space for a longer period of time in cases treated with chest tube. Eddy et al. (9) emphasized that in emergency tube thoracostomy, the tube remained in the pleural space for a longer time due to inadequate drainage, and 5% empyema developed as a result.

In the diagnosis and treatment of traumatic thoracic pathologies, studies related to video-assisted thoracoscopic surgery (VATS) have been carried out. VATS is recommended as a reliable method in the diagnosis and treatment of patients with hemodynamically stable and suspected hemothorax, hemopneumothorax, or diaphragmatic laceration or hernia (10, 11). In the treatment of traumatic hemothorax/pneumothorax, VATS seems to be superior in comparison to classical tube thoracostomy, in terms of providing direct diagnosis with diagnostic thoracoscopy, performing the treatment by providing the opportunity to intervene in the primary pathology, and preventing complications such as empyema, fibrothorax, and prolonged air leakage. These cases can be discharged early because the duration of chest tube stay and hospital stay are shorter (13).

Thoracoscopy with sedation and regional nerve blockade without the use of general anesthesia is a procedure that has started to evolve in recent years to avoid the complications of general anesthesia, and many surgical interventions, including lobectomy, can be performed with this method (14).

In our study, we aimed to analyze whether the application of thoracoscopy with early regional block and sedation in patients who underwent tube thoracostomy due to traumatic hemothorax/pneumothorax is superior compared to classical tube thoracostomy.

2. Material and Methods

After approval from the local ethical committee (ID Number: E.Kurul-E-16-761, Date: 04.02.2016), between 07.01.2015 and 31.01.2016; medical form of patients who were in our hospital due to traumatic hemothorax/pneumothorax; underwent tube thoracostomy and did not improve radiologically or clinically on the first day after the procedure, were evaluated. Patients were over the age of 18 and did not need emergency thoracotomy or mechanical ventilator. Patients with following criteria were excluded: under the age of 18; who were connected to a mechanical ventilator; who needed emergency thoracotomy; who had undergone tube thoracostomy due to chronic reasons; or who recovered radiologically and clinically on the first day after tube thoracostomy.

In the study, there were 20 patients who were followed up with classical methods after tube thoracostomy and 20 patients who underwent thoracoscopy on the first day after tube thoracostomy. All patients were informed about the procedure and consent was obtained. Age, gender, trauma type, tube thoracostomy indication and presence of additional traumas were recorded. Drain removal time, hospital stay, complication development status, need for thoracotomy, white blood cell (WBC) on the 3rd day after the procedure, percentage of neutrophils (%NEU), erythrocyte distribution with (RDW), partial oxygen pressure (pO2), partial pressure of carbon dioxide (pCO2) and oxygen saturation value (SO2) were examined in both groups. Thoracoscopic findings were also recorded in the thoracoscopy group.

Hemogram and routine biochemistry tests were performed; bleeding-coagulation times were measured, blood gas values were followed, and echocardiography was performed for all patients followed-up by tube thoracostomy. Posteroanterior (PA) chest radiographs were taken for indication purposes before tube application, immediately after application and 1 day later for control purposes. Daily control and followed-up was continued with PA chest radiographs and routine blood tests.

A thoracic epidural block catheter was inserted between the T5-T6 vertebrae by the anesthesia team to the patients who will undergo thoracoscopy.

For premedication purposes; IV 50 mcg fentanyl and 1 mg midazolam were administered and additionally, 13 ml of bupivacaine and 25 mcg of fentanyl were administered through the epidural catheter. Before the procedure, 5 cc bupivacaine with unilateral stellate ganglion blockade was also applied to the side where the procedure would be performed on these patients. Thus, the cough reflex that may develop due to contact with the lung parenchyma during exploration was temporarily blocked. Thoracoscopy procedure was performed with epidural block and sedation without intubating the patient. No new incisions were made in the patients and only the existing tube thoracostomy incision was used as a port.

After the appropriate lateral decubitus position was placed, a 15 mm trocar was inserted. Exploration of the thoracic cavity and lung parenchyma was achieved with a 2.5 mm or 5 mm optical camera through this incision. When intrathoracic pathologies such as hematoma, active bleeding, and adhesions were detected and it was necessary to intervene, the incision was expanded by 1 cm and the procedure was continued. During the procedure, the patient's vital signs, saturation value, and pain status were closely monitored. After the procedure, the patient underwent tube thoracostomy through the same incision. In order to prevent tube malposition; 3-4 new holes were made on the chest tube with the help of scissors, and the thoracoscope was inserted into the tube through one of these holes. Using the thoracoscope as a guide, the chest tube was placed in the appropriate position and the procedure was terminated. After the procedure, the patients were followed up with breathing exercises, appropriate analgesics and medication throughout the hospital stay.

After tube thoracostomy, the group, which was followed-up with the classical method, was observed with daily PA chest radiographs and daily blood tests. During their hospitalization, these patients were followed up with breathing exercises, appropriate analgesics and medication.

Statistical analyses

The data of both groups in our study were analyzed with SPSS Windows 18 version. The distribution of variables was checked with the Kolmogorov Smirnov test. Mean, standard deviation and frequency values were used in the descriptive statistics of the data. Student T-test was used in the analysis of numerical nonparametric data. Pearson Chi-square test and Fisher's Chi-square test were used in the analysis of qualitative data. A p value of <0.05 was considered statistically significant.

3. Results

The first group consists of patients who underwent thoracoscopy. The mean age of patients in first group was 38.7 ± 12.3 years, and the mean age of the control group, the second group, was 47.2 ± 16.4 years. There was no statistically significant difference between the groups in terms of age (p: 0.075). In the first group; there were18 (90.0%) male and 2 (10%) female. In the control group, there were 17 (85.0%) male and 3 (15.0%) female. There was no significant difference between the groups in terms of gender (p > 0.05).

9 (22.5%) of the patients underwent tube thoracostomy due to the development of hemothorax/pneumothorax after sharp trauma and 31 (77.5%) of the patients underwent after blunt trauma. In the first group; tube thoraxotomy was performed as a result of pathology due to blunt traumain 13 (65.0%) of the patients and due to sharp trauma in 7 (35%) of the patients. In the control group, tube thoraxotomy was performed as a result of pathology due to blunt traumain 18 (90.0%) of the patients and due to sharp trauma in 2 (10%) of the patients. There was no significant difference between the groups in terms of trauma type (p > 0.05).

Considering the indications for tube thoracostomy; in the first group, 2 (10.0%) of the patients were underwent due to pneumothorax, 6 (30.0%) due to hemothorax and 12 (60%) due to hemopneumothorax. In the control group, 8 (40.0%) of patients were underwent due to pneumothorax, 5 (25.0%) due to hemothorax and 7 (35%) due to hemopneumothorax. There was no significant difference between the groups in terms of tube thoracostomy indications (p > 0.05).

Among the patients included in this study, 9 (45.0%) of the patients in the first group had additional trauma, while 14 (70.0%) of the patients in the control group had additional trauma. There was no significant difference between the groups in terms of additional trauma (p > 0.05).

Tube malposition was present in 14 (35%) of all patients included in our study. 9 (45.0%) of the patients in the first group and 5 (25.0%) of the patients in the control group had tube malposition. There was no significant difference between the groups in terms of tube malposition (p > 0.05).

According to the thoracoscopic findings of the patients who underwent thoracoscopy the following were found: Non-draining hematoma in 10 (50%) patients; lung parenchymal laceration with non-draining hematoma in 2 (10%) patients; adhesions in 2 (10%) patients; adhesion and displaced rib fracture in 1 (10%) patient; diaphragm and lung parenchyma laceration in 1 (5%) patient; displaced rib fracture with non-draining hematoma in 1 (5%) patient; adhesion with displaced rib fracture in 1 (5%) patient; active bleeding at the incision site in 1 (5%) patient; and mediastinal hematoma in 1 (5%) patient (Table 1).

Table 1. Findings of the patients who underwent thoracoscopy

	N(%)
Non-drained hematom	10 (50)
Laseration of lung parenchyma with non-drained hematoma	2 (10)
Cohesions	2 (10)
Cohesion and displaced rib fractures	1 (5)
Laserations of diaphragma and lung parenchyma	1 (5)
Non-drained hematom and displaced rib fractures	1 (5)
Displaced rib fractures with cohesions	1 (5)
Active bleeding at stab incision	1 (5)
Mediastinal hematoma	1 (5)

The mean tube duration of the patients was 4.7 ± 1.5 days in the first group and 6.9 ± 1.9 days in the control group. The mean hospitalization time of the patients was 7.1 ± 2.0 days in the first group and 9.3 ± 3.3 days in the control group. Hospitalization time and tube insertion time were significantly shorter in patients who underwent thoracoscopy ($p < 0.05$) (Table 2).

Table 2. Duration of chest tube staying and duration of hospital stay at the patients to whom thoracoscopy applied and not applied

	VATS (n:20) AVERAGE +SD	CONTROL(n:20) AVERAGE +SD	P
Chest tube duration	4.7 ± 1.5	6.9 ± 1.9	**< 0.001**
Hospital stay duration	7.1 ± 2.0	9.3 ± 3.3	**0.014**

Student t-test

The mean WBC value of the patients was 10.7 ± 1.5 10 µl in the first group, and 11.6 ± 3.5 µl in the control group. The mean neutrophil percentage of the patients was 75.9 ± 7.2 in the first group, and 75.9 ± 8.4 in the control group. The mean RDW value of the patients in the first group was 13.5 ± 1.2, and 13.6 ± 1.9 in the control group. There was no statistically significant difference between the groups in terms of WBC, neutrophil percentage and RDW ($p > 0.05$) (Table 3).

Table 3. Comparison of WBC, neutrophile percentage and RW values of the patients to whom thoracoscopy applied and not applied

	VATS (n:20) AVERAGE + SD	CONTROL (n:20) AVERAGE + SD	P
WBC	10.7 ± 3.2	11.6 ± 3.5	0.391
Neutrophile	75.9 ± 7.2	75.9 ± 8.4	0.970
RDW	13.5 ± 1.2	13.6 ± 1.9	0.880

Student t-test

The mean pO2 value of the patients was 82.4 ± 10.6 mmHg in the first group, and 84.5 ± 15.6 mmHg in the control group. The mean pCO2 value of the patients who underwent VATS was 36.2 ± 4.5 mmHg, and 36.0 ± 4.5 mmHg in the control group. The mean SO2 value of the patients who underwent VATS was 93.7 ± 1.7, and 94.4 ± 3.0in the control group. There was no statistically significant difference between the groups in terms of pO2, pCO2 and SO2 values (p > 0.05) (Table 4).

Table 4. Comparison of pO_2, pCO_2 ve SO_2 values at blood gas examination of the patients to whom thoracoscopy applied and not applied

	VATS (n:20) AVERAGE + SD	CONTROL (n:20) AVERAGE + SD	p
pO_2	82.4 ± 10.6	84.5 ± 15.6	0.615
pCO_2	37.2 ± 3.3	36.2 ± 4.5	0.439
SO_2	93.7 ± 1.7	94.4 ± 3.0	0.352

Student t-test

patient (5%) in the control group was treated with thoracotomy 1 week later due to non-draining hematoma. In the first group, 1 patient (5%) was treated with thoracotomy because of the detection of diaphragmatic rupture, which could not be seen in radiological examinations. No statistically significant difference was found between the two groups in terms of thoracotomy requirement (p > 0.05).

4. Discussion

Pneumothorax is the accumulation of positive air in the space between the visceral and parietal pleura in the thorax and the development of lung collapse accordingly; it is more common in penetrating traumas than in blunt traumas (14). Hemothorax is the accumulation of blood between the leaves of the pleura and may develop after both penetrating and blunt traumas (15). Thoracic trauma is responsible for approximately 25% of trauma-related deaths (16, 17). While very few of these patients require urgent thoracotomy; treatment,in approximately 85-90% of the patients, is provided with pain control, tube thoracostomy and respiratory physiotherapy (18). However, some complications that develop in the acute or chronic period, such as coagulum occurring in 18-30% of patients with traumatic hemothorax and prolonged air leakage in 4-24% of patients with traumatic pneumothorax, require surgical treatment (19).

Following chest tube administration, chest tube removal is planned after lung expansion on the PA chest radiograph, open monitoring of the costophrenic sinuses, and cessation of air and blood drainage from the chest tube. Failure to withdraw the chest tube due to expansion defect, non-draining hematoma, and prolonged air leakage causes complications such as empyema and fibrothorax (20). Therefore, it is important to with draw the chest tube early without a collection of air or fluid in the pleural space.

If an emergency thoracotomy was not required after tube thoracostomy, hospitalization and monitoring of the patients is the standard treatment. However; despite tube thoracostomy, conditions such as non-draining hematoma and expansion defect require surgical intervention in order to prevent complications such as empyema and fibrothorax. While there were subsidiary treatment methods such as the application of the second and, if necessary, the third tube or exploration with thoracotomy, since the beginning of the 1990s experience accumulated in thoracoscopic interventions and early thoracoscopic interventions have started to be preferred (21, 22). It has started to be preferred especially because of its advantages over thoracotomy; such as less pain in the postoperative period, less impact on respiratory functions, reduction in hospital stay and costs (23, 24). In our study, it was observed that the duration of removal of chest tubes and the length of hospitalization of the patients in the first group were statistically significantly decreased compared to the control group.

Thoracoscopy is a very valuable diagnostic method because it provides direct examination. It can be preferred together with laparoscopy for diagnosis, especially in diaphragmatic injuries and radiologically inadequate cases. The diagnostic value of thoracoscopy is between 98-100% (25). In our study, a diaphragmatic rupture of approximately 2 cm in width, which could not be detected radiologically, was observed in a patient who underwent thoracoscopy, and the patient was subsequently operated with thoracotomy and diaphragmatic repair was achieved.

Thoracoscopy with sedo-analgesia is a method that has been started to be applied to protect the patient from the risks of general anesthesia, muscle relaxants and intubation, and enable a faster return to daily life. This method has become widespread in recent years, from simple effusion drainages to lobectomies and segmentectomies (26, 27). Studies show that thoracoscopy with sedation and regional block is a safe and convenient method. In this group of patients, intrathoracic vagal block or satellite ganglion blockade has been an effective method for cessation of cough reflex. Although long-term results have not been revealed completely yet, it is seen as an alternative to classical thoracoscopy performed with one-lung ventilation under general anesthesia (28). In our study, we applied thoracoscopy to trauma patients with epidural block, stellate ganglion block and sedation, and we saw that it can contribute both in the diagnostic sense and in the primary intervention of simple pathologies.

5. Conclusion

As a result, this study showed us that sedo-analgesia and regional blocks may allow us to perform thoracoscopic surgeries and may help us on avoiding side effects of general anesthesia. In addition, we found that thoracoscopy may be a very helpful procedure on treatment of the patients to whom chest tube has been applied because of traumatic haemothoraks or pneumothorax. Besides, it may decrease the complication ratio by shortening the treatment period. And finally we can say that early thoracoscopic surgeries may give us the chance to diagnose soma patologies like diagraphmatic laseration and intrathoracic haemotoma.

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Research Article / Araştırma Makalesi

Yaşlı Diyabetik Hastalarda Malnutrisyonun Klinik Sonuçları ve Önemi

The Clinical Implications and Importance of Malnutrition in Elderly Diabetic Patients

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Özet

Diabetes mellitus ve malnutrisyon, yaşlı hastalarda sık görülen sağlık problemleridir. Her ikisi de çok sayıda olumsuz sağlık durumlarıyla ilişkilidir. Çalışmamızın amacı, yaşlı diyabetik hastalarda malnutrisyon ile ayrıntılı geriatrik değerlendirme parametreleri arasındaki ilişkiyi değerlendirmektir. Kesitsel araştırma tasarımı kullanıldı. Çalışmaya geriatri polikliniğine başvuran ≥ 65 yaş, 506 diyabetik hasta dahil edildi. Hastaların demografik verileri, komorbiditeler, kullanılan ilaç sayısı, üriner inkontinans, ortostatik hipotansiyon varlığı ve laboratuar tetkikleri kaydedildi. Tüm hastalara ayrıntılı geriatrik değerlendirme yapıldı. Nörokognitif değerlendirme için Mini Mental Durum Değerlendirme testi (MMSE), duygu durum değerlendirmesi için Geriatrik Depresyon Skalası (GDS), fonksiyonellik değerlendirmesi için Temel Günlük Yaşam Aktiviteleri (TGYA) ve Enstrümantal Günlük Yaşam Aktiviteleri (EGYA) ölçekleri, yürüyüş ve denge fonksiyonları değerlendirmesi için Tinetti Denge ve Yürüme Testi ile Kalk ve Yürü testi (KYT), uyku durumu değerlendirmesi için Uykusuzluk Şiddet İndeksi (UŞİ) ve kas gücü için el kavrama gücü (EKG) testi dosya verileri kullanıldı. Çalışma grubu Mini Nutrisyonel Değerlendirme skorları>23,5, 17-23,5 ve <17 olması sırasıyla normal nutrisyon, malnutrisyon riski ve malnutrisyon olarak kategorize edildi. Katılımcıların yaş ortalaması 76,86 ± 6,97 yıl ve %74,7'si kadın idi. Normal nutrisyonel durum, malnutrisyon riski ve malnutrisyon prevalansı sırasıyla %60,8, %30,43'ü ve %8,7 idi. Ayrıntılı geriatrik değerlendirme parametreleri gruplar arasında lojistik regresyon analizine göre değerlendirildiğinde malnütrisyon olan grupta TGYA, EGYA, Tinetti yürüme ve denge skorları, MMSE ve EKG skorları anlamlı olarak düşük iken, GDS, UŞİ ve KYT skorları anlamlı olarak yüksek saptandı (p<0,05). Yaşlı diyabetik hastalarda malnütrisyon fonksiyonel gerileme, yürüme-denge bozuklukları, kognisyon ve duygu durum bozuklukları, el kavrama gücünde azalma ve uyku bozuklukları için bir risk faktörüdür. Yaşlı diyabetik hastalarda diyabet tedavi ilkeleri gözetilirken nutrisyonel değerlendirmenin de göz önünde bulundurulması gerekmektedir.

Anahtar Kelimeler: Diyabetes mellitus; malnutrisyon; ayrıntılı geriatrik değerlendirme; yaşlı

Abstract

Diabetes mellitus and malnutrition are common health problems in older adults. Both are associated with numerous adverse health conditions. The aim of our study is to evaluate the relationship between comprehensivez geriatric assessment parameters and malnutrition in elderly diabetic patients. A cross-sectional study design was used. A total of 506 diabetic outpatients aged ≥ 65 years were included. Demographic data, comorbidities, number of drugs used, urinary incontinence, orthostatic hypotension and laboratory tests were recorded. All patients underwent comprehensive geriatric assessment. Mini mental state examination (MMSE) test was used for neurocognitive assessment, Geriatric Depression Scale (GDS) for mood assessment, Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL) scales for functionality assessment, Tinetti Balance and Gait Test and Time up and go test (TUG) for gait and balance assessment, Insomnia Severity Index (ISI) for sleep status assessment and hand grip strength for muscle strength assessment. Mini Nutritional Assessment (MNA) scores>23.5, 17-23.5, or <17 were categorized as normal nutritional status, malnutrition risk, and malnutrition, respectively. The mean age of the participants was 76.86 ± 6.97 years and 74.7% were women. Prevalence of normal nutritional status, malnutrition risk, and malnutrition were 60.8%, 30.43%, and 8.7%, respectively. Comprehensive geriatric assessment parameters were evaluated according to logistic regression analysis between the groups. BADL, IADL, Tinetti walking and balance scores, MMSE and hand grip strength test scores were significantly lower in the malnourished group, while GDS, ISI, and TUG scores were significantly higher (p<0.05). Malnutrition is a risk factor for functional decline, gait-balance disorders, cognition and mood disorders, decreased hand grip strength and sleep disorders in elderly diabetic patients. Nutritional assessment should be considered while evaluating elderly diabetic patients for diabetes treatment principles.

Keywords: Diabetes mellitus; malnutrition; comprehensive geriatric assessment; older adults

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1. Giriş

Tip 2 Diyabetes Mellitus (DM) tüm dünyada yaygın olarak görülen önemli bir halk sağlığı sorunudur (1). Prevalansı yaşam süresinin uzamasıyla doğru orantılı olarak artış gösteren DM'nin yaşlı hastalarda yönetimi gençlere göre daha zordur (2). Örneğin, 65 yaş üstü diyabetik yaşlı hastalar, genç diyabetik hastalarla ile karşılaştırıldığında; yaşlılarda mikrovasküler komplikasyon gelişme riski benzer olmakla birlikte makrovasküler komplikasyonlar açısından mutlak riskleri, diyabetik genç hastalara göre önemli ölçüde yüksektir (3). Fiziksel aktivite, beslenmenin düzenlenmesi ve ilaç tedavisi kombinasyonlarını içeren iyi bir metabolik denetim, hastalığın progresyonunu geciktirmekte ve komplikasyon oranını azaltmaktadır. Fakat tedavinin olmazsa olmazlarından olan yaşam tarzı değişikliklerinin başında gelen fiziksel aktivitenin arttırılması, yaşlılarda sık görülen osteoartirit, düşme korkusu ve ortostatik hipotansiyon gibi durumlardan dolayı sıklıkla etkin bir şekilde gerçekleştirilememektedir (3). Yaşlılarda görülen polifarmasi, demans, geriatrik depresyon ve tremor gibi geriatrik sendromlar, hastaların ilaç uyumunu ya da insülin tedavisinin uygulanmasını olumsuz etkileyebilir (2,4). Diğer yandan optimum glukoz regülasyonunu sağlama amacıyla gelişebilecek hipogliseminin yaşlılarda düşme ve buna bağlı kırıklar, hospitalizasyon, kardiyovasküler olaylar ve tüm bu nedenlere bağlı mortalitede artışa sebep olabilmesi yaşlı diyabetik hastaların komplikasyon gelişmeden tedavi edilmesini zorlaştırmaktadır (5).

DM'nin yönetimindeki en önemli faktörlerden biri diyet modifikasyonudur. Ancak, malnutrisyon, malnutrisyon riski ve mikronutrient eksiklikleri zaten yaşlılarsa sık görülmektedir (6). Yaşlanmayla birlikte fizyolojik olarak azalan organ fonksiyonları, psikolojik, sosyal ve ekonomik değişiklikler bu hastalarda beslenme bozukluklarına yol açabilir. Malnutrisyon mevcut tıbbi tabloyu şiddetlendirmekte, hastanede kalış süresini, maliyeti ve ölüm oranını daha da artırmaktadır (7). 65 yaş üstü diyabetik hastaların %26'sında malnutrisyon görülebilmektedir (8).

DM'nin kendisi, diyabetle ilişkili komplikasyonlar ve diyabet tedavisinde kullanılan ilaçlar hastalarda beslenme durumunu bozarak malnutrisyona neden olabilir. Özellikle yaşlı hastalarda pankreas rezervinin azalmasıyla birlikte eksilen insülin hormonu, iskelet kasında glikoz kullanımını bozmakta, yağ ve kas yıkımını artırmakta ve buna bağlı gelişen ketozis ise mide bulantısı ve anoreksiye yol açarak malnutrisyona katkıda bulunmaktadır (9). Bunun yanında birçok yaşlı diyabetik hasta kilo kontrolü için katı ya da uygunsuz diyet yaparak malnurisyon gelişimine zemin hazırlamaktadır (10). Bildiğimiz kadarıyla literatürde yaşlı diyabet hastalarının beslenme ve bununla ilgili klinik durumunu değerlendiren çok az sayıda çalışma vardır.

Çalışmamızın temel amacı, geriatri polikliniğe başvuran yaşlı diyabetik hastalarda malnütrisyon prevalansını araştırmak ve malnutrisyon ile ayrıntılı geriatrik değerlendirme parametreleri arasındaki ilişkiyi değerlendirmektir.

2. Gereç ve Yöntem

Hasta Seçimi

Çalışma için Kasım 2019-Ocak 2021 tarihleri arasında Bezmi Alem Üniverisitesi Tıp Fakültesi Hastanesi Geriatri Polikliniği'ne başvuran, 65 yaş ve üstü, ayrıntılı geriatrik değerlendirme yapılmış olan ve çalışma dizaynına uygun olan 506 diyabetik hastanın dosyaları retrospektif olarak incelendi.

- ✓ Dışlama Kriterleri
- ✓ 65 yaşın altında olanlar,
- ✓ Çalışmaya katılmayı reddedenler,
- ✓ Terminal hastalığı olanlar,

Bireyin genel sağlık durumunu bozabilecek ciddi hastalığı olanlar (Örneğin; akut serebrovasküler hastalık, sepsis, gastrointestinal kanama, akut böbrek yetmezliği, akut koroner sendrom, akut karaciğer yetmezliği, akut solunum yetmezliği, akut enfeksiyonlar, kanser gibi)

Muayene sırasında iletişimi ve komutları anlamayı engelleyen ileri derecede demansı

veya ileri derecede görme ve işitme bozukluğu olan hastalar,

Alkol ve/veya madde bağımlılığı olanlar çalışmadan dışlanmıştır.

Hasta özellikleri

Hastaların demografik verileri (yaş, cinsiyet), mevcut kronik hastalıkları (hipertansiyon, kronik obstruktif akciğer hastalığı, konjestif kalp yetmezliği, kronik böbrek yetmezliği, osteoartrit, iskemik kalp hastalığı, tiroid hastalığı, serebrovasküler olay, periferik arter hastalığı), kullanılan ilaç sayısı, son bir yıl içindeki düşme sayısı, yatarken ve ayağa kalınca ölçülen sistolik ve diyastolik kan basıncı ölçümleri hasta dosyalarından kaydedildi. Vücut kitle indeksi (VKİ), kilogram cinsinden vücut ağırlığının, metre cinsinden vücut boyunun karesi (kg/m2) değerine bölünmesiyle hesaplandı.

Ayrıntılı Geriatrik Değerlendirme (11)

Hastalara ayrıntılı geriatrik değerlendirme kapsamında uygulanmış olan nörokognitif değerlendirme için MMSE, duygu durum değerlendirmesi için Geriatrik Depresyon Skalası (GDS) (12), fonksiyonellik değerlendirmesi için Temel Günlük Yaşam Aktiviteleri Ölçeği (TGYA) ve Enstrümantal Günlük Yaşam Aktiviteleri (EGYA) ölçekleri (11), yürüyüş ve denge fonksiyonları değerlendirmesi için Tinetti Denge ve Yürüme Testi ile Kalk ve Yürü testi, uyku durumu değerlendirmesi için Uykusuzluk Şiddet İndeksi (13) ve el kavrama gücü (14) verilerine hasta dosya kayıtlarından ulaşılarak kayıt edildi. Üriner inkontinans, idrar yolu enfeksiyonu olmaksızın son 3 ayda istemsiz idrar kaçırma olarak tanımlandı (15). Ortostatik hipotansiyon, oturur veya sırt üstü yatar pozisyondan ayağa kalkıldıktan 3 dakika sonra ölçülen kan basıncında sistolik kan basıncında ≥20 mmHg ve/veya diyastolik kan basıncında ≥10 mmHg düşüş olarak tanımlandı (16). Jamar el dinamometresi ile ölçülen el kavrama gücünün (ortalama 3 ölçüm) erkeklerde <28 kg, kadınlarda <14 kg olması düşük kas gücü olarak tanımlandı (14).

Nutrisyonel Değerlendirme

MNA-Kısa Form skorları ≥12 olsa bile tüm hastalarda malnütrisyon riskini saptamak için Mini Nutritional Assessment (MNA) yapıldı. Toplam puan>23,5, 17-23,5 veya <17 skorları sırasıyla normal nutrisyonel durum grubu (Grup 1), malnütrisyon riski olan grup (Grup 2) ve malnütrisyon grubu (Grup 3) olarak kabul edildi. MNA testi basit ölçümlerden ve 10 dakikadan kısa sürede tamamlanabilen 18 kısa sorudan oluşur. MNA testindeki sorular; vücut kitle indeksi, kilo kaybı, kol çevresi ve baldır çevresi ile ilgili antropometrik ölçüm soruları, genel değerlendirme (yaşam tarzı, ilaç tedavisi ve mobilite ile ilgili 6 soru), diyet anketi ve subjektif değerlendirme (yemek sayısı, yiyecek ve sıvı alımı, beslenmenin özerkliği, sağlık ve beslenmenin kendi algısı ile ilgili 8 soru) (17) sorularından oluşmaktadır.

Laboratuvar Bulguları

Hastaların biyokimyasal, metabolik ve beslenme durumunu değerlendirmek için bazı laboratuvar testleri yapıldı. Tiroid uyarıcı hormon (TSH), kolesterol düzeyleri, serum glukoz, hemoglobin (Hb) ve HbA1c düzeyleri için laboratuvar kayıtları değerlendirildi. Tüm bu biyokimyasal testler, Diagnostic Modular Systems oto analizörü (Roche E170 ve P-800) kullanılarak yapıldı.

B12 Vitamini, Folat ve D Vitamini değerlendirmesi

Yetersiz alımın biyokimyasal kanıtlarını ve metabolik durumun değerlendirmek için, en az 8 saatlik açlıktan sonra sabah kan örnekleri alındı. Serum B12 vitamin eksikliği, B12 düzeyi <200 pg/mL olarak değerlendirildi (18). Folat eksikliği folat düzeyi <3 ng/mL olarak değerlendirildi (19). Kan örneği alındıktan sonra jel tüpler 1 saat içinde santrifüj edildi ve serum vitamin D analizi için -20°C'de saklandı. 25(OH)D radyoimmünoanaliz yöntemi kullanılarak ölçüldü. 25(OH)D <30 ng/mL olan hastalarda D vitamini eksikliği olduğu kabul edildi (20).

Çalışmanın Etik Boyutu

Çalışma, Bezmi Alem Üniversitesi Tıp Fakültesi Hastanesi Girişimsel Olmayan

Araştırmalar Etik Kurulu'nun 15/01/2020 tarih 97706721-900 protokol nolu kararı ile uygun bulunmuş ve Helsinki Deklarasyonu ile uyumlu olarak yürütülmüştür. Çalışmaya dahil edilen katılımcılardan veya yasal vasilerinden bilgilendirilmiş gönüllü olur formu alındı.

İstatistiksel Analiz

Çalışmada istatistiksel analizler için IBM SPSS istatistik 22.0 programı kullanılmıştır. Çalışma verileri değerlendirilirken tanımlayıcı istatistiksel yöntemler (ortalama, standart sapma, medyan, frekans) kullanıldı. Verilerin normal dağılımını değerlendirmek için çarpıklık ve basıklık değerleri Shapiro-Wilk testi ile birlikte kullanılmıştır. Normal dağılım gösteren ikiden fazla değişkeni karşılaştırmak için tek yönlü ANOVA testi kullanılırken, normal dağılım göstermeyen ikiden fazla değişkeni değerlendirmek için Kruskal Wallis testi kullanıldı. Değişkenler arasındaki ilişkiyi değerlendirmek için ki-kare testi kullanıldı. Veriler arasındaki korelasyonu değerlendirmek için normal dağılım gösteren veriler için pearson korelasyon analizi, normal dağılım göstermeyen veriler için spearman korelasyon analizi kullanıldı. Yaş etkisi ortadan kaldırılarak, normal nutrisyonu olanlarla malnutrisyon riski; malnutrisyon ve malnutrisyon ve malnutrisyon riski olan gruplar arasında, ayrıntılı geriatrik değerlendirme parametreleri açısından farklılık devam edip edilmediği lojistik regresyon analizi ile ayrı ayrı değerlendirildi. Sonuçlar %95 güven aralığında ve anlamlılık $p<0,05$ düzeyinde değerlendirildi.

3. Bulgular

Çalışmaya dahil edilen 506 hastanın yaş ortalaması 76,86 ± 6,97 yıl idi. Çalışmaya dahil edilen 506 diyabetik hastanın yaş ortalaması 76,86 ± 6,97 yıl idi. Hastaların %74,7'si kadın, %25,3'ü erkekti. Çalışma grubunun MNA skorlarının ortalaması 23,68 ± 4,16 idi. Katılımcıların 308' inde (%60,8) normal nutrisyonel durum mevcut iken 154'ünde (%30,43) malnutrisyon riski ve 44'ünde (%8,7) ise malnutrisyon mevcut idi.

MNA skor gruplarına göre bakıldığında, hipertansiyon, iskemik kalp hastalığı ve kronik obstrüktif akciğer hastalığı sıklığı açısından gruplar arasında anlamlı fark tespit edilmez iken ($p > 0,05$), konjestif kalp yetmezliği ve kronik böbrek hastalığı sıklığı malnütrisyonu olan hastalardan oluşan Grup 3'te anlamlı şekilde yüksekti ($p<0,05$). MNA grupları ile yaş, ilaç sayısı, BMI ve laboratuvar verileri arasındaki ilişki Tablo 1'de gösterilmiştir. MNA grupları ile geriatrik değerlendirme parametreleri arasındaki ilişki Tablo 2'de gösterilmiştir. Yaş etkisi ortadan kaldırılarak, normal nutrisyonu olanlarla malnutrisyon riski; malnutrisyon ve malnutrisyon ve malnutrisyon riski olan gruplar arasında, ayrıntılı geriatrik değerlendirme parametreleri açısından farklılık devam edip edilmediği lojistik regresyon analizi ile değerlendirildi. Malnutrisyon riski olanlar, normal nutrisyonu olanlarla karşılaştırıldığında sadece Geriatrik depresyon skalası skoru, kalk ve yürü testi süresi, el kavrama gücü ve uykusuzluk şiddeti indeksi skorlarının arasındaki farklılığın devam ettiği saptandı ($p<0,05$). Sadece malnutrisyon ya da malnutrisyon riski ve malnutrisyonu olan gruplar, normal nutrisyonu olanlarla karşılaştırıldığında ise tüm ayrıntılı geriatrik değerlendirme parametrelerinde anlamlılık devam etti ($p<0,05$).

MNA grupları arasında ortostatik hipotansiyon, sistolik ortostatik hipotansiyon, diastolik ortostatik hipotansiyon ve üriner inkontinans varlığı açısından gruplar arasında anlamlı fark saptanmaz iken ($p>0,05$), 1 yıl içindeki düşme varlığı açısından gruplar arasında anlamlı fark saptandı ($p<0,05$). 1 yıl içinde düşme sıklığı Grup 3'te en yüksek oranda saptanırken Grup 1'de en düşük düzeydeydi ($p<0,05$).

Tablo 1. MNA grupları ile yaş, ilaç sayısı, VKİ ve laboratuvar verileri arasındaki ilişkinin değerlendirilmesi

	Grup 1 MNA > 23,5 (n:308)	Grup 2 MNA :17-23,5 (n:154)	Grup 3 MNA < 17 (n:44)	P değeri
Yaş (Yıl)	75,89±6,74	78,67±7,07	81,90±6,52	**0,001**
VKİ (Kg/m^2)	32,98±6,08	32,16±6,32	32,55±6,30	**0,043**
İlaç sayısı	5,85±3,03	6,76±2,98	6,85±3,71	**0,005**
Glukoz (mg/dL)	156,88±69,74	159,98±79,3	169,38±87,51	0,633
HbA1c (%)	7,68±1,65	7,42±1,70	6,82±1,52	**0,012**
Trigliserid (mg/dL)	186,78±107,96	183,70±154,81	150,83±65,4	0,382
LDL-Kolesterol (mg/dL)	119,92±42,65	127,26±41,55	111,32±44,69	0,152
HDL-Kolesterol (mg/dL)	48,41±20,76	48,41±13,53	43,92±11,51	0,576
Hb (g/dL)	13,59±1,67	12,77±1,65	11,81±1,57	**0,001**
TSH (mIU/L)	1,86±2,42	1,80±1,96	1,90±2,11	0,965
Folik asid (ng/mL)	9,62±4,14	8,83±3,90	7,70±4,91	**0,022**
Vitamin B12 (pg/mL)	322,12±249,32	382,60±363,32	464,13±367,22	**0,006**
Vitamin D (ng/mL)	19,05±12,39	22,07±18,25	25,25±17,96	**0,036**

Hb: Hemoglobin; HbA1c: Glikolize hemoglobin; HDL-K: High-density lipoprotein-Kolesterol, LDL-Kolesterol: Low-density lipoprotein-Kolesterol; MNA: Mini Nutrisyonel Değerlendirme; TSH: Tiroid situmulan hormon; VKİ: Vücut kitle indeksi.

Tablo 2. MNA grupları ile geriatrik değerlendirme parametreleri arasındaki ilişkinin değerlendirilmesi

	Grup 1 MNA > 23,5 (n:308)	Grup 2 MNA:17-23,5 (n:154)	Grup 3 MNA < 17 (n:44)	P değeri
TGYA	90,40±11,41	83,02±17,49	60,34±31,05	**0,001**
EGYA	18,85±4,70	15,04±6,37	7,93±7,20	**0,001**
Tinetti Denge	14,57±2,77	12,59±4,11	8,49±5,73	**0,001**
Tinetti Yürüme	11,13±1,92	9,71±3,27	6,58±4,31	**0,001**
Tinetti Total	25,74±4,36	22,31±7,01	15,01±9,97	**0,001**
GDS	3,29±3,45	7,21±4,24*	8,21±4,24	**0,001**
MMSE	25,82±3,10	23,67±4,65	21,49±6,08	**0,001**
KYT (sn)	12,44±6,64	17,27±10,13*	31,44±29,02	**0,001**
EKG (Kg)	24,1±8,77	18,20±6,49*	12,33±7,09	**0,001**
UŞİ	12,07±9,06	16,41±8,80*	18,27±9,01	**0,002**

EGYA: Enstrümantal günlük yaşam aktiviteleri; EKG: El kavrama gücü; GDS: Geriatrik depresyon skalası, KYT: Kalk ve yürü testi; MMSE: Mini Mental Durum Değerlendirme; MNA: Mini Nutrisyonel Değerlendirme; TGYA: Temel günlük yaşam aktiviteleri; UŞİ: Uykusuzluk şiddeti indeksi.
**Yaşın etkisi ortadan kaldırılan Lojistik regresyon analizi sonrasında, malnutrisyon riski ile normal nutrisyon arasındaki anlamlılığın devam ettiği parametreleri (p<0,05).*

4. Tartışma ve Sonuç

Çalışmamızda yaşlı diyabetik hastalarda malnutrisyon ve malnutrisyon riski prevelansı sırasıyla %8,7 ve %30,43 olarak saptandı. Diyabetik yaşlı hastalarda malnütrisyon ile fonksiyonellik, yürüme ve denge fonksiyonları, kognisyon, duygu durum, el kavrama gücü ve uyku durumu üzerine anlamlı oranda olumsuz etkilerinin olduğu saptandı.

Malnutrisyon, besin emilimindeki yetersizlik ve/veya besin alımında azalma ile karakterize olup bu durum tedavi edilmezse veya tedavi ertelenirse, fiziksel ve mental fonksiyonlarda

düşüş, yaşam kalitesinde bozulma, kırılganlık, hastane başvurularında artış ve uzun hastane yatış süreleri gibi fiziksel ve psikososyal sonuçlara yol açabilen bir geriatrik sendromdur (21, 22). Genç diyabetik hastalarda tip 2 DM ortaya çıkışı genellikle obezite ve insülin direncine bağlı olduğu için optimal glisemik kontrol için güncel tedavi yaklaşımı yaşam tarzı modifikasyonu ve ilaç tedavisidir (23). Ancak bu yaklaşım diyabetik yaşlı hastalarda malnutrisyonla sonuçlanabilir. Yaşlanmanın kendisi vücut ağırlığı ve gıda alımında azalma ile ilişkili olabileceğinden (24) diyabetik olan ve olmayan yaşlı hastalarda malnutrisyon prevelansı yüksek olarak görüldüğü bilinmektedir (25). Çalışma grubumuzda malnutrisyon ve malnutrisyon riski prevalansı sırasıyla %8,7 ve %30,43 idi. Diyabetik yaşlı hastalarda malnutrisyon ve malnutrisyon riski varlığı klinik pratikte sıklıkla göz ardı edilse de çalışma sonuçlarımıza göre oldukça yüksek prevalansa sahip olduğu görülmektedir. Literatür incelendiğinde; 146 geriatrik diyabetik hastanın prospektif olarak değerlendirildiği bir çalışmada malnutrisyon ve malnutriyon riski prevelansı bizim çalışmamızdan yüksek saptanmıştır (sırasıyla %13,9 ve %75) (26). Bu farklılık bahsedilen çalışmada nutrisyonel durumun MNA-kısa form ile değerlendirilmiş olduğundan ve yaş ortalamasının 82,5±7,3 yıl olmasından kaynaklanıyor olabilir.

Çalışma sonuçlarımıza göre, yaşlı diyabetik hastalarda malnutrisyonu olan grupta HbA1c düzeyi anlamlı olarak düşük saptandı. Ulaşılan bu sonuç iyi glisemik kontrolün işaretlerinden biri olarak kullanılan HbA1c düzeyinin geriatrik yaş grubunda malnutrisyonun da işaretlerinden biri olabileceği yönündeki verileri desteklemektedir (26). Yapılan bu prospektif gözlemsel çalışmada, glisemik ve nutrisyonel parametreleri değerlendirilmiş olup iyi glisemik kontrol (HbA1c <%7,5) durumundaki hastalarda MNA skorlarının ve VKİ'nin anlamlı derecede düşük olduğu saptanmıştır. Başka bir çalışmada ise, hastanede yatarak tedavi gören diyabetik olmayan yaşlı hastalarda düşük insülin direncinin malnutrisyonla ilişki olduğu gösterilmiştir (27). Malnutriyon riski ve malnutrisyon gruplarında ortalama kan şekeri düzeyi kontrol grubuna göre anlamlı olarak yüksek olmasına rağmen HbA1c daha düşük bulunmuştur ($p<0,05$). Bu durum malnütrisyon ve malnutrisyon riski gruplarında Hb düzeyinin normal nutrisyon grubuna göre anlamlı olarak daha düşük saptanmasından kaynaklanabilir. Diğer yandan malnutrisyon, HbA1c değerlerinde azalmaya ve muhtemelen düşük insülin direncinin bir sonucu olarak oral hipoglisemik tedavi gereksinimlerinin azalmasına katkıda bulunabilir.

Miknonutrient eksiklikleri Tip 2 DM olan hastalarda ve yaşlı hastalarda sık olarak görülmektedir. Tip 2 DM olan hastalarda B12 vitamin eksikliği %22 (28) ve D vitamin eksikliği %85–90 (29) sıklıkta görüldüğü bildirilmiştir. Yaşlı hastalarda özellikle malnutrisyon varlığında B12 vitamin, folik asit ve D vitamin eksikliği sık olarak görülmektedir (30). Çalışma verilemiz mikronutrient düzeyleri açısından değerlendirildiğinde malnutrisyon grubunda serum folat düzeyi anlamlı olarak düşük iken serum B12 vitamini ve serum 25(OH) D vitamini düzeyi anlamlı olarak yüksek idi. Bunun sebebi serum vitamin B12 ve serum 25(OH) D vitamini düzeylerinin, birinci basamak sağlık kuruluşlarında rutin olarak değerlendirilmesi ve replasman tedavilerinin başlanması ya da diyabetik polinöropati tedavisinde bazen vitamin b12 preperatlarının kullanılması olabilir.

Malnutrisyon fonksiyonellikte bozulma, mobilite bozukluğu, düşme, kognitif bozukluk, sarkopeni, duygu durum ve uyku bozuklukları gibi çok sayıda komplikasyona yol açabilen bir geriatrik sendrom olarak bilinmektedir (31,32). Yaşlı diyabetik hastalarda da malnutrisyonu olanlarda bu komplikasyonların gelişebileceği yapılan çalışmalarda gösterilmiştir. Örneğin, diyabetik yaşlı hastalar ile yapılan çalışmalarda malnutrisyonu olan hastalarda retinopati, periferal nöropati ve nefropati gibi mikrovasküler komplikasyonların da katkısıyla fonksiyonellikte gerileme ve sarkopeniye yol açabileceği bildirilmiştir (25, 33, 34). Ayrıca bu hastalarda inflamatuar sitokinler, komorbiditeler, malnutrisyon ve düşük fiziksel aktivitenin kas kitlesinde kayıp, kas gücü ve fonksiyon kaybı ile yürüme-denge bozuklukları ve düşmelere yol

açabileceği bilinmektedir (35). Vasküler endotelyal disfonksiyon, inflamasyon, kan beyin bariyer hasarı, demyelinasyon ve aksonal kayıp gibi nedenlerden dolayı yaşlı diyabetik hastalarda kognitif fonksiyonlar da olumsuz etkilenmektedir (36). Kognitif disfonksiyonun ise hastaları özellikle ilerleyen yaş ile malnutrisyon riski ile karşı karşıya getirdiği bilinmektedir (37). Nokturmal solunum bozukluklarının tekrarlayan oksijen desatürasyonu ve uyku bölünmelerine yol açarak glukoz metabolizma bozukluklarına yol açabileceği gösterilmiştir (38). Özellikle yaşlılarda uyku bozuklukları iştahı, gıda alımını, melatonin salınımını ve sirkadyen ritmi etkileyerek malnutrisyon ile sonuçlanabilir (17,32). Çalışma sonuçlarımız tüm bu verileri destekler nitelikte olup yaşlı diyabetik hastalarda malnutrisyon varlığının, yürüme ve denge fonksiyonları, kognitif durum, duygu durum, el kavrama gücü ve uyku durumunun da dahil olduğu tüm geriatrik değerlendirme parametrelerini olumsuz etkilediği gösterilmiştir. Diğer çalışmalardan farklı olarak bahsedilen tüm geriatrik değerlendirme parametreleri tek bir çalışmada değerlendirilip malnutrisyonun yaşlı diyabetik hastalardaki olumsuz etkileri ortaya koyulmuştur.

Çalışmamızın güçlü yanları yüksek örneklem sayısı, tüm hastalara ayrıntılı geriatrik değerlendirme testleri yapılması ve komorbid hastalıkların değerlendirilmesidir. Çalışmanın belli noktalarda kısıtlılıkları mevcuttur. Bunlardan en önemlisi çalışmanın kesitsel ve retrospektif bir çalışma olmasıdır. Diğer yandan DM tedavisinde kullanılan ilaçların ve hastanın almakta olduğu mikronutrient replasman tedavilerinin değerlendirilmemesi kısıtlılıklar olarak değerlendirilebilir.

5. Sonuç

Çalışma sonuçlarımız yaşlı diyabetik hastalarda malnütrisyonun fonksiyonel gerileme, yürüme ve denge bozuklukları, kognisyon ve duygu durum bozuklukları, el kavrama gücünde azalma ve uyku bozuklukları için bir risk faktörü olabileceğini göstermektedir. Yaşlı diyabetik hastalarda DM tedavi ilkeleri gözetilirken nutrisyonel değerlendirmenin yapılması gerekmektedir. Yaşlı diyabetik hastalarda sıkı diyet kontrolünün malnutrisyon ve malnutrisyon ilişkili sağlık sorunları ile sonuçlanabileceği akılda bulundurulmalıdır. Zaten duyarlı olan yaşlı diyabetik hastaların nutrsiyonel açıdan değerlendirilmesi ve malnutrisyonun taranması, erken dönemde tanınması ve tedavisi önemlidir.

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Research Article / Araştırma Makalesi

Yüksek Centor Skorunu Belirlemede Hemogram Parametrelerinin Kullanımı

The Usage of Hemogram Parameters for Determining High Centor Score

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Özet

Modifiye Centor Kriterleri bakteriyel-viral tonsilofaranjit ayrımında sıklıkla kullanılmaktadır. Bu puanlama sistemi anamnez ve fizik muayene bulguları gibi subjektif verilere dayanmaktadır. Bu çalışmada yüksek centor skorunu belirlemede hemogram parametrelerinin kullanımı araştırılmıştır. 01/01/2019-31/12/2019 tarihleri arasında boğaz ağrısı şikayeti ile kulak burun boğaz polikliniğine başvurmuş ve akut tonsilofaranjit tanısı alan hastalar retrospektif olarak tarandı. Bu hastalardan bu başvurularında hemogram tetkiki istenmiş olanlar çalışmaya dahil edildi. Tüm hastaların kayıtlı anamnez ve fizik muayene bulguları incelenerek modifiye centor skoru hesaplandı. Centor skoru 4 olanlar yüksek centor grubunu oluştururken, centor skoru 0 ve 1 olanlar düşük centor grubunu oluşturdu. Herbir grupta 30 hastanın olması sağlandı. İki grup hemogram parametreleri açısından karşılaştırıldı. Ortalama beyaz küre sayısı, nötrofil sayısı, monosit sayısı yüksek centor grubunda (10.96±3.49, 7.91±3.43, 1.06±0.34, sırasıyla) düşük centor grubundan (7.94±2.11, 5.10±1.94, 0.66±0.23, sırasıyla) daha yüksek saptanmıştır. Bu farklar istatistiksel olarak anlamlıdır (p<0.001, p<0.001, p<0.001,sırasıyla). Yüksek centor grubunda saptanan ortalama MCV ve MPV değerleri (84.17±5.48, 9.44±0.99, sırasıyla) düşük centor grubunda saptanan değerlerden (86.89±4.49, 10.14±0.78, sırasıyla) daha düşüktür. Bu farklar da istatistiksel olarak anlamlıdır (p=0.008, p= 0.004, sırasıyla). Ayrıca ortalama RDW değeri yüksek centor grubunda (13.88±1.44) düşük centor grubuna göre (13.06±0.92) daha yüksek bulunmuştur (p=0.012). Hesaplanan veriler incelendiğinde ortalama nötrofil-lenfosit oranı ve ortalama monosit-lenfosit oranı yüksek centor grubunda (5.25±4.41, 0.62±0.21, sırasıyla) düşük centor grubuna göre (3.17±3.04, 0.39±0.24, sırasıyla) daha yüksek saptanmıştır (p<0.001, p<0.001, sırasıyla). Hemogram parametreleri hem yüksek centor skorunu belirlemede hem de akut tonsilofaranjit etiyolojisinde bakteriyel-viral ayrımını yapmakta kullanılabilir. Hemogram parametrelerinin modifiye centor puanlama sistemiyle birlikte kullanımı bu puanlama sisteminin duyarlılık ve özgüllüğünü arttırabilir.

Anahtar Kelimeler: Modifiye centor skoru; hemogram; akut tonsilofaranjit; grup A streptokok

Abstract

Modified Centor Criteria are frequently used to differantiate bacterial-viral tonsilopharyngitis. This scoring system is based on subjective data such as history and physical examination. In this study, the use of hemogram parameters in determining high centor score was investigated. Patients who applied to otolaryngology outpatient clinic with complaint of sore throat between 01/01/2019-31/12/2019 and were diagnosed with acute tonsilopharyngitis were retrospectively scanned. Of these patients, those who were requested to have hemogram at their admission were included in study. Modified centor score was calculated by examining recorded anamnesis and physical examination. Those with a centor score of 4 formed high centor group, while those with a centor score 0 and 1 formed low centor group. It was ensured that there were 30 patients in each group. Two groups were compared in terms of hemogram parameters. Mean white blood cell, neutrophil and monocyte counts were higher in high centor group (10.96±3.49, 7.91±3.43, 1.06±0.34, respectively) than in low centor group (7.94±2.11, 5.10±1.94, 0.66±0.23, respectively). These differences are statistically significant (p<0.001, p<0.001, p<0.001, respectively). Mean MCV and MPV values found in high centor group (84.17±5.48, 9.44±0.99, respectively) were lower than values found in low centor group (86.89±4.49, 10.14±0.78, respectively). These differences are also statistically significant (p=0.008, p= 0.004, respectively). In addition, mean RDW value was found to be higher in high centor group (13.88±1.44) than in low centor group (13.06±0.92, p=0.012). When calculated data were analyzed, mean neutrophil-lymphocyte and monocyte-lymphocyte ratios were found to be higher in high centor group (5.25±4.41, 0.62±0.21, respectively) than in low centor group(3.17±3.04, 0.39±0.24, p<0.001, p<0.001, respectively). Hemogram parameters can be used both to determine high centor score and to differentiate bacterial and viral etiology in acute tonsilopharyngitis. Usage of hemogram parameters together with modified centor scoring system can increase sensitivity and specificity of this scoring system.

Keywords: Modified centor score; hemogram; acute tonsilopharyngitis; group A streptococcus

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1. Giriş

Akut tonsilofaranjit tedavisinde etiyolojide bakteriyel-viral ayrımını yapmak en kritik basamaktır. Bakterilere bağlı meydana gelen tonsilofarenjitlerin tedavisinde antibiyotikler kullanılırken virüslere bağlı meydana gelen tonsilofarenjitlerin tedavisinde semptomatik tedavi uygulanmaktadır. Bakteriyel tonsilofaranjitlerin özellikle grup A beta hemolitik streptokokların (GABHS) antibiyotik ile tedavi edilmesi, hem süpüratif komplikasyonların hem de akut romatizmal ateş, akut glomerülonefrit gibi non süpüratif komplikasyonların önlenmesi açısından önemlidir (1). Bu nedenle akut tonsilofaranjit etiyolojisinde bakteriyel-viral ayrımını yapmak en kritik basamaktır. Bu amaçla GABHS tanısının klinik ve epidemiolojik bulgularla beraber labaratuar testlerine dayandırılması önerilmektedir (2). Modifiye Centor Kriterleri bu amaçla kullanılan fizik muayene ve anamnez bulgularına dayanan puanlama sistemlerinden biridir. Bu puanlama sistemi ile elde edilen puanların artmasıyla beraber hastada GABHS'a bağlı tonsilofaranjit görülme riski de artmaktadır (3,4). Bu puanlama sistemi anamnez ve fizik muayene bulgularına dayanmaktadır, bu nedenle subjektiftir. Boğaz kültürü ve hızlı antijen testleri daha objektif testler olmasına karşın bu tetkikler hem daha uzun sürede sonuçlanmaktadırlar hem de daha maliyetlidirler. Bu nedenle akut tonsilofaranjit etiyolojisinde bakteriyel-viral ayrımını yapmakta kullanılabilecek objektif ve düşük maliyetli tetkiklere ihtiyaç duyulmaktadır.

Hemogram tetkiki birçok patolojinin tanı ve takibinde sıklıkla kullanılan basit, kolay ulaşılabilir ve ucuz bir tetkiktir. Bu nedenle bu tetkiki akut tonsilofaranjit etiyolojisinde bakteriyel-viral ayrımını yapmak amacıyla kullanmak mantıklı görünmektedir. Hemogram tetkikinde incelenen birçok parametre bu amaçla kullanılabilir. Eğer bu parametrelerden bazıları yüksek centor skorunu belirlemede faydalı bulunursa bakteriyel-viral tonsilofaranjit ayrımında da kullanılabilecektir. Ayrıca yüksek centor skorunun hemogram tetkiki ile desteklenmesi bu puanlama sisteminin duyarlılık ve özgüllüğünü de arttırabilir.

Bu çalışmada yüksek Modifiye Centor Skoru olan hastalar düşük skoru hastalar ile hemogram parametreleri açısından karşılaştırılmıştır

2. Gereç ve Yöntemler

Bu çalışma lokal etik kurul onayı alındıktan sonra üçüncü basamak bir hastanenin kulak burun boğaz bölümünde yapıldı (Karar No:2017-KAEK-189_2021.09.22_07). 01/01/2019-31/12/2019 tarihleri arasında kulak burun boğaz polikliniğine başvurmuş ve akut tonsilofarenjit tanısı alan hastalar hastane otomasyon sisteminden tarandı. Bu hastalardan bu başvurusunda hemogram tetkiki istenmiş olanlar çalışmaya dahil edildi. Hastaların otomasyon sisteminden elde edilen anamnez bilgilerine ve fizik muayene bulgularına göre Modifiye Centor Skoru belirlendi. Modifiye Centor Skoru yüksek olan hastalar Modifiye Centor Skoru düşük olan hastalar ile hemogram parametreleri açısından karşılaştırıldı. Herbir grupta 30 hasta olacak şekilde toplam 60 hasta çalışmaya dahil edildi. Hematolojik hastalığı olanlar, kronik hastalığı olanlar, hemogram parametrelerini etkileyebilecek ilaç kullanım öyküsü olanlar, malignitesi olanlar, kronik akciğer ve kalp hastalığı olanlar, 18 yaşından küçükler, 65 yaşından büyükler çalışmaya dahil edilmedi. Başvuru sırasında hastaların akut tonsilofaranjit için herhangi bir tedavi almıyor oldukları teyit edildi. Hastaların 32'si kadın iken, 28'i erkekti. Hastaların yaş ortalaması 32.42±12.69 saptandı. İki grup arasında yaş ve cinsiyet açısından istatistiksel olarak anlamlı bir fark yoktu (Tablo 1). Hastaların tüm demografik verileri Tablo 1' de verilmiştir.

Tablo 1. Çalışmaya dahil edilen hastaların demografik verileri

	Yüksek Centor Grubu	Düşük Centor Grubu	*p*
Cinsiyet			
Erkek	16	12	0.301[a]
Kadın	14	18	
Yaş	30.00±8.37	34.83±15.67	0.143[b]
Centor Puanına Göre Hasta Dağılımı			
0 puan		14 hasta	
1 puan		16 hasta	
4 puan	30 hasta		

a=Pearson Ki-Kare Testi
b=Bağımsız Gruplar T-testi

Modifiye Centor Kriterleri akut tonsilofaranjit tanısı alan hastalarda bakteriyel ve viral etiyolojiyi ayırmak amacıyla kullanılan, anamnez ve fizik muayene bulgularına dayanan bir puanlama sistemidir. Bu puanlama sisteminde 5 kriter puanlanmaktadır. Bu puanlama sistemine göre ateşin 38˚C nin üzerinde olması +1 puan, hastada ağrılı büyümüş ön servikal LAP'ların olması +1 puan, tonsillerde hipertrofi veya eksuda olması +1 puan, öksürük bulunmaması +1 puan, yaşın 3-14 yaş arasında olması +1 puan, 15-44 yaş arasında olması 0 puan, 44 yaşın üzerinde olması -1 puan olarak puanlanır (Tablo 2). Bu puanlama sonucunda elde edilen toplam puan arttıkça akut tonsilofaranjitin GABHS'a bağlı meydana gelme ihtimali de artmaktadır (4). Bu nedenle yüksek centor skorlu hastaların antibiyotikle tedavi edilmesi önerilirken düşük centor skorlu hastalara semptomatik tedavi verilir. Bu çalışmada da yüksek Modifiye Centor Skoru olan hastalar (toplam puanı 4 olanlar), düşük Modifiye Centor Skoru olan hastalar ile (toplam puanı 0 veya 1 olanlar) hemogram parametreleri açısından karşılaştırılmıştır. Yüksek centor skorunu belirlemede hemogram parametrelerinin kullanılabilirliği araştırılmıştır.

Table 2. Modifiye centor kriterleri ve puanlaması

Kriterler	Puan
Ateş (38˚C<)	+1 puan
Ağrılı büyümüş ön servikal LAP	+1 puan
Tonsillerde hipertrofi veya eksuda	+1 puan
Öksürüğün bulunmaması	+1 puan
Yaş	
3-14 yaş arası	+1 puan
15-44 yaş arası	0 puan
44 yaş üstü	-1 puan

İstatistiksel Analiz

İstatistiksel analiz Statistical Package for Social Sciences (SPSS) version 15 kullanılarak yapıldı. Değişkenlerin normal dağılıp dağılmadığına karar vermek için görsel (histogram, probability plots) ve analitik metodlar (Kolmogorov-Simirnov testi) kullanıldı. İki grubun hemogram parametreleri Mann Whitney-U testi/ Bağımsız Gruplar T-testi kullanılarak karşılaştırıldı. İki gruptaki kategorik verilerin karşılaştırılmasında Pearson Ki-Kare testi kullanıldı. $p<0.05$ istatistiksel olarak anlamlı kabul edildi.

3. Bulgular

Yüksek Centor grubunda ortalama beyaz küre sayısı 10.96±3.49 iken Düşük Centor grubunda ortalama beyaz küre sayısı 7.94±2.11 saptanmıştır. Yüksek Centor grubunda ortalama nötrofil sayısı 7.91±3.43 iken Düşük Centor grubunda ortalama nötrofil sayısı 5.10±1.94'dür. Benzer şekilde Yüksek Centor grubunda Düşük Centor grubuna göre daha yüksek ortalama monosit sayısı elde edilmiştir (1.06±0.34, 0.66±0.23, sırayla). Tüm bu farklar istatistiksel olarak anlamlı bulunmuştur (p<0.001, p<0.001, p<0.001, sırayla, Tablo 3)

Yüksek Centor grubunda ortalama MCV değeri 84.17±5.48 iken Düşük Centor grubunda ortalama MCV değeri 86.89±4.49 saptanmıştır. Bu fark istatistiksel olarak anlamlıdır (p=0.008, Tablo 3). Benzer şekilde Yüksek Centor grubunda ortalama MPV değeri 9.44±0.99 iken Düşük Centor grubunda ortalama MPV değeri 10.14±0.78 bulunmuştur. Bu fark da istatistiksel olarak anlamlı bulunmuştur (p=0.004, Tablo 3). Yüksek Centor grubunda (13.88±1.44) Düşük Centor grubuna (13.06±0.92) göre daha yüksek ortalama RDW değeri saptanmıştır. Bu fark istatistiksel olarak anlamlıdır (p=0.012, Tablo 3).

Tablo 3. Yüksek ve düşük centor grubunun hemogram parametreleri açısından karşılaştırılması

	Yüksek Centor Grubu (Mean±SD)	Düşük Centor Grubu (Mean±SD)	*P*
Beyaz Küre Sayısı	10.96±3.49	7.94±2.11	<0.001[a]*
Nötrofil Sayısı	7.91±3.43	5.10±1.94	<0.001[b]*
Lenfosit Sayısı	1.83±0.72	1.99±0.76	0.423[a]
Monosit Sayısı	1.06±0.34	0.66±0.23	<0.001[a]*
Eritrosit Sayısı	5.05±0.34	4.83±0.49	0.053[a]
Hemoglobin Değeri	14.32±1.59	13.90±1.49	0.301[a]
Hematokrit Değeri	42.54±4.13	42.05±3.74	0.636[a]
Mean Corpuscular Volume (MCV)	84.17±5.48	86.89±4.49	0.008[b]*
Red Cell Distribution Width (RDW)	13.88±1.44	13.06±0.92	0.012[a]*
Platelet Sayısı	248.53±88.16	255.13±53.60	0.728[a]
Mean Platelet Volume (MPV)	9.44±0.99	10.14±0.78	0.004[a]*
Platelet Distribution Width (PDW)	11.25±1.47	11.62±1.68	0.420[b]
Nötrofil/Lenfosit	5.25±4.41	3.17±3.04	<0.001[b]*
Platelet/Lenfosit	151.41±74.98	143.27±59.73	0.779[b]
Monosit/Lenfosit	0.62±0.21	0.39±0.24	<0.001[b]*

a= Bağımsız Gruplar T-testi
b= Mann Whitney-U testi
**= İstatistiksel olarak anlamlı*

Hesaplanan veriler incelendiğinde Yüksek Centor grubunda ortalama nötrofil-lenfosit oranı 5.25±4.41 iken, Düşük Centor grubunda ortalama nötrofil-lenfosit oranı 3.17±3.04 saptanmıştır. Yüksek Centor grubunda ortalama monosit-lenfosit oranı 0.62±0.21 iken Düşük Centor grubunda ortalama monosit-lenfosit oranı 0.39±0.24'dir. Bu farklar istatistiksel olarak anlamlı bulunmuştur (p<0.001, p<0.001, sırayla, Tablo 3). Platelet-lenfosit oranı açısından Yüksek Centor grubu (151.41±74.98) ve Düşük Centor grubu (143.27±59.73) arasında fark saptanmamıştır (p=0.779, Tablo 3).

İki grup arasında lenfosit sayısı, eritrosit sayısı, hemoglobin değeri, hemotokrit değeri, platelet sayısı, PDW değeri açısından istatistiksel olarak anlamlı bir fark saptanmamıştır (Tablo 3).

4. Tartışma

Akut tonsilofaranjitler çoğunlukla virüslere bağlı meydana gelmekle birlikte bakteriler de akut tonsilofaranjit oluşumunda rol oynarlar (5). Bakteriyel tonsilofaranjitlerin büyük çoğunluğu GABHS nedeniyle oluşur (6). GABHS tedavisi romatizmal ateşin ve süpüratif komplikasyonların önlenmesi, semptomların azaltılması, hastalığın yayılımının önüne geçilmesi açısından önemlidir (7). Bu nedenle bakteriyel tonsilofaranjitlerin antibiyotik ile tedavi edilmesi gerekirken viral tonsilofaranjitlerin tedavisinde semptomatik tedavi yeterlidir. Akut tonsilofaranjit tedavisinde bakteriyel-viral ayrımını yapmak en önemli basamaktır. Bu ayrımı yapmakta çeşitli tetkikler ve puanlama sistemleri kullanılmaktadır. Streptokokkal tonsilofaranjit tanısını koymak için hızlı antijen testi ve/veya boğaz kültürü ile beraber klinik tanı kriterlerinin kullanılması önerilmektedir (8). Öte yandan birçok çalışmada yüksek Centor skoru ile direkt ampirik antibiyotik tedavisinin başlanması gerektiği ileri sürülmektedir (5,9). Yani tüm Centor Kriterlerinin puan alması durumunda ampirik antibiyotik başlanması geçerli ve yaygın bir uygulamadır (10). Ayrıca centor puanlama sisteminin kullanılması uygun antibiyotik kullanımını arttırmakta ve antibiyotik kullanım oranını azaltmaktadır (10). Boğaz kültürü bakteriyel-viral etiyolojiyi ayırdetmekte kullanılan altın standart yöntemdir. Fakat boğaz kültüründe patojenlerin üremesi 48 saati bulabilmektedir (6). Bu da tedavinin gecikmesine yol açmaktadır. Özellikle gelişmiş ülkelerde bakteriyel-viral tonsilofaranjit ayrımında hızlı antijen testleri kullanılmaktadır. Bu testlerin literatürede sensitivite oranları ile ilgili değişik sonuçlar verilse de hızlı sonuç vermesi en büyük avantajıdır (6). Fakat bu testlerin de maliyetinin yüksek olması özellikle gelişmemiş ve gelişmekte olan ülkelerde kullanımının önünde önemli bir engeldir (6). Ayrıca çalışmalar boğazdan örnek alınmasının tonsilofaranjit tedavisinde yaygın olarak kullanılmadığını göstermektedir (10). Bu nedenle maliyeti olmayan, hastanın anamnez ve fizik muayene bulgularına dayanan Modifiye Centor Kriterleri gibi puanlama sistemleri akut tonsilofaranjit tedavisinde bakteriyel-viral ayrımını yapmakta sıklıkla kullanılmaktadır. Çalışmalarda, hekimlerin akut tonsilofaranjitin GABHS'lara bağlı olup olmadığını bilmeksizin sadece klinik özellikleri değerlendirerek antibiyotik yazma eğiliminde oldukları ileri sürülmektedir (11). Centor puanlama sistemi akut tonsilofaranjitli hastalarda GABHS riskini belirlemek amacıyla kullanılmaktadır (7). Centor Kriterleri 1981 yılında ilk defa yayınlandıktan sonra 1998 yılında Modifiye Centor Kriterleri oluşturulmuştur (12,13). Modifiye Centor Kriterleri'nde diğer adıyla Mc Isaac Kriterleri' nde Centor Kriterlerine ek olarak hastanın yaşı da puanlamaya dahil edilmektedir. Böylelikle Centor Kriterleri'nde maksimum alınabilen puan 4 iken Modifiye Centor Kriterleri'nde maksimum alınabilen puan 5 olmuştur. Çalışmamızda dahil edilen hastaların tamamının 18-44 yaş aralığında olması nedeniyle tüm hastalar bu bölümden 0 puan almıştır bu nedenle çalışmamızda her iki puanlama sistemine göre de maksimum alınan puan 4 olmuştur. Yüksek Centor Grubunu centor skoru 4 olan hastalar oluştururken, Düşük Centor Grubunu centor skoru 0 ve 1 olan hastalar oluşturmuştur. Daha önce de belirtildiği gibi Modifiye Centor Puanlama Sistemi hastanın anamnez ve fizik muayene bulgularına dayanmaktadır. Literatürde yapılan bir çalışmada ateş ve öksürük yokluğu gibi hastanın anamnezine dayalı öğelerin puanlamasının hasta veya ebeveynleri ile doktorlar arasında benzer olduğu saptanmıştır. Öte yandan boyunda ağrılı lenf nodu ve tonsiller eksuda gibi fizik muayene bulgularına dayanan öğelerin puanlamasının hasta veya ebeveynleri ile doktorlar arasında daha az benzer olduğu ortaya konmaktadır (7). Ayrıca bu kriterlerin herbirinin GABHS tanısını koymada veya ekyartasyonundaki etkisi farklı bulunmuştur (14). Bu da diğer tetkiklere nazaran Modifiye Centor Puanlama sisteminin daha subjektif olduğunu gösterir. Bu nedenle sıklıkla hızlı antijen testiyle veya boğaz kültürü ile doğrulanması önerilir. Çalışmamızda da yüksek centor skorunu belirlemede hemogram parametrelerinin kullanımı araştırılmıştır. Yüksek Centor grubunda Düşük Centor grubuna göre daha yüksek beyaz küre sayısı, nötrofil sayısı,

monosit sayısı ve RDW değeri elde edilirken, daha düşük MCV ve MPV değerleri elde edilmiştir. Önceki çalışmalar centor skorunun artmasıyla GABHS pozitifliğinin arttığını ortaya koymaktadır (7). Yüksek Centor grubunda bakteriyel tonsilofaranjit sayısı daha fazla olacağından beyaz küre sayısında ve nötrofil sayısında daha yüksek değerler elde etmek şaşırtıcı değildir. Öte yandan Yüksek Centor grubunda daha yüksek monosit, RDW değerleri ve daha düşük MCV, MPV değerleri elde edilmiştir. Bu bulgular literatür için yeni bulgulardır. Tüm bu parametreler yüksek centor skorunu belirlemek veya teyit etmek amacıyla kullanılabilir. Ayrıca hemogram parametrelerinden yararlanılarak hesaplanan nötrofil-lenfosit oranı, monosit-lenfosit oranı da yüksek centor grubunda daha yüksek saptanmıştır. Bu veriler de bakteriyal-viral tonsilofaranjit ayrımında kullanılabilir.

Yukarıda da belirtilen kısıtlılıklar nedeniyle akut tonsilofaranjitte bakteriyel-viral ayrımını boğaz kültürü veya hızlı antijen testleriyle yapmak her zaman mümkün olmamaktadır. Bu nedenle Modifiye Centor Puanlama sistemi klinisyenler tarafından sıklıkla tercih edilmektedir. Öte yandan Modifiye Centor Kriterleri'nde ateş, boyunda ağrılı lap, öksürük olmaması gibi puanlanan kriterler sıklıkla hastanın beyanına dayanmaktadır. Bu da puanlamanın subjektif olmasına neden olmaktadır. Ayrıca Shaikh ve ark. yaptıkları çalışmada hiçbir puanlama sisteminin mikrobiyolojik inceleme ihtiyacını ortadan kaldıracak düzeyde yeterince sensitivitesinin ve spesifitesinin olmadığını ortaya koymaktadır (15). Bu nedenle bu subjektif puanlama sisteminin daha objektif tetkiklerle doğrulanması ve sensitivite/spesifitesinin arttırılması gerekmektedir. Bu çalışmada hemogram tetkikinin yüksek centor skorunu belirlemede kullanılması araştırılmıştır. Gelecek çalışmalarda yüksek centor skorunu belirlemede başka tetkiklerin de etkisinin araştırılması literatüre bu konuda katkı sağlayacaktır. Hatta gelecek çalışmalarda Centor gibi puanlama sistemlerine hemogram gibi basit objektif tetkikler eklenerek sensitivitesi ve spesifitesi daha güçlü olan puanlama sistemleri oluşturulabilir.

Çalışmamızda yüksek centor grubunu centor skoru 4 olan hastalar oluştururken, düşük centor grubunu centor skoru 0 veya 1 olan hastalar oluşturmuştur. İki grubun skor olarak birbirine yakın olmaması iki grubun klinik olarak da belirgin farklı olmasını sağlamıştır. Bu çalışmamızın güçlü tarafı olarak görülebilir. Öte yandan hasta sayısının az olması ve retrospektif bir çalışma olması bu çalışmanın kısıtlılıklarıdır. Daha çok hasta sayısını içeren prospektif çalışmalar literatüre daha çok katkı sağlayabilir.

5. Sonuç

Hemogram parametreleri hem yüksek centor skorunu belirlemede hem de akut tonsilofaranjitte bakteriyel-viral ayrımında kullanılabilir. Hemogram parametrelerinin modifiye centor puanlama sistemiyle birlikte kullanımı bu puanlama sisteminin duyarlılık ve özgüllüğünü arttırabilir.

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Research Article / Araştırma Makalesi

Yüksek Syntax Skoruna Sahip Kronik Koroner Sendromlu Olgularda Cerrahi, Perkütan Müdahale ve Medikal Tedavi

Surgery, Percutaneous Intervention, and Medical Treatment in Cases with Chronic Coronary Syndrome with High Syntax Scores

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Özet

Yüksek SYNTAX skorlu olgulara genellikle cerrahi revaskülarizasyon önerilmektedir ve cerrahi riski yüksek olgularda güvenilir bir "B planı"nın olması girişimsel kardiologların en büyük arzusudur. Bu sebeple çalışmamızda kronik koroner sendrom (KKS)'lu SYNTAX skoru ≥33 olan olgularda tek başına medikal tedavi(MT), cerrahi-medikal tedavi(CABG) ve perkütan-medikal tedavi(PCI) kollarını karşılaştırmayı amaçladık. Gözlemsel kayıt çalışmamıza KKS'li çok damar hastası ve SYNTAX skoru ≥33 olan olgular dahil edildi. Her üç tedavi kolundaki olguların hem kısa (30 günlük) hem de uzun dönem sonlanımları değerlendirildi. Birincil sonlanım noktası kardiyak ve tüm nedenlere bağlı mortalite iken, ikincil sonlanım noktası akut miyokart infarktüsü(AMİ), ilave revaskülarizasyon, serebrovasküler olay(SVO) olarak belirlendi. 33 hasta MT, 24 hasta PCI, 79 hasta ise CABG kolunda istatistiksel analize dahil edildi. Ortalama takip süresi 48,25±26,37 ay olarak saptandı. Uzun dönemde CABG kardiyak ve tüm nedenlere bağlı ölüm açısından MT ve PCI kollarına üstün olduğu görüldü(sırasıyla CABG vs MT p=0,001, CABG vs PCI p=0,001; CABG vs MT p=0,002, CABG vs PCI p=0,002). Bu bağlamda MT ve PCI kolları arasında fark görülmedi (sırasıyla p=0,085, p=0,065). AMİ ve SVO sonlanım noktalarında da CABG kolunun superior olduğu saptandı(sırasıyla CABG vs MT p=<0,001, CABG vs PCI p=<0,001; CABG vs MT p=0,04, CABG vs PCI p=0,015). CABG kolu ilave revaskülarizasyon açısından da PCI'a üstün bulundu(p=<0,001). AMİ MT'de PCI koluna göre daha fazla görülürken (p=0,025), SVO açısından iki kol arasında fark görülmedi(p=0,65) daha fazl İlave revaskülarizasyon açısından da yine CABG daha üstün olarak görüldü(CABG vs PCI p=<0,001) KKS'lu SYNTAX skoru ≥33 olan olgularda CABG, tek başına MT ve everolimus kaplı stentlerle yapılan PCI'ya göre uzun dönemde kardiyak ölüm, tüm nedenlere bağlı ölüm, AMİ ve SVO açısından daha üstündür.

Anahtar Kelimeler: Koroner bypass, Everolimus, Perkütan koroner müdahale , SYNTAX skoru, çok damar hastalığı.

Abstract

Generally, surgical revascularization recommended for patients who have high SYNTAX scores, but it is the greatest desire of invasive cardiologists to have a reliable "Plan B" in cases with high surgery risk. For this reason, the purpose of the present study was to compare medical treatment alone, surgical-medical treatment, and percutaneous-medical treatment options in CCS cases with a SYNTAX score of ≥33. In an observational registry study, we included patients with multivessel disease and SYNTAX score of ≥33. Both short (30-day) and long-term outcomes of subjects in all three treatment arms were evaluated. The primary outcome was allcause and cardiac mortality. Myocardial infarction, revascularization, and stroke constituted our secondary outcomes. 33 patients in the MT arm, 24 in the PCI arm, and 79 in the CABG arm were included in the analyses. Mean follow-up was 48.25±26.37 months. CABG arm was superior to both arms in terms of cardiac death (CABG vs MT p=0.001, CABG vs PCI p=0.001) and PCI and MT did were similar (p=0.085), CABG was superior in allcause detah (CABG vs MT p=0.002, CABG vs PCI p=0.002) again no statistical differences were detected between MT and PCI arms (p=0.065) in long term follow-up. In terms of acute myocardial infarction(AMI) (CABG vs MT p=<0.001, CABG vs PCI p=<0.001), cerebrovascular event(CVE) (CABG vs MT p=0.04, CABG vs PCI p=0.015) , additional revascularization CABG was superior side again (CABG vs PCI p=<0.001). AMI was higher in MT group compare to PCI (p=0.025). CVE were similar in MT and PCI groups (p=0.65). İn cases with CCS and ≥33 SYNTAX score, CABG is superior to MT alone and PCI which is performed with everolimus-eluting stents in terms of cardiac death, allcause mortality, AMI and CVE in long term follow-up.

Keywords: Coronary artery bypass, Everolimus, Percutaneous coronary intervention, SYNTAX score, Multivessel disease

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1. Giriş

Günümüzde kronik koroner sendrom (KKS) tedavisinde optimal-medikal, perkütan ve cerrahi yöntemlerden ister ayrılıkta isterse de hibrit şekilde yararlanmaktayız. Medikal tedavinin esas görevi trombotik olayların önlenmesi, semptomların ve aterosklerotik progresyonun azaltılmasıdır. Miyokardiyal revaskülarizasyondaki esas amaç ise semptomların giderilmesi ve prognozun iyileştirilmesidir(1). 2018 ESC/EACTS Revaskülarizasyon rehberinde de belirtildiği üzere kılavuz bilgisi ile sabit optimal medikal tedaviye rağmen semptomatik olan olgularda revaskülarizasyon önerilmektedir. Ancak revaskülarizasyon, bir çok çalışmada semptom kontrolü, efor kapasitesinde artış ve hayat kalitesinde iyileşmede tekbaşına medikal tedaviye oranla daha başarılı bulunmuştur(2,3). Dolayısıyla klinik pratiğimizde bu yöntemleri gerektiğinde kombine şekilde kullanmanın daha çok fayda sağladığını düşünmekteyiz. Özellikle çok damar hastalığında yüksek SYNTAX skoruna sahip olguların prognoz açısından revaskülarizasyona yönlendirilmesi büyük önem taşımaktadır(4). Revaskülarizasyona karar verildikten sonraki adım perkütan veya cerrahi seçeneğin değerlendirilmesidir. Burada esas olan hangi yöntemle tam revaskülarizasyonun sağlanabileceğidir(5,6). Ayrıca revaskülarizasyon işleminin kısa ve uzun dönem başarısı eşlik eden hastalık, ejeksiyon fraksiyonu, renal fonksiyon, yaş gibi etkenleri içinde bulunduran STS ve EUROSCORE gibi cerrahi riski belirleyen skorlara da bağlıdır. Yani tam revaskülarizasyon hedeflenerek perkütan veya cerrahi işlem riski karşılaştırılarak yöntem belirlenmiş olur(7,8,9). KKS'da medikal tedavinin rolü bir çok çalışmaya konu olsa da, çok damar ve ≥33 SYNTAX skoruna sahip olgulardaki tek başına etkisi bilinmemektedir. Nitekim bu olgulara genelde son güncel kılavuzlar gereği cerrahi uygulandığından perkütan tedavinin tek başına veya medikal tedaviye eklenmiş şekilde etkisi de çok az bilinmektedir. İkinci nesil ilaç kaplı özellikle de everolimus kaplı stentlerin ölüm riskini, miyokart enfarktüsünü, stent trombozunu birinci nesil ilaç kaplı ve çıplak metal stentlere göre belirgin olarak düşürdüğü gösterilmiştir(10,11). Çok damar hastalarında everolimus kaplı stentlerle sağlanan revaskülarizasyon olgularının cerrahi ile karşılaştırıldığında benzer ölüm riskine sahip olduğu gösterilmiştir(12). Uzun süreli deneyim ve özellikli malzemeler kullanılması günümüzde perkütan tedavi ile tama yakın revaskülarizasyon imkanı sağladığından yüksek SYNTAX skorlu hastalarda da everolimus kaplı stent kullanımının cerrahi ile karşılaştırılması yapılabilir. Son yıllarda yeni ve eski antianjinal ilaçların kullanımı yaşam kalitesinde artış ve semptomların giderilmesi ile KKS olgularının yönetimine büyük katkı sağlamaktadır(13). Antiagregan, antihiperlipidemik, antianjinal ilaçların tek başına ve cerrahi yada perkütan revaskülarizasyona eklenerek çok damar hastalığı ve ≥33 SYNTAX skoruna sahip en riskli KKS popülasyonunda rolü cazip araştırma konusudur. Nitekim yüksek SYNTAX skorlu olgulara cerrahi revaskülarizasyonun önerildiği alışageldiğimiz durum olduğundan cerrahi riski çok yüksek olan durumlarda güvenilir "B planı"nın olması invazif kardiologların en büyük arzusudur(14). Dolayısıyla biz çalışmamızda ≥33 SYNTAX skoruna sahip KKS olgularında tek başına medikal, cerrahi-medikal ve perkütan-medikal tedavi seçeneklerini karşılaştırmayı hedefledik.

2. Gereç ve Yöntemler

Hasta seçimi

Dünyadaki bir çok merkez gibi bizim merkezde de tek damar, düşük riskli yani kısmen "kolay" görülen vakalar kateter laboratuarında en az iki invazif kardiolog tarafından diyagnostik koroner anjiografi (KAG) sonrası değerlendirilerek gerekli ise perkütan revaskülarizasyona geçilir. Ancak çok damar, eşlik eden komorbit durumlar, yüksek SYNTAX skoru ve s. gibi durumlarda kalp takımı ile birlikte değerlendirilme amacıyla olgu konseye sunulur. Konseyin aldığı ortak karar hastaya deklare edilir ve hastanın rızası varsa karar uygulanır. Bu durumda hastaların çoğu doğal olarak konsey kararına uyar. Ancak karara uymayanlar da mevcuttur. Nitekim cerrahi revaskülarizasyonu kabul etmeyen hastalara detaylı bilgi verilerek yüksek riskli perkütan

müdahale önerilir. Hasta perkütan işlemi de kabul etmiyor ise medikal tedavi ile devam edilir. Merkezimizde bu tür hastalar 1. ve 3. aylarda ve ardından rutin 6 aylık aralıklarda takibe çağrılır. Yukarıda belirttiğimiz şekilde çalışan bir merkezde, çalışmamızı gözlemsel çalışma olarak dizayn ettik. Çalışma Eskişehir Osmangazi Üniversitesi Etik Kurulu tarafından onaylandı. Dahil edilen hastaların tamamı Eskişehir Osmangazi Ünversitesi kardiyoloji kliniğinde 1 ocak 2012 ve 31 aralık 2017 yılları arasında yeni ismi ile KKS tanısıyla yapılan KAG sonrasında kalp takımı tarafından değerlendirilmek üzere konseye sunulan hastalaradan oluşmaktadır. Çalışmaya konseye sunulan ve izole cerrahi revskülarizasyon kararı verilen çok damar hastası, ≥33 SYNTAX skoruna sahip olguları dahil ettik. SYNTAX skorlarının hesaplanmasında 4 invazif kardiolog görev edindi. İnvazif kardiologlar iki gruba ayrılıp, birbirinden bağımsız olarak 2018 ESC/EACTS Revaskülarizasyon rehberinde belirtildiği üzere SYNTAX skorlarını hesapladı. Eğer bir olgunun skoru iki gruptan birinde ≤33 bulunmuşsa hasta çalışma dışı bırakıldı. Cerrahi tedaviyi kabul etmeyen hastalara yüksek riskli perkütan tedavi önerilmiş, eğer perkütan tedaviyi de kabul etmemişse sadece medikal tedavi uygulanmış. Böylelikle hastalar cerrahi, perkütan ve medikal tedavi olarak üç kolda çalışmaya dahil edildi. Her iki revaskülarizasyon kolundaki hastalarda kılavuzlara uygun olarak antitrombotik, antihiperlipidemik ve ihtiyaç halinde antianjinal ilaçlar kullanıldı.

Hasta dahil etme ve dışlama kriterleri

Çalışmaya (1)KKS öntanısıyla KAG uygulanan (2) en az 3 epikardiyel koroner arterde ciddi stenoza (≥70%) sahip, (3) SYNTAX skoru ≥33, (4) ejeksiyon fraksiyonu ≥ 40 olan ve (5) kalp takımı tarafından konseyde izole cerrahi revaskülarizasyon önerilen, (6) perkütan revaskülarizasyonda everolimus kaplı stent kullanılan, (7) konseyde kararlaştırılan damarların hepsinin ister cerrahi isterse de perkütan olarak tam revaskülarize edildiği hastalar çalışmaya dahil edildi.

(1) Ciddi sol ana koroner stenozu (≥50%), (2) önceden perkütan veya cerrahi revaskülarizasyon öyküsü, (3)geçirilmiş miyokart enfarktüsü kanıtının bulunması (EKG ve eski kardiyak marker yüksekliği), (4) konjenital kalp hastalığının varlığı, (5) tanı konulmuş ve devam eden malignite, (6)glomerüler filtrasyon hızının(GFH) 50 ml/dk altında olması, (7)fiziksel veya zihinsel sekel bırakmış serebrovasküler olay (SVO) öyküsü dışlama kriterleri olarak belirlendi.

Hasta takibi

Çalışamaya alınan hastaların laboratuar, 2D ekokardiyografi, ilaç , takipte oluşan hastalık bilgileri hastane bilgi sisteminden ve ülkedeki bütün özel ve kamu sağlık kuruluşlarından anlık biriken anamnez, tahlil sonuçları, epikriz, reçete bilgilerini kapsayan medulla eczane ve e- nabız sisteminden elde edilmiştir. Her üç koldaki olgulara antiagregan, antihiperlipidemik ve gerektiği ölçüde antianjinal tedavi verilmiştir. Düzenli ilaç kullanmayan, birinci ay ve birinci yıl sonunda klinik bilgileri olmayan olgular çalışma dışı bırakılmıştır. Hastaların taburculuk ve poliklinik kontrolünde bütün kan değerleri kaydedildi. Yukarıda bahsi geçen bilgi sistemlerinden yararlanılarak birinci ay, birinci yıl takip bilgileri elde edildi. Aynı zamanda son kez 26 şubat 2020'de hastane bilgi sistemi, e-nabız ve medulla eczane sisteminden son ilaç, olay ve ölüm bilgileri toplanmıştır.

Sonlanımlar

Hem kısa (30 günlük) hem de uzun dönem sonlanımlar değerlendirildi. Çalışmamızın birincil sonlanım noktası uzun dönem tüm nedenlere bağlı ve kardiyak nedenli ölüm olarak belirlendi. Miyokart enfarktüsü, tekrar revaskülarizasyon, inme ise ikincil sonlanım noktamızı oluşturdu. Miyokart enfarktüsü index işlemin hemen sonrasında ve takip sırasında MI tanımı kılavuzunda belirtildiği üzere kardiyak marker, EKG değişikliği ve hastanın şikayetinin değerlendirilmesi sonucu tespit edilmiştir(15). Tekrar revaskülarizasyon konseyde ve hemen akabinde hedeflenmiş koroner arterlere tekseferde veya aşamalı işlemlerin tamamlanması sonrasında ihtiyaç duyulan, yani önceden planlanmamış işlem olarak belirlendi. İnme tanısı ise hastanın işlem

sırasında, sonrasında veya takip sırasında nörolog tarafından muayene, cerebral BT veya diffüzyon MR bulguları sonucu konulmuştur.

İstatistiksel analiz

Sürekli veriler Ortalama ± Standart Sapma ve Medyan (Q1 - Q3) olarak verilmiştir. Kategorik veriler ise sıklık ve yüzde (%) olarak verilmiştir. Verilerin normal dağılıma uygunluğunun araştırılmasında Shapiro Wilk testinden yararlanılmıştır. Normal dağılım gösteren grupların karşılaştırılmasında grup sayısı üç ve üzerinde olan durumlar için Tek yönlü varyans analizi (One-Way ANOVA) kullanılmıştır. Normal dağılıma uygunluk göstermeyen grupların karşılaştırılmasında grup sayısı üç ve üzerinde olan durumlar için Kruskal-Wallis H testi kullanılmıştır. Oluşturulan çapraz tabloların analizinde Pearson Ki-Kare ve Pearson Kesin (Exact) Ki-Kare analizleri kullanılmıştır. Analizlerin uygulanmasında IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) programından yararlanılmıştır. İstatistiksel önemlilik için $p<0,05$ değeri kriter kabul edilmiştir.

3. Bulgular

Belirtilmiş zaman aralığında kronik koroner sendrom(KKS) tanısıyla koroner anjiografi(KAG) uygulanmış 820 hastanın görüntüleri izlendikten sonra dahil etme kriterlerini karşılayan 190 hasta seçildi. Ancak başlangıçta PCI koluna dahil edilmiş 22 hasta revaskülarizasyonun everolimus kaplı stentlerle gerçekleştirilmemesi ve tam revaskülarizasyon sağlanamaması nedeniyle çalışma dışı bırakıldı. Böylelikle medikal tedavi(MT) koluna 37 , PCI koluna 30 ve CABG koluna 101 olgu olmakla çalışmaya toplamda 168 hasta alındı. Ancak düzensiz ilaç kullanımı ve kayıp veriler nedeniyle istatistiğe MT kolunda 33, PCI kolunda 24 ve CABG kolunda 79 hasta dahil edildi. Çalışmaya dahil edilme kriterleri oldukça sıkı olduğundan her üç grubun da demografik, laboratuar ve komorbiditeleri arasında belirgin fark görülmedi(Tablo 1.). 1. yıl ortalama EF değerlerinin CABG grubunda diğer iki gruba nazaran daha az düştüğü görüldü. 2. yıl kontrolünde ise bu fark istatistiki öneme ulaşmadı(CABG vs MT P=0,080, CABG vs PCI P=0,089). Hem 1. hem de 2. yıl EF değerleri açısından MT ve PCI kolları arasında fark izlenmedi(p=0,885, p=0,999).

Tablo 1. Grupların temel özellikleri.

	Medikal (n=33)	*PCI (n=24)*	*CABG (n=79)*	*P değeri*
Değişkenler				
Yaş (yıl)	70.25±6.73	68.33±8.91	67.43±9.99	0.086
Erkek, n/%	25/75.8	16/66.7	54/68.4	0.689
VKİ, kg/m^2	25.48±2.17	26.01±2,37	26.52±2.10	0.077
Aile öyküsü, n/%	2/6.1	0/0.0	5/6,3	0.453
Sıgara kullanımı, n/%	2/6.1	2/8.3	11/13.9	0.431
Tıbbi öykü				
HT, n/%	25/75.8	13/54.2	51/64.6	0.231
DM, n/%	17/51.5	12/50.0	34/43.0	0.660
HL, n/%	6/18.2	4/16.7	17/21.5	0.840
KOAH, n/%	1/3.0	4/16.7	6/7.6	0.171
Laboratuvar değerleri				
Hgb(g/dL)	12.76±1,83	12.12±1.57	13.0±1.64	0.087
CrCL(ml/dk)	65.40±13.1	68.81±9.5	71.03±12.1	0.071
Total kolesterol(mg/dL)	178.72±36.66	177.83±35.67	172.21±40.30	0.659
LDL(mg/dL)	123.39±32.22	115.08±41.74	118.47±38.56	0.698
HDL(mg/dL)	41.33±7.77	41.33±9.56	41.94±10.08	0.934
EF(%)	51.51±8.82	50.33±8.71	54.51±8.42	0.088
Syntax 1	34.93±0.65	34.75±0.94	34.64±0.87	0.246

Kısaltmalar; PCI-perkütan koroner müdahale , CABG- koroner arter bypass greft, DM- diabetes mellitus,HT-hipertansiyon, KOAH- kronik obstruktif akciğer hastalığı, VKİ- vücut kitle indeksi, LDL- düşük dansiteli lipoprotein, HDL- yüksek dansiteli lipoprotein, EF-ejeksiyon fraksiyonu.

Tedavi kollarında kullanılan ilaçlardan ACE/ARB, betablokör, kalsiyum kanal blokörü kullanım oranları açısından fark görülmezken (sırasıyla p=0,855, p=0,685, 0,850), statin kullanım oranı CABG kolunda daha düşük saptandı (CABG vs MT p=0,045, CABG vs PCI p=0,050). İstatistiğe dahil edilen hastaların tamamının en az bir antiagregan aldığı görüldü. KAG sonrası bütün hastaların en az 1 sene ikili antiagregan aldığı saptandı. MT tedavi kolundaki olguların %88 oranda nitrat ,%85 oranda trimetazidin ve %68 oranda ise ranolazin aldığı tespit edildi. Antianjinal ilaç kullanımının en az olduğu kol ise CABG kolu olarak belirlendi(CABG vs MT p=<0,001, CABG vs PCI p=0,010, MT vs PCI p=0,024).

Erken Dönem Sonlanımlar

30 günlük takip sırasında MT kolunda serebrovasküler olaya (SVO) rastlanmadı. CABG kolunda 2(%2,53) hastada cerrahi sonrası yoğun bakım sürecinde, PCI kolunda ise 1(%4,16) hastada işlem sırasında SVO görüldü. Erken dönemde akut miyokart enfarktüsü CABG kolunda görülmezken MT kolunda 4(%12,12), PCI kolunda ise 2(%8,33) hastada izlendi. CABG ve MT kolunda ilave revaskülarizasyon yapılmazken, PCI kolunda 2(%8,33) hastaya uygulanmıştır. Erken dönemde CABG kolunda kardiyak ölüm görülmedi. MT ve PCI kolunda ise sırasıyla 2(%6,06), 3(%12,50) hastada kardiyak ölüm gerçekleşti. Tüm nedenlere bağlı mortalite CABG grubunda 5(%6,32) hastada görüldü, bunlardan da 1'i operasyon sırasında, 4 hasta ise yoğun bakım sürecinde kaybedildi. PCI ve MT kollarında ise erken dönemde sadece kardiyak ölüm görüldüğünden tüm nedenlere bağlı ölüm yüzdesi kardiyak ölümlere eşit olmuştur (Tablo 2).

Table 2. 30 günlük sonlanımlar.

	Medikal (n=33)	*PCI (n=24)*	*CABG (n=79)*	*P değeri*
Tüm nedenlere bağlı mortalite ,%	2/6.06	3/12.50	5/6.32	0.040* 0.245** 0.045***
Kardiyak ölüm ,%	2/6.06	3/12.50	0/0	0.040* <0.001** <0.001***
İlave Revaskülarizasyon ,%	0/0	2/8.33	0/0	<0.001* <0.001***
AMİ,%	4/12.12	2/8.33	0/0	0.065* <0.001** <0.001***
SVO,%	0/0	1/4.16	2/2.53	<0.001* <0.001** 0.025***

**PCI vs Medikal, ** CABG vs Medikal , **CABG vs PCI*
Kısaltmalar; AMİ- akut miyokart infarktüsü, SVO- serebrovasküler olay, PCI- perkütan koroner müdahale.

Uzun Dönem Sonlanımlar

Median takip süresi 41, ortalama takip süresi ise 48,25±26,37 ay olarak hesaplandı. Bu süre zarfında CABG kolunda 4(%5,06) olguda SVO görüldü. Diğer iki tedavi koluyla karşılaştırıldığında bu oranın anlamlı derecede daha az olduğu izlendi(CABG vs MT p=0,04, CABG vs PCI p=0,015) . MT ve PCI kolları arasında ise SVO açısından anlamlı fark görülmedi(p=0,65). AMI açısından da CABG kolunun diğer iki koldan belirgin olarak üstün olduğu izlendi(CABG vs MT p=<0,001, CABG vs PCI p=<0,001). MT ve PCI kollarının karşılaştırılmasında ise üstün taraf PCI kolu oldu(p=0,025). MT kolunda AMİ geçiren 13 olgunun sadece 1'i ST elevasyonlu(STEMI) (yüksek lateral MI) olduğu saptandı. STEMI' li bu olgu PCI ve litik tedaviyi kabul etmediğinden 7 gün ikili antiagregan tedavi ve enoksaparin tedavisi sonrasında taburcu edilmiş. PCI kolunda ise 7 olgunun tamamının STEMI olduğu görüldü. CABG kolunda 74(%93,7) olguda LIMA grefti kullanılmıştı. CABG kolunda AMİ geçiren 3 hastanın sadece 1'ının STEMI ile başvurduğu görüldü. AMİ geçirenlerin LIMA grefti kullanılmayan olgular olduğu saptandı.

MT kolunda hiçbir hastaya gerekli olsa dahi kabul etmediğinden ilave revaskülarizasyon uygulanmamıştır. CABG kolunda 5(%6,32) , PCI kolunda ise 10(%41,66) olguya endikasyon nedeniyle ilave revaskülarizasyon uygulanmıştır. Revaskülarizasyon ihtiyacının CABG kolunda PCI koluna nazaran ciddi oranda daha düşük olduğu saptanmıştır(p=<0,001).

Uzun dönemde MT kolunda 18(%54,54), PCI kolunda 12(%50), CABG kolunda ise 12(%15,18) olguda kardiyak ölüm gerçekleşmiştir. CABG kolunun bu açıdan her iki kola nazaran üstün olduğu (CABG vs MT p=0,001, CABG vs PCI p=0,001), PCI ve MT kolları arasındaki farkın ise istataistiki anlama ulaşmadığı saptandı(p=0,085). CABG kolunun üstünlüğü kendini tüm nedenlere bağlı ölümde de gösterdi (CABG vs MT p=0,002, CABG vs PCI p=0,002). MT ve PCI kolları arasında yine istatistiksel fark görülmedi(p=0,065) (Tablo 3).

Table 3. 48.25±26.37(median 42) aylık takip sonlanımları.

	Medikal (n=33)	*PCI (n=24)*	*CABG (n=79)*	*P değeri*
Tüm nedenlere bağlı mortalite ,%	22/66.66	14/58.33	17/21.51	0.065* 0.002** 0.002***
Kardiyak ölüm ,%	18/54.54	12/50	12/15.18	0.085* 0.001** 0.001***
İlave Revaskülarizasyon ,%	0/0	10/41.66	5/6.32	<0.001* 0.001** 0.001***
AMİ,n/%	13/39.39	7/29.16	3/3.79	0.025* <0.001** <0.001***
SVO,n/%	3/9.09	3/12.50	4/5.06	0.065* 0.040** 0.015***

**PCI vs Medikal, ** CABG vs Medikal , **CABG vs PCI*
Kısaltmalar; AMİ- akut miyokart infarktüsü, SVO- serebrovasküler olay, PCI- perkütan koroner müdahale.

4. Tartışma ve Sonuç

Çalışmadan çıkan en önemli sonuçlar: (1) CABG ile yapılan revaskülarizasyon tekbaşına MT ve PCI'a göre 1. yıl sonunda EF'nin korunmasında daha üstün, (2) erken dönemde (30 gün) CABG her iki tedavi koluyla kıyaslandığında daha düşük MI ve kardiyak ölüm oranlarına sahip, (3) uzun dönem takipte CABG seçeneği daha düşük MI, SVO, kardiyak ölüm ve tüm nedenlere bağlı ölüm ile ilişkili bulunmuştur. Bilgimize göre literatürde 3 damar, SYNTAX skoru ≥33 olan olgularda revaskülarizasyon metotları ile tekbaşına medikal tedaviyi karşılaştıran çalışma yoktur. Nitekim bu olgulara revaskülarizasyon ve öncelikle de CABG önerildiğinden herhangi bir hastaya tekbaşına medikal tedavi vererek revaskülarizasyondan mahrum bırakmak tıbbi etiğin bir gereği olarak mümkünsüzdür. Ancak çalışmayı dizayn ederken ilham kaynağımız bu karşılaştırmanın literatürde olmaması değil, hasta işlemi kabul etmezse tekbaşına medikal tedavi veya yeni nesil everolimus kaplı stentlerle yapılan revaskülarizasyonun CABG'ye alternatif olma ihtimalini araştırmaktı. Çalışmanın retrospektif olması bize bu imkanı tanımıştır.

Kronik koroner sendrom olgularında revaskülarizasyonun tekbaşına medikal tedavi ile karşılaştırılması bir çok çalışmaya konu olmuştur. Nitekim Windecker ve ark. yayınladıkları metaanalizde CABG ve yeni jenerasyon ilaç kaplı stentler ile yapılan revaskülarizasyonun tekbaşına medikal tedaviye kıyasla ölüm ve MI riskini azalttığını, bu azalmanın balon anjioplasti , çıplak metal ve birinci nesil ilaç kaplı stentlerle sağlanamadığını rapor etmişler(16). Hızla gelişen revaskülarizasyon yöntem ve araçları ile bu sonuç kabul edilir olsa da , 3 damar hastası ve SYNTAX skoru ≥33 olan olgularda bu faydayı gösteren veriler kısıtlıdır. Bizim çalışma popülasyonumuzu oluşturan bu olgularda erken dönemde MT koluna nazaran PCI kolunda daha çok ilave revaskülarizasyon, SVO, tüm nedenlere bağlı ve kardiyak ölüm görüldü. Uzun dönem takipte bu popülasyonda PCI'ın faydası yine gösterilemedi. Chang ve ark. CABG ve PCI'yı karşılaştıran çok damar hastalarında uzun

dönem sonlanımlar açısından belirgin olarak cerrahinin daha üstün olduğunu belirtmiştir. Özellikle farkın ilk 2 yılda belirgin olmadığı ancak 5 yıllık sağkalıma bakıldığında ibrenin ciddi oranda CABG lehine değiştiği rapor edilmiştir. Ancak primer sonlanım noktası tüm nedenlere bağlı ve kardiyak ölüm olan bu çalışmanın alt grup analizlerine bakıldığında SYNTAX skoru ≥33 olan olgularda CABG ve PCI kolları arasındaki fark istatistiksel anlama ulaşmamıştır(17). Fikrimizce bu fark bu alt gruplardaki olgu sayılarının az olmasına bağlıdır. Bizim çalışmamızda ise CABG ister kısa isterse de uzun dönemde kardiyak ve tüm nedenlere bağlı ölüm açısından PCI' a üstün bulunmuştur. Bu üstünlük erken dönemde tüm nedenler bağlı ölüm hariç MT kolu üzerinde de gösterilmiştir. Nitekim 30 günlük kısa dönemde girişimsel bir tedavinin enfeksiyon, intraoperatif ve yoğun bakım komplikasyonları gibi nedenlerle medikal tedaviye üstünlük sağlayamaması anlaşılandır. Çalışmadan elde ettiğimiz CABG'nin sağkalımı arttırdığı ana bulgusu birçok randomize çalışma ile desteklenmektedir(18-20). Bu açıdan önemli bir yere sahip olan SYNTAX çalışmasının 5 yıllık sonuçlarına göre 3 damar hastalarında CABG ile ölüm, MI, tekrarlayan revaskülarizasyon oranları daha düşük oranda görülmüştür(21). Randomize çalışmaların gücü ve kanıt düzeyi yüksek olsa da bias olabileceği her zaman akılda tutulması gerekir. Bu açıdan retrospektif ve gözlemsel çalışamaların da bu fikri desteklemesi önem arzetmektedir. Weintraub ve ark.(22) büyük ölçekli gözlemsel çalışmada CABG ve PCI arasında 1 yılın sonunda belirgin mortalite farkı olmadığını ancak 4 yılın sonunda CABG'nin belirgin olarak mortalitede fayda sağladığını rapor etmişler. Ancak daha sonra yayınlanan başka bir gözlemsel çalışmada Bangalore ve ark.(8) 2.9 yıllık takipte everolimus kaplı stentlerle yapılan PCI ve CABG'nin ölüm riski açısından benzer olduğunu bildirmiştir. Çalışmamızda everolimus kaplı stent kullanmamıza rağmen, fikrimizce SYNTAX skorunun ≥33, takip süremizin daha uzun ve daha ciddi dahil etme kriterlerimizin olması sonuçları güvenilir kılar ve daha önce vurguladığımız çalışmalarla çelişmemesine neden olmuştur.

Kısa ve uzun dönemde CABG kolunda AMI görülme sıklığı MT ve PCI koluna göre daha az saptanmıştır , bu da daha önceki çalışmaları destekler niteliktedir(17,23). CABG ile yapılan revaskülarizasyonun AMI sıklığını azaltması çok damar ve multidarlık olan damarlarda bütün ciddi darlıklar bypass edildiğinden mantığa uygun bir sonuçtur(24).

Postopertaif SVO CABG'nin önemli komplikasyonudur. Çok damar hastalarında ilaç kaplı stentlerle yapılan revaskülarizasyonda tekrarlayan revaskülarizasyon ve kardiyovasküler olay riskinin CABG'ye nazaran daha yüksek olduğu literatürde sıklıkla vurgulansa da, uzun dönem sağkalım, erken mortalite ve inme ile ilgili çelişkili sonuçlar mevcuttur(25). Athappan ve ark.(26) erken dönemde CABG kohortunda PCI'ya nazaran daha fazla görülen SVO'nun, geç dönemde benzer oranda görüldüğünü rapor etmiştir. Ancak bu iki revaskülarizasyon stratejilerinde erken veya geç dönemde benzer SVO oranlarının olduğu bir çok çalışmada gösterilmişir(17,23,27). Elde edilen bu farklılıkların çalışma dizaynı, alınan hasta özellikleri ve medikal tedavi farklılıklarından kaynaklandığını düşünüyoruz. Bizim çalışmamızda erken dönemde MT kolunda SVO saptanmadı. CABG kolu ise PCI'ya nazaran daha üstün olarak görüldü. Ancak bu erken dönem sonuçlarının az sayıda olay üzerinden ortaya çıktığını belirtmek gerekir. Hem CABG hem de PCI kolundaki SVO'lar işlem kaynaklı gelişmişti. MT tedavi kolunda işlem yapılmadığından bu bulgularla CABG veya PCI'ya tercih edilmelidir sonucu çıkarılamaz. Uzun dönem izlemde SVO açısından CABG her iki koldan üstün olarak görüldü. Biz bu farkın çok damar ve yüksek SYNTAX skorlu olguların EF düşüşü ve iskeminin tetikleyeceği AF kaynaklı olduğunu düşünmekteyiz. Nitekim 1. Yıl sonunda EF düşüşü MT ve PCI kollarında daha fazlaydı.

Çok damar hastalarındaki bir diğer önmeli sorun ise tekrarlayan revaskülarizasyon ihtiyacıdır. Çalışmamızda erken dönemde sadece 2 hastaya stent trombozu nedeniyle tekrarlayan revaskülarizasyon ihtiyacı olmuştur. Ancak CABG kolunda ilave revaskülarizasyon ihtiyacı olmamıştır. Bu tür

riskli popülasyonda yeni nesil ilaç kaplı stentler kullanılsa da tromboz riski her zaman olduğundan sonuç anlaşılandır. Uzun dönem takipte bu revaskülarizasyon ihtiyacının PCI kolunda belirgin olarak fazla olduğu saptandı. Bu sonuç da yine uzun takip süresi olan 3 damar hastalarından oluşan randomize kontrollü çalışmalarda gösterilmiştir(21).

Sonuç olarak CABG, 3 damar ve SYNTAX skoru ≥33 olan olgularda everolimus kaplı stentlerle yapılan PCI ve MT'ye kıyasla uzun dönemde tüm nedenlere bağlı ve kardiyak mortalite, AMI ve SVO açısından daha üstündür.

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Araştırma Makalesi / Research Article

Diabetes Health Promotion Self-Care Scale: Reliability and Validity of the Turkish Version

Diyabet Sağlığını Geliştirme Öz Bakım Ölçeği: Türkçe Formunun Güvenirlik ve Geçerliliği

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Abstract

This study was carried out to put the Diabetes Health Promotion Self-Care Scale for patients with Type 2 diabetes mellitus (DM) into use for nursing and medical literature. The sample of this methodological design research consisted of 620 patients diagnosed with type 2 DM. The data were collected with Personal Information Form and the Diabetes Health Promotion Self-Care Scale. In the validity and reliability stage of the scale, exploratory and confirmatory factor analyzes, and structural equation modeling was used for the item analyzes, internal consistency, and structural validity. The statistical analysis showed that the reliability coefficient of the scale was Cronbach α=0.922. The sub-factors of the Diabetes Health Promotion Self-Care Scale consisting of 27 items and 7 sub-factors were determined as "Interpersonal Relationships", "Blood glucose self-monitoring", "Personal Health Responsibility", "Exercise", "Diet", "Adherence to the Recommended Regime", and "Foot Care". As a result of the analysis, the Diabetes Health Promotion Self-Care Scale was found as a valid and reliable scale to be applied to Turkish society.

Keywords: Diabetes health promotion self-care, instrument development, reliability, validity, type 2 diabetes mellitus

Özet

Bu çalışma, Tip 2 diabetes mellitus (DM) hastalarına yönelik Diyabet Sağlığı Geliştirme Öz Bakım Ölçeği'nin hemşirelik ve tıp literatürüne kazandırılması amacıyla yapılmıştır. Bu metodolojik tasarım araştırmasının örneklemini tip 2 DM tanısı almış 620 hasta oluşturmuştur. Veriler Kişisel Bilgi Formu ve Diyabet Sağlığı Geliştirme Öz Bakım Ölçeği ile toplanmıştır. Ölçeğin geçerlik ve güvenirlik aşamasında, madde analizleri, iç tutarlılık ve yapı geçerliliği için açımlayıcı ve doğrulayıcı faktör analizleri ile yapısal eşitlik modellemesi kullanılmıştır. İstatistiksel analiz, ölçeğin güvenirlik katsayısının Cronbach α=0,922 olduğunu göstermiştir. 27 madde ve 7 alt faktörden oluşan Diyabet Sağlığı Geliştirme Öz Bakım Ölçeği'nin alt faktörleri şu şekilde belirlenmiştir: "Kişilerarası İlişkiler", "Kan şekeri kendini izleme", "Kişisel Sağlık Sorumluluğu", "Egzersiz", "Diyet" olarak belirlenmiştir. ", "Önerilen Rejime Uyum" ve "Ayak Bakımı". Analiz sonucunda Diyabet Sağlığı Geliştirme Öz Bakım Ölçeği'nin Türk toplumu için geçerli ve güvenilir bir ölçek olduğu görülmüştür.

Anahtar Kelimeler: Diyabette sağlığın teşviki ve geliştirilmesi özbakım, araç geliştirme, güvenilirlik, geçerlik, tip 2 diabetes mellitus

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1. Introduction

Diabetes Mellitus (DM) is a serious metabolic disease due to its prevalence and complications (1). DM affects 25% of the world population, and approximately 90% of all diabetic patients are type 2, and 10% are type 1 diabetes patients (2). According to the studies carried out by the Turkish Diabetes Epidemiology project group between 1997 and 1998, diabetes prevalence was 7.2%, and prevalence of prediabetes was 6.7% in our country (3).

Diabetes causes high health costs and complications that affect people in many ways. Individuals' compliance and self-care behaviors constitute 98% of diabetes care for the prevention of complications and diabetes treatment (4). Even though the importance of these behaviors is well-understood by both patients and health professionals, successful implementation of these behaviors is generally not achieved (5,6). Self-efficacy is regarded as the most significant indicator of self-care in between type 2 DM cases. (7).

Self-care is defined to actions which people take for their care within their environmental conditions by Orem (8). Although the term health promotion is not defined in Orem's Self Care Deficit Theory, it is considered as the outcomes achieved through self-care. Protection and promotion of health is an indispensable part of nursing care. Nursing practices, education, and research should clarify the activities for health promotion and ensure their applicability (9).

People with diabetes who encounter complex and challenging activities due to diabetes control generally experience emotional problems, and their quality-of-life decreases (10). Therefore, in diabetes management, in addition to physical issues, psychosocial issues should also be considered (11,12). Health promotion focuses on improving physical and psychosocial well-being. Implementing health-promoting behaviors is a significant strategy for the maintenance and improvement of the quality of life in people who have chronic disabilities (13).

Various instruments have been created to evaluates self-care behaviors that strengthen the health of people with diabetes like the Summary of Diabetes Self-Care Measures (SDSCA) and Self-Care Inventory-Revised (SCI-R) form (14). The recently revised 11-item SDSCA evaluates diet, blood glucose testing, foot care, and smoking behavior (15). SCI-R, on the other hand, is a 14-subject scale which measure people' perceptions of compliance with therapeutics recipes (16). Both SDSCA and SCI-R measure disease control self-care behavior but overlook the measurement of psychosocial health-related self-care behavior. Diabetes Self-Care Scale (DSCS) is another scale that was developed in the USA and adapted to Turkish culture as the Diabetes Self-Care Scale (DSCS) (17). The scale consists of 35 items, including information about diabetes and its complications but ignores the psychosocial situation. The Diabetes Management Self-Efficacy Scale (DHPSC) is recommended as the most appropriate tool for eventual usege in practice and research. The quantification equability over languages, measurement mistake, and responsiveness of this tool is suggested to be evaluated (18). DHPSC, created by Wang et al. for type 2 diabetes mellitus patients, consists of sub-items that question physical activity, nutrition, self-monitoring of blood glucose, adherence to regimens, foot care, personal health responsibility, and interpersonal relationships. The scale is reported to be supplementary in promoting the DM patient’s physical and psychosocial health (19).

Health-promoting behavior is a multi-dimensional model of self-induced activitiess and sensationss that which to resume or improve health. Despite different reinforcement approaches and modern monitoring devices, many people still have challenges with self-management of diabetes (20). Moreover, individual health responsibleness is a major condition to strengthening of DM people (21). Our study aimed to form, examine, and adapt the psychometric resources of the DHPSC developed for individuals with DM.

2. Material and Methods

Research design and sample

The study was performed within a methodological model to improve and test the psychometric properties of the DHPSC developed by Wang et al. (19) for individuals with Type 2 DM and adapt it to the Turkish language.

The population was composed of adult type 2 diabetes patients admitted to a university hospital diabetes polyclinic in Kocaeli between May 2021 and July 2021. The entire population was tried to be reached without performing a sample selection. The data of the study were obtained from voluntary patients with type 2 diabetes on the specified dates.

When adopting a scale to another culture, the case extent for a definitive factor analysis should be at least 5 to 10 times bigger than the number of scale units (22). Based on this suggestion, 620 individuals with Type 2 DM volunteering to take part in our academic work and acknowledged to the survey were inclusived in the study. The response rate was 65.2%. The patients fitting the inclusion criteria were chosen by using a random sampling method. We adopted DHPSC to Turkish culture in three phases: (a) language validity, (b) scale validity, and (c) scale reliability.

The DHPSC has seven behavior dimensions: diet, exercise, blood glucose self-monitoring, adherence to recommended regimens, foot care, interpersonal relationships, and personal health responsibility.

Data collection

The data were collected between May 2021 and July 2021 after obtaining written and verbal consent from volunteer participants with diabetes by filling out the forms together. It took about 5-7 minutes to proper all the data collection form. The Personal Information Form and the DHPSC were used for data collection.

Instruments

The personal information form: It includes 4 socio-demographic questions as age, gender, marital status, educational status, and 3 questions regarding essences of the illness, including duration of diabetes, treatment method in diabetes, and body mass index.

Diabetes Health Promotion Self-Care Scale: DHPSC was improved by Wang et al. in 2012 and includes 7 parts as diet (three items), exercise (three items), blood glucose self-monitoring (five items), adherence to the recommended regime (three items), foot care (two items), interpersonal relationships (seven items) and personal health responsibility (five items). The DHPSC scale is a 28-item scale with seven behavioral dimensions. The scale has a 5-point assessment, ranging from ‘always’ (5 points) to ‘never’ (1 point). High scores indicate that health care behaviors were better. The Cronbach alpha reliability coefficients of the scale and its sub-factors were found to be α=0.922, and α=0.689-0.925, respectively (Table 1).

Table 1. Correlations and Cronbach α values for the Sub-Factors of the DHPSC

r (p)*		Interpersonal Relationships **(Factor 1)**	Blood Glucose Self-Monitoring **(Factor 2)**	Personal Health Responsibility **(Factor 3)**	Exercise **(Factor 4)**	Diet **(Factor 5)**	Adherence to the Recommended Regimens **(Factor 6)**	Foot Care **(Factor 7)**	**Cronbach α**
Factor 1	r	-	0.264	0.371	0.208	0.242	0.266	0.325	0.896
	p		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Factor 2	r		-	0.579	0.359	0.548	0.374	0.375	0.831
	p			**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Factor 3	r			-	0.298	0.514	0.374	0.415	0.856
	p				**<0.001**	**<0.001**	**<0.001**	**<0.001**	
Factor 4	r				-	0.465	0.122	0.332	0.925

	p	**<0.001**	**0.002**	**<0.001**	
Factor 5	r	-	0.358	0.403	0.689
	p		**<0.001**	**<0.001**	
Factor 6	r		-	0.248	0.893
	p			**<0.001**	
Factor 7	r			-	0.886
	p				

**: Pearson correlation analysis*

Subfactors of the scale

Factor 1- Interpersonal Relationships: The interpersonal relationships section consists of 7 items that show positive communication and sharing with the family and the people around you.

Factor 2 - Blood Glucose Self-Monitoring: There are 5 items in this section that examine the adaptation of knowledge, attitudes, and behaviors regarding the measurement of blood glucose and urinary glucose levels to social life and preventing hypoglycemia during exercise.

Factor 3 - Personal Health Responsibility: Personal health responsibility sub-factor includes 5 items as attitudes and behaviors in situations that require consultation, interest in training programs, and blood glucose monitoring.

Factor 4 – Exercise: The exercise section has 3 items that question compliance with the exercise program.

Factor 5 – Diet: It consists of 3 items, including knowledge, attitudes, and behaviors related to diet.

Factor 6 - Adherence to the Recommended Regimens: In this section, two items question the correct use of the prescribed drugs.

Factor 7 - Foot Care: This section consists of 2 items as foot care practices and shoe/socks selection.

Based on these seven factors, items loaded on each factor were added as individual scores of diabetics and sub-factors were created.

Language validity

In the first phase, three independent translators who can speak English translated the scale into Turkish. Then, the researchers examined the translations and formed a single version. In the next step, the translation of the scale back to English was done by three expert trainers in the concerned area and are competent in both languages fine. The first shape of the scale and its back translation were compared and each of unıt were analysed. Finally, the Turkish version of the scale was finished since there was no gap in the accessibility of the scale items.

Analysis

Statistical evaluation was done with IBM SPSS 20.0 (IBM Corp., Armonk, NY, USA) and Linear Structural Relationships package programs (LISREL v8.8, Inc. SSI. Lincoln, IL, USA). The compliance of numerical variables to normal distribution was evaluated with the Kolmogorov-Smirnov Test. Numerical variables were given as median (25.-75.) and frequency (percentages). To evaluate the language comprehensibility of the scale questions, it was first translated into Turkish, and then back to English, which was the original language, and sent to the expert who developed the scale to get an opinion. For the clearness of the questions, the Pearson correlation coefficient was calculated for test-retest reliability performed at two-week intervals. For the internal consistency of the DHPSC and sub-factors, Cronbach α coefficient was calculated separately. Exploratory Factor Analysis was conducted to test the validity of the scale's structure in Turkish culture. To determine the factors and, appropriate factors, the principal components analysis method and the Varimax factor rotation method were performed, respectively. The suitability of the sample was tested with the Kaiser-Meyer-Olkin coefficient. The Bartlett's Sphericity Test was used for the suitability of the data for factor analysis. The criteria to retain all the factors with

Eigenvalues greater than 1 (Kaiser Criterion) was used. The compatibility of the sub-factors with the original variables was measured using Confirmatory Factor Analysis. To check the newly created constructive model, the Structural Equation Modeling (SEM) method was used. The relationship between the sub-factors of the DHPSC's was calculated by Pearson's correlation coefficient. $p<0.05$ was considered sufficient for statistical significance in two-way tests.

3. Results

Sample characteristics

The sociodemographic aspects of the patients are given in Table 2.

Table 2. Disease-related characteristics and The DHPSCsub-factor and total score averages (n=620)

Characteristics	n	%
Gender		
Female	412	66.5
Male	208	33.5
Marital Status		
Married	486	78.4
Single	134	21.6
Education level		
Illiterate	49	7.9
Literate	59	9.5
Elementary school	289	46.6
High school	133	21.5
Associate /Undergraduate Degree	90	14.5
Duration of diabetes		
Less than 1 year	64	10.3
1-5 years	158	25.5
6-10 years	197	31.8
11-20 years	144	23.2
21 years and over	57	9.2
Diabetes treatment type		
Diet	41	6.6
OAD	265	42.7
Insulin	212	34.2
OAD and Insulin	75	12.1
Alternative Treatments	3	0.5
Body Mass Index		
No treatment	24	3.9
Underweight	3	0.5
Normal weight	106	17.1
Overweight	511	82.4
Total	620	100.0
	Median	**Percentiles**
The DHPSC Sub-Factors		25. percentile / 75. percentile
Interpersonal Relationships	29.00	25.25 / 33.00
Personal Health Responsibility	19.00	15.00 / 21.75
Diet	10.00	7.00 / 12.00
Exercise	6.00	3.00 / 9.00
Foot Care	7.00	5.00 / 9.00
Blood glucose self-monitoring	17.00	13.00 / 21.00
Adherence to the Recommended Regime	10.00	8.00 / 10.00
Total Scale Score	96.00	84.00 / 109.00

OAD: Oral Antidiabetic; DHPSC: Diabetes Health Promotion Self-Care Scale

Reliability analysis

Cronbach's α inner consistence coefficient technique is performed to examine the reliability of Likert-type scales. The Cronbach's α coefficient was determined for DHPSC. The item-total correlation coefficients were explored for the relationship

between the scores in the DHPSC test items and the total score of the test. In this study, Cronbach that evaluates the inner consistency value of the scale was found to be α=0.922. It was determined that the scale was sufficient to protect and enhance the health of individuals with DM, to evaluate personal care behaviors comprehensively, and the inner consistence of the scale was ensured.

Validity analysis

Exploratory Factor Analysis (EFA) was applied to test the validity of the DHPSC. As a result of the EFA, a structure explaining 72.66% of the total variance of the data structure used in the scale consisting of seven factors and 27 items emerged. The Kaiser-Meyer-Olkin index was determined to be 0.89, supporting the suitability of the data for factor analysis. Bartlett's sphericity test was found to be significant ($\chi 2=10851.575$; $p<0.001$). The principal components method and the Varimax factor rotation method were utilized to determine the factors and the appropriate factors, respectively. It was seen that the scale has 7 sub-factors to show the DHPSC in patients. The rotated factor loads matrix is presented in Table 3.

Table 3. Factor Matrix Loads According to the Varimax Rotation Method (AFA)

Items	Interpersonal Relationships (Factor 1)	Blood Glucose Self-Monitoring (Factor 2)	Personal Health Responsibility (Factor 3)	Exercise (Factor 4)	Diet (Factor 5)	Adherence to the Recommended Regimens (Factor 6)	Foot Care (Factor 7)
Item 1	0.727						
Item 2	0.787						
Item 3	0.837						
Item 4	0.835						
Item 5	0.793						
Item 6	0.757						
Item 7	0.638						
Item 21		0.821					
Item 22		0.824					
Item 23		0.780					
Item 24		0.823					
Item 25		0.637					
Item 8			0.796				
Item 9			0.808				
Item 10			0.773				
Item 11			0.420				
Item 12			0.574				
Item 16				0.854			
Item 17				0.912			
Item 18				0.900			
Item 13					0.820		
Item 14					0.844		
Item 15					0.622		
Item 26						0.871	
Item 27						0.881	
Item 19							0.809
Item 20							0.781
Exploratory percentage (%)	33.75	12.23	8.47	5.42	4.95	4.06	3.78

EFA: Exploratory Factor Analysis

Confirmatory factor analysis

Confirmatory factor analysis was used to test the appropriateness of the structure explained by the exploratory factor analysis. Based on the Confirmatory Factor Analysis, a structural equation model of 7 sub-factors emerged. The fit measures that were used to examine the validity of the Structural Equation Model were root mean square error of approximation (RMSEA)=0.072 (CI 95%=0.068; 0.076), AGFI=0.83, GFI=0.87. These results support the validity of the model. The 7 sub-factors were named "Interpersonal relationships, Personal health responsibility, Diet, exercise, Footcare, Blood glucose self-monitoring, and Adherence to the recommended regimens" (Figure 1).

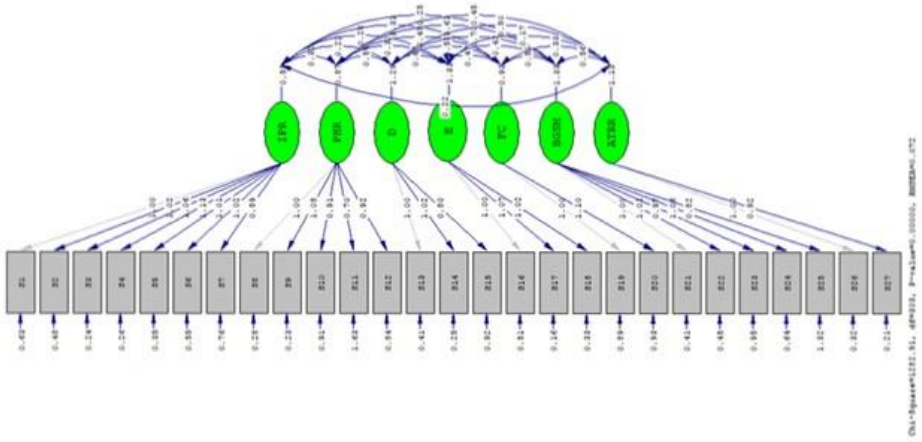

Figure 1. The Structural Equation Model of Diabetes Health Promotion Self-Care Scale

Sub-Factors: Fac 1- IPR: Interpersonal Relationships; Fac 2- BGSM: Blood Glucose Self-Monitoring; Fac 3- PHR: Personal Health Responsibility; Fac 4- E: Exercise; Fac 5- D: Diet; Fac 6- ATRR: Adherence to the Recommended Regimens; Fac 7- FC: Foot Care

The DHPSC items, subfactors and item statistics, total scale scores, and subfactor scores are shown in Table 4.

Table 4. Diabetes Health Promotion Self-Care Scale Items and Item Statistics

Factor	Our Study	Mean	SD	Item Correlations TSS	SFS
Interpersonal Relationships **(Factor 1)**	1. Spend time with intimate friends.	3.85	1.08	0.414	0.761
	2. Find ways to satisfy the needs of intimate relationships.	4.07	1.02	0.402	0.762
	3. Keep in touch and communicate with people about whom you are concerned.	4.30	0.92	0.455	0.780
	4. Maintain meaningful relationships with other people.	4.13	0.98	0.500	0.822
	5. Express care, love, and warmth to others.	4.20	0.95	0.447	0.768
	6. Praise the strength and virtues of other people.	4.01	1.05	0.437	0.773
	7. Resolve conflicts with others through discussion and negotiation when having.	3.95	1.09	0.460	0.700
Blood Glucose Self-Monitoring **(Factor 2)**	21. Measure blood glucose or urine glucose according to the suggestions of healthcare providers.	3.69	1.31	0.656	0.848
	22. Increase the frequency of testing blood glucose or urine glucose when feel uncomfortable.	3.71	1.34	0.651	0.849
	23. Write down the results of each blood glucose or urine glucose testing.	3.06	1.48	0.631	0.841
	24. Check the blood glucose or urine glucose as usual even when away from home.	3.29	1.46	0.678	0.875
	25. Prevent hypoglycemia according to suggestions of healthcare providers when exercising.	3.04	1.49	0.649	0.754
Personal Health Responsibility **(Factor 3)**	8. Discuss personal health issues with healthcare providers (not only limited to diabetes.	4.05	1.07	0.585	0.768
	9. Report healthcare providers any unusual signs or symptoms (not only limited to diabetes).	3.99	1.12	0.619	0.803
	10. Discuss with healthcare providers about their suggestions when not clearly understood.	3.51	1.27	0.549	0.795
	11. Consult healthcare providers about methods of practicing self-care (not only limited to diabetes).	2.89	1.43	0.552	0.697
	12. Actively visit the doctor when blood glucose is not well controlled.	3.72	1.25	0.636	0.762
Exercise **(Factor 4)**	16. Keep exercising regularly.	2.55	1.34	0.540	0.934
	17. Push self to exercise even though feeling lazy.	2.26	1.29	0.503	0.936
	18. Find time to exercise even on busy schedule.	2.16	1.30	0.480	0.908
Diet **(Factor 5)**	13. Follow the rules of diet control for diabetes when having a meal out or in an unfamiliar setting.	3.25	1.30	0.622	0.895
	14. Follow the rules of diet control when having meals.	3.34	1.26	0.633	0.914
	15. Make sure to substitute foods within the same category.	3.14	1.32	0.672	0.825
Adherence to the Recommended Regimens **(Factor 6)**	26. Take diabetic medicine on time even when out..	4.24 4.40	1.201.	0.482	0.969
	27. Take medications at the prescribed times.		07	0.466	0.886
Foot Care **(Factor 7)**	19. Wear appropriate shoes and socks when out or traveling.	3.64	1.34	0.510	0.846
	20. Perform self-examination of feet or apply foot cream according to suggestions of healthcare providers	3.10	1.43	0.543	0.890

SD: Standard Deviation; TSS: Total Scale Score; SFS: Sub-Factors Score

Table 5. DHSC Items and Item Statistics

English Version (Wang et al. 2012) Factor	Items	**Turkish Version** Factor	Items
Interpersonal relationships	1. Spend time with intimate friends 2. Find ways to satisfy the needs of intimate relationships 3. Keep in touch and communicate with people about whom you are concerned 4. Maintain meaningful relationships with other people 5. Express care, love, and warmth to others 6. Praise the strength and virtues of other people 7. Resolve conflicts with others through discussion and negotiation when having	**Kişilerarası İlişkiler** (Faktör 1)	1. Yakın arkadaşlarıma zaman ayırırım. 2. Yakınlarımın ihtiyaçlarını karşılamak için yollar bulurum. 3. Değer verdiğim kişilerle temas ve iletişim halinde olurum. 4. İnsanlarla anlamlı ve doyumlu ilişkiler sürdürürüm. 5.Diğer insanlara özen, sevgi ve sıcaklık gösteririm. 6. Diğer insanların güçlü ve erdemli yönlerine övgüde bulunurum. 7. Başkalarıyla yaşanan çatışmaları konuşarak ve uzlaşarak çözerim.
Blood glucose self-monitoring	21. Measure blood glucose or urine glucose according to the suggestions of healthcare providers 22. Increase the frequency of testing blood glucose or urine glucose when feel uncomfortable 23. Write down the results of each blood glucose or urine glucose testing 24. Check the blood glucose or urine glucose as usual even when away from home 25. Prevent hypoglycemia according to suggestions of healthcare providers when exercising	**Kendi Kendine Kan Şekeri Takibi** (Faktör 2)	21. Sağlık ekibi önerilerine göre kan şekeri ya da idrar şekeri ölçerim. 22. Rahatsız hissettiğimde kan şekeri ya da idrar şekeri ölçüm sıklığımı arttırırım. 23. Her ölçtüğüm kan şekeri ya da idrar şekeri sonuçlarımı kaydederim. 24. Evden uzakta olduğum durumlarda bile kan şekeri ve idrar şekeri takiplerime her zamanki gibi devam ederim. 25. Sağlık ekibi üyelerinin önerilerine göre egzersiz sırasında hipoglisemiyi önlerim.
Personal health responsibility	8. Discuss personal health issues with healthcare providers (not only limited to diabetes) 9. Report healthcare providers any unusual signs or symptoms. (not only limited to diabetes) 10. Discuss with healthcare providers about their suggestions when not clearly understood 11. Consult healthcare providers about methods of practicing self-care (not only limited to diabetes) 12. Actively visit the doctor when blood glucose is not well controlled	**Kişisel Sağlık Sorumluluğu** (Faktör 3)	8. Sağlık ekibi üyelerine kişisel sağlık sorunlarımı danışırım. 9. Herhangi bir olağandışı belirti ve bulguyu sağlık ekibi üyelerine bildiririm. 10. Net olarak anlaşılamayan durumlar hakkındaki önerilerimi sağlık ekibi üyeleri ile tartışırım (konuşurum). 11. Bireysel sağlık bakımı ile ilgili sağlık ekibinin verdiği eğitim programına katılırım. 12. Kan şekeri kontrolü iyi olmadığında düzenli olarak doktora muayene olurum.
Exercise	16. Keep exercising regularly 17. Push self to exercise even though feeling lazy 18. Find time to exercise even on busy Schedule	**Egzersiz** (Faktör 4)	16. Düzenli egzersiz yaparım. 17. Tembel hissettiğim anlarda bile kendimi egzersiz yapmaya zorlarım. 18. Yoğun programlarda bile egzersiz için zaman ayırırım.
Diet	13. Follow the rules of diet control for diabetes when having a meal out or in an unfamiliar setting 14. Follow the rules of diet control when having meals 15. Make sure to substitute foods within the same category	**Diyet** (Faktör 5)	13. Dışarda veya yabancı ortamda yemek yenildiğinde diyet kuralarını takip ederim. 14. Öğünlerde diyet kontrol kurallarına uyarım. 15. Aynı grupta birbirinin yerine geçebilen kuralları iyi bilirim.
Adherence to the recommended regimens	26. Take diabetic medicine on time even when out 27. Take medications at the prescribed times 28. Take prescribed doses of medication	**Önerilen Rejime Uyma** (Faktör 6)	26. Dışarıdayken bile diyabet ilaçlarını düzenli alırım. 27. İlaçları reçete edilen zamanlarda alırım. **28. madde ölçekten çıkarıldı.**
Foot care	19. Wear appropriate shoes and socks when out or traveling 20. Perform self-examination of feet or apply foot cream according to suggestions of healthcare providers	**Ayak Bakımı** (Faktör 7)	19. Dışarıda ya da seyahat sırasında uygun ayakkabı ve çorap kullanırım. 20. Sağlık ekibi üyelerinin önerilerine göre ayaklarımı kendi kendime muayene ederek krem uygularım.

The relationship between the DHPSC subfactors was determined using the Pearson correlation factor, and a significant relationship between each of the subfactors was observed in table 1 ($p<.001$). Table 1 also gives Cronbach α values demonstrating the contribution of subfactors to the scale. The contribution of the "Diet" sub-factor to the scale was found lower compared to other sub-factors.

Original scale subfactors and Turkish version scale subfactors and items are given in Table 5.

4. Discussion and Conclusion

The DHPSC can significantly contribute to the assessment of certain aspects of patients' health promotion self-care behaviors by nurses and to make particular interference for individuals with DM after this assessment (19). The scale includes 7 critical issues that individuals with diabetes should pay attention to in their self-care. It consists of 7 independent parts, and each question is short, concise, and understandable, so the implementation period is short. Individuals with diabetes can apply the scale themselves without the help of any healthcare staff.

DHPSC scale consists of 7 parts as diet (three items), exercise (three items), blood glucose self-monitoring (five items), adherence to recommended regimens (three items), foot care (two items), interpersonal relationships (seven items), and personal health responsibility (five items).

In this study, the Turkish validity and reliability of the scale improved by Wang et al. (19) were tested to determine the health-promoting self-care behavior of individuals with diabetes to present the Turkish literature a scale that can reveal accurate, consistent, and valid data. The data were collected from the sample of individuals with Type 2 DM admitted to a public university hospital, and analysis studies were conducted on these data. The conclusions provided a significant idea about the diabetes self-management of patients. However, the lack of a sufficient few studies in which the validity and reliability of DHPSC were conducted to evaluate the health promotion self-care behaviors of individuals with Type 2 DM made it challenging to discuss the findings in detail.

This part handles the evidence of the study performed to test the reliability and validity of the "DHPSC" under the following headings:

Discussion of the results on the reliability of the DHPSC

The reliability of the DHPSC was found as Cronbach $\alpha=0.922$, which shows that this is a highly reliable scale to measure diabetes self-management in individuals with Type 2 DM. While the Cronbach α value was found to be 0.88 in the study of Wang et al. (19), it was determined as 0.71 in a cross-sectional study (n=304) in which Nie et al. (23) examining disease perception, risk perception, and health promotion self-care behaviors in Chinese patients with type 2 DM. Consistent with the literature studies, the reliability of this study was determined to be high. The reliability values of the sub-factors in the study of Wang et al. (19) and in this study were determined as follows respectively; the sub-factor of "Interpersonal Relationships" was $\alpha=0.90$, in this study $\alpha=0.896$; the sub-factor of "Blood Glucose Self-Monitoring" was $\alpha=0.84$, in this study $\alpha=0.831$; the sub-factor of "Personal Health Responsibility" $\alpha=0.80$, in this study $\alpha = 0.856$; the sub-factor of "Exercise" $\alpha=0.94$, in this study $\alpha = 0.925$; the sub-factor of "Diet" $\alpha=0.90$, in this study $\alpha=0.689$; the sub-factor of "Adherence to the Recommended Regime" was $\alpha=0.78$, in this study, $\alpha=0.893$; the sub-factor of "Foot Care" could not be determined among the individuals study, $\alpha=0.886$ in this study. In the study of Nie et al. (23), the alpha reliability coefficient ranged between 0.64 and 0.93.In the study conducted by Wang et al. (19), the reliability of the "Foot Care" sub-factor could not be determined, the "Adherence to the Recommended Regime" factor was determined to be $\alpha=0.78$, and in our study the "Diet" sub-factor was $\alpha=0.689$.It is emphasized that patients with diabetes who can follow dietary self-care advice generally have better glycemic control, resulting in less diabetic complications. However, it is emphasized that it is challenging to motivate

patients to achieve self-care behaviors with diet and requires ongoing efforts between patients and a multidisciplinary team (24). Relevant studies noted that the compliance of individuals with diabetes to dietary recommendations is not at the desired level (24,25). In parallel to the literature (24,25), it was determined in this study that 6.6% of individuals with diabetes were on a diet, and the median of "diet" mean score was lower than the other sub-factors. In our study, the findings related to diet in Table 2 are thought to have an effect on the low alpha reliability coefficient obtained in the "diet" sub-factor. However, since the "diet" sub-factor is a significant therapeutic approach in promoting health in individuals with diabetes, it was not excluded from the scale despite its low alpha reliability coefficient. It can be said that obtaining low alpha reliability coefficients for different sub-factors in the study of Wang et al. (19) and our study is due to the treatment approaches used by patients in the treatment of diabetes, the cultural differences of countries, and the number of different samples included in the studies.

Discussion of the results on the validity of the DHPSC

For the structural validity of the scale, EFA analysis was performed for the data belonging to the patient group. As a outcome of the analysis, 7 sub-factors emerged, which was consistent with the original scale. The "Adherence to the Recommended Regime" sub-factor in the original scale consists of 3 items (items 26, 27, and 28). However, the 28th item "Take prescribed doses of medication" was removed in our study because its contribution to the scale was very low. Oral antidiabetic drug (OAD) treatment is the main treatment method used especially in the early phases of diabetes management in individuals with type 2 diabetes whose insulin secretion ability has not yet been exhausted (26,27). The effectiveness of the treatment depends on the individual's adherence to drug treatment. Adherence to drug treatment includes the patient's adherence to medical recommendations, believing and accepting the treatment, taking responsibility for his/her own treatment, participating in treatment-related training if necessary, performing his/her treatment properly and on time, and attending regular health checks. However, the literature on oral drug use in individuals with diabetes has reported that patients confuse their medications, take medication at the wrong dose or at the wrong time, stop using the medication on their own, and make mistakes such as using non-prescription medication (28,29).This study determined that 42.7% of individuals with diabetes used OAD, and the average score of "Adherence to the Recommended Regime" was lower than other sub-factors (Table 2). The reason why item 28 was excluded from the scale in our study was the inability of diabetic individuals to comply with the "Take prescribed doses of medication" item due to their education levels or to perform them adequately. However, it was determined that the items belonging to other sub-factors were collected under the same factors as the items designed in the original scale (Table 5).

As a result of the EFA applied to determine the structural validity of the DHPSC, it was seen that the scale was in the form of a structure that explained 72.66% of the total variance. In EFA, the scale was divided into 7 sub-factors named "Interpersonal Relationships", "Blood Glucose Self-monitoring", "Personal Health Responsibility", "Exercise", "Diet", "Adherence to the Recommended Regime" and "Foot Care". The explanatoriness of the variances of the sub-factors were 33.75%, 12.23%, 8.47%, 5.42%, 4.95%, 4.06%, and 3.78%, in turn. All the questions contribute significantly to the whole scale. This result shows that the data structure is suitable for factor analysis. Similar to our study, in the study of Wang et al. (19), the scale was also divided into 7 sub-factors. The authors named the sub-factors "Interpersonal Relationships", "Blood Glucose Self-monitoring", "Personal Health Responsibility", "Exercise", "Diet", "Adherence to the Recommended Regime" and "Foot Care". The explanatoriness of the variances of the sub-factors were found as 21.30%, 16.81%, 27.04%, 38.44%, 39.69%, 9.30%, and 68.89%, respectively. In the study conducted by Wang et al. (19) on Taiwanese patients (n=489), it was determined that the

"Foot Care" subfactor made the highest contribution to the scale, and in our study, it was the "Interpersonal Relations" The results show that Taiwanese patients with Type 2 diabetes regarded "foot care" behavior as essential in health promotion self-care behavior, and our study "interpersonal relationships" behavior. The difference between Wang et al.'s (19) study and our study on the item that made the highest addition to the scale may have resulted from the health system of countries and the cultural differences of the patients and countries included in the sample. In a relevant study, health promotion behavior is stated to be affected by culture (30), so DHPSC should be evaluated for use in different countries.

Structural Equation Modeling is an analysis that explores the addition of sub-factors developed by confirmatory factor analysis to the model and verifies the findings (31,32). When the validity of the model confirmed for the DHPSC was tested with compliance criteria, it was determined that the factor structure that emerged in the applied structural equation model was compatible according to the results of the factor analysis. Fit measures of the DHPSC's Structural Equation Model were found as RMSEA=0.072 (CI 95%=0.068; 0.076) AGFI=0.83 and GFI=0.87, and the results reveal that the model is a scale that can be utilized to determine self-care management in patients with Type 2 diabetes.

Study Limitations

The study evaluates only the data of patients admitted to a university hospital diabetes outpatient clinic. It does not include the health-promoting self-care habits of patients who apply to private centers.

5. Conclusion

It is concluded in the study that DHPSC was a valid and reliable scale to be applied to Turkish society. Nurses can apply the DHPSC to evaluate the health promotion self-care behaviors of patients with Type 2 diabetes, and they can provide effective interventions to promote the habits of patients with Type 2 diabetes.

However, for the validity and reliability of the scale, further comprehensive studies on different sample groups (such as state, university, private hospitals, private diabetes centers), in different countries and cultures are required.

Declarations

Ethics approval and consent to participate: For the scale to be used in this study permission was obtained from the author "Ruey-Hsia Wang" and necessary revisions were made according to the suggestions. Ethics committee approval was procued from the Kocaeli University Non-Interventional Clinical Research Ethics Committee on 02.05.2021 with the decision number GOKAEK-2021/9.14, 2021/164. It was conducted between May and July 2021 after obtaining the permissions from Kocaeli University Research and Training Hospital, where the research was conducted. All the participants have been reported permission previous to their involvement to the study.

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Olgu Sunumu / Case Report

Bilateral Incus Body Pneumatization

Bilateral İnkus Gövdesinde Pnömotizasyon

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Abstract

Embryological development of middle ear ossicles is a complex process and congenital abnormalities and variations are very rare. Therefore, adding new knowledge to this conditions is highly important. This case report describes a rare case of variation consisting of bilateral pneumatization in the incus body in a patient with left-sided mixed-type hearing loss. These incus variations were detected incidentally during the examination performed for an otological problem. This paper discusses the possible embryological mechanism for the occurrence of this rare incus variation and its significance.

Keywords: middle ear, variation, middle ear ossicles, incus, computed tomography

Özet

Orta kulak kemikçiklerinin embriyolojik gelişimi karmaşık bir süreçtir ve konjenital anormallikler ve varyasyonlar çok nadirdir. Dolayısıyla bu durumda yeni bilgilerin eklenmesi son derece önemlidir. Sol tarafta mikst tip işitme kaybı yakınması ile başvuran her iki inkus gövdesinde pnömotizasyon şeklinde nadir bir varyasyonu bulunan olgu sunulmaktadır. Bu inkus varyasyonu otolojik problem için yapılan muayenede tesadüfen tespit edildi. Bu yazı, bu nadir inkus varyasyonunun oluşumu için olası embriyolojik mekanizmayı ve önemini tartışmaktadır.

Anahtar Kelimeler: orta kulak, varyasyon, orta kulak kemikçikleri, inkus, bilgisayarlı tomografi

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1. Introduction

The malleus, incus and stapes are the smallest bones in the body. They are arranged in the middle ear in this order and ensure that the sound is transmitted mechanically from the outer ear to the inner ear. The incidence of ear malformations is approximately 1 per 15 000 in newborns1. Goldenhar syndrome, Treacher Collins syndrome, branchio-auto-renal syndrome, prenatal infection, and drug use during pregnancy are associated with malformation in the ossicles2. Isolated congenital ossicular malformations are even rarer1. Stapes malformation is reported to be the most common ossicular anomaly, while malformations including incus are among the rarest cases described3. In the postpartum period, cholesteatoma, chronic otitis media, and trauma may also cause ossicular deformity4.

In this report, we present a patient, who, rather than having a malformation or deformity, had pneumatization in the incus body, which can be defined as a normal developmental variation. In a recently published case report, a similar appearance located at the incus body was reported, however it was evaluated as pneumatization5. To our knowledge, the literature contains no other similar case. The aim of publishing this case report was to ensure that this appearance, whether defined as a pneumatization, is known as a variation and no invasive procedure is performed in patients with this variation.

2. Case report

A 27-year-old male patient presented to the hospital with progressive left-sided hearing loss that had started 18 months earlier. The patient had no other symptoms, such as otalgia and ear discharge. The otoscopic examination showed a normal ear canal and intact tympanic membrane. There was no history of ear disease, otologic surgery, significant head trauma, or family history of hearing loss. The audiogram revealed a left-sided moderate mixed-type hearing loss.

Further investigation was performed with high-resolution computed tomography (HRCT) of the temporal bone, which showed no otological pathology that would indicate the reason for the hearing loss. However, it demonstrated bilateral pneumatization of incus bodies (Figure). No personal information of the patient were used in the case report. Therefore no consent was obtained.

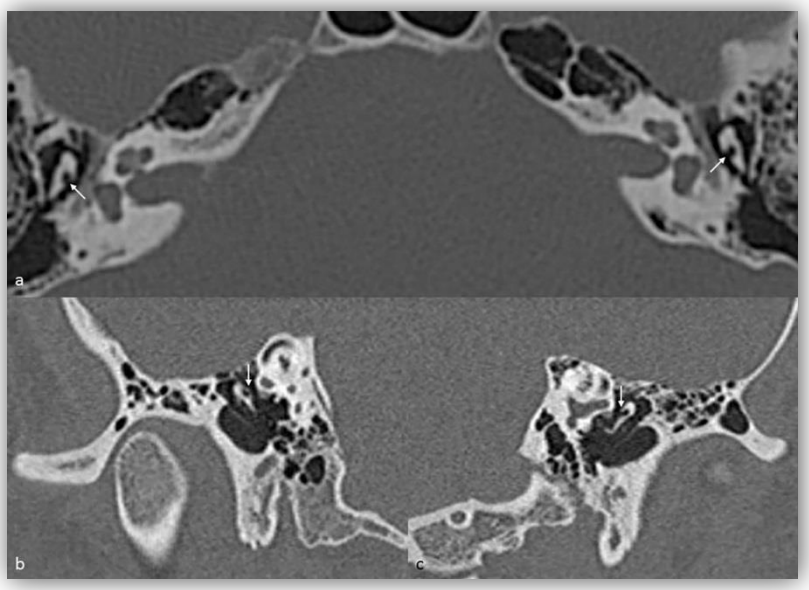

Figure. Axial (a) and coronal oblique (b and c) reconstructed high-resolution computed tomographic images showing bilateral cleft formation in the incus body (arrows).

3. Discussion

In a study in which the variations and clinical significance of middle ear ossicles were evaluated, the most frequent variation was found in the stapes followed by the malleus, and the least variation was observed in the incus. In the incus, the triangular shape of the long process accompanying the small body and a small notch in the short process were detected6. In a case report of Bhatt et al.5, pneumatization was observed in the incus body, as in the current case. The authors considered that this pneumatization detected in the incus was most likely a developmental variation5.

The embryological development of the middle ear is a complex process. The skeletal elements of the middle ear have been claimed to develop from the mesenchyme of the first two branchial arches. Although many different hypotheses have been postulated, in general it is well accepted that the first branchial arch forms the bodies of the malleus and incus above the neck of these ossicles, while the second branchial arch forms the parts of the ossicles below the neck of the malleus and the body of the incus, including the crura of the stapes, which grow to merge with the stapes footplate, the lenticular process and long process of the incus, and the manubrium of the malleus, which is induced separately. With further development, the ossicles first separate from the remainder of the arch cartilages, and then join to form the ossicular chain. The cartilaginous ossicles grow only throughout the first half of intrauterine life, and then ossify, each from a single center. The center for the incus appears at the 16th fetal week, the center for the malleus at the mid-16th fetal week, and that of the stapes at the 18th fetal week7.

While there is chondrogenesis in the ossicles, the entire middle ear is filled with soft tissue consisting of the mesenchyme derived from the neural crest and a single layer of endodermal epithelium that runs along the inner surface of the tympanic membrane and along the ventral areas of the soon-to-emerge middle ear cavity. This mesenchyme regresses and leaves the ossicles suspended in air8. It can be considered that the small airspaces in the primitive bone marrow cavities in the incus and malleus allow for the migration of the mesenchyme to the ossicles, thus leaving a small pneumatic air void after regression. Microscopic examination reveals pneumatization in 0.2% of the 1500 temporal bones in the body and long process of the incus5’9. This mechanism may explain the formation of the pneumatization seen in the incus. The observed variation being bilateral also supports the idea that it is a developmental variation.

A pneumatized incus, which was previously described only in one other case report, should not be treated incorrectly as a defect. If the middle ear is to be operated on for other purposes, the surgeon should be warned of the existence of this variation.

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Olgu Sunumu / Case Report

Elizabethkingia Meningoseptica'ya Bağlı Bir Neonatal Bakteriyemi Olgusu

Elizabethkingia Meningoseptica'ya Bağlı Bir Neonatal Bakteriyemi Olgusu

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Özet

Elizabethkingia meningoseptica (Chryseobacterium meningosepticum) is a rare nosocomial infection that can show multiple antimicrobial resistance. It has been shown to cause epidemics in neonatal units. This case is presented to discuss this rare cause of *Elizabethkingia meningoseptica* growth in the blood culture of a patient followed in the neonatal intensive care unit due to asphyxia and hypothermia. This case was presented because *Elizabethkingia meningoseptica* was detected in the blood culture of a patient followed in the neonatal intensive care unit due to difficult delivery and asphyxia, and the patient was successfully treated with vancomycin.

Anahtar Kelimeler: *Elizabethkingia meningoseptica*; bacteremia; infection; neonatal

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Abstract

Elizabethkingia meningoseptica (Chryseobacterium meningosepticum), nadir görülen ve çoklu antimikrobiyal direnci görülebilen bir hastane enfeksiyonu etkenidir. Yenidoğan ünitelerinde salgınlara yol açtığı gösterilmiştir. Bu olgu, zor doğum ve asfiksi nedeniyle yenidoğan yoğun bakım ünitesinde takip edilen bir hastanın kan kültüründe *Elizabethkingia meningoseptica*'nın saptanması ve hastanın vankomisin ile başarılı bir şekilde tedavi edilmesi nedeniyle sunulmak istenmiştir.

Keywords: *Elizabethkingia meningoseptica*; bakteriyemi; enfeksiyon; yenidoğan

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1. Giriş

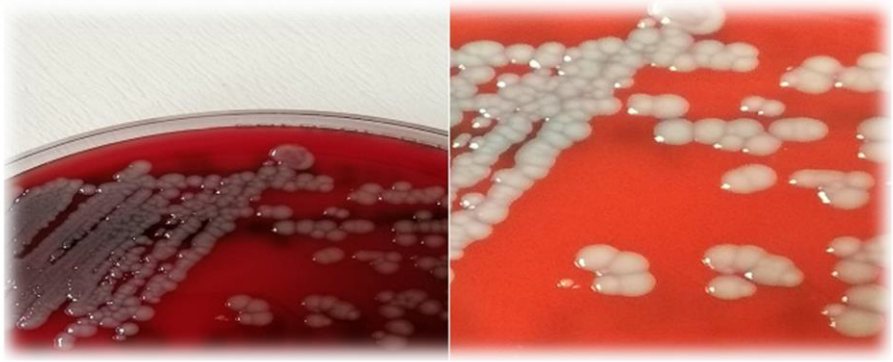
Elizabethkingia meningoseptica (*E. meningoseptica*) glukozu fermente etmeyen, hareketsiz, oksidaz pozitif, Gram negatif aerobik basildir. Önceleri *Flavobacterium meningosepticum* ve *Chryseobacterium meningosepticum* olarak adlandırılmıştır(1). *Chryseobacterium*'un doğal habitatları, hastane florası da dahil olmak üzere toprak, bitkiler, gıda maddeleri ve su kaynaklarıdır(2). Birçok *E. meningoseptica* enfeksiyonu vakası, hastane musluk suyu, dezenfektanlar, salin, antibiyotik solüsyonları, lipid solüsyonu, lavabo drenajları ve solunum ekipmanının kontaminasyonuna bağlı olarak bildirilmiştir(3,4). *E. meningoseptica* çoklu antimikrobiyale direnç gösterebilmesi ve ciddi enfeksiyonlara yol açması ile gündeme gelmektedir. Özellikle yenidoğan yoğun bakım ünitelerinde bu etkene bağlı sepsis ve menenjit salgınları bildirilmektedir(3). *E.meningoseptica,* birincil olarak bağışıklığı baskılanmış bireyleri enfekte eder ve yüksek mortalite (∼% 20 - 40) ile ilişkilidir(5). Çalışmamızda yenidoğan bir erkek hastada nadir rastlanan *E. meningoseptica*'ya bağlı bir bakteriyemi olgusu sunulmuştur.

2. Olgu

Hasta 30 yaşındaki annenin 3. gebeliğinden normal vajinal yol ile 38 haftalık olarak doğmuştur. Doğum ağırlığı 4600 gram olup zor doğum ve asfiksi öyküsü olan hasta yenidoğan yoğun bakım ünitesine yatırılmış ve entübe olarak takip edilmeye başlanmıştır. Asfiktik durumdaki hasta Sarnat & Sarnat Sınıflaması'na göre evre I-II kabul edilmiş ve 72 saat boyunca hipotermi tedavisine alınmıştır. Ek olarak sağ kolunda şişlik ve ekimozları bulunan hastanın çekilen direkt radyografisinde sağ klavikuler kırığı tespit edilmiştir. Sağ kol için elevasyon, soğuk uygulama, dolaşım takibi ve Velpau bandajı uygulanmıştır. Hastanın yatışının 3.gününde CRP (C-reaktif protein) değerinin 2 mg/l'den 14,5 mg/l'ye, prokalsitonin değerinin 0,21 µg/L'den 1,29 µg/L'ye ve beyaz küre sayısının 13500/mm^3'e yükselmesinin üzerine ampirik olarak vankomisin ve amikasin tedavisi başlanmış ve kan kültürü gönderilmiştir. Kan kültüründe *E.meningoseptica* tespit edilen hastanın bu süre zarfında vankomisin ve amikasin tedavisine devam edilmiştir. Antibiyotik tedavisinin 10.gününde lökosit, CRP ve prokalsitonin değerlerinin normal sınırlara gelmesi üzerine antibiyotik tedavisi kesilmiştir. Takibinde oral alıma geçen ve genel durumu iyi seyreden hasta taburcu edilmiştir.

İzolatın tanımlanması ve antimikrobiyal duyarlılığı

Laboratuvarımıza gelen kan kültürü şişeleri kan kültürü cihazına (BACTEC FX TOP, Becton, Dickinson and Company, ABD(Amerika Birleşik Devletleri) yüklenmiştir. Pozitif sinyal veren örneklerin Gram boyaması yapılmış ve koyun kanlı agar (BD(Becton, Dickinson and Company) Columbia Agar with 5% Sheep Blood, ABD), çikolata agar (BD Chocolate Agar, GC II Agar with IsoVitaleX, ABD), eosin metilen blue (EMB) agar (BD EMB Agar (Eosin Methylene Blue Agar), Modified ,ABD) besiyerlerine ekim yapılarak 37°C'de 24 saat süre ile inkübe edilmiştir. Gram boyamada Gram-negatif basiller saptanmıştır. İnkübasyon sonunda koyun kanlı agarda küçük, mat ve beyaz koloniler üremiştir (Resim 1). EMB(Eosin Methylene Blue) agarda küçük, laktoz negatif koloniler üremiştir. Üreyen koloniler konvansiyonel yöntemler kullanılarak, oksidaz pozitif, katalaz pozitif, hareketsiz olarak tespit edilmiştir. İzolatın kesin tanısı için otomatize tanımlama ve antimikrobiyal duyarlılık sistemi (BD Phoenix 100, Becton, Dickinson and Company, ABD) kullanılmıştır (Tablo1). Antimikrobiyal sonuçların duyarlılık tespiti için The European Committee on Antimicrobial Susceptibility Testing (EUCAST) kılavuzunda non fermenter bakteriler için tanımlanan kriterler kullanılmıştır (6).



Resim 1. Koyun kanlı agarda E. Meningoseseptica kolonileri

Tablo 1. *E. meningoseptica*'nın antimikrobiyal duyarlılığı

Antimikrobiyal madde	Sonuç / MİK (µg/ml)
Amikasin	Dirençli (>32)
Kolistin	Dirençli (>4)
Gentamisin	Dirençli (>8)
İmipenem	Dirençli (>8)
Meropenem	Dirençli (>8)
Levofloksasin	Duyarlı (1)
Siprofloksasin	Dirençli (>1)
Piperasilin/tazobaktam	Duyarlı (<=4/4)
Sefepim	Dirençli (>8)
Seftazidim	Dirençli (>8)

MİK: minimum inhibitör konsantrasyon

Kültürden izole edilen *E. meningoseptica*'nın moleküler tanımlaması için BAK2(5'GGACTACHAGGGTATCTA-AT3') ve BAK11(3'AGTTTGATCMTGGCTCAG5') primerleri kullanılarak 16S rRNA(Ribozomal Ribonükleik Asit) PCR(Polimeraz zincir reaksiyonu) yöntemi uygulanmıştır. Sanger sekanslama analizi (Applied Biosystem 3130 Genetic Analyzer, Applied Biosystems, Fisher Scientific, Waltham, MA, ABD) ile nükleotid dizisi belirlenmiştir. Sekans sonuçları BLAST (Basic Local Alignment Search Tool) programında analiz edilmiştir. İzole edilen *E. meningoseptica*'ya ait nükleotid dizisi GenBankaKSU-Cifo adıyla ve MZ221765 aksesyon numarasıyla kaydedilmiştir (7).

Çalışmamız Etik Kurul Komitesinin 05.04.2021 tarihli, Karar No:10 ve Oturum:2021/13 ile onaylanmıştır. Çalışmaya dahil edilen hastanın ebeveyni tarafından bilgilendirilmiş onam formu imzalanmıştır.

3. Tartışma ve Sonuç

E. meningoseptica hastane ortamında entübasyon tüplerini ve solunum cihazlarını kontamine edebilmektedir. Hastanede entübe olarak yatmakta olan özellikle yenidoğan ve bağışıklığı baskılanmış hasta gruplarında nadir ama ciddi bir enfeksiyon etkenidir(1,8). Tekerekoğlu ve ark. tarafından yapılan bir çalışmada, yenidoğan yoğun bakım ünitesinde meydana gelen bir salgında intravenöz beslenme sıvılarının enfeksiyon kaynağı olduğu belirtilmiştir(3). Nadir bir hastane enfeksiyonu etkeni olmakla birlikte özellikle son on yılda *E. meningoseptica'*ya bağlı nozokomiyal enfeksiyonlarda artış tespit edilmiştir (9). *E.meningoseptica'*nın bulaş yolu, virülans faktörleri, etkili tedavi rejimleri ve antimikrobiyal direnç paternleri hakkında henüz yeterli bilgi bulunmamaktadır(8). Bundan ötürü *E. meningoseptica'*nın yol açtığı enfeksiyonların halen yüksek mortaliteye (%20-40) neden olduğu belirtilmektedir(10).

*E.meningoseptica'*nın yenidoğan yoğun bakım ünitelerinde sepsis ve menenjit salgınlarına yol açtığı bilinmekte olup, risk faktörleri arasında çoklu komorbiditeye sahip olma, immunsüpresyon, ventilatör desteği, prematürite yer almaktadır(11). Olgumuzdaki hasta asfiksi ve zor doğum gibi komorbiditeleri bulunup klinik durumu nedeniyle entübe edilmiştir. Hastanın kan kültüründen *E. meningoseptica* izole edilmesinde bu faktörlerin de etkili olduğu düşünülmektedir.

*E. meningoseptica'*nın çoklu ilaç direncine sahip olması nedeniyle, tedavi planında mutlaka antimikrobiyal duyarlılık sonuçları göz önüne alınmalıdır. Tedavide florokinolonlar, trimetoprim-sülfametoksazol, minosiklin, piperasilin-tazobaktam gibi seçenekler bulunmaktadır(10). Aminoglikozit grubu antibiyotikler, karbapenemler ve kolistin gibi antimikrobiyaller ise tedavide daha az etkilidir(12). Olgumuzda izole edilen suş kolistin, gentamisin, imipenem ve meropeneme dirençli; levofloksasin ve piperasilin-tazobaktama duyarlı bulunmuştur. *E. meningoseptica* Gram negatif bir etken olmakla birlikte vankomisin ile *E. meningoseptica* tedavisinde başarılı olunduğuna dair çalışmalar da mevcuttur(2,13). Olgumuzda hastaya ampirik olarak başlanan vankomisin tedavisinin sonucunda hastanın kliniğinde ve laboratuvar parametrelerinde belirgin düzelme olması bu çalışmalarla uyumlu niteliktedir.

Sonuç olarak, *E. meningoseptica'*nın nemli ve ıslak ortamlarla temas sonucu hastane kaynaklı enfeksiyonlara neden olduğu bilinmektedir. Bundan dolayı hastanelerde entübasyon, kateterizasyon gibi girişimsel işlemlerde ve ventilasyon gibi tıbbi cihazların kullanımında gerekli dezenfeksiyon kurallarına uyulması önemlidir. Nadir görülmekle birlikte bağışıklığı baskılanmış hastalar ve yenidoğanlarda, ampirik antibiyotik tedavisine cevap vermeyen ciddi enfeksiyonlarda, Gram negatif basil izole edildiğinde *E.meningoseptica* da akla getirilmelidir. Böylelikle bakterinin hızlı bir şekilde tanımlanması ve antibiyogram sonuçlarına uygun şekilde tedavisi mümkün olacak, yüksek morbidite ve mortalite önlenebilecektir.

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Olgu Sunumu / Case Report

Surgical Repair of Fistula Between Right Coronary Artery and Main Pulmonary Artery: Case Report

Sağ Koroner Arter ile Ana Pulmoner Arter Arasında Görülen Fistülün Cerrahi Onarımı: Olgu Sunumu

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Abstract

Coronary artery fistulas (CAF) are uncommon cases. They may cause myocardial ischemia, arrhythmia, pulmonary hypertension, and heart failure. Treatment options are controversial and not clear. In this article we report surgical management of a case with right coronary artery fistula and concurrent coronary artery disease. A sixty-years-old male patient with stable angina symptoms admitted to our medical center. Coronary angiography examination showed a right coronary artery to pulmonary artery fistula and significant right coronary artery lesion located after the fistula's origin. CAF ligated epicardially and right coronary revascularization was performed. Coronary arterial fistulas cause important hemodynamic problems. Surgical and transcatheter interventional treatments are treatment options. Therefore indications for treatment are very important for these patients. The best therapeutic strategy (surgery or transcatheter intervention) is debatable. The surgical treatment is controversial especially for asymptomatic and small fistulas. However, there is consensus that large and symptomatic fistulas should be treated. Further research is necessary to deepen these observations.

Keywords: Coronary artery fistula, right coronary artery, pulmonary artery, coronary artery disease

Özet

Koroner arter fistülleri (KAF) nadir vakalardır. Miyokardiyal iskemi, aritmi, pulmoner hipertansiyon ve kalp yetmezliğine neden olabilirler. Tedavi seçenekleri tartışmalı ve net değildir. Bu yazıda sağ koroner arter fistülü ve eşlik eden koroner arter hastalığı olan bir olgunun cerrahi tedavisini sunuyoruz. Altmış yaşında erkek hasta, stabil anjina semptomları ile tıp merkezimize başvurdu. Koroner anjiyografide, pulmoner artere doğru sağ koroner arter fistülü ve fistülün başlangıcından sonra yer alan belirgin sağ koroner arter lezyonu görüldü. KAF epikardiyal olarak kliplerle ligature edildi ve sağ koroner arter revaskülarizasyonu yapıldı. Koroner arter fistülleri önemli hemodinamik sorunlara neden olur. Cerrahi ve transkateter girişimsel işlemler tedavi seçenekleridir. Bu nedenle bu hastalar için tedavi endikasyonları çok önemlidir. En iyi tedavi stratejisi (cerrahi veya transkateter müdahale) hala net değildir. Özellikle asemptomatik ve küçük fistüllerde cerrahi tedavi tartışmalıdır. Ancak büyük ve semptomatik fistüllerin tedavi edilmesi gerektiği konusunda fikir birliği vardır. Bu gözlemleri derinleştirmek için daha fazla araştırmaya ihtiyaç vardır.

Anahtar Kelimeler: Koroner arter fistül, Sağ koroner arter, Pulmoner arter, Koroner arter hastalığı

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1. Introduction

Coronary artery fistula (CAF) is a rare anomaly. According to the references, coronary anomalies have an incidence of 0.2-1.2% in the general population (1,2). Most of the coronary artery fistula is delivered to the right heart with a single fistula in 95% of cases and nearly all of them are small and asymptomatic (2). About 90% of CAFs drain to the right heart chambers/circulation (2). Large fistulas may cause heart failure, arrhythmias, pulmonary hypertension, endocarditis and angina pectoris (2,3). Surgical closure of CAF with sternotomy or thoracotomy has been described as a safe and effective mode of therapy (4). In this report, we present surgical treatment of a fistula from the right coronary artery (RCA) to the pulmonary artery.

2. Case Presentation

A sixty-year-old male patient was admitted to the cardiology out-patientclinic with stable angina and dyspnea. The electrocardiography (ECG) results showed negative T waves in the inferior leads. No ST segment change, pathological Q wave, branch block or rhythm disturbances were encountered. Echocardiography showed minimal mitral insufficiency and tricuspid insufficiency while both ventricular sizes were normal. The ejection fraction (EF) was not affected (EF: %60) and no sign of pulmonary hypertension or right ventricular overload were found. Coronary angiography was planned due to 2 packs per day for 20 years of cigarette smoking and a history of 10 years of type 2 diabetes mellitus disease. Coronary angiography showed a fistula arising from the right coronary artery and draining into the main pulmonary artery and a significant right coronary lesion located after the fistula's origin (Figure-1). Left system angiography was evaluated naturally. The treatment management was discussed in the cardiology and cardiovascular surgery council. It was concluded that the patient's complaints might be caused by both lesions and that it is difficult to differentiate the exact cause of patient's complaints. There is no definitive information in asymptomatic CAFs about surgical closureor percutaneous closure. This issue is still controversial. The presence of an untreated RCA and an unclosed CAF in the future may lead to ventricular dysfunction, pulmonary hypertension or stealing syndrome from the right coronary artery. For this reason, it was accepted that it would be beneficial to complete the treatment (RCA revascularization and closure of CAF) in order to avoid repetitive procedures and avoid aforementioned complications. Transcatheter treatment was considered to be first option (Stenting RCA (99% occlusion) and re-evaluation of the fistula afterwards). However, open surgery decision was taken considering the risk of early stent occlusion after percutaneous procedure (5,6). Informed consent was obtained from the patient. Laboratory tests and pre-operative anesthesiology examination were assessed as normal before the operation. Under general anesthesia a median sternotomy was done. Aorta and two stage (unicaval) venous cannulations were performed. Cardiopulmonary bypass (CPB) was applied under normothermia. The fistula was easily identified in the epicardium after opening the pericardium. The fistulous communication was directly ligated epicardially by titanium clips (Ethicon Endo-Surgery 36 LIGACLIP®LT200) (Figure-2). Further exploration of pulmonary artery was carried outto exclude the possibility of another existing fistula. No other fistula communication was observed and pulmonary artery was repaired and right coronary revascularization was performed. Follow up was uneventful, and the patient was discharged after one week post operatively. No problems occurred during the 2-year follow-up (2018-2020) after the operation.

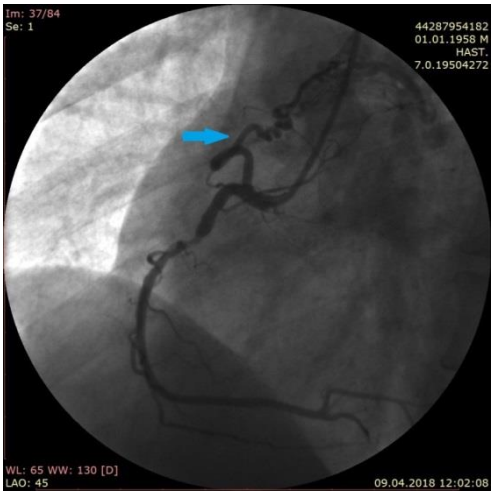

Figure 1. Right coronary artery fistula angiographic image

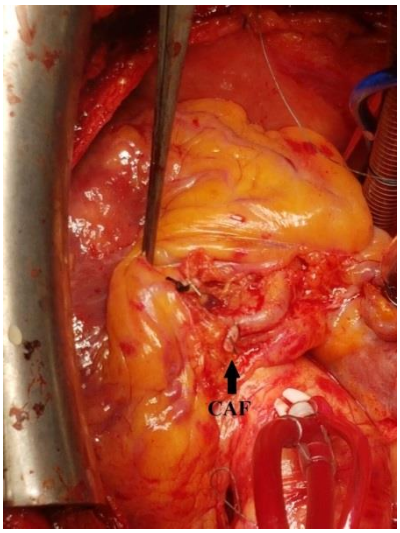

Figure 2. Surgical closure of the right coronary artery fistula

3. Discussion

Coronary artery fistulas have been extensively published in the English literature explaining the origin of coronary artery fistulas, their terminations and mode of treatments. It has been reported that coronary artery fistulas originating from the right coronary artery are encountered the most common with a rate of 52% (2,7,8). But, some authors referred that CAFs originate mostly from left anterior descending coronary artery (LAD) and left coronary system (3,9).

Clinical manifestations of coronary artery fistulas (CAF) usually depend on the hemodynamic and anatomical features. Fistula size, drainage site and the origin of the CAF effects the symptoms and complications (10,11). Pathophysiology includes flow changes and steal phenomenon resulting in oxygenation imbalance, myocardial ischemia or infarction (2). Fistulas draining into the left chambers cause increase in left ventricular volume and subsequently heart failure, whereas fistulas draining into the right heart or pulmonary circulation cause left-to-right shunt and subsequently right ventricular and pulmonary arterial volume overload (10). In addition, CAF's causes atherosclerosis because of coronary flow changes2. In

particular, accompanying coronary artery disease further increases symptoms.

Indications for operation are not clear. It is controversial whether asymptomatic patients and small fistulas should be operated. However, we think that the large fistulas, symptomatic fistulas and patients with additional coronary pathologies should be treated. Delaying operation will lead to CAF-induced complications. This will increase the mortality and morbidity of surgical intervention (8).

Treatments include catheter-mediated stenting, embolization and surgical ligation (12). Transcatheter closure (occlusion devices, coils) may be preferred in patients without coronary artery disease, especially those with a single CAF. Vascular accesses are also important in the percutaneous repair of CAFs. In particular, radial access has been shown to reduce hemorrhagic events and mortality rates compared to transfemoral access (13).

Complications include transient arrhythmia, coronary artery spasm, fistula dissection, ST-T wave change and coil embolization. Transcatheter and surgical applications show similar early efficacy on morbidity and mortality. Surgical ligation is one of the ideal treatments with low mortality rate (1.4%) compared to other surgical techniques (14). CPB is the most commonly used method in surgical ligation. However, it may not be used in lesions that are epicardial and easily visible (2,3,10). Coronary artery fistula ligation can be performed safely in patients with additional coronary lesions, who have additional cardiac problems and large CAFs. However, postoperative bleeding, embolism, cardiac ischemia, and cardiopulmonary bypass complications are important aspects of the procedure.

According to our limited view and experience, the most important point to be determined in CAFs is identifying of treatment indications for coronary artery fistulas. CAFs should be evaluated according to the characteristics of the patients, presence of additional coronary lesions,anatomy of the coronary system and the localization of the fistulas. Large and symptomatic CAFs should be treated accordingly. Transcatheter intervention should be considered as the first choice in patients, but if surgical procedure is considered, early surgical procedure maintains the long-term functional capacity of these patients.

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Derleme / Review

The Prevalence of Ground-Glass Opacity and Consolidation Symptoms of Covid-19 By Meta-Analysis

Covid 19 İçin Buzlu Cam Opasitesi ve Konsolidasyon Belirtileri Prevalansının Meta Analizi

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Özet

Bu çalışmada, bilgisayarlı göğüs tomografisinde en yaygın görüntüleme bulguları olan buzlu cam opasitesi (GGO) ve konsolidasyon sonuçları incelenerek daha kesin Covid-19 tespitini sağlamak için yayınlanan çalışmalardan elde edilen sonuçlar kullanılarak meta analiz yönteminin uygulanması amaçlanmıştır. Çalışmaya gerçek zamanlı polimeraz zincir reaksiyonu (rRT-PCR) pozitif vakaların görüntü özelliklerini bildiren ve SARS-Cov-2 enfeksiyonunu doğrulayan yayınlanmış hakemli makaleler dahil edilmiştir. Bu makalelerin çalışma türü vaka serisi, geriye dönük veya ileriye dönük kohort şeklindedir. Araştırma kapsamındaki çalışmalara, Covid-19, şiddetli akut solunum yolu sendromu corona virüsü 2 (SARS-Cov-2), bilgisayarlı göğüs tomografisi, konsolidasyon ve GGO anahtar kelimelerinin radyografik araştırma veri tabanı Secure Australia (RNSA), The Science Direct ve National Library of Medicine'de araştırılması ile ulaşılmıştır. Arama terimleri sonucunda üç veri tabanından toplam 310 makale toplandı ve makaleler tarandı. Buzlu cam opasitesi ve konsolidasyon bilgilerinin olmaması nedeniyle 250 makale çıkarıldı. Geriye kalan makalelerden, çalışma türü nedeniyle 24 makale, gün kriterini sağlamaması nedeniyle 7 makale, eksik ve yanlış veriler nedeniyle 9 makale çıkarıldı. Sonuçta 20 makale meta-analiz çalışmamıza dahil edildi. Bilgisayarlı göğüs tomografisi pozitif olan bulgularda, buzlu cam opasitesinin 5 güne kadar mevcut olduğu, beşinci ve sonraki günlerde konsolidasyona dönüştüğü görülmüştür. Analiz sonuçlarına göre; Covid-19'un erken evresi için buzlu cam opasitesinin prevalansı %82 ve konsolidasyonun prevalansı %40'tır.

Anahtar Kelimeler: Meta analiz, Covid-19, rRT-PCR test, bilgisayarlı göğüs tomografisi

Abstract

In this study, it was aimed to apply the meta-analysis method of the results obtained from the published studies to provide a more precise Covid-19 detection by examining the results of ground glass opacity (GGO) and consolidation, which are the most common imaging findings in chest computed tomography (CT). Published peer-reviewed articles reporting the image characteristics of real-time reverse transcription–polymerase chain reaction (rRT-PCR) positive cases and confirming Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) infection were included in the study. The study type of articles were case series, retrospective or prospective cohort studies. The studies under the scope of the research were reached from the National Library of Medicine, the research network for a Secure Australia (RNSA) and The Science Direct databases by searching the keywords Covid-19, SARS-Cov-2, computed chest tomography, Consolidation and GGO. As a result of the search terms, in total 310 articles were collected from three databases and articles were scanned, 250 articles were removed due to lack of GGO and Consolidation information, 24 studies were eliminated due to study type, 7 studies were unsuitable for day criteria, and 9 studies were eliminated due to missing and incorrect data. After all, 20 studies were included in our meta-analysis study. In the positive CT findings, it is known that the GGO is present for up to 5 days, the GGO turns into consolidation on the fifth and the following days, and according to the analysis result; for the early stage of Covid-19, the GGO Prevalence is 82% and Consolidation Prevalence is 40%.

Keywords: Meta-analysis, Covid-19, rRT-PCR test, chest computed tomography

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1. Introduction

Meta-analysis is a statistical analysis providing the presentation of the studies, conduction for the same purpose from a single source, determining the causes of inconsistency and heterogeneity between the studies and obtaining statistically more precise results from the studies conducted with small sample groups.(1) Meta-analysis is a quantitative statistical analysis of several separate but similar experiments or studies in order to test the pooled data for statistical significance. (2)

1.1.Weighting of Studies Participate in Meta Analysis by Fixed Effect and Random Effect Models

It is important to understand the two concepts when combining studies.

True Effect Size: It refers to the effect size in the population.

Observed Effect Size: It refers to the effect size of the added studies.

If the number of studies participating in the meta-analysis is too large, the "Observed Effect = True Effect" situation arises. The difference between the true effect and the observed effect is called sampling error.

Observed Effect of i-th study:

$$Y_i = \theta_i + \varepsilon_i \quad (1)$$

$$Y_i = Observed\ Effect \quad (2)$$

$$\theta_i = True\ Efect \quad (3)$$

$$\varepsilon_i = Sampling\ Error\ Between\ Studies \quad (4)$$

$\varepsilon_i \sim N(0, vi)$. Therefore the Yi's are assumed to be unbiased and normally distributed of their corresponding true effect. (3)

$$\theta_i = \mu + \zeta_i \quad \text{True Effect} \quad (5)$$

"ζ_i" shows the variability of effect size between studies and "ε_i" variability of sampling error within studies.

In condition $\zeta_i = 0$ then $\theta_i = \mu$ and $Y_i = \mu + \zeta_i + \varepsilon_i = \theta_i + \varepsilon_i = \mu + \varepsilon_i$ occurs. It means the observed effects size of studies and true effect size are equal.

The distance of observed effect size from the population mean (μ) is expressed by $\boldsymbol{\tau}$

(Standart deviation) and $\boldsymbol{\tau^2}$ = the population variance**,** the total amount of heterogeneity among the true effects. The variance value plays a role in the determination of the weights when calculating the population effect value.

$V_i = \varepsilon_i^2$ = The variance of Y_i. (The Sampling Variance) (6)

If the Population Variance is $\tau^2 = 0$ then the weight function should be

$$w_i = \frac{1}{Vi_{Yi}} \quad Fixed\ Effect\ Model. (3) \quad (7)$$

If the Population Variance is $\tau^2 \neq 0$ then the weight function should be

$$w_i = \frac{1}{Vi_{Yi} + \tau^2} \quad Random\ Effect\ Model. (3) \quad (8)$$

When calculating the effect size in the model, the random efect model or the fix effect occurs according to the presence or absence of the variance (τ^2) between the studies resulting from the real effect variability (ζ_i) of the studies. While analyzing studies in homogeneous structure, it should be calculated by fixed effect model; otherwise analyzing heterogeneous studies should be calculated by random effect model. The fixed or random effect model is highly determinative on the amount of population impact size.

Population effect size function is:

$$\mu = \frac{\sum_{i=1}^{k} w_i * Y_i}{\sum_{i=1}^{k} w_i} \quad (9)$$

$$V_M = \frac{1}{\sum_{i=1}^{k} w_i} \quad \text{Variance of Total Effect Size} \quad (10)$$

$$SE_M = \sqrt{V_M} \quad \text{Standard Error of Total Effect Size} \quad (11)$$

$\%\ 95\ CI = \mu \pm 1.96 * SE_M$ The Confidence Interval of Total Effect Size (12)

1.2.Calculating Prevalence with Meta Analysis

Calculating prevalence with meta-analysis methods is based on the inverse variance method (4,5)

$p_i = log\left(\frac{a/n}{1-a/n}\right)$ a=number of event and

n=number of observation (5)

Prevalence equation

$V_i = \varepsilon_i{}^2$ = The variance of p_i (The Sampling Variance). (14)

$w_i = \frac{1}{Vi_{pi}}$ The weight function for i'th study. (15)

Thus, the pooled prevalence estimate P, according to the inverse variance method, then becomes:

$P_{pooled} = \frac{\sum_{i=1}^{k} w_i * P_i}{\sum_{i=1}^{k} w_i}$ the pooled prevalence equation (4,6) (16)

$V_{(p)} = \frac{1}{\sum_{i=1}^{k} w_i}$ the variance of meta-analysis (17)

$SE(P) = \sqrt{V_{(p)}}$ the standard error (18)

$CI(P) = P \pm Z\alpha_{/2} SE(P)$ confidence interval (19)

$Z\alpha_{/2}$ denotes the appropriate factor from the standard normal distribution for the desired confidence percentage.

1.3.The Heterogeneity Test Cochran Q

Cochran's Q test is the traditional test for heterogeneity in meta-analyses, allows us to decide whether to combine the effect size into a single population.

The test hypotheses are:

$H_0: \theta_i = \theta_2 \ldots \ldots = \theta_k = 0$ or $H_0: \sigma_B^2 = 0$ (B=Between) $H_0: \sigma_W^2 = 0$ (w=within)

H_1: At least one variance differs.

Cochran Q test statistic is calculated as follows.

$Q = \sum_{i=1}^{k} W_i (Y_i - \mu)^2$ and (20)

$\mu = \frac{\sum_{i=1}^{k} W_i Y_i}{\sum_{i=1}^{k} W_i}$ (13)(21)

If Q test value < χ^2 critical value, then we accept that H_0 hypothesis and meta-analysis effect size calculation type should be calculated with the homogeneity fixed effect model.

In December 2019, Covid-19 with agent Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-Cov-2) occurred in Wuhan, a city of China, and spread all over the world.

According to the China Government's guide for the SAR-Cov-2 infection, the key indicator for hospitalization must be reverse transcription polymerase chain reaction (RT-PCR) or gene sequencing for respiratory or blood specimens (National Administration of Traditional Chinese Medicine). (7)

Viruses most commonly cause lung infections. Viral pneumonia images are different from other respiratory infections and inflammatory lung diseases. Viruses in the same viral family share a similar pathogenesis: therefore, CT imaging is important in the diagnosis of lung diseases for distinguishing patterns. (8)

The studies include images were analyzed for the following aspects: Presence of Ground-Glass Opacity (GGO): defined by increase in lung density but without covering the pulmonary blood vessels and bronchial walls; Presence of lung consolidation: defined by higher density than GGO and blurred margins of pulmonary blood vessels and bronchial tubes.

Limitation sample collection and kit performance the viruses may not be detected

in the upper respiratory samples, mostly 0-7 days after illness onset. Some severe cases viral ribonucleic acids (RNAs) could not be detected in the upper respiratory samples while positive in the bronchoalveolar lavage fluid. Except that, computed tomography (2) images of some cases showed typical viral pneumonia with GGO, whereas viral Ribonucleic Acid infections (RNAs) were not detected by throat swap samples. In this context, chest CT may provide benefit for diagnosis of Covid-19. (9)

Typical radiographic features of all Covid-19 patients included GGO and multifocal patchy consolidation. With RT-PCR results as reference, the sensitivity, specificity, accuracy of chest CT to diagnose Covid-19 infections were 97%, 25%, and 68%, respectively.(9) Another study's result for the sensitivity and specificity of chest CT with repeated RT-PCR was 95% and 35%. (10)

Incubation period of Covid-19 disease is 1 to 14 days, mostly three to seven days. General symptoms are fever, fatigue and dry cough.

In 0-2 days of symptoms onset, chest CT tends to be normal or Broncho vascular markings may start. *The early/initial stage* of the disease (0-4 days) shows the previously identified and best recognized features of Covid-19 infection, which consists of peripheral-based GGOs without subpleural sparing. *The progressive stage* of disease (5-8 days) shows an increasing amount of GGO relative to early stage. There can be vascular thickening and associated intralobular septal thickening "crazy paving pattern". *The peak stage* (10-13 days) includes consolidation and may include secondary complications of the disease. This step may include an even less specific pattern. The distinctive feature of *the absorption stage* (≥14 days) is the improvement of the aeration of the lungs with resolving features of "crazy paving", continuous solubility of GGO and parenchymal bands. In addition, there may be changes in fibrosis at this stage. (11)

In a suspected clinical case with typical clinical symptoms and previous exposure to individuals with SARS-Cov-2, a combination of chest CT imaging and RT-PCR assay may help to increase the Covid-19 diagnosis. For this reason, it is of crucial importance to define imaging patterns of Covid-19 pneumonia in order to diagnose the viral infection promptly in acute stages and to lead to the correct work-up. (12) Figure 1 shows the CT results of **A**: 28-year-old man who had a cough and fever for 3 days and **B**: 79-year-old male whose PCR test was positive.(28)

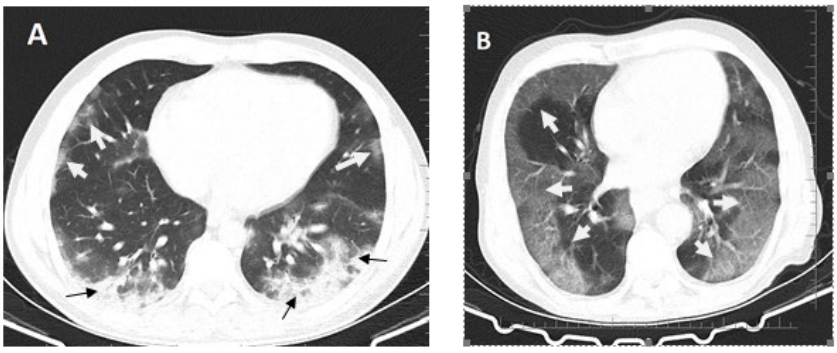

Figure 1. ***A****: 28-year-old male patient with complaints of nausea and vomiting for 10 days, fever and cough for the last three days.Non-contrast enhanced chest CT showed multiple peripheral patchy ground glass opacities in bilateral multiple lobular and subsegmental with obscure boundary (white arrows). In addition, areas of consolidation in the bilateral lower lobes were observed on the CT scan (black arrows).* ***B****: A 79-year-old male patient is admitted to the emergency room with fever and cough. The patient whose PCR test was positive, showed multiple peripheral patchy view glass opasities (white arrows) in the thorax CT examination. (28)*

Although rarely the RT-PCR negative patients had early stage (0-4 days) opacification, which is the most obvious lung finding of SARS-Cov-2, on chest CT imaging made us think about the importance of imaging for the diagnosis of Covid-19 disease. With the

progression of the disease, consolidation begins to form in the lungs. In order to contribute to the diagnosis and prognosis of Covid-19 disease, we considered it appropriate to investigate the prevalence of Consolidation and Opacification in 0-4 days which we call early stage.

In this meta-analysis, we aim to summarize the results from published studies quantitatively to provide a more precise detection Covid-19 by GGO and Consolidation which are the most common imaging findings on chest CT of patients, in other word we try to get the prevalence of related symptoms.

In this study, our question is what the consolidation and opacification rate is in the computed tomography within the first 4 days of hospitalization of disease whose Covid-19 rRT-PCR test positive and have symptom fever.

2. Material and Methods

2.1. Protocol and Registrations

The subject and method of our research were determined on 7-15 April 2020. Meta-analysis was the most appropriate method to answer our research question, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The purpose of the PRISMA Statement is to help the authors to develop their systematic review and meta-analysis reports. The critical evaluation of the research conducted by PRISMA, when it is compared to randomized studies, is clearer. However, the PRISMA checklist is not an assessment tool that can be used to measure the quality of the review. (13)

2.2. Eligibility Criteria

We included published peer-reviewed articles that reported image characteristics of rRT-PCR positive cases confirmed SARS-Cov-2 infection. Appropriate study designs to evaluate imaging characteristics are case control, retrospective or prospective cohort studies and case series. Article language limit was not set, we included publications from January 1, 2020 to May 25, 2020. Letters, opinion articles and studies that did not provide original data were excluded.

2.3. Information Sources And Search Strategy

The studies included in Meta-Analysis were taken from The National Library of Medicine (www.ncbi.nlm.nih.gov/pubmed), the publication of radiographic The Research Network for a Secure Australia (RNSA) (ww.pubs.rnsa.org) and The Science Direct (www.sciencedirect.com) databases. The publication related to Covid-19, SARS-Cov-2, chest CT, Consolidation and GGO were completely reviewed, these features were also search terms we used.

2.4. The Properties of Study Selection

The research criteria were clear and Covid-19 articles were open to share in databases, thus made literature review easier. Initial selection articles strategy was first screen by title and abstract. Limiting the research to three databases is a precaution to avoid bias. Any descriptive features that characterize the patients included in the study were not taken into account (age, smoking status etc.)

For this reason, articles which were studied with specific patient groups such as pediatric, pregnant, heart disease, kidney transplant were not included in the study. The articles in which numerical values were inconsistent and made by different people using the same data were excluded. Case Reports were not included in study, but the findings of these cases were compared with the results of the study. PRISMA method was used for the quality of the study. A total of 20 study met inclusion criteria. The PRISMA 2009 Flow Diagram is shown in Figure 2. (13)

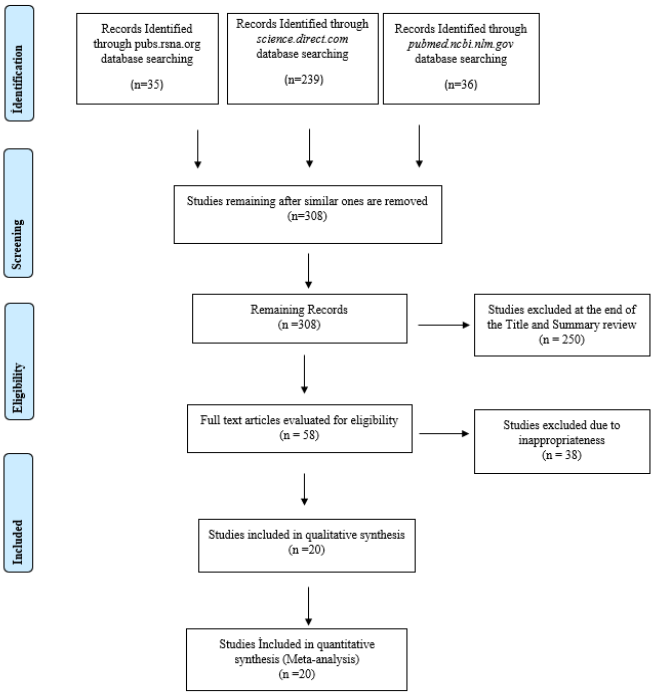

Figure 2. *PRISMA 2009 Follow Diagram*

2.5. Assessment of Methodological Quality and Risk of Bias

Calculation was made with the log values of the research findings and the confidence interval value of each study was given. Funnel plot and Egger's test were applied to investigate bias. Apart from three databases, any article was not included in the study and these databases were examined in detail for collecting data.

We used inverse variance method for counting the effect size of each study. The most used methods Mantel-Haenszel and One-step Peto's do not require to estimate the variance. For this reason, Mantel Haenszel only applies a fixed effect model. Also Peto's method only allows us to get odds ratio. (1) Statistical heterogeneity between studies was evaluated by Cochran's Q test, I2, H2, Tau2 indexes. For Q satatistic p< 0.100 was considered statistically significant for heterogeneity, I2>50%, H2 >1.15, for Tau2>0.130 (according to (14)) was considered to have moderate heterogeneity. For puplication bias, we conducted funnel pilot and it was checked by Edger's test that p<0.05 was considered statistically significant. For all statistical analysis used by R statistical software with package "meta" and "metafor" program.

3. Results

3.1 Study Selection and Characteristics

First, a total 310 articles were collected from three databases because of search terms. After screening those articles, 250 articles were excluded due to the lack of information of GGO and Consolidation. 24 studies were eliminated due to the study type (case record), 7 of them were eliminated due to the inappropriate day criterion and 9 of them were eliminated due to the missing and incorrect data. The design of the studies which were included in meta-analysis; 15 were retrospective studies, 2 were prospective studies and 3 were case series. Properties of studies which were included to the Meta-analysis for Prevalance of GGO is shown in Table 1. Properties of studies which were included to the Meta-analysis for Prevalence of Consolidation is shown in Table 2.

Table 1: Properties of studies which were included to the Meta Analysis for Prevalance of GGO

Study No	Authors	Ground Glass Opacities		Sample Size	CT Day	Study Design	Reference
		GGO+	GGO-	N			
1	Chung, M., et al.	19	2	21	on admission	Retrospective	(19)
2	Caruso, D., et al.	58	4	62	on admission	Prospective	(15)
3	Wang, Y., et al.	49	30	79	on admission	Prospective	(20)
4	Bai, H.X., et al.	200	56	256	on admission	Retrospective	(18)
5	Bernheim, A., et al.	45	24	69	on admission	Retrospective	(21)
6	Wang, K., et al.	80	34	114	on admission	Retrospective	(22)
7	Huang, L., et al.	6	2	8	on admission	Case Series	(23)
8	Luo, Z., et al.	9	3	12	on admission	Retrospective	(24)
9	Fang, X., et al.	11	3	14	on admission	Case Series	(25)
10	Peng, S., et al.	10	1	11	on admission	Case Series	(26)
11	Guan, C.S., et al.	47	6	53	on admission	Retrospective	(27)
12	Xu, X., et al.	65	25	90	on admission	Retrospective	(28)
13	Shi, H., et al.	31	5	36	on admission	Retrospective	(29)
14	Ding, X., et al.	36	11	47	on days 0. and 3.	Retrospective	(30)
15	Lomoro, P., et al.	40	2	42	on days 0. and 3.	Retrospective	(12)
16	Li, X., et al.,	106	25	131	on days 0. and 3.	Retrospective	(31)
17	Wang, X., et al.	863	149	1012	on days 0. and 4.	Retrospective	(32)
18	Zhou, Z., et al.	33	1	34	on days 0. and 4.	Retrospective	(33)
19	Nie, W., et al.	150	13	163	on days 0. and 4.	Retrospective	(34)
20	Liu, Z., et al.	59	13	72	on days 0. and 4.	Retrospective	(35)

Table 2. Properties of studies which were included to the Meta-analysis for Prevalence of Consolidation

Study No	Authors	Consolidation		Sample Size	CT Day	Study Design	Reference
		Cons+	Cons-	N			
1	Chung, M., et al.	6	15	21	on admission	Retrospective	(19)
2	Moher, D., et al.	42	20	62	on admission	Prospective	(15)
3	Wang, Y., et al.	18	61	79	on admission	Prospective	(20)
4	Bai, H.X., et al.	150	106	256	on admission	Retrospective	(18)
5	Bernheim, A., et al.	24	45	69	on admission	Retrospective	(21)
6	Wang, K., et al.	80	34	114	on admission	Retrospective	(22)
7	Huang, L., et al.	5	3	8	on admission	Case Series	(23)
8	Luo, Z., et al.	4	8	12	on admission	Retrospective	(24)
9	Fang, X., et al.	6	8	14	on admission	Case Series	(25)
10	Peng, S., et al.	2	9	11	on admission	Case Series	(26)
11	Guan, C.S., et al.	30	23	53	on admission	Retrospective	(27)
12	Xu, X., et al.	12	78	90	on admission	Retrospective	(28)
13	Shi, H., et al.	2	34	36	on admission	Retrospective	(29)
14	Ding, X., et al.	12	35	47	on days 0. and 3.	Retrospective	(30)
15	Lomoro, P., et al.	25	17	42	on days 0. and 3.	Retrospective	(12)

16	Li, X., et al.,	91	40	131	on days 0. and 3.	Retrospective	(31)
17	Wang, X., et al.	54	958	1012	on days 0. and 4.	Retrospective	(32)
18	Zhou, Z., et al.	12	22	34	on days 0. and 4.	Retrospective	(33)
19	Nie, W., et al.	125	38	163	on days 0. and 4.	Retrospective	(34)
20	Liu, Z., et al.	50	22	72	on days 0. and 4.	Retrospective	(35)

The 13 of studies have CT findings on admission, seven of them on days 0. and 4. days. There were 2326 (N) Covid-19 patients with positive rRT-PCR test and chest CT finding GGO and Consolidation of patients during the first 0-4 days of fever onset or within the 0-4 days of admission to the hospital. 100 % of all cases included in our study have positive rRT-PCR test results. The research question is: "Should there be a finding of Consolidation accompanying to the diagnosis of chest CT within the first 4 days of fever or hospitalization? Is the rate of opacity and the consolidation same in the early stage Covid-19 positive patients?

3.2 Imaging Outcomes

Outcomes for Ground Glass Opacities: The Prevalence of GGO occurrence in studies included in the analysis is 82% (95% CI 61-92%). There is two study which are outlier, one is study "3" (20) and the other is study "19" (34), shown in Figure 3B. When outliers are corrected, the prevalence turns into 81% (95% CI 65-91%). The Line Charts of Outlier Studies for Ground Glass Opacity shown in Figure 3A and The Scatter Plot of Outlier Studies for Ground Glass Opacity shown in Figure 3B.

According to the prevalence results, the variability between studies is statistically significant (Estimate=1.49, se=0.15, Z=10.20, p< 0.001 CI 95% 1.21-1.78), and it is supported by Cochran's Q test's results that the heterogeneity detected is statistically significant (Q=85.44, df=19, p<0.001). The other test results that measure heterogeneity also support the Q test. Tau2= 0.26 (SE=0.1849) (CI 95% 0.12- 1.02), I2= 77.76% (CI 95% 63.09-93.31%) and H2= 4.50 (CI 95% 2.71-14.94). After the study is found to be heterogeneous, the random effect model is used in the meta-analysis where Prevalence is calculated, and The Prevalence of Ground Glass Opacity are shown with Figure 3C.

The funnel plot is the distribution graphic of the studies included in the meta-analysis according to the standard deviation and prevalence values and evaluate the presence of bias. To evaluate the bias of the Funnel Chart, Egger Regression Model was chosen in accordance with our data because the model evaluates on weights. Test for Funnel plot's asymmetry with value p<0.05 showed presence of bias (t=2.25, df=18, p=0.022), The Funnel Plot for Ground Glass Opacity shown in Figure 3D. To solve the bias in the study, we looked at the Funnel by removing the extreme values, but the result did not change (Egger test: t=2.29, df=15, p=0.018).

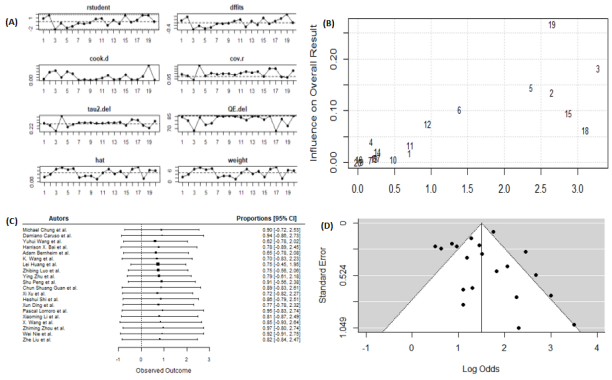

Figure 3. *GGO Results*

Sub-groups of the study were examined to investigate bias. Two groups were created according to CT imaging days, one was “on admission” and the other was “on 0 - 4 days”. For “on admission” Cochran Q test results showed heterogeneity (Q=33.70, df=12, p<0.050) and Prevalence=77% (95% CI PLO=71-82%). The Egger Regression Test for asymmetry of Funnel plot had the same bias (t=2.34, df=11, p=0.018). For CT images taken “on days 0 and 4” the Cochran Q test results had the same heterogeneity (Q=16.88, df=6, p<0.050) and there were no bias at this time for finding of CT images taken on days zero and fourth (Egger test: t=1.82, df=6, p=0.060). The prevalence for “on days 0 and 4” is 87% (95% CI PLO=82-90%).

Outcomes for Consolidation

The percentage of consolidation is 40 % (95% CI 25-56%). Study 17. (32) and 13. (29) outlier values, after correcting outliers the percentage turns into 47% (95% CI 37% - 57%). The Line Charts of Outlier Studies for Consolidation shown in Figure 4A and The Scatter Plot of Outlier Studies for Consolidation shown in Figure 4B.

According to the prevalence of consolidation, with Cochran’s Q test’s results shows that the heterogeneity detected is statistically significant (Q=602.53, df=19, p<0.001). The other test results that measure heterogeneity also support the Q test. Tau2 = 2.04 (CI 95% 0.70- 2.94), I2 = 96 % (CI 95% 91-97%) and H2 = 31.71 (CI 95% 11.58-45.53). After the study is found to be heterogeneous, the random effect model is used in the meta-analysis where prevalence is calculated, and the results are the prevalence of consolidation shown in Figure 4C .

The images belong to the funnel plot shows the studies spread all over the chart. The funnel plot for consolidation shown in Figure 4D. To examine the bias of the Funnel Chart, the Egger Regression Model (model=”lm”) result shows no presence of bias (t=-1.10, df=18, p=0.270). Sub-groups of the study were examined for consolidation prevalence, CT images of “on admission” have Prevalence=38% (95% CI PLO=26% -51%) and CT images taken “on days 0 and 4” have Prevalence= 48% (95% CI PLO=15% -83%).

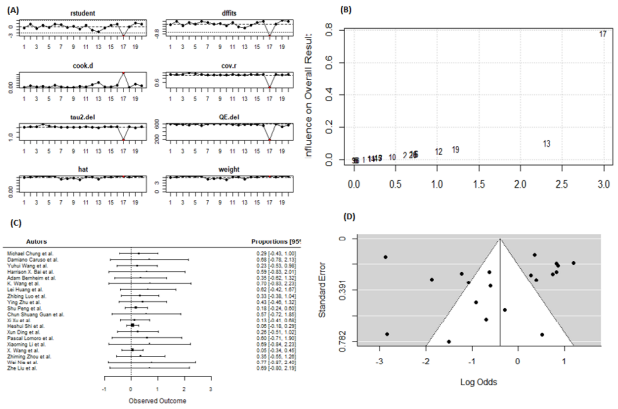

Figure 4. *Consolidation Results*

4. Discussion

The contribution of lung findings to Covid-19 disease diagnosis cannot be ignored, therefore many studies have been conducted on the sensitivity and specificity, by using RT-PCR as a reference and using chest CT images of Covid-19 as positive predictive value or as negative predictive value, just like Caruso, D., et al. found sensitivity 97% and specificity 56% or Dashraath, P., found 97% for sensitivity and 25% for specificity. Himoto, Y., et al.conducted a study with a series of 51 patients by founding chest CT and RT-PCR assay performed in 3 days, the sensitivity was 98% for CT and 71% for RT-PCR (p<0.001). (15-17)

In a study conducted in China, of 1014 patients, 59% had positive RT-PCR results, and 88% had positive chest CT scans. The sensitivity of chest CT in suggesting Covid-19 was 97% (95% CI, 95-98%). With negative RT-PCR result 75% (308/413) had positive chest CT finding; of 308, 48% were considered as highly likely cases, with 33% as probable cases that ultimately all cases received a positive test result. Another output of the same study: In the first CT measurements, the initial negative RT-PCR returned to positive with an average of 5.1 ± 1.5 days and initial positive and then negative RT-PCR the conversion took an average of 6.9 ± 2.3 days. (9)

At Hunan, China a study conducted for differentiating 219 Covid-19 patients from 205 patients with pneumonia without Covid-19, diagnostic capabilities of radiologists and three Chinese radiologists had sensitivity of 72%, 72%, 94% and specificity of 94%, 88%, 24%; four United States radiologists had a sensitivity of 93%, 83%, 73% and 73% and specificity of 100%, 93%, 93% and 100%. The most discriminating features for Covid-19 pneumonia were peripheral distribution (with 80% and 57%, p<0.001), GGO (91% and 68%, p<0.001) and vascular thickening (58% and 22%, p<0.001). (18)

It is understood that GGO is a very important parameter for diagnosis of Covid-19 disease in CT images. As a radiological finding in the lung, GGO turns to into Consolidation, which is a histopathological structure within an average of 0-4 days.

The percentage of GGO occurrence in studies included in our meta-analysis is 82 % (%95 CI 61-92 %). At the same time the percentage of consolidation is 40% (95% CI 37-92). Respectively in studies 3., 5., 6., 12., 17. with number of samples (n) 79, 256, 114, 90, 1012 the represent of GGO was 62%, 78%, 70%, 72%, 85% and consolidation was 29%, 58%, 70%, 13%, 5%. (20,21,22,28,32)

By showing observed value and variants of the studies: There were extreme values at study 12. with value yi=1.69, vi=0.076; study 13. (29) with value yi=2.74, vi=0.476, study 17. (yi=2.77, vi=0.017). (28,29,32)

According to the GGO prevalence results, the variability between studies is statistically significant (Estimate=1.49, se=0.15, Z=10.20, p< 0.001 CI 95% 1.21—1.78), and it is supported by Cochran's Q test's results that the heterogeneity detected is statistically significant (Q=85.44, df=19, p<0.001, I2=77.76%). Cochran's Q test's results for the prevalence of consolidation shows heterogeneity (Q=602.53, df=19, p<0.001, I2=96%).

In the positive CT findings, we know that GGO is present up to 5 days, on the fifth and the later days GGO changes into consolidation. This meta-analysis also shows same result; the Prevalence of GGO for early stage of Covid-19 is 82% and Consolidation's Prevalence is 40%.

5. Conclusion

This meta-analysis has provided an overview of early Chest CT findings of Covid-19 patients. In the analysis which the random effect model was applied, an inference about the population Prevalence value of GGO and Consolidation has been gained. The long incubation period explains the heterogeneity of analysis.

In the early stage of SARS-Cov-2 when fever and cough are observed, radiological findings have become vital in the rapid and early diagnosis. Chest CT can be a great benefit to the patients and to the public health surveillance at SARS-Cov-2 infection.

ABBREVIATIONS

GGO	:	Ground-Glass Opacity
CT	:	*Computed Tomography*
rRT-PCR	:	Real-Time Reverse Transcription–Polymerase Chain Reaction
SARS-Cov-2	:	Severe Acute Respiratory Syndrome Coronavirus 2
RNSA	:	The Research Network for a Secure Australia
RT-PCR	:	Reverse Transcription Polymerase Chain Reaction
RNAs	:	Viral Ribonucleic Acids
PRISMA	:	Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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