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RESEARCH ARTICLE

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The Role of Meteorological Parameters in COVID-19 Infection

ABSTRACT

Objective: The SARS-CoV-2 infection outbreak was given the name Coronavirus Disease 2019 (COVID-19) by the World Health Organization. Meteorological parameters are one of the most important factors affecting infectious diseases. The aim of this study is to analyze the correlation between meteorological parameters and the COVID-19 pandemic.

Methods: One hundred ninety-seven COVID-19 patients diagnosed and treated in the Turkish province of Duzce between 29.03.2020 and 04.05.2020 were included in this study.

Results: We found the relationship between air quality parameters and COVID-19 case numbers revealed significant negative correlation between positive patient number and air temperature, relative humidity, and NO_2, and significant positive correlation with air pressure, but no correlation with PM_{10}, $PM_{2.5}$, SO_2, NO, or CO.

Conclusions: Our findings are important as a preliminary study, since interactions between air pollutants and meteorological factors may be involved in the transmission and pathogenesis of COVID-19, and large-scale studies should now be designed for a better understanding of these interactions.

Keywords: Infection, COVID-19, Meteorological Parameters

COVID-19 Enfeksiyonunda Meteorolojik Parametrelerin Rolü

ÖZET

Amaç: SARS-CoV-2 enfeksiyonu salgınına Dünya Sağlık Örgütü tarafından Coronavirus Hastalığı 2019 (COVID-19) adı verildi. Meteorolojik parametreler bulaşıcı hastalıkları etkileyen en önemli faktörlerdendir. Bu çalışmanın amacı meteorolojik parametreler ile COVID-19 salgını arasındaki ilişkiyi incelemektir.

Gereç ve Yöntem: Türkiye Düzce ilinde 29.03.2020 ve 04.05.2020 tarihleri arasında tanı ve tedavi edilen 197 COVID-19 hastası çalışmaya alındı.

Bulgular: Hava kalitesi parametreleri ile COVID-19 olgu sayıları arasındaki ilişkinin, Pozitif hasta sayısı ile hava sıcaklığı, bağıl nem ve NO2 arasında anlamlı negatif korelasyon olduğu ve hava basıncı ile anlamlı pozitif korelasyon olduğu, ancak PM_{10}, $PM_{2.5}$ SO_2, NO veya CO ile korelasyon olmadığı saptandı.

Sonuç: Bulgularımız bir ön çalışma olarak önemlidir, çünkü hava kirleticileri ile meteorolojik faktörler arasındaki etkileşimler COVID-19'un bulaşması ve patogenezinde rol oynayabilir ve bu etkileşimlerin daha iyi anlaşılması için büyük ölçekli çalışmalar tasarlanmalıdır.

Anahtar Kelimeler: İnfeksiyon, COVID-19, Hava Parametreleri

INTRODUCTION

The SARS-CoV-2 infection outbreak was given the name Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO). COVID-19 then spread rapidly to many countries, and the WHO officially declared it a pandemic on 11 March, 2020 (1).

Viruses do not replicate outside the living cell, but the virus can survive on environmental surfaces it has contaminated, that survival being significantly affected by temperature and moisture (2).

Meteorological parameters are one of the most important factors affecting infectious diseases. Previous studies have suggested that environmental air pollutants make humans more susceptible to pathogens by carrying micro-organisms and are risk factor for respiratory tract diseases by affecting the body's immunity (3-5).

Various studies have been performed to investigate the factors affecting SARS-CoV-2 transmission in order to control the spread of COVID-19 (6). Several factors affect the transmission, such as the incubation period, the length of infectiousness, the virus load, the incidence and infectiousness of asymptomatic cases, transmission pathways other than droplets, and the length at which the agent can maintain infectivity in external environments (7). Air quality parameters may therefore play a role in the transmission and infectivity of the virus.

Meteorological conditions have been proposed as important factor in predicting epidemic trends, in addition to population mobility and human-to-human contact. Meteorological factors, such as humidity, visibility, and wind speed, can affect droplet stability in the environment, or affect the survival of viruses in the same way as air temperature, thus impacting on epidemic transmission. Air temperature and absolute humidity have been reported to significantly affect the transmission of COVID-19 (8).

Information concerning the survival of SARS coronavirus at different temperature and humidity conditions is of great importance to understanding the transmission of the virus. In addition to human-to-human transmission, both epidemiological and laboratory studies have shown that environmental temperature is an important factor in the transmission and survival of coronaviruses (9,10). The aim of this study is to analyze the correlation between meteorological parameters and the COVID-19 pandemic.

MATERIAL AND METHODS

Study Population: One hundred ninety-seven COVID-19 patients diagnosed and treated in the Turkish province of Duzce between 29.03.2020 and 04.05.2020 were included in this study.

Data Collection: The air monitoring measurement parameters published by the National Air Quality Network [PM10 (particulate matter less than 10 μm), PM2.5 (particulate matter less than 2.5 μm), SO2 (sulfur dioxide), NO2 (nitrogen dioxide), NO (nitrogen oxide), CO (carbon monoxide), air temperature, air pressure, relative humidity] were obtained from the relevant web site (http://laboratory.cevre.gov.tr/Default.ltr.aspx).

The study was conducted in full accordance with the local Good Clinical Practice (GCP) guideline and current legislation, while permission for the use of patient data for publication purposes was obtained from Düzce University Faculty of Medicine Ethics Committee.

Polymerase Chain Reaction (PCR) Method: Combined nasopharyngeal-oropharyngeal swab, sputum or tracheal aspirate samples were collected from suspected cases of COVID-19. These were then sent to the laboratory under appropriate conditions in viral transport medium, where they were processed in the biosafety cabinet. Nucleic acid extractions were performed manually using Bio-speedy viral nucleic acid extraction buffer (Bioeksen R&D Technologies, Turkey). PCR testing was then performed using a SARS-CoV-2 (2019-nCoV) RT-qPCR detection kit (Bioeksen R&D Technologies, Turkey) and Montania® Real-Time PCR instruments (Anatolia Geneworks, Turkey). PCR test results were evaluated and reported by the laboratory manager.

Statistical Analysis: Statistical analysis was performed on SPSS-21 software. Descriptive statistics were calculated as frequency and mean, median, and standard deviation values. Pearson's correlation analysis was applied to determine correlations between patient numbers at the beginning of each week over the five-week study period and mean air pollution, air temperature, relative humidity, and air pressure values. p values <0.05 were regarded as statistically significant.

RESULTS

Women constituted 51.8% (n: 102) of the 197 COVID-positive patients, and men 48.2% (n:95). Mean ages were 44.8 ± 17.8 (min:1, max:88, median 43) for women and 44.8 ± 17.7 (min:2, max: 96, median 43) for men (p=0.990). Five-week mean air parameter and pollution values are shown in Table 1).

Table 1. Five-week mean air parameter and pollution (29 April-5 May 2020)

	First week n=26	2nd week n=55	3rd week n=45	4th week n=28	5th week n=34
Temperature ºC	10.6 ± 1.4	12.0 ± 0.9	13.0 ± 1.8	14.7 ± 3.8	17.9 ± 1.8
Relative humidity	90.6 ± 6.2	-	68.2 ± 12.4	74.6 ± 13.3	67.2 ± 6.6
Air pressure	997.1± 2.6	-	1002.3±2.6	999.8± 2.6	995.2±2.8
PM_{10}	46.0 ± 25.9	59.4 ± 22.5	74.9 ± 32.1	58.6 ± 17.7	68.2 ± 8.1
$PM_{2.5}$	24.5 ± 10.7	28.5 ± 9.8	36.4 ± 15.6	28.5 ± 8.6	33.0 ± 3.7
SO_2	2.9 ± 0.7	3.7 ± 0.6	3.6 ± 0.7	4.4 ± 1.3	4.8 ± 0.4
NO	12.5 ± 7.8	11.3 ± 6.5	12.0 ± 5.2	10.3 ± 3.0	13.7 ± 6.3
NO_2	9.7 ± 4.6	8.4 ± 3.8	10.7 ± 3.6	9.4 ± 3.1	15.5 ± 2.3
CO	334.1±235.7	405.9±261.2	558.7±214.5	409.5±182.2	562.7±76.6

PM_{10}: particulate matter less than 10 μm, $PM_{2.5}$: particulate matter less than 2.5 μm, SO_2: Sulfur dioxide, NO: Nitrogen oxide, NO_2: Nitrogen dioxide, CO: Carbon Monoxide

Significant negative correlation was found between positive patient number and air temperature (r= -.247, p= 0.001), relative humidity (r= -.358, p<0.001) and NO2 (r= -.225, p= 0.002) (Figures 1-3). Significant positive correlation was determined between positive patient number and air pressure (r= .444, p<0.001) (Figure 4). No correlation was determined between patient numbers by weeks and PM10, PM2.5, SO2, NO, or CO. (p and r values r=.136 p=.076, r=.047 p=.572, r=-.133 p=.068, r= -.044 p=.549, and r=.040 p= .584, respectively).

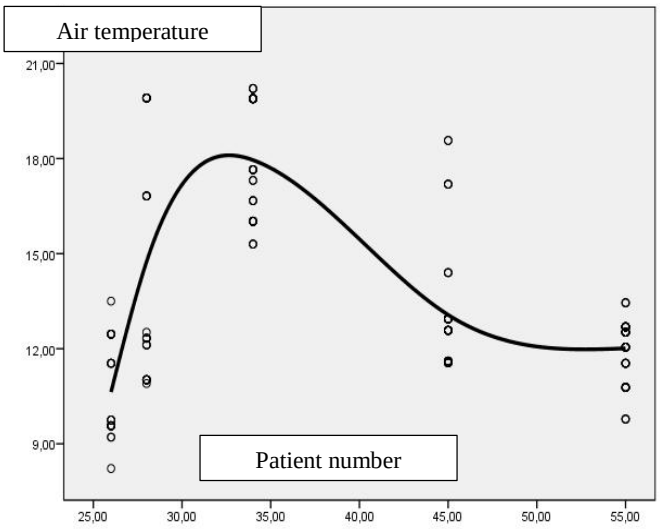

Figure 1. Negative correlation curve between air temperature and COVID-19-positive patient number. Air temperature/patient number (r=-.247, p=.001)

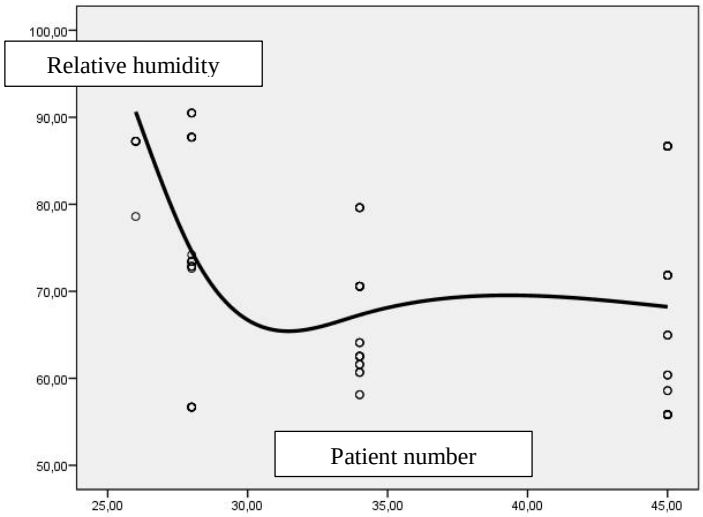

Figure 2. Negative correlation curve between patient number and relative humidity

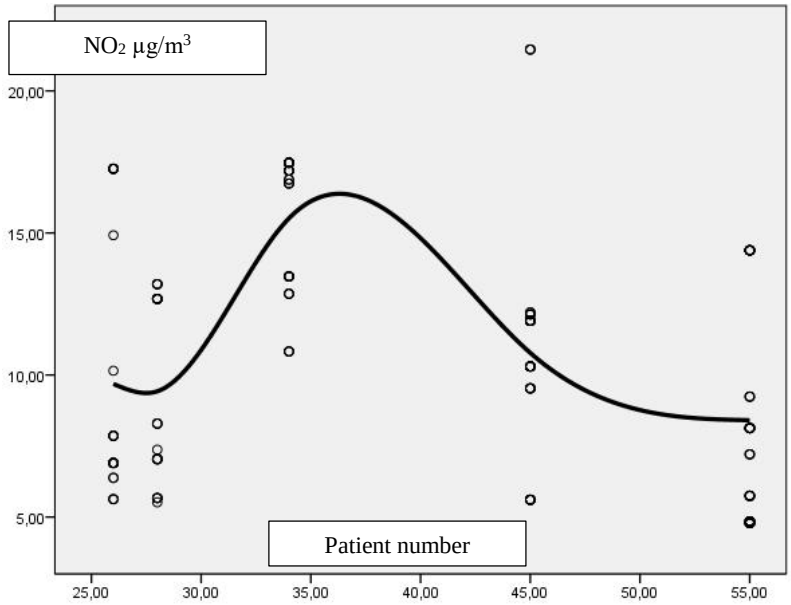

Figure 3. Negative correlation curve between positive patient number and NO2 (r=-.225, p=0.002)

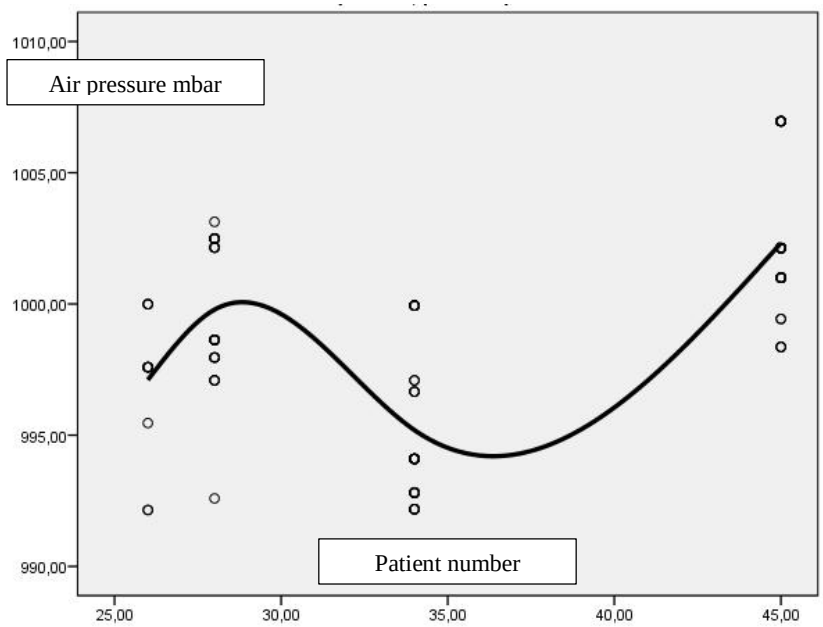

Figure 4. Significant positive correlation curve between positive patient number and air pressure (r=.444, p<0.001)

DISCUSSION

This study investigating the relationship between air quality parameters and COVID-19 case numbers revealed significant negative correlation between positive patient number and air temperature, relative humidity, and NO_2, and significant positive correlation with air pressure, but no correlation with PM_{10}, $PM_{2.5}$, SO_2, NO, or CO.

It is very important to examine the effect of meteorological parameters in outbreaks involving human-to-human transmission. However, the results of studies performed in the field of the COVID-19 pandemic are discrepant. Studies of parameters associated with air pollution have generally involved the effect on COVID-19 infection mortality (11-13). However, mortality outcomes were not evaluated in the present study. In their study of the effect of air pollution of COVID-19 mortality, Xiao Wu et al. (12) reported that a small increase in long-term exposure to $PM_{2.5}$ led to a large increase in the COVID-19 death rate.

Zhu et al. (6) investigated the association between air pollutants and COVID-19 by examining data for 120 cities, and reported significantly positive correlations between $PM_{2.5}$, PM_{10}, CO, NO_2 and O_3 and COVID-19 confirmed

cases, while SO_2 exhibited negative correlation with the number of daily confirmed cases. No significant association between PM_{10}, $PM_{2.5}$, SO_2, NO, and CO and case numbers was found in the present study. This may be due to our low case number and to our cases being included only in the Spring, and this is also a limitation of this study.

One study of case numbers and temperature in China reported that every 1 °C increase at a mean temperature of <3 °C led to an increase in case numbers, but that no such relationship was found when the mean temperature exceeded 3 °C (10). Since the increase in case numbers in China was observed in Winter, the inconsistency with our study results is an expected finding. Temperature values in Turkey in March and April were at higher levels.

Chan et al. (2) examined the stability of the SARS CoV virus at different temperatures and relative humidities and reported better stability in a low temperature and low humidity environment.

Oliveiros et al. (14) examined temperature, humidity, rainfall, and wind speed in terms of modulation of the doubling of COVID-19 cases. They reported that the time to doubling was inversely proportional with temperature and humidity. They calculated that these variables explained 18% of the change in the disease doubling time, the remaining 82% possibly being associated with limitation precautions, general health policies, population density, transport, and cultural factors.

One study examining the relationship between weather and COVID-19 in terms of nine cities in Turkey considered the five main factors of temperature, dew point, humidity, wind speed, and population. Similarly to the present study, those authors found a negative correlation between case numbers and temperature, with case numbers rising as temperature decreased (15).

Biqing Chen et al. (16) examined the effect of four meteorological parameters (air temperature, relative humidity, wind speed, and visibility) on COVID-19 infection and reported that the values for the previous 14 days were correlated with case numbers. However, they did not think that changes in a single weather factor such as temperature or humidity could be well linked to case numbers. Based on their study finding, the authors stated that governments could employ these meteorological factors in outbreak control.

The principal limitation of this study is that exposure to air pollution relied on estimation. Home specific exposure assessments could not be performed since exact addresses were unavailable. The monitoring was also limited by the number of observations taken by the National Air Quality Monitoring Network stations.

Despite these limitations, our findings are important as a preliminary study, since interactions between air pollutants and meteorological factors may be involved in the transmission and pathogenesis of COVID-19, and large-scale studies should now be designed for a better understanding of these interactions.

Conflict of Interest: Authors declared no conflict of interest.

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RESEARCH ARTICLE

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Evaluation of the Attitudes of the Students of the Faculty of Health Sciences towards Healthy Nutrition and Physical Activity

ABSTRACT

Objective: The foundations of a healthy life are laid during youth, and healthy nutrition and regular physical activity are not only two key determinants of health but also two main factors decreasing age-related health risks. Universities are the ideal environments for increasing this awareness and educating university students that constitute the majority of young population on healthy behavioral choices. This study aimed to evaluate the factors affecting the attitudes of the students of the Faculty of Health Sciences (Department of Physiotherapy and Rehabilitation and Department of Nutrition and Dietetics) at a foundation university towards healthy nutrition and physical activity.

Methods: The total number of students in the Department of Physiotherapy and Rehabilitation and Department of Nutrition and Dietetics was 467. The study aimed to reach the whole universe and was conducted with 339 students (73%) that consented to participate. Study data were collected via face-to-face surveys that covered the sociodemographic data form, demographic data questions of the modified survey by the University of North Florida on Diet and Exercise and the survey including the Body Image Scale. The study received an approval from the Scientific Researches Ethics Council of the School of Medicine of Trakya University (TÜTF-BAEK 2019/163). Study data were analyzed using SPSS 25.0 program. Significance level was $p<0.05$. Chi-square analysis was used for group comparisons as the data were categorical variables.

Results: While the Cronbach's α coefficient was 0.91 in the original Body Image Scale, it was 0.959 in our study. In addition, while prediction point was 135 in the original scale, it was 134.5 according to our ROC analysis. 49.6% of students stated that they did not exercise; 27.1% of those associated it with "lack of time" while 17.1% cited "lack of willpower". 54% of students considered their diets unhealthy. There was a statistically significant difference between lack of exercise and gender ($p<0.05$). 81% of females did not exercise at all while 19% of males did not exercise. Among students whose body image perception was below average, the number of those not exercising (n=52) was higher than those exercising (n=36), and this was statistically significant ($p<0.05$).

Conclusions: According to results of this study, university students should be provided with awareness programs on healthy nutrition and exercise to promote healthy lifestyle behaviors.

Keywords: Exercise, Body Image, Dietary Habits.

Sağlık Bilimleri Fakültesi Öğrencilerinin Sağlıklı Beslenme ve Fiziksel Aktiviteyle İlgili Tutumlarının Değerlendirilmesi

ÖZET

Amaç: Sağlıklı yaşamın temelleri gençlik döneminde atılır. Dengeli beslenme ve düzenli fiziksel aktivite sağlığın önemli iki belirleyicisi olmanın yanında yaşlanmayla ilgili sağlık risklerini azaltmada etkili iki temel unsurdur. Üniversiteler bu farkındalığı artırmak için ideal ortamlardır. Bu çalışma Sağlık Bilimleri Fakültesi öğrencilerinin sağlıklı beslenme ve fiziksel aktiviteyle ilgili tutumlarını etkileyen faktörlerin değerlendirilmesi amacıyla yapılmıştır.

Gereç ve Yöntem: Beslenme ve Diyetetik, Fizyoterapi ve Rehabilitasyon bölümlerinde toplam 467 öğrenci bulunmaktaydı. Evrenin tamamına ulaşılması hedeflendi. Sadece 339 (%73) öğrenci çalışmaya katıldı. Veriler; sosyo-demografik veriler, Modifiye Edilmiş North Florida Üniversitesi Diyet ve Egzersiz Anketi'nin demografik içerikli soruları ve Beden Algısı Ölçeği'ni içeren anket formu ile yüz yüze toplandı. Verilerinin analizinde SPSS 25.0 programı kullanıldı. Anlamlılık düzeyi $p<0,05$ alındı. Bulgular: Çalışmada kullandığımız Beden Algısı Ölçeğinin orijinalinde 0.91 olan Cronbach α katsayısı çalışmada 0.959 olarak hesaplandı. Ayrıca orijinal ölçekte 135 olarak hesaplanan kestirim noktası yapılan ROC analizi sonucunda 134.5 olarak bulundu. Öğrencilerin %49,6'sı egzersiz yapmadığını belirtirken bunların %27,1'i bu durumu zaman kısıtlılığına %17,1'i ise irade zayıflığına bağlamaktaydı. Öğrencilerin %54'ü sağlıklı beslenmediğini düşünmekteydi. Egzersiz yapmama ile cinsiyet arasında istatistiksel olarak anlamlı farklılık saptandı ($p<0,05$). Beden algısı ortalama değerin altında olan öğrencilerde egzersiz yapmayanların sayısının (n=52) yapanlardan (n=36) yüksek olması istatistiksel olarak anlamlı bulundu ($p<0,05$).

Bulgular: PNP olan hastalarda glikolize hba1c oranı, açlık kan şekeri PNP olmayan hastalara göre anlamlı olarak yüksek bulundu. ($p < .001$) PNP' si olan hastalarda HDL oranı PNP'si olamayan hastalara göre düşük saptanırken ($p < 0.01$), TG/HDL oranı daha yüksek saptandı ($p < 0.05$). PNP olan hastalarda glikolize üre ($p < 0.001$) ve kreatinin ($p < 0.01$), PNP olmayan hastalara göre anlamlı olarak yüksek saptandı. PNP olan hastalarda 25(OH) vitamin D düzeyi, PNP olmayan hastalara göre anlamlı olarak düşüktü. ($p < 0.05$). PNP olan hastalarda ferritin, olmayan hastalara göre anlamlı olarak daha yüksek saptandı ($p <0 .01$).

Sonuç: Çalışma sonuçları doğrultusunda üniversite öğrencilerine sağlıklı beslenme ve egzersiz konulu farkındalık programları sunularak sağlıklı yaşam biçimi davranışları teşvik edilmelidir.

Anahtar Kelimeler: Egzersiz, Beden Algısı, Beslenme Alışkanlıkları

INTRODUCTION

The foundations of a healthy life are laid during youth, and healthy nutrition and regular physical activity are the two key determinants of health (1,2,3). Diet and physical activity are the effective factors in minimizing age-related health risks (4). Chronic diseases, which are the leading causes of death, affect both adults and the young (5). Studies reported that behaviors such as unhealthy diets, physical inactivity, tobacco use and excessive use of alcohol pose health risks starting from early ages (6,7). Particularly university students, who are one of the first groups that pass from adolescence to adulthood, leave their families and become exposed to external effects in the process, which also requires from them to make individual decisions (8).

As the first years of university coincide with adolescence, the visible acceleration of growth and development along with the changing lifestyle can affect the dietary habits of university students. According to studies, university students in Turkey are undernourished and malnourished, and this is due to two main reasons (9). These are lack of information (9) and lack of economic means (8). Eating junk food, dieting excessively, and consuming high-calorie and low-nutrition foods due to these reasons lead to unhealthy nutrition (10).

Eating out more and particularly consuming fast-food may lead to undernourishment and malnutrition, and negative body image may cause various eating disorders (1). Body image is the dynamic idea that someone has of what their own body looks and feels rather than the external evaluation of others (11-13). Each person has a different and separate idea of his or her own body image, and this idea covers body shape, size, mass, structure, functions, whole body and body parts (14). It can also be affected by environment, cultural messages and social appearance standards (11,12).

According to a study examining social factors, media has a big impact on body image (15). Moreover, media is reported to be a strong contributing force due to the time the population (especially adolescent population) spends using various aspects of it, including internet, television, magazines, video games, and smart phones (16). There are increased presentations of idealized beauties in the mass media. Thinner bodies are considered to be acceptable for females while heavily muscular bodies are presented as likeable for men. Since university students face a new social environment that is in less contact with their families and open to prevalent and dominant social models and representation, body image dissatisfaction is triggered in people whose body images do not fit those (17).

Another risk factor for the health of university students is the lack of physical activity (18). Due to its increased prevalence and negative health effects, physical inactivity is a major public health problem that should be fought against (19-22). A study in 2012 reported that the rate of diseases preventable by physical activity were 9.3% for coronary heart diseases; 11.5% for type 2 diabetes; 16.6% for colon cancer; 16.3% for breast cancer; and their overall rate was 15.0% (23). Another study in 2004 reported that while students were aware of the benefits of exercise, only 35% exercised regularly (10).

Physical activity affects our psychological and physical health in all stages of our lives (24) and young people with insufficient physical activity is a risk group for hypertension, diabetes, obesity, coronary heart diseases and some types of cancer (25).

University students constitute the majority of young population and can change their behaviors with environmental influences (26). Students should be healthy, physically active (2) and eat well (6) to succeed in their academic studies.

According to studies, universities are the best environments to raise awareness and educate students on healthy behavioral choices such as healthy diets, regular physical activity and weight control (25,6). Positive changes made by university students in their exercise and dietary habits will continue in their adulthood (10,8). Therefore, it is important to identify their behaviors related to eating and exercising and help them improve those in a health way at university (26).

Due to all those reasons, this study aimed to evaluate the factors affecting the attitudes of the students of the Faculty of Health Sciences (Department of Physiotherapy and Rehabilitation and Department of Nutrition and Dietetics) at Istanbul Esenyurt University towards healthy nutrition and physical activity. In line with this purpose, the study will contribute to science and society by creating awareness that healthy nutrition and exercise can prevent chronic diseases caused by poor diets and sedentary lifestyle, which are important community health problems, and to literature by setting an example for new studies.

MATERIAL AND METHODS

There were 467 students in the Faculty of Health Sciences (Department of Physiotherapy and Rehabilitation and Department of Nutrition and Dietetics) of a foundation university, where the study was conducted, in the 2019-2020 academic year. The study aimed to reach the whole universe and was conducted with 339 students (73%) that consented to participate. Study data were collected via face-to-face surveys that covered the sociodemographic data form, demographic data questions of the modified survey by the University of North Florida on Diet and Exercise and the survey including the Body Image Scale. The study received an approval from the Scientific Researches Ethics Council of the School of Medicine of Trakya

University (TÜTF-BAEK 2019/163). Study data were analyzed using SPSS 25.0 program. Significance level was $p<0.05$. As the data were categorical variables, chi-square analysis was used for group comparisons. While the Cronbach's α coefficient was 0.91 in the original Body Image Scale, it was 0.959 in our study. In addition, while prediction point was 135 in the original scale, it was 134.5 according to our ROC analysis.

RESULTS

According to the distribution of demographic variables, 73.2% of participants were female. 87% were in the age range of 17-22. Department of Physiotherapy and Rehabilitation had 178 students. Department of Nutrition and Dietetics had 161 students. 65.5% of students stayed at houses, and 33.3% stayed at private and state dormitories. Of those staying at houses, 48.7% lived with their parents, and 36.6% lived with friends. The allowance of 68.7% was 1000 TL and below.

According to the distribution of the variables of smoking and alcohol consumption, 75.8% of students did not smoke and never smoked before. 19.5% consumed alcohol and 95.4% of those consumed alcohol 0-7 times a week (Table 1).

Table 1. Distribution of the variables of smoking and alcohol consumption

Variables		Number (N)	Percentage (%)
Do you smoke	No, I don't smoke. I have never smoked.	257	75.8
	I smoke	60	17.7
	I used to smoke. I quitted it.	22	6.5
How many cigarettes do you smoke per day	1-5	19	5.6
	6-10	24	7.1
	11-15	9	2.7
	16-20	8	2.4
	21 and more	1	0.3

H1: There is a significant relationship between gender and breakfast consumption.

In our study, breakfast was the most commonly skipped meal. 12 participants never have breakfast while 112 participants always have breakfast. Of those having breakfast, 75.9% were female and 24.1% were male. There was no statistically significant relationship between gender and breakfast consumption ($p>0.05$). 50.4% of students stated that they exercised.

25.7% stated that its frequency was 0-2 times a week (Table 2). When we questioned students on why they exercised, the most common response was "staying fit" (25.1%) with 85 participants, and the second one was "losing weight" (13.3%) with 45 participants.

Table 2. Distribution of the variable of exercising

		Number (N)	Percentage (%)
Do you exercise	No	168	49.6
	Yes	**171**	**50.4**
What is the frequency of your exercise	0-2 times a week	87	25.7
	3-4 times a week	62	18.3
	5 or more times a week	23	6.8

49.6% of participants did not exercise. Their reasons for not exercising included lack of time (27.1%), lack of willpower (17.1%) and lack of motivation (14.2%).

In addition, 54% of participants considered their diets unhealthy. Of those with healthy diets, 73.1% stayed at houses, 3.2% stayed at state dormitories and 23.7% stayed in private dormitories.

According to the distribution of snacks consumed in a day, the foods consumed most by students were chips, crackers, hazelnuts, peanuts (53.9%); ice cream, cookies, candies (14.3%); fast food (16.7%); chocolate (5%); raisins, roasted chickpeas, walnuts (6.9%) and others (2.9%).

H2: There is a significant relationship between gender and emotional eating.

There was a statistically significant relationship between male and female participants in terms of emotional eating ($p<0.05$). The number of females that exhibited emotional eating habits (n=40) was significantly higher than the number of males (n=4).

H3: There is a significant relationship between gender and waist circumference classification.

There was no statistically significant relationship between male and female participants in terms of waist circumference classification ($p<0.05$). The ratio of females was higher in the risk and high-risk groups but it was not statistically significant.

Participants were divided into two groups according to their body image satisfaction (low or high) based on the results of the Body Image Scale. According to this, 74% of participants were satisfied with their body images (Table 3).

Table 3. Body image satisfaction

	Number	Percentage (%)
Body image satisfaction is low	88	26.0
Body image satisfaction is high	251	74.0
Total	339	100.0

H4: There is a significant relationship between gender and genital appearance satisfaction.

29 participants out of 339 did not reply this question. Evaluations were made with the replies of 310 participants. There was a statistically significant difference between gender and genital appearance satisfaction ($p<0.05$). The number of females who were dissatisfied with genital appearance (n=64) wash higher than the number of males (n=49) and this was statically significant ($p<0.05$). The females who were highly satisfied with genital appearance constituted 28.8% of total female participants. The males who were highly satisfied with genital appearance constituted 55.7% of total male participants. Moreover, 40 participants did not answer the "my sexual activities" part in the Body Image Scale, and 37 of them were female. 29 participants did not answer the "my sexual organs" part, and 26 of them were female. Similarly, 32 participants did not answer the "my sexual potency" part, and 31 of them were female.

H5: There is a significant difference between gender and exercising.

There was a statistically significant relationship between gender and exercising ($p<0.05$). 81% of females and 19% of males never exercised. There was no statistically significant relationship between exercising and class ($p>0.05$). 171 participants exercised while 168 participants did not.

H6: There is a significant relationship between exercising and the departments of students.

The number of students that exercised was higher in the Department of Physiotherapy and Rehabilitation, and this was statistically significant (Table 4).

Table 4. Distributions of exercising students by departments

Variables		**Exercising**					
		No		**Yes**		**Total**	
		n	%	n	%	n	%
Department	Physiotherapy	77	45.8	101	59.1	178	52.5
	Nutrition	91	54.2	70	40.9	161	47.5
	Total	168	100	171	100	339	100
	Test values	$p=0.015$ $\chi^2=5.949$ sd = 1 $p<0.05$*					

DISCUSSION

Studies reported that eating and physical activity behaviors of university students affect both their academic success and whether they will develop chronic diseases in the future (6-8).

An examination of the dietary habits of adolescents reported that they skipped meals and the skipped meals were usually breakfast and lunch (27). Studies reported that breakfast played a big role in nutrition, and skipping breakfast had a negative effect on students' school success (28,1). A study on the memory and blood glucose of university students reported that memory function correlated with blood glucose concentrations, and breakfast consumption facilitated this process (29). Another study covering female university students in 2010 found that 44.1% of them had breakfast every day (30). In the study by Sakamaki et al. (2005), 66.8% of males and 82.3% of females reported eating breakfast regularly (31). A study made in 2015 found that 72.1% of females and 64.7% of males skipped meals (32). According to Chi-square analysis, there was no significant relationship between skipping breakfast and gender. We had similar results in our study as we found that breakfast was the most commonly skipped meal and there was no statistically significant relation between eating breakfast and the variables of gender and place of residence ($p>0.05$). That means, according to our study, a person's gender or place of residence is not a determinant for eating breakfast.

The relationship between gender and snacking:

In terms of exhibiting emotional eating habits, the number of females (n=40) was significantly higher than the number of males (n=4). According to Mudd (2002), females have a different psychological and mental structure and they are the more emotional party in the society (33). The study by Akdevelioğlu (2019) found that emotional eating score was significantly higher in females than males, and this result was parallel to our finding (34). In addition, the higher levels of snacking in females can be caused by the decreased blood glucose, which starts in females two weeks before the menstruation period, and the associated emotional exhaustion.

Obesity has become a severe health problem in recent years. The rate of obesity is generally higher in females than males in our country, which is also the case throughout the world (35). Our study found that the number of female students was higher than the number of male students in the risk and high-risk groups in terms of waist circumference classification, but this result was not statistically significant.

Our study found that genital appearance satisfaction was lower in female students than male

students. There was not a similar finding in the studies on university students according to our literature review. However, body image in females is generally more affected by the social standards of appearance, and gender-related cultural stereotypes and roles are adopted particularly for females along with gender characteristics. In addition, media considers thinner bodies as acceptable and desirable stereotypes and popularizes this body image. In that context, a failure to fit into this body image triggers a body image dissatisfaction in females, which in turn causes the abovementioned result.

In our study, students that did not reply the questions related to "my sexual activities", "my sexual organs" and "my sexual potency" in the Body Image Scale were mostly female. This indicates that female students were shier than male students in replying sexuality-related questions. In our opinion, this derives from gendered social and cultural norms.

A study examining the relationship between gender and physical activity found that vigorous, moderate and total physical activities were higher in males than females (36). The study by Savcı et al. (2006) examined the physical activity levels of university students and found that males had higher scores than females in vigorous, moderate and total physical activities as well as walking (37). Another study made in 2015 among university students in 23 countries found that males exercised more intensively than females in all countries except for six countries (38). They reported that Turkey was among the exceptional countries. However, studies made among university students in Turkey reported that the habit of exercising regularly was lower among females than males. Various studies made in our country and other countries found that physical activity level was higher in males than females (39,40). One study made with 2729 Australian college students found that 47% of females and 32% of males were insufficiently active (41). Our results were similar to the results of those studies.

In terms of physical activity levels among the students of different departments included in our study, the number of students that exercised was higher in the Department of Physiotherapy and Rehabilitation, and this was statistically significant ($p<0.05$). The importance of exercise is taught for four years in health-based departments such as the Department of Physiotherapy and Rehabilitation so this result supported the idea that the level of exercises increases as knowledge on its benefits increases.

CONCLUSION

Our study indicated that most students skipped meals, that breakfast was the most commonly skipped meal, and that most students did not exercise. According to those results, university management has a big role to play in creating positive effects on students' lives. Environmental conditions play an important role in physical activity so we recommend increasing the number of sportive and social areas where students can perform different physical activities. University cafeterias can become more attractive with healthy and affordable menus. In addition, healthy lifestyle behaviors should be promoted by providing seminars and awareness programs on health nutrition and exercise.

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RESEARCH ARTICLE

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Investigation of Protective Effects of Dehydroepiandrosterone (DHEA) Against Toxic Damage Caused by Doxorubicin in Rat Ovaries

ABSTRACT

Objective: Our aim is to evaluate whether dehydroepiandrosterone has a protective effect on doxorubicin-induced ovarian damage.

Methods: The rats were divided into three groups. Group 1 (the control Group): no treatment was administered. Intact ovarian tissue was removed, and blood samples were taken for the anti-Mullerian hormone (AMH) test. Group 2 (the doxorubicin Group): Rats received doxorubicin intraperitoneally at a single dose of 3 mg/kg. Group 3 (the doxorubicin + DHEA Group): Rats received doxorubicin intraperitoneally at a single dose of 3 mg/kg at baseline and DHEA subcutaneously for 10 days at a dose of 60 mg/kg daily. Rats in groups 2 and 3 were sacrificed at the end of 10 days, ovarian tissues were removed and blood samples were taken for AMH test.

Results: While normal ovarian tissue damage scores were zero except hemorrhage, doxorubicin showed significant damage and histopathological changes in all rats. Doxorubicin and Doxorubicin + DHEA groups had higher edema, vascular congestion, cellular degeneration, and total damage scores than the normal ovarian group. The number of antral follicles and ovarian volume decreased in the doxorubicin group compared to the normal ovarian group ($p = 0.011$ and 0.002, respectively). In the doxorubicin + DHEA group, ovarian volume was similar to the normal ovary ($p = 0.091$), but the number of antral follicles was significantly lower in this group ($p = 0.002$). AMH values did not differ between the normal ovarian group and the other groups.

Conclusions: It was concluded that DHEA was not effective in preventing ovarian damage caused by doxorubicin.

Keywords: Doxorubicin, Dehydroepiandrosterone, Anti-Mullerian Hormone, Ovary, Rat

Rat Overlerinde Doksorubisinin Neden Olduğu Toksik Hasara Karşı Dehidroepiandrosteronun (DHEA) Koruyucu Etkilerinin Araştırılması

ÖZET

Amaç: Amacımız, dehidroepiandrosteronun (DHEA) doksorubisine bağlı over hasarı üzerinde koruyucu bir etkisinin olup olmadığını değerlendirmektir.

Gereç ve Yöntem: Ratlar üç gruba ayrıldı. Grup 1 (kontrol grubu), tedavi uygulanmadı. Sağlam over dokusu çıkarıldı ve Anti-Mulleran Hormon (AMH) testi için kan örnekleri alındı. Grup 2 (doksorubisin grubu), ratlara 3 mg/kg'lık tek bir dozda intraperitonal yoldan doksorubisin verildi. Grup 3 (doksorubisin + DHEA grubu), ratlara intraperitonal yolla 3 mg/kg'lık tek bir dozda doksorubisin ve günde 60 mg/kg'lık bir dozda subkutan olarak DHEA verildi. Grup 2 ve 3'teki ratların onuncu günün sonunda yumurtalık dokuları alındı ve AMH testi için kan örnekleri alındı.

Bulgular: Normal over doku hasarı skorları kanama dışında sıfır olmakla birlikte, doksorubisin tüm deneklerde anlamlı hasar ve histopatolojik değişiklikler gösterdi. Doksorubisin ve Doksorubisin + DHEA gruplarında normal over grubundan daha yüksek ödem, vasküler konjesyon, hücresel dejenerasyon ve toplam hasar skorları vardı. Antral folikül sayısı ve yumurtalık hacmi doksorubisin grubunda normal over grubuna göre azaldı (sırasıyla $p = 0.011$ ve 0.002). Doksorubisin + DHEA grubundaki over hacmi, normal over hacmine benzerdi ($p = 0.091$), ancak antral folikül sayısı bu grupta anlamlı olarak daha düşüktü ($p = 0.002$). AMH değerleri normal over grubu ile diğer gruplar arasında farklılık göstermedi.

Sonuç: DHEA'nın doksorubisinin neden olduğu over hasarını önlemede etkili olmadığı sonucuna varıldı.

Anahtar Kelimeler: Doksorubisin, Dehidroepiandrosteron, Anti-Mulleran Hormonu, Over, Rat

INTRODUCTION

Recent developments in cancer management and early diagnosis of cancer have led to an improvement in the quality of life and overall survival of pediatric and young females with cancer.(1) All these advancements have increased the life expectancy of patients diagnosed with cancer.(2) Currently, the survival rate has increased to 80%–90% for certain types of cancer such as breast cancer and childhood leukemia.(3, 4) In fact, the 5-year survival rate for pediatric cancer, which was 58% in the mid-1970s, has now increased to 83%.(5) With the increase in the survival rate for cancer, the side effects of cancer treatments are drawing more concern.(6)

In oncology, a conventional approach is defined as an untargeted and non-selective therapy as the initially developed therapeutic agents rapidly affect cell division, thereby impacting normal and cancerous cells.(7) Cytotoxic chemotherapy is the basis for the treatment of various childhood malignancies; however, these treatment methods are known to have several side effects.(8) Doxorubicin is a prototype agent of anthracycline antibiotics.(9) Anthracycline antibiotics are used for the treatment of several human malignant neoplasms such as various solid tumors (ovarian, breast, lung and liver cancer), Hodgkin's disease, Kaposi sarcoma, leukemia, lymphoma and childhood cancer.(10-12) Despite being a commonly used medication with high efficacy, the clinical use of doxorubicin has been limited due to its side effects.(13-16) Ovarian toxicity due to chemotherapy is a critical problem for children (0–15 years) and patients of reproductive age (15–44 years).(17) Chemotherapeutic chemicals are known to cause reproductive toxicity, damage ovarian follicles and increase the risk of premature ovarian failure and premature menopause.(18-20)

Dehydroepiandrosterone (DHEA) is a weak androgenic steroid primarily secreted from the adrenal glands as well as the ovaries and peripheral feedback.(21) Many tissues can intake DHEA and its sulfated metabolite (DHEA-S) after they are metabolized into active androgenic and estrogenic sterol compounds, which are required for growth and development.(22) DHEA has drawn the interest of specialists in recent years for increasing fertility.(23, 24) An international survey showed that in 26% cases of in vitro fertilization (IVF), clinicians used DHEA as an auxiliary agent for such women.(25)

In a meta-analysis, Ji et al. showed that DHEA supplementation before IVF could improve pregnancy rate and increase the number of oocytes collected, although it did not affect miscarriage rate and the total gonadotropin dose used.(26)

The present study aimed to investigate whether DHEA had protective effects on doxorubicin-induced ovarian damage.

MATERIAL AND METHODS

This study was conducted at the Animal Testing Laboratory of University in July 2019 after obtaining the approval of the Ethics Committee.

Laboratory Animals and the Care of Animals in Research: Ten-twelve week-old female Wistar Albino (Rattus Norvegicus species) rats weighing 180 to 220 grams were used in this study. Rats received light exposure 12 hours a day (from 08:00 to 20:00) and had access to food (standard rodent pellet) and drinking water (tap water) without restriction and were kept at a room temperature of 21 to 23ºC with a humidity of 40 to 50%. Rats were housed 4 or 5 per cage. The number of rats was chosen in line with previous studies. Rats were randomly assigned to four groups of 8. Considering bowel transit time, rats were not fed within 6 hours before laparotomy to empty the gut and allow surgery but had access to drinking water.

Study Groups: Group 1 (the control Group): These rats underwent a laparotomy procedure at baseline, and their ovaries were removed. Blood was drawn from the inferior vena cava for AMH testing.

Group 2 (the doxorubicin Group): Rats received doxorubicin intraperitoneally at a dose of 3 mg/kg at baseline(27) and underwent an oophorectomy procedure at the end of day 10 of the study. After sacrificing the rats, at least 2-3 ml of blood was collected for AMH testing. Then, laparotomy was performed, and both ovaries were excised for histopathological examination.

Group 3 (the doxorubicin + DHEA Group): Rats received doxorubicin intraperitoneally at a dose of 3 mg/kg at baseline. Also, they received DHEA (Cayman Chemical, Michigan, USA, CAS registry no: 53-43-0, item no:15728) subcutaneously for 10 days at a dose of 60 mg/kg daily as dissolved in 0.1 ml of sesame oil.(28, 29) After sacrificing the rats, at least 2-3 ml of blood was collected for AMH testing. Then, laparotomy was performed, and both ovaries were excised for histopathological examination.

Doxorubicin Dose and Preparation: Doxorubicin was administered intraperitoneally at a dose of 3 mg/kg only at baseline. While preparing the drug, we used the central drug preparation unit of our hospital (with Robotic Chemotherapy Drug Preparation System) in a closed environment where microbiological contamination and employee exposure risks are eliminated under conditions in compliance with national and international standards. Negative pressure indoor air environment complied with ISO 5 and had Class 100 and GMP Class A double HEPA filter air cleaning system, safe waste management system, high capacity laminator current, and dose sensitivity information (gravimetric and volumetric) measurement, and the barcode system was performed.

Surgical Procedures: Sterile, powder-free, latex gloves were used during all surgical procedures. The procedure was performed while the rats were lying in a supine position. The abdominal area was shaved before the procedure, and the surgical site was prepared using a 10% Povidone-iodine solution (Batticon; Adeka Laboratories, Istanbul, Turkey). A 5 cm median (on the line between the xiphoid process and pubis) incision was made to enter into the abdominal cavity, and each surgical procedure lasted 5 to 10 minutes to protect the drying effect of the room air. After the removal of ovaries for histological examination, animals were decapitalized and disposed of in red waste containers (Figure 1).

Histopathological Examinations: Surgically excised ovaries were fixed in 10% formalin. Paraffin blocks were prepared 24 hours after the oophorectomy procedure. Tissue sections of 5 micrometers were taken, and follicular activity was assessed in 5 randomly selected samples from each ovary. Slides were stained with hematoxylin-eosin and examined under a light microscope. The paraffin blocks were sectioned using a microtome blade (Leica, Nussloch, Germany). Every slide was blindly assessed by the same pathologist. A light microscope (Olympus Clinical Microscope, Tokyo, Japan) was used to analyze the sections.

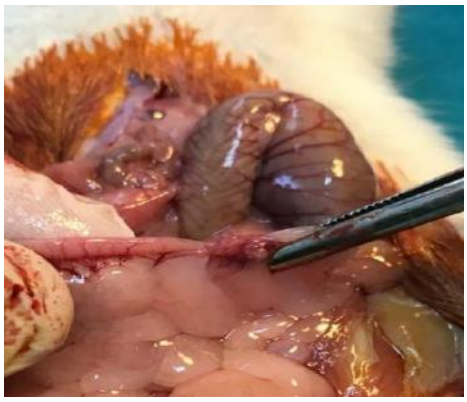

Figure 1. Excision of the ovary

Edema, vascular congestion, inflammation, cellular degeneration, and hemorrhage were examined as histopathological injury scores (figure 1). The scores were evaluated as described by Celik et al.(30). Pathological findings were rated. Grade 0 indicated normal alterations and no abnormal findings; Grade 1 indicated mild edema, mild vascular congestion, absence of hemorrhage or leukocyte infiltration; Grade 2 indicated moderate edema, moderate vascular congestion, absence of hemorrhage or leukocyte infiltration; Grade 3 indicated severe edema, severe vascular occlusion, minimal hemorrhage, and minimal leukocyte infiltration, and Grade 4 indicated severe edema, severe vascular occlusion, hemorrhage, and leukocyte infiltration. (Figure 2)

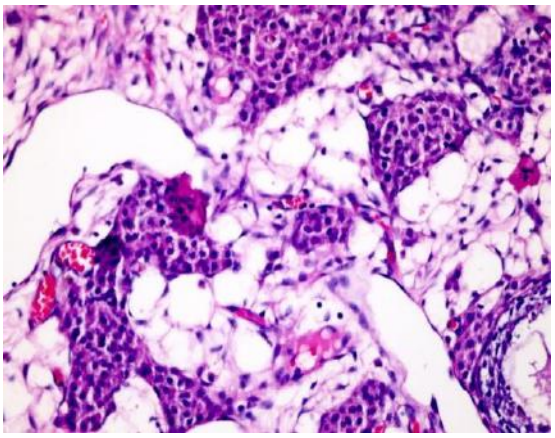

Figure 2. Significant edema x400 hematoxylin-eosin

All follicles were counted to assess ovarian reserve. Primordial, primary, secondary (pre-antral), tertiary (antral), and atretic follicles were counted (Figures 3, 4). Follicles were evaluated as described by Parlakgumus et al.(31).

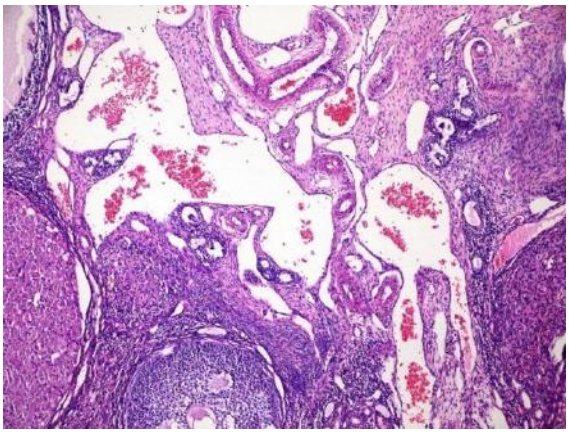

Figure 3. Veins with marked dilatation x200 hematoxylin-eosin

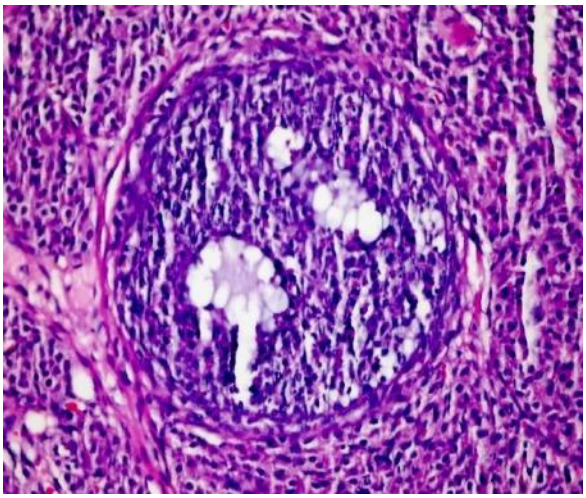

Figure 4. Degenerated follicle x400 hematoxylin-eosin

Primordial, primary, secondary (pre-antral) and tertiary (antral) follicles were counted. Primordial follicle is described as an oocyte with only one surrounding epithelial cell layer, and the primer follicle is surrounded by one or more layers of cuboidal granulosa cells. Secondary/ pre-antral follicle is surrounded by more than two cell layers and consists of antrum follicles and zona pellucida. The tertiary follicle is defined if there are antrum, stratum granulosum and surrounding cumulus oophorus layers. In an atretic follicle, the basement that separated the oocyte from granulosa cells often thickens to become the glassy membrane. Fibrous material replaces the granulosa cells, and loss of cohesion may occur in granulosa cells.

AMH Assays: Blood samples were collected into tubes containing lithium heparin (BD Vacutainer Plasma tubes, Manchester, England). The concentration of the Lithium Heparin additive in these tubes is 17 international units of heparin/ml of blood. The blood samples were centrifuged within 30 minutes of sampling. After 15 minutes of centrifugation at 1000xg, serum was removed, and the remaining plasma was transferred into an Eppendorf tube and stored frozen at -20ºC until the time of analysis. AMH concentrations were measured in "ng/ml" plasma using the ELISA method. The rat AMH kit used in the study had a sensitivity of 0.10 g/mL, a detection range of 0.16 to 10 ng/mL and a coefficient of variation less than 10% (Elabscience, Rat AMH kit; Houston, Texas, ABD). The laboratory technician of the laboratory of the university hospital was blinded to the study groups and unaware of which samples belonged to which rat. All samples were analyzed in the same assay.

Statistical Analysis: SPSS version 17.0 was used for statistical analyses. The normal distribution of variables was evaluated using histograms and Kolmogorov–Smirnov test. Mean, standard deviation, median, and interquartile range are used to present descriptive statistics. Non-normally distributed (non-parametric) variables were compared between two groups using Mann–Whitney *U*-test. Spearman's correlation test was used for the analysis of measurement data. A *p*-value <0.05 was considered statistically significant.

RESULTS

Histopathological damage scores were compared between the groups. While ovarian tissue damage scores were 0, except in cases of hemorrhage, significant damage and histopathological changes were observed in the ovarian tissues of rats that were administered doxorubicin. Edema, vascular congestion, cellular generation, and total damage scores of the doxorubicin and doxorubicin+DHEA groups were found to be higher than those of the normal ovary group. Further, their inflammation and hemorrhage scores showed no increase compared to those of the normal ovary group (Table 1).

Table 1. Comparison of histopathological damage scores of normal ovary vs doxorubicin and doxorubicin + DHEA groups

	Normal ovary	Doxorubicin	*P**	Doxorubicin +DHEA	*P***
Edema					
Mean SD	0,00±0,00	0,75±0,71	**0,010**	1,50±0,53	**<0,001**
Median- IQR	0,00(0,00-0,00)	1,00(0,00-1,00)		1,50(1,00-2,00)	
Vascular congestion					
Mean SD	0,00±0,00	0,88±0,64	**0,003**	1,25±0,71	**0,001**
Median- IQR	0,00(0,00-0,00)	1,00(0,50-1,00)		1,00(1,00-2,00)	
Inflammation					
Mean SD	0,00±0,00	0,13±0,35	0,317	0,00±0,00	1,000
Median- IQR	0,00(0,00-0,00)	0,00(0,00-0,00)		0,00(0,00-0,00)	
Cellular degeneration					
Mean SD	0,00±0,00	0,75±0,89	**0,027**	0,50±0,53	**0,025**
Median- IQR	0,00(0,00-0,00)	0,50(0,00-1,50)		0,50(0,00-1,00)	
Hemorrhage					
Mean SD	0,13±0,35	0,00±0,00	0,317	0,00±0,00	0,317
Median- IQR	0,00(0,00-0,00)	0,00(0,00-0,00)		0,00(0,00-0,00)	
Total score					
Mean SD	0,13±0,35	2,50±1,41	**0,001**	3,25±1,16	**<0,001**
Median- IQR	0,00(0,00-,00)	2,00(1,50-3,50)		3,50(2,00-4,00)	

*, ** Mann-Whitney U Test

Primordial, primary, secondary, tertiary, and atretic follicle counts were compared with ovarian volume. The results revealed that the doxorubicin group had decreased antral follicle count (AFC) and ovarian volume than the normal ovary group (p = 0.011 and 0.002, respectively). The doxorubicin+DHEA and normal ovary groups had similar ovarian volume (p=0.091); however, AFC was significantly lower in the doxorubicin+DHEA group (p=0.002; Table 2).

Table 2. Comparison of normal ovary vs Doxorubicin, Doxorubicin + DHEA groups in terms of follicle count and AMH values

	Normal ovary	Doxorubicin	P*	Doxorubicin +DHEA	P**
Primordial follicle					
Mean SD	12,75±1,91	8,25±5,68	0,091	9,25±5,73	0,339
Median- IQR	12,50(11,50-14,00)	7,00(3,00-13,00)		9,00(5,00-14,00)	
Primer follicle					
Mean SD	10,50±2,33	9,88±5,46	0,833	10,50±6,09	0,792
Median- IQR	11,00(8,50-12,00)	9,50(6,00-14,00)		12,00(4,00-15,50)	
Secondary (pre-antral) follicle					
Mean SD	12,25±1,83	9,63±4,24	0,114	11,13±3,00	0,363
Median- IQR	12,50(10,50-13,50)	8,50(6,50-13,00)		10,50(10,00-13,00)	
Tertiary (antral) follicle					
Mean SD	21,50±3,21	13,88±5,19	**0,011**	14,00±2,27	**0,002**
Median- IQR	22,00(19,50-23,50)	13,00(10,00-16,50)		14,00(12,00-16,00)	
Atretic follicle					
Mean SD	,25±,46	,88±1,13	0,223	,75±1,04	0,268
Median- IQR	,00(,00-,50)	,50(,00-1,50)		,50(,00-1,00)	
AMH (ng/mL)					
Mean SD	3,42±,79	3,02±,94	0,401	2,49±,88	0,074
Median- IQR	3,37(2,64-4,06)	2,96(2,39-3,62)		2,46(1,76-3,26)	
Ovary volume (mm3)					
Mean SD	55,49±9,14	34,49±8,05	**0,002**	47,57±14,04	0,091
Median- IQR	54,12(50,19-55,53)	32,59(28,83-39,38)		46,72(37,64-53,09)	

*, ** Mann Whitney U Test

For both study groups, AMH was evaluated for any correlation with rat weight, ovarian volume, total damage score, atretic follicle count, and preantral+antral follicle count. In the normal ovary group, there was a strong positive correlation between AMH and ovarian volume (Table 3).

Table 3. Correlations between rat weights, over volume, total damage score, number of atretic follicles, and AMH levels

	Normal AMH	Doxorubicin AMH	Doxorubicin +DHEA AMH
Ratweight (grams)	0,443	-0,647	-0,467
Ovaryvolume (mm3)	**0,778***	-0,262	0,132
Total damagescore	0,082	0,160	-0,630
Pre-antral+ antralfolliclecount	-0,072	0,452	-0,337

Spearman's Correlation Test *p<0.050

DISCUSSION

The risk of developing amenorrhea following doxorubicin treatment ranges between 40% and 80% depending on age (high incidence at ≥40 years; moderate incidence at 30–39 years).(32, 33) To date, doxorubicin-induced pathomechanisms such as apoptosis, oxidative stress, and inflammation have been extensively studied.(34, 35) The chemical structure of doxorubicin causes cell damage, induces oxidative stress due to the production of free radicals(36), and leads to tissue damage as a result of these effects. The doxorubicin and doxorubicin+DHEA groups had higher edema, vascular congestion, cellular generation, and total damage scores than the normal ovary group. Chemotherapy was found to cause significant histopathological damage to ovarian tissues. However, DHEA appears to have no protective effect on such damage possibly due to the differences between the mechanism by which doxorubicin causes damage and the mechanism of action of DHEA. Doxorubicin has been shown to damage mitotically active granulosa cells, induce follicular apoptosis and eventually disrupt ovarian function and efficiency(2, 32, 37). Suitable agents are required to prevent such damage. Certain studies have shown improvements in AFC, ovarian volume and follicular activity after DHEA supplementation even in women with premature ovarian failure.(38) In the present study, the doxorubicin group had significantly decreased AFC and ovarian volume compared to the normal ovary group. In the doxorubicin+DHEA group, while there was no decrease in the ovarian volume, AFC showed a significant decrease.

DHEA is converted into testosterone in ovarian connective tissues (theca/stroma) and then processed by granulosa cells to be converted into estradiol. Therefore, the prohormone state of an endogenous precursor and a metabolic intermediate product is assumed to be involved in follicular steroidogenesis.(39, 40) This mechanism underlies the effects of DHEA. In the present study, primordial, primary, and preantral follicles were present in similar amounts in the doxorubicin+DHEA and normal ovary groups.

Many studies have verified and

confirmed that AMH is a reliable molecular bioindicator of ovarian reserve.(41, 42) Its decrease to minimal levels can be correlated with decreased follicle counts.(43) AMH expression is seen in the granulosa cells of small growing follicles (preantral and small antral follicles).(44) In the doxorubicin group, the AMH level was similar to that of the normal ovary group. The absence of significant damage to preantral follicles might have led to this result. Besides, a decrease in the AMH level might not have accompanied chemotherapy at an early stage. Evaluation of the long-term results can be beneficial to gain a complete understanding of this subject.

In the present study, there was a strong positive correlation between AMH level and ovarian volume in the normal ovary group. Only the doxorubicin group exhibited a significant decrease in the ovarian volume compared to the normal ovary group. There was no decrease in the ovarian volume in the doxorubicin+DHEA group. AMH is known to have a positive correlation with ovarian volume and peripheral follicular distribution.(45) Preservation of ovarian volume and follicles can affect AMH levels.

Taken together, the results indicated that the additional use of DHEA in rats administered doxorubicin could not decrease ovarian tissue damage scores or prevent follicle loss and did not lead to changes in AMH levels.

CONCLUSION

The use of DHEA was not effective in the prevention of doxorubicin-induced ovarian damage in rats.

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RESEARCH ARTICLE

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Local Anesthetic Systemic Toxicity Knowledge of Emergency Medicine Residents: A Cross-Sectional Study

ABSTRACT

Objective: Local anesthetics (LAs) are starting to be used after the discovery of cocaine, which is used in medical practice. Now LAs are used many procedures in many clinics, especially in emergency departments (EDs). The extensive use of LAs was brought side effects and toxicity. Local anesthetic systemic toxicity (LAST) have been reported from simple allergic conditions to cardiovascular and neurological complications that can be fatal. The study aims to evaluate the level of knowledge and awareness of LAST among emergency medicine residents (EMRs).

Methods: This was a questionnaire-based cross-sectional study. The questionnaires were sent to EMRs via e-mail, and responses were collected. The participants who gave informed consent included in the study, and who didn't use LAs in their daily practice were excluded. All of the participants responded all of the questions and responses were analyzed.

Results: 92 EMRs were included in the study. The median age of the participants was 29 (24-50) years, and 48.9% were women. In the research, no one could recognize all LAST symptoms, ranging from mild to severe. Only 16.3% of the participants answered all treatment options of the LAST correctly, and 27.2% knew the intravenous lipid emulsion dosage accurately.

Conclusions: The level of knowledge and awareness of the EMRs on LAST were insufficient. EMRs training rates on LAs and LAST were found to be low. In addition, it was stated that the patient's informed consent was not appropriately obtained from the vast majority of patients undergoing LA procedure. As the first study on LAST among EMRs, we believe that necessary arrangements should be made regarding the detected deficiencies.

Keywords: Local Anesthetics, Local Anesthetic Systemic Toxicity, Emergency Medicine Residents, Intravenous Lipid Emulsion

Acil Tıp Asistanlarının Lokal Anestetik Sistemik Toksisitesine İlişkin Bilgi Düzeyleri: Kesitsel Bir Çalışma

ÖZET

Amaç: Lokal anestetikler (LA) kokainin keşfiyle birlikte, özellikle acil servisler olmak üzere birçok klinik tarafından, birçok prosedürde kullanılmaktadır. LA' in yaygın kullanımı, beraberinde yan etki ve toksisite vakalarını da getirmiştir. Lokal anestetik sistemik toksisitesi (LAST) basit alerjik durumlardan ölümcül olabilecek kardiyak ve nörolojik komplikasyonlara kadar geniş bir yelpazede bildirilmiştir. Literatürde acil tıp asistanları (ATA)' nın LAST konusunda bilgi ve farkındalıklarını ortaya koyan çalışma bulunmamaktadır. Bu çalışmada ATA' nın LAST bilgi ve farkındalık düzeylerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma anket tabanlı kesitsel bir çalışmadır. Anket formları e-mail yoluyla ATA' na gönderildi ve cevapları kayıt edildi. Aydınlatılmış onam veren ATA çalışmaya dahil edildi ve günlük pratiğinde LA kullanmayan ATA çalışmadan dışlandı. Tüm katılımcılar, bütün sorulara yanıt verdiler ve yanıtların analizleri yapıldı.

Bulgular: 92 ATA çalışmaya katıldı. Katılımcıların yaş ortancası 29 (24-50) ve %48,9 u kadındı. Çalışmamızda, hafiften ağıra doğru sıralanmış LAST semptomlarının tamamına ATA' nın hiçbiri doğru yanıt veremedi. Katılımcıların sadece %16,3 ü tüm LAST tedavi seçeneklerini ve %27,2 si intravenöz lipid emülsiyonu dozunu doğru olarak cevapladılar.

Sonuç: ATA' nın LAST konusunda bilgi ve farkındalık düzeyleri yetersizdir. LA ve LAST konusunda ATA' nın eğitimleri düşüktür. Ayrıca, LA kullanılan prosedürlerin çoğunda uygun aydınlatılmış onam alınmamaktadır. ATA arasında yapılan ilk çalışma olması nedeniyle, tespit edilen eksikliklere yönelik gerekli düzenlemelerin yapılacağına inanıyoruz.

Anahtar Kelimeler: Lokal Anestetikler, Lokal Anestetik Sistemik Toksisitesi, Acil Tıp Asistanları, İntravenöz Lipid Emülsiyonu

INTRODUCTION

Local anesthetics (LAs), which appeared from the beginning of the 20th century with the use of cocaine as an analgesic during surgical procedures, are continuing to be used commonly with intravenous and topical forms in peripheral blocks, spinal and epidural anesthesia, regional anesthesia, postoperative pain control, minor and major surgical procedures (1-3). This process, which started with the discovery of cocaine, brought addiction, other side effects, and risk of mortality (4, 5). Over time, new LAs such as lidocaine, mepivacaine, prilocaine, and bupivacaine have been developed for reducing the side effect potentials. However, there is not enough awareness about the side effects and toxicity of LAs, which are commonly used by non-anesthetists clinicians (emergency medicine physicians, surgeons, dentists, estheticians, dermatologists, etc.) in minor procedures (6). Although current guidelines contain recommendations to prevent local anesthetic systemic toxicity (LAST), it is unfortunately still seen as a frequently encountered clinical entity that is difficult to diagnose (3). The reported incidence of LAST ranges from 1/500 to 1/10.000 and the potential reasons for this wide range are the lack of standard definition, lack of reporting, and diagnostic failures due to a broad spectrum of LAST findings (3).

LAs complications have been reported in a wide range from simple allergic conditions to cardiovascular and neurological complications that can be fatal (3, 7). There are also cases that have been successfully treated following the recommendations of the clinical guidelines (8-10). Protocols for ensuring airway safety, assessment of circulation, and intravenous lipid emulsion (ILE) treatment are included in LAST treatment (3, 7). ILE treatment has taken place in laboratory studies and international guidelines (3, 7, 11, 12).

LAs are widely used in emergency departments (EDs), from minor surgical procedures to peripheral blocks. However, to the best of our knowledge, there is no study in the literature evaluating LAST knowledge and awareness of emergency medicine residents (EMRs). Consequently, in this study, we aimed to evaluate the LAST knowledge and awareness of residents working in the ED.

MATERIAL AND METHODS

Study Design: In this study, the internet-based assessment survey was used. After obtaining approval of the local ethics committee (2019/453), EMRs working in the ED of our country between November 1, 2019, and May 1, 2020, and giving informed consent for the study were included. EMRs who did not use LAs in their daily practice were excluded from the study. The questions in the questionnaire were prepared based on similar studies of the literature and our past experiences. The survey collected participants' demographic informations, LA usage practices, knowledge levels in diagnosis, and LAST treatment. In order to evaluate the scope and clarity of the survey, it was piloted with 20 EMRs beforehand. These participants were excluded from the study not to affect the results.

Data Collection: The questionnaire forms were sent to 250 EMRs via e-mail and asked to answer all questions. 120 EMRs that provided informed consent and answered all questions were included in the study. 28 EMRs were excluded from the study because they did not use LAs in their daily practice. The responses of a total of 92 EMRs were recorded and analyzed. The flow diagram of the study is demonstrated in Figure 1.

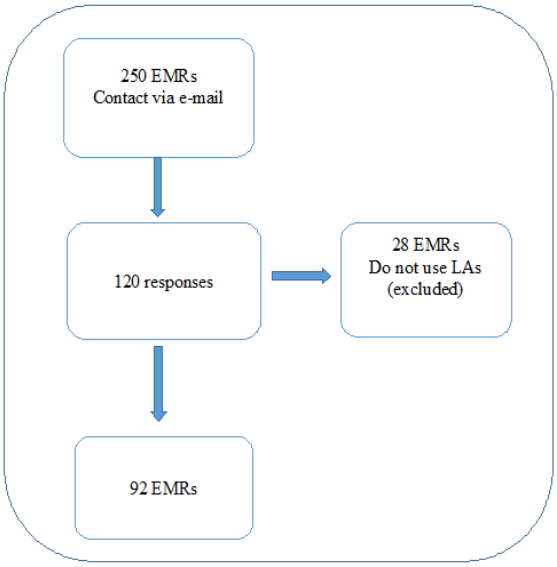

Figure 1. Flow diagram of the study. EMRs: Emergency medicine residents, LAs: Local anesthetics

Data Analysis: Descriptive statistics were summarized in numbers and percentages. Numerical variables were presented with median (min-max). Kolmogorov-Smirnov test was used to evaluate the distribution of numerical data. Pearson's chi-square test was used for categorical variables. IBM SPSS for Windows version 21 was used for statistical analyses. The statistical significance was accepted as $p < 0.05$.

RESULTS

92 EMRs participated in the study and answered all questions. The median age of the EMRs was 29 (24-50), and 48.9% were women. Demographic information, years of professional experience, and LAs usage practices of the participants are demonstrated in Table 1. In the research, no one could recognize all LAST symptoms, ranging from mild to severe. Only 16.3% of the participants answered all treatment options of the LAST correctly, and 27.2% knew the proper dose of the ILE. The percentages of

participants' responses to questions about LAST symptoms and treatment options are indicated in Table 2.

Table 1. Demographic data and local anesthetic use of the participants

Female, %	48.9
Age (years), median (min-max)	29 (24-50)
Total working time in ED (years), median (min-max)	3 (1-22)
Total working time as a resident (years), median (min-max)	2 (1-4)
Institution type, %	
Training and Research hospital	35.9
University hospital	62.0
Private hospital	2.2
Use of local anesthetics, %	
Lidocaine	66.3
Prilocaine	91.3
Bupivacaine	5.4
Lidocaine + Prilocaine	52.2
Lidocaine + Prilocaine + Bupivacaine	5.4
Alone	85.9
With adrenaline	32.6
Alone and with adrenaline	18.5
Administration route of LAs, %	
Intravenous	6.5
Subcutaneous	90.2
Intramuscular	15.2
Topical	44.6
Intranasal	2.2
Intraarticular	4.3
Procedure type of LAs usage, %	
Minor procedure	97.8
Regional block	34.8
Frequency of LAs usage, %	
Every day	39.1
≥2/week	27.2
1/week	25.0
1/month	8.7
Interventions to prevent toxicity, %	
Ultrasound guided	6.5
Negative aspiration	70.7
Test dose	13.0
Incremental injection	30.4
With adrenaline	8.7
Nothing	17.4

ED: Emergency department

No significant correlation was found between identifying all of the LAST treatment options and the proper dose of ILE, and the type of institution, frequency of use of LAs, and training about LAs. However, when we look at the answers of those who stated that they knew LAST treatment or who had encountered LAST before, there is a significant correlation between this group and correct response to ILE dosage properly.

But there is no correlation between this group and knowing LAST treatment options. In other words, accurate answers to ILE dosage were found to be significantly higher among those who thought they knew LAST treatment or who had encountered LAST before. The relationship between correctly responding to the LAST treatment options and the appropriate dose of ILE and the type of institution, frequency of use of LAs, training on LAs, state of believing to know LAST treatment, and state of encounter with LAST in the past is shown in Table 3. While 20.7% of the participants stated that they encountered before, the rate of those who stated that they knew LAST treatment and that they could treat LAST was 44.6% and 76.1%, respectively.

Table 2. Responses to symptoms and treatment of LAST

Symptoms of LAST (%)	
Allergy/Anaphylaxis	83.7
Metalic taste	42.4
Circumoral numbness	45.7
Dizziness	47.8
Tinnitus	37.0
Loss of consciousness	66.3
Seizure	62.0
Arrhythmia	81.5
Hypotension	81.5
Cardiovascular collapse	78.3
Recognize all the symptoms of LAST correctly	0.0
Treatment of LAST (%)	
Symptomatic	79.3
Antihistamines	56.5
Methylene blue	31.5
ILE	75.0
Resuscitation	71.7
Identifying all treatment options of LAST correctly	16.3

LAST: Local anesthetic systemic toxicity, ILE: Intravenous lipid emulsion

Regarding the answers given to the questions about LAs, 34.8% of the participants stated that they received training on LAs. 83.7% of the participants reported they did not calculate the dose before the procedure for patients with or without additional comorbidity. The rate of those who stated that they knew max and ml/mg doses of the LAs they used were 35.9% and 42.4%, respectively. Also, 84.8% of the participants stated that they did not explain the possible risks and receive consent from the patients before the procedure. In questions about ILE, 64.1% of the participants stated that ILE could be used in the LAST cases. However, 57.6% of the participants indicated that they had ILE in their departments, the rest reported that they did not have ILE in their departments or had no idea about it. Answers to questions about ILE are shown in Table 4.

Table 3. The relationship between correct answers and type of hospital, frequency of LAs usage, educational status, and LAST experience

	LAST treatment		ILE dose	
	C	p	C	p
Instution type, n (%)				
Training and Research	6 (18.2)	0.374	10 (30.3)	0.628
University	8 (14.0)		15 (26.3)	
Private	1 (50.0)		0 (0.0)	
Frequency of LAs use, n (%)				
Everyday	4 (11.1)	0.700	12 (33.3)	0.758
2/w	5 (20.0)		6 (24.0)	
1/w	4 (17.4)		5 (21.7)	
1/m	2(25.0)		2 (25.0)	
Education on LAs, n (%)				
Yes	4 (12.5)	0.748	13 (40.6)	0.106
No	7 (17.5)		8 (20.0)	
Don't remember	4 (20.0)		4 (20.0)	
Do you know the treatment of LAST?				
Yes	9 (22.0)	0.189	17 (41.5)	**0.006**
No	6 (11.8)		8 (15.7)	
Have you ever encounter LAST?				
Yes	2 (10.5)	0.519	12 (63.2)	**<0.001**
No	13 (18.6)		13 (18.6)	

LAs: Local anesthetics, LAST: Local anesthetic systemic toxicity, ILE: Intravenous lipid emulsion, C: Correct, the values considered statistically significant were shown in bold font (p <0.05).

Table 4. Responses to ILE treatment

Have you heard of ILE treatment? (%)	
Never heard of it	9.8
I have heard of it but I can't recall	26.1
I have read a scientific paper on it	23.9
I know when and how it is used	40.2
ILE treatment dose (%)	
1.5 ml/kg IV bolus, 0.25 ml/kg/min IV infusion	27.2
Have you ever used ILE? (%)	
No	64.1
Yes, I have used to treat LAST	18.5
Yes, I have used to treat another toxicity except LAST	26.1
Yes, I have used to treat both LAST and another toxicity	8.7

ILE: Intravenous lipid emulsion, LAST: Local anesthetic systemic toxicity

DISCUSSION

LAs are widely used in emergency medicine practice. Early diagnosis and treatment of possible toxicity findings of a group of drugs that are used so frequently and whose toxicity can cause mortality and severe morbidity is essential. In our study, we found that EMRs' knowledge and awareness on LAST was low.

None of the EMRs were recognized all of the symptoms related to the LAST. 16.3% of the participants identified all of the treatment options of LAST. In the study conducted by Karasu et al. among 102 residents, 15.8% of them were EMRs, LAST knowledge levels were found to be low, similar to our study (2). While the proportion of people using LAs "every day" was 44.4% in their study, it was found to be 39.1% in our study

When the answers to the questions about LAST symptoms were evaluated, questions about severe LAST findings such as arrhythmia, hypotension, cardiovascular collapse, seizure, and allergy/anaphylaxis were answered at high rates. Still, mild findings of LAST such as metallic taste, paresthesia around the mouth, and tinnitus were responded to less accurately (13). This situation constitutes a serious obstacle to the early diagnosis and treatment of LAST.

Comparing to the study by Urfalıoğlu et al. which conducted among ophthalmologists, EMRs tend to prefer ILE more frequently as a treatment option, and the answers are similar in other treatment options (13). It can be argued that this difference is based on the fact that ILE is an agent that can be used in different toxicity situations and that toxicology cases constitute an essential place in emergency medicine practice. However, when both LAST symptoms and responses to treatment options were evaluated in general, low rates of correct answers were obtained. Also, in the study conducted by Karasu et al., 19.8% of the participants stated that they received training on LAs, which was found to be 34.8% in our study (2). Undoubtedly, this rate is not enough. In this case, it is necessary to review the content and quality of the institutional and national emergency medicine education syllabus. 27.2% of the participants responded correctly to the appropriate treatment dose of ILE recommended by international guidelines. When the results of our study are evaluated in general, we can assume that EMRs have serious information deficiencies in the diagnosis and treatment of LAST.

No significant correlation was found between knowing all of the LAST treatment options and ILE dosage correctly and the type of institution, frequency of use of LAs, and training about LAs. In

this case, it can be said that LAST knowledge levels are not affected by the institution, the frequency of use of LAs, and previous training about LAs. However, EMRs who had encountered LAST cases or thought that they knew LAST treatment responded significantly higher to the ILE treatment dose. In this case, it can be said that the LAST experience contributed to the level of knowledge of the ILE treatment, rather than the institution and the training. It is also necessary to underline the importance of practice in emergency medicine residency training.

In terms of toxicity prevention measures, 70.7% of the EMRs preferred negative aspiration, while this rate was 6.1% in the study of Urfalıoğlu et al. (13). Negative aspiration can be applied quickly at the bedside, which may be the main reason for preference. Besides, although negative aspiration is recommended by international guidelines to prevent LAST, it can be said that the compliance of EMRs is not complete, or they were not given sufficient importance on that matter (7).

In our study, 20.7% of the participants stated that they had encountered LAST before, and 44.6% of them stated they knew about the LAST treatment. The rate of those who stated that they could manage LAST was 76.1%. It can be said that EMRs have high self-confidence in LAST because of the high rate of participants who think they can manage LAST despite their low level of knowledge and experience about LAST. Our study found that most of EMRs did not calculate the max and mg/ml doses of LAs they used before the procedure. In addition, the rate of EMRs who stated that they did not know the max and mg/ml doses of LAs they used were higher than the result of the study of Öksüz et al. conducted among dentists (14). The fact that the emergency medicine clinics are better equipped than dental clinics, and the EMRs have high self-confidence may be the reason why they act less cautiously in procedures using LAs. In conclusion, when we compare our results with the results of Öksüz et al.'s study, it can be said that dentists encounter less LAST and have more information about the LAs compared to EMRs (14).

Also, 84.8% of the participants stated that they did not receive informed consent by discussing the risks with the patients before the procedure. This situation undoubtedly carries the risk of causing some medico-legal conditions. In a study by Gaeta et al., it was found that EMRs did not receive formal training on informed consent (15). In this case, we can say that EMRs working in our country were suffering from the same problem.

While 67.4% of the participants stated that they did not have an idea about ILE treatment in the study conducted by Karasu et al., assessment of the questions about ILE showed that this rate was 9.8% in our study (2). Also, in our study, 64.1% of the participants stated that ILE therapy could be used in the treatment of LAST, while 40.2% reported that they know when and how to use it. It is obvious that EMRs have insufficient knowledge about ILE dosage as well as their awareness about ILE is not at the desired level. The knowledge and awareness of the diagnosis and treatment options of the toxicity of such frequently used agents in daily practice should be high.

LIMITATIONS

The first limitation of our study is that it was a questionnaire study, and participation was voluntary. We reached many EMRs, but some did not agree to participate. Since no questions were measuring LAs knowledge levels in the questionnaire, no comments could be made about the knowledge levels of EMRs about LAs. The limited number of studies in the literature related to LAST knowledge and awareness level may have caused limitations in evaluating the data. There is also a need for larger studies on this subject.

CONCLUSIONS

The knowledge and awareness of the EMRs about LAST were low and, unfortunately, insufficient. EMRs training rates on LAs and LAST were found to be low. In addition, informed consent was not obtained properly by EMRs from the vast majority of patients undergoing LA procedure. Due to being the first study on LAST among EMRs, we believe that necessary regulations should be made regarding the deficiencies detected. There is a need for national and international multi-centered studies on this subject.

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RESEARCH ARTICLE

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Development of Valid and Reliable Scale of Vaccine Hesitancy in Turkish Language

ABSTRACT

Objective: Anti-vaccine movement has been increasing in recent years, leading to poor health outcomes. There are some scales to measure the vaccine hesitancy but most of them have limitation and may not be proper for Turkey. The aim of this study is to develop a Turkish scale of vaccine hesitancy.

Methods: Two cross sectional studies were conducted. Purposive sampling method was used to reach participants in hospital and its surroundings. Study1: Explanatory factor analysis involved 315 participants, whose 61.3% were female mean age was 33.3±11.6 years. The draft scale with 36 items were applied face to face. Study 2: Confirmatory factor analysis involved 214 participants for the long form and 200 for short form. Of the participants, 62.0% was female and the mean age was 33.9±11.3 for short form. Of the participants, 65.4% was female and the mean age was 34.5±11.4 for the long form. Goodness of fit indexes of both forms were compared with literature.

Results: The long form with 21 items in 4 factors and the short form with 12 items in 3 factors were selected as they best explained the data. Explained variance by long form and short form were 57.4%and 65.3% respectively. Cronbach Alpha values for long form and short form were 0.905 and 0.855, respectively.

Conclusions: It is important to understand vaccine hesitancy at local levels because differences in sociocultural structure have major effect. In this study, two forms of reliable vaccine hesitancy scale were presented in Turkish as first in literature.

Keywords: Vaccine Refusal, Antivaccination Movement, Reliability And Validity, Scale, Turkey

Geçerli ve Güvenilir Türkçe Aşı Karşıtlığı Ölçeği Geliştirilmesi

ÖZET

Amaç: Aşı karşıtlığı son yıllarda artarak kötü sağlık sonuçlarına neden olmaktadır. Literatürde aşı karşıtlığı ölçekleri bulunsa da bunlar Türkiye için uygun olmamakla birlikte kısıtlılıkları bulunmaktadır. Bu çalışmanın amacı, Türkçe aşı karşıtlığı ölçeğini geliştirmektir.

Gereç ve Yöntem: İki farklı kesitsel çalışma yürütüldü. Hastane ve çevresindeki katılımcılara ulaşmak için amaçlı örnekleme yöntemi kullanıldı. Çalışma 1: Açıklayıcı faktör analizi, %61,3'ü kadın ve ortalama yaşı 33,3±11,6 yıl olan 315 katılımcıyı içermektedir. Otuz altı maddeli taslak ölçek yüz yüze uygulanmıştır. Çalışma 2: Doğrulayıcı faktör analizi, uzun form için 214 katılımcı ve kısa form için 200 katılımcıdan oluşmaktadır. Kısa form katılımcılarının %62,0'ı kadındı ve ortalama yaş 33,9±11,3 idi. Uzun form katılımcılarının %65,4'ü kadındı ve ortalama yaş 34,5±11,4 idi. Her iki formun uyum iyiliği indeksleri literatürle karşılaştırıldı.

Bulgular: Yüksek açıklayıcılıkları nedeniyle 4 faktörde 21 maddeden oluşan uzun form ve 3 faktörde 12 maddeden oluşan kısa form seçilmiştir. Uzun formun ve kısa formun açıkladığı varyans sırasıyla %57,4 ve %65,3 idi. Uzun form ve kısa form için Cronbach Alpha değerleri sırasıyla 0,905 ve 0,855 idi.

Sonuç: Sosyokültürel yapıdaki farklılıkların büyük etkisi olduğu için aşı karşıtlığını yerel düzeylerde anlamak önemlidir. Bu çalışmada literatürde ilk kez, geçerli ve güvenilir olarak iki farklı Türkçe aşı karşıtlığı ölçeği geliştirilmiştir.

Anahtar Kelimeler: Aşı Reddi, Aşı Karşıtlığı Hareketi, Güvenilirlilik Ve Geçerlilik, Ölçek, Türkiye

INTRODUCTION

Vaccination is one of the greatest achievements of public health interventions (1). But when vaccination has been started at early 1800s, concurrently vaccine hesitancy has also started (2). Anti-vaccine movement has been increasing in recent years, leading to poor health outcomes as well as waste of resources (3,4). Strategic Advisory Group of Experts on Immunization work group of World Health Organization has described vaccine hesitancy as "delay in acceptance or refusal of vaccines despite availability of vaccine services. Vaccine hesitancy is complex and context specific, varying across time, place, and vaccines" (5). There are studies commenting that it would be wrong to express the vaccine hesitancy by just behaviors, namely "vaccine refusal" (6), because even some of the vaccine recipients may have vaccine hesitancy (7). Vaccine hesitancy is a continuum between accepting and rejecting all vaccines (8). Five different groups were identified in this spectrum; 1) Immunization Advocate, 2) Go Along to Get Along, 3) Health Advocate, 4) Fence-sitter and 5) Worried. The group of fence sitters has the largest variance, including people that have higher level of vaccine advocacy than those in the Immunization Advocate group or higher level of vaccine hesitancy than those in the Worried group (9). Directly targeting the people who refuse vaccine can result in backfire, so it seems more effective to target the fence sitters (10,11). If we can measure vaccine hesitancy even in vaccine recipients, we can find true fence sitters and take the necessary interventions. In addition, by measuring the vaccine hesitancy, factors related to vaccine hesitancy can be revealed, the current status of vaccine hesitancy can be determined objectively, and the effectiveness of intervention strategies can be monitored.

The vaccine hesitancy scales in the literature have limitations such as involving only parents (12-17), studying in specific age groups (18), measuring vaccine hesitancy in terms of specific vaccines (19-22), or studying only one aspect of vaccine hesitancy (23). Recently, holistic scales of vaccine hesitancy have been arising (24,25), but Horne at al.'s scale has received structural criticism (26). In addition, socio-cultural characteristics that vary among countries affecting vaccine hesitancy, so it isn't a good way to evaluate vaccine hesitancy in developing / undeveloped countries by criterion of developed countries where most of vaccine hesitancy studies are conducted (27).

The aim of this study is to develop a valid and reliable Turkish scale that will be used to measure the level of vaccine hesitancy of individuals.

MATERIAL AND METHODS

Revealing the technical features of a measurement tool is only possible by describing these features. Descriptive research serves the descriptive purpose of science and at the same time provides insight into generating experiments for subsequent research.

This is a descriptive study revealing the technical features of presented measurement tool. The development process of scale was completed by following the path suggested in the literature (28). Study consisted of two major parts, Explanatory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA).

This study was conducted in accordance with Declaration of Helsinki - Medical Research Involving Human Subjects. Ethical approval was taken from the Clinical Research Ethics Committee of Canakkale Onsekiz Mart University with the number of 2019-07. Informed consents were obtained from every participant before surveys.

Explanatory Factor Analysis

Sample and Design: First, the desired issue to be revealed with the scale was defined. For this purpose, literature and social media were examined in the context of vaccine hesitancy and items were identified. These items were presented to the opinion of three experts in the field of family medicine and vaccination and one expert in the field of measurement and scale development. Following the determination of the aim and target group, 36 items were listed in the draft scale. The responses of the participants to the items in the measurement tool were obtained with a 5-point Likert scale including "exactly disagree", "disagree", "partially agree", "agree" and "exactly agree".

Everitt (29) states that the number of participants should be at least ten times the number of items that included in survey. So, in this study, it was taken care that the number of samples was ten times the number of items in the scale. The form with 36 items was applied to 315 individuals in May and June 2019. Participants were selected by purposive sampling method, in the hospital and surroundings (canteen, street, garden, bus stop) with the appropriate characteristics of target group of the scale. The participants' mean age was 33.3±11.6 years and 61.3% of them were female. Sociodemographic characteristics of the participants of EFA is shown in Table 1 with details.

Data Analysis: A few missing values were tested with EM Missing Value Analysis which showed that the missing values were randomly distributed. The missing data were completed with the most preferred (mode) values. Kaiser Meyer Olkin (KMO) and Bartlett's Test of Sphericity tests were used to determine whether the data file was suitable for factor analysis. KMO is a test for adequacy of sampling (30). In addition, Doornik-Hansen Multivariate Normality Test was applied to the items in the scale by the STATA statistics software.

Table 1. Sociodemographic characteristics of participants

		EFA		CFA (Short Form)		CFA (Long Form)	
Variables		***n***	***%***	***n***	***%***	***n***	***%***
Gender	Female	193	61.3	124	62.0	140	65.4
	Male	122	38.7	76	38.0	74	34.6
	Total	315	100	200	100	214	100
Education	None	1	0.3	2	1.0	4	1.9
	Primary	32	10.2	22	11.0	23	10.7
	Secondary	135	42.9	64	32.0	63	29.4
	University	124	39.4	90	45.0	109	50.9
	Postgraduate	20	6.3	22	11.0	14	6.5
	Unspecified	3	1.0	0	0.0	1	0.5
	Total	315	100	200	100	214	100
Marital status	Married	172	54.6	108	54.0	134	62.6
	Single	134	42.5	79	39.5	67	31.3
	Widow	8	2.5	13	6.5	12	5.6
	Unspecified	1	0.3	0	0.0	1	0.5
	Total	315	100	200	100	214	100
Income Status	Good	59	18.7	42	21.0	47	22.0
	Moderate	220	69.8	124	62.0	136	63.6
	Poor	30	9.5	32	16.0	29	13.6
	Unspecified	6	1.9	2	1.0	2	0.9
	Total	315	100	200	100	214	100
Child Status	No	147	46.6	98	49.0	59	27.6
	Yes	168	53.4	102	51.0	155	72.4
	Total	315	100	200	100	214	100

CFA: Confirmatory factor analysis, EFA: Explanatory factor analysis, n: Number

As a result of the test, it was determined that the items do not violate the multivariate normality ($p > .05$). The possible factorization in the EFA was tested with Varimax Axis Rotation. There are many methods (such as test-retest) to determine the reliability of the scales. Cronbach Alpha reliability coefficient can be used for measuring reliability for Likert type-items that include more than two level. So, Cronbach Alpha reliability coefficient, which gives information about reliability in terms of internal consistency, was calculated in this study.

All analysis was performed on Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. and IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. softwares.

Confirmatory Factor Analysis

Sample and Design: As a result of EFA, two forms were selected as they best explained the data, the long form with 21 items in 4 factors and the short form with 12 items in 3 factors.

In this study, it was considered that the number of samples was ten times the number of items in the scale in accordance with the literature. In August and September 2019, 200 individuals for short form and 214 individuals for long form were reached. Purposive sampling method was used, and the participants were selected from the hospital and surroundings (canteen, street, garden, bus stop). The scale developed after EFA was applied face-to-face.

Of the participants of the short form, 62.0% was female and the mean age was 33.9±11.3 years. Of the participants of the of the long form, 65.4% was female and the mean age was 34.5±11.4 years. Sociodemographic characteristics of the participants of CFA is shown in Table 1 in details.

Data Analysis: A few missing values were tested with EM Missing Value Analysis which showed that the missing values were randomly distributed. The missing data were completed with the most preferred (mode) values. The CFA

statistics in this study were examined with the goodness of fit indexes. Accepted reference values according to literature for a scale were given in Table 2.

Table 2. Goodness of Fit Index in literature

Goodness of Fit Index	Limits of Acceptance	Limits of Excellence	Reference
RMSEA	0.050≤RMSEA≤0.080	0.000≤RMSEA≤0.050	(38,39)
RMR	0.050<RMR≤0.080	0.000≤RMR≤0.050	(38–40)
GFI		0.900 and above	(39,40)
AGFI		0.900 and above	(39,40)
NFI		0.950 and above	(38,40)
IFI	0.900≤IFI≤0.940	0.950 and above	(38)
CFI	0.900≤CFI≤0.940	0.950 and above	(38,39)
X^2/df	2.000<X^2/df≤5.000	0.000≤X^2/df≤2.000	(30,33,40)

AGFI: Adjusted Goodness of Fit Index, **CFI:** Comparative Fit Index, **df:** Degree of freedom, **GFI:** Goodness of Fit Index**, IFI:** Incremental Fit Index, **NFI:** Normed Fit Index, **RMR:** Root Mean Square Residual**, RMSEA:** Root mean Square Error of Approximation, **X^2:** Chi square

All analysis was performed on Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC. and IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. softwares.

RESULTS

Explanatory Factor Analysis: In EFA, it was tested whether the draft scale of vaccine hesitancy would show a structural integrity. Thirty-six items were handled together, and then the structure was tested. As a result of the exploratory factor analysis conducted with principal axis factoring method (31), the scale revealed a structure of 7-factor. KMO value was over 0.500 and Bartlett's Test of Sphericity value was found to be significant ($p< 0.05$). These results showed that the dataset was appropriate for factor analysis (32,33). The scree plot was examined to obtain a simpler solution. It was decided to repeat the factor analysis with the four factors that have the highest slope at the scree plot. The KMO value was 0.903 for the EFA which was conducted as four factors. Bartlett's Test of Sphericity value is 2785.318 (df = 210.0, $p<0.05$). As previously mentioned, these values were good enough according to the literature.

As a next step, item total correlations and factor loadings were examined. Before the EFA, item total correlations were examined in order to determine the contribution of the items to the scale. As a result of the examination, it was found that the item total correlations for items 4, 9, 12, 22, 23, 25, 26, 29, 34, 35 and 36 were low (below 0.300). So, these items were excluded out of the vaccine hesitancy scale because of low contribution.

According to item total correlations, it was determined that items 11 and 20 correlated with multiple factors. It was appropriate to remove these items from the scale. There were four factors with eigenvalue greater than 1. Varimax Axis Rotation resulted in four factors. These factors and the loading values of the items were summarized in Table 3. As can be seen in Table 3, the remaining 21 items were grouped under four factors. Of these items;

- 1, 2, 3, 5 and 8 formed first factor. These items were related to the "benefit and protective value of vaccine".
- 10, 14,16, 17, 18 and 19 formed second factor. These items were related to the "vaccine repugnance".
- 27, 28, 30, 32 and 33 formed third factor. These items were related to the "solutions for non-vaccination".
- 6, 7, 13, 15 and 21 formed fourth factor. These items were related to "legitimization of vaccine hesitancy".

The Cronbach's alpha reliability coefficients was calculated to determine internal consistency of the four factors and were presented in Table 3. The Cronbach's alpha reliability coefficients of the four factors and the total scale ranged between 0.75 and 0.91 and correspond to high reliability levels (33). After these analyses, the researchers conducted another EFA to obtain a shorter, more useful form for ease of application with the items that gave the highest correlation value and the highest contribution to the scale. As a result of the analysis conducted in this direction, a short form consisting 12 items in three factors were reached. The statistics are shown in Table 4 As can be seen in Table 4; the 12 items were grouped under three factors. Of these items;

- 1, 2, 3 and 5 formed first factor, related to the "benefits and protective value of vaccines".
- 14, 16, 17, 18 and 19 formed second factor, related to the "vaccine repugnance".
- 32, 33 and 34 formed third factor, related to the "solutions for non-vaccination".

The Cronbach's alpha reliability coefficients were calculated to determine internal consistency of the three factors. The reliability values are summarized in Table 4. The Cronbach's alpha reliability coefficients of the three factors and the total scale ranged between 0.71 and 0.86 and correspond to high reliability levels (33).

Table 3. Factors and item total correlations with loading values of items (long form)

Item (English translation)		Corrected Item-Total Correlation	Factor			
			1	2	3	4
2	Herkes aşılanırsa hastalıklar azalır. (If everyone is vaccinated, the diseases will decrease.)	0.613	0.859			
1	Aşı sağlığı korumak için etkili bir yöntemdir. (Vaccination is an effective method to maintain health.)	0.587	0.846			
3	Devlet tarafından önerilen aşılara güvenirim. (I trust the vaccines supplied by the government.)	0.517	0.753			
5	Salgın hastalıklara karşı en güçlü önlem aşıdır. (The most powerful measure against epidemics is the vaccine.)	0.542	0.695			
8	Aşı sağlığımız için önemli bir güvencedir. (Vaccination is an important guarantee for our health.)	0.603	0.585			
16	Aşıların yan etkileri beni endişelendiriyor. (I worry about the side effects of the vaccines.)	0.492		0.757		
19	Aşının otizm veya öğrenme bozukluğuna yol açmasından korkuyorum. (I am afraid the vaccine will cause autism or learning disability.)	0.575		0.697		
17	Aşı birçok hastalığa neden olabilir. (The vaccine can cause many diseases.)	0.542		0.676		
14	Aşı insanların sağlığından çok aşı üretenlere kazanç sağlar. (Vaccination is more beneficial for pharmaceutical industry than for human health.)	0.494		0.638		
10	Aşıların yararı kadar zararı da vardır. (Vaccines have disadvantages as much as their advantage)	0.406		0.614		
18	Aşıların içeriğinde zehirli maddeler vardır. (Vaccines contain toxic substances.)	0.576		0.526		
27	Atadan kalma yöntemler aşıdan daha iyi korur. (Ancestral methods protect health better than the vaccines.)	0.533			0.723	
30	Bağışıklık kazanmak için aşı yaptırmaktansa hastalığı geçirmeyi tercih ederim. (To gain immunity, I would rather having the disease instead of getting the vaccine.)	0.578			0.697	
28	Elimden gelse aşı zorunluluğunu kaldırırım. (If I can, I will remove the vaccination obligation.)	0.585			0.606	
32	Aşı zorunlu değil isteğe bağlı olmalıdır. (The vaccine should be optional, not mandatory.)	0.471			0.588	
33	Çocukluğuma dönsem aşı olmazdım. (If I were a child, I would not get vaccinated.)	0.614			0.552	
15	İğneden korktuğum için aşı olmam. (I may refuse vaccination because I am afraid of injections.)	0.449				0.759
21	Dini inancım nedeniyle aşı olmam. (I may refuse vaccination because of my religious belief.)	0.534				0.735
13	Aşılar kalıcı hastalık yapabileceğinden çocuğumu aşılatmam. (I do not make my child vaccinated because vaccines can cause permanent illness.)	0.518				0.666
6	Diğer çocuklar aşılandığı için benim çocuğumun aşılanmasına gerek yok. (My child does not need to be vaccinated because other children are vaccinated.)	0.542				0.495
7	Bulaşıcı hastalıklar az görüldüğü için aşılanmak gereksizdir. (Since infectious diseases are rare, vaccination is unnecessary.)	0.482				0.493
Explained variance			16.296	14.163	14.014	12.958
Cronbach Alpha			0.866	0.809	0.780	0.753
Variance explained by all factors together =57.431						
Cronbach Alpha value of 21 items =0.905						
KMO = 0.903. Bartlett's Test of Sphericity = 2785.318 (df = 210.0, p <0.05)						

Table 4. Factors and total item correlations with loading values of items (short form)

Item (English translation)		Corrected Item-Total Correlation	Factor 1	2	3
1	Aşı sağlığı korumak için etkili bir yöntemdir. (Vaccination is an effective method to maintain health.)	0.571	0.877		
2	Herkes aşılanırsa hastalıklar azalır. (If everyone is vaccinated, the diseases will decrease.)	0.602	0.895		
3	Devlet tarafından önerilen aşılara güvenirim. (I trust the vaccines supplied by the government.)	0.537	0.762		
5	Salgın hastalıklara karşı en güçlü önlem aşıdır. (The most powerful measure against epidemics is the vaccine.)	0.516	0.722		
14	Aşı insanların sağlığından çok aşı üretenlere kazanç sağlar. (Vaccination is more beneficial for pharmaceutical industry than for human health.)	0.495		0.741	
16	Aşıların yan etkileri beni endişelendiriyor. (I worry about the side effects of the vaccines.)	0.526		0.710	
17	Aşı birçok hastalığa neden olabilir. (The vaccine can cause many diseases.)	0.534		0.766	
18	Aşıların içeriğinde zehirli maddeler vardır. (Vaccines contain toxic substances.)	0.548		0.693	
19	Aşının otizm veya öğrenme bozukluğuna yol açmasından korkuyorum. (I am afraid the vaccine will cause autism or learning disability.)	0.576		0.716	
32	Aşı zorunlu değil isteğe bağlı olmalıdır. (The vaccine should be optional, not mandatory.)	0.446			0.640
33	Çocukluğuma dönsem aşı olmazdım. (If I were a child, I would not get vaccinated.)	0.574			0.835
34	Aşı sırasında çocuğum ağladığı için çocuğuma aşı yaptırmam. (I do not make my child vaccinated because my child cries during the vaccination.)	0.511			0.850
Explained variance			23.951	24.089	17.287
Cronbach Alpha			0.863	0.809	0.712
Variance explained by all factors together=65.327					
Cronbach Alpha value of 12 items =0.855					
KMO=0.836. Bartlett's Test of Sphericity=1652.255. df=66. p<.05					

Confirmatory Factor Analysis: CFA was performed to determine whether the structures of the scale's long and short forms indicated by EFA were valid. Goodness of fit indexes provide important information about the validity of the structure in CFA. Goodness of fit indexes calculated in the CFA were summarized in Table 5 in comparison with the literature. Diagrams of CFA were given for long form in Figure 1 and for short form in Figure 2. Observed Goodness of Fit Indexes of vaccine hesitancy scale (long and short form) were at the desired level. So, it can be considered as an evidence for the validation of structures revealed previously by EFA.

Table 5. Goodness of Fit Index of Confirmatory factor analysis

Goodness of Fit Index	Limits of Acceptance	Limits of Excellence	Observed Value (long form)	Observed Value (short form)	Reference
RMSEA	0.050≤RMSEA≤0.080	0≤RMSEA≤0.050	0.077	0.070	(38,39)
RMR	0.050<RMR≤0.080	0≤RMR≤0.050	0.076	0.070	(38–40)
GFI		0.900 and above	0.840	0.930	(39,40)
AGFI		0.900 and above	0.800	0.880	(39,40)
NFI		0.950 and above	0.940	0.970	(38,40)
IFI	0.900≤IFI≤0.940	0.950 and above	0.960	0.980	(38)
CFI	0.900≤CFI≤0.940	0.950 and above	0.960	0.980	(38,39)
X2/df	2.000<X^2/df≤5.000	0.000≤X^2/df≤2.000	2.260	1.980	(30,33,40)

AGFI: Adjusted Goodness of Fit Index, **CFI:** Comparative Fit Index, **df:** Degree of freedom, **GFI:** Goodness of Fit Index**, IFI:** Incremental Fit Index, **NFI:** Normed Fit Index, **RMR:** Root Mean Square Residual**, RMSEA:** Root mean Square Error of Approximation, **X^2:** Chi square

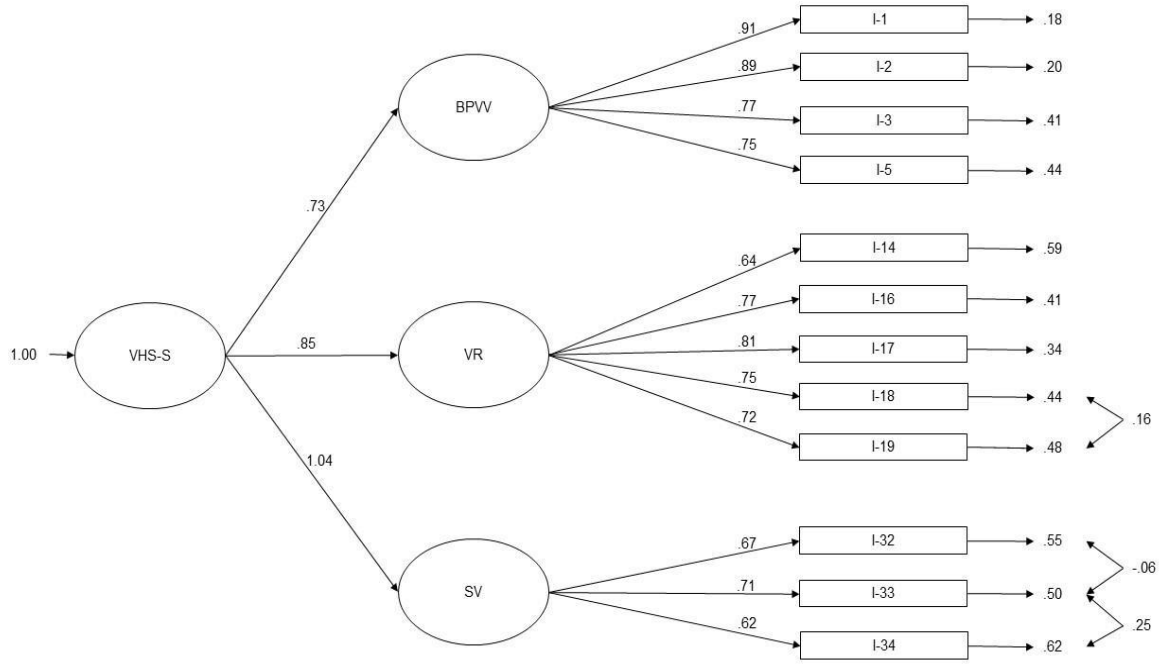

Figure 1. Path diagram of confirmatory factor analysis (standardized values) of vaccine hesitancy scale-long form (Chi-Square= 416.37, df= 184, p value< 0.001, RMSEA= 0.077)
BPVV: Benefits and protective value of vaccines, **df:** Degree of freedom, **I:** Item, **LVH:** Legitimization of vaccine hesitancy, **RMSEA:** Root mean Square Error of
Approximation, **SV:** Solutions for non-vaccination, **VHS-L:** Vaccine hesitancy scale-long form, **VR:** Vaccine repugnance.

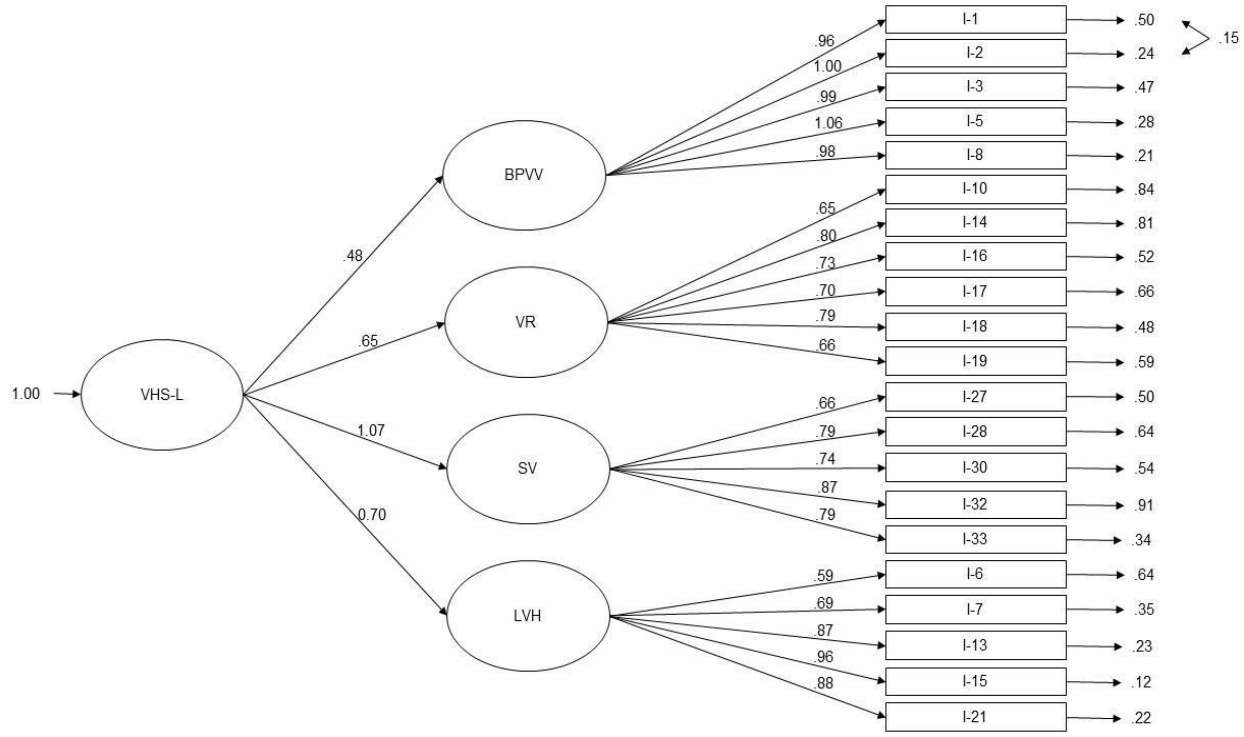

Figure 2. Path diagram of confirmatory factor analysis (standardized values) of vaccine hesitancy scale-short form (Chi-Square= 95.23, df= 48, p value< 0.001, RMSEA= 0.070)
BPVV: Benefits and protective value of vaccines, **df:** Degree of freedom, **I:** Item, **RMSEA:** Root mean Square Error of Approximation, **SV:** Solutions for non-vaccination,
VHS-S: Vaccine hesitancy scale-short form, **VR:** Vaccine repugnance.

DISCUSSION

The World Health Organization states that the extent and nature of vaccine hesitancy needs to be better understood at local levels (34). In this study, a Turkish vaccine hesitancy scale in two forms were developed in order to better understand and objectively measure the vaccine hesitancy. The long form was constituted by 21 items and 4 factors: 1) benefit and protective value of the vaccine 2) vaccine repugnance 3) solutions for non-vaccination and 4) legitimize vaccine hesitancy; the short form was constituted by 12 items and 3 factors: 1) benefit and protective value of the vaccine: 2) vaccine repugnance and 3) solutions for non-vaccination. The scales developed in our study had remarkably high internal consistency and explained a significant part of the variance. As Gorsuch (35) strongly recommends, each factor of our scales contains at least 3 items. The scales we developed are not specific to any predefined group (parents, etc.) (12-17), or to age group (18), or to vaccine (19-22) such as many other vaccine hesitancy scales in the literature. Our scales measure the vaccine hesitancy holistically.

The long form has four factors and provides more multidirectional information about vaccine hesitancy than the three-factor short form. While, short form can be easily used in the measurement of vaccine hesitancy by explaining the higher variance with less items.

Strategic Advisory Group of Experts on Immunization of the World Health Organization supports the development of different scales in high, middle- or low-income countries (36). This study was conducted in Turkey that is a developing country. According to our knowledge, our scales are the first vaccine hesitancy scales that were developed in Turkey. After considering that the socio-cultural structure highly influences the vaccine hesitancy; for Turkey it will be more accurate to use our scale instead of using the scales prepared with the data of developed countries. As shown previously (37), it may be appropriate to use our scales in other Turkish speaking countries and countries that have sociocultural structure similar as Turkey.

The items address emotions or perceptions and beliefs work well in the scale. It was seen that excluded items mostly contain gerunds or long sentences which make the item obscure. One of the general principles in the scale development literature is that the items should be as simple as possible with single meaning. When we evaluate some excluded items, it was seen that they have structures that question technical information

For scoring the scale, each item is scored as 1 point for “exactly disagree”, 2 point for “disagree”, 3 point for “partially agree, 4 point for “agree” and 5 point for “exactly agree”. Then scores of all items are added up to get total score of scales. Total score of the long form can vary between 21 and 105, while total score of the short form can vary between 12 and 60. The higher score on the scales means the higher vaccine hesitancy of participants. The issue that should be considered while scoring and interpretation of the scales is that for both the long form and the short form, a factor represents attitudes favorable to vaccination, not opposing vaccine. However, other factors and whole scales measure the vaccine hesitancy. Therefore, when scoring the scale, “Benefit and protection of vaccine” factor of the long form and the short form should be coded and interpreted in reverse way. Because getting higher score in both the long form and the short form of the scale will imply the higher level of vaccine hesitancy.

In our study, purposive sampling method was used as in other studies of vaccine hesitancy scale. So, results should be generalized cautiously. While this scale is used for future research in different samples, researchers can repeat factor analysis or reliability analysis in their own study groups. By this way, they can provide additional evidence for the validity and reliability of the scales and contribute to evolution process of the scales.

CONCLUSION

In summary, two Turkish vaccine hesitancy scales were developed, one of which was a long form (21 items) and one was a short form (12 items). Vaccine hesitancy challenge must be coped in order to achieve the required level of vaccination. The long form provides more detailed information about the multiple dimensions of vaccine contrast by its four factors, while the short form is easily applicable as it consists of less items with a higher rate of explained variance. With the scales we developed, it has become possible to measure the level of vaccine hesitancy, to determine related factors, to plan intervention studies for these related factors, and to observe the effectiveness of intervention studies in our country also as well as other Turkish speaking countries or countries that have sociocultural structure similar as Turkey after necessary validity and reliability studies will done.

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RESEARCH ARTICLE

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Vaccine Rejection in a University's Training Family Health Centers

ABSTRACT

Objective: It was aimed to determine the vaccine rejection rates and affecting factors in the Training Family Health Centers (TFHC) affiliated with a department of family medicine.

Methods: This study was designed as a mixed research and conducted in two TFHC of Department of Family Medicine of Atatürk University. In 2018, parents who did not receive at least one of the vaccines required under the Ministry of Health's Extended Immunity Program were included. Semi-structured interview technique was used on the telephone as the data collection method. Content analysis was applied statistically. An in-depth interview was done with 6 volunteering parents.

Results: The mean age was 30±1.2 years for both parents. All parents (n=6) who refused vaccination were university graduates. 66.7% of the parents (n=4) had high monthly income. According to the medical records of 749 children between 0-16 ages who were supposed to be vaccinated in 2018, it was observed that in nine children (1.2%), at least one vaccine was missing. Four children were not vaccinated due to distrust to the vaccine. Three of the parents refused vaccination due to complications developed after previous vaccinations.

Conclusions: Vaccine rejection rates were found low in our TFHCs and socioeconomic levels of them were high. The most important factors affecting vaccine rejection were the lack of confidence in the vaccine content and insufficient information about vaccines.

Keywords: Vaccine Rejection, Vaccine Hesitancy, Anti-Vaccination Parents, Family Health Center

Bir Üniversitenin Eğitim Aile Sağlığı Merkezlerinde Aşı Reddi

ÖZET

Amaç: Bu çalışmada bir Aile Hekimliği Anabilim Dalı'na bağlı Eğitim Aile Sağlığı Merkezleri'nde (EASM) aşı reddi oranlarının ve etkileyen faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma karma bir araştırma olarak tasarlanmış ve Atatürk Üniversitesi Aile Hekimliği Anabilim Dalı'nın iki EASM'sinde yürütülmüştür. Çalışmaya 2018 yılında Sağlık Bakanlığı'nın Genişletilmiş Bağışıklık Programı kapsamında yapılması gerekli aşılardan en az birini almayan ebeveynler dahil edilmiştir. Veri toplama yöntemi olarak telefonda yarı yapılandırılmış görüşme tekniği kullanılmış ve içerik analizi uygulanmıştır. Çalışmaya katılmaya gönüllü 6 ebeveyn ile derinlemesine bir görüşme yapılmıştır.

Bulgular: Her iki ebeveyn için ortalama yaş 30±1.2 yıldı. Aşı reddi yapan tüm ebeveynler (n=6) üniversite mezunuydu. Ebeveynlerin %66,7'si (n=4) yüksek gelir düzeyine sahipti. 2018 yılında aşılanması gereken 0-16 yaş arası 749 çocuğun tıbbi kayıtlarına göre, 9 çocukta (%1,2) en az bir aşının eksik olduğu gözlendi. Dört çocuğa aşıya güvensizlik nedeniyle aşı yapılmamıştı. Ebeveynlerden üçü ise önceki aşılardan sonra gelişen komplikasyonlar nedeniyle aşılamayı reddetmişti.

Sonuç: EASM'lerde aşı reddi oranları düşük bulundu ve aşı reddi yapan ebeveynlerin sosyoekonomik düzeyleri yüksekti. Aşı reddini etkileyen en önemli faktörler, aşı içeriğine duyulan güvensizlik ve aşılar hakkında yetersiz bilgi idi.

Anahtar Kelimeler: Aşı Reddi, Aşı Kararsızlığı, Aşı Karşıtı Ebeveynler, Aile Sağlığı Merkezi

INTRODUCTION

Vaccination is an essential preventive health service that has been used for many years to control infectious diseases and prevent complications and sequelae (1, 2). The World Health Organization (WHO) reported that 2 to 3 million deaths are prevented annually with vaccines, and 1.5 million more deaths can be prevented if vaccination reaches the desired levels (3). Thanks to the effectiveness of the vaccines, smallpox has been eradicated in the world, Turkey has received the "Polio-Free Zone" certificate, and maternal and neonatal tetanus has not been observed in Turkey for a long time (4).

The WHO has accepted vaccine rejection as one of the 10 global threats in 2019 (3). Despite all the known benefits of vaccines, anti-vaccine attitudes are increasing in the world (4-7). It is anticipated that vaccine rejection is gradually rising in Turkey, and if this rate continues, vaccination rates will decrease below 80% after five years (4). It is expected that this will impair social immunity and that there may be significant increases in the incidence of rare infectious diseases; even eradicated diseases may reappear (4, 8).

Studies on vaccine rejection are limited in Turkey. There are no official and precise data on vaccine rejection rates. It is known that there are differences between countries regarding vaccine rejection and its reasons; even regional differences exist in the same country (9). The implementation of the first two years of childhood vaccinations in Turkey is performed by the family health centers (FHC), while the task of immunization of the school children is accomplished by the community health centers. If school vaccines cannot be administered, the child is asked to be vaccinated by the registered FHC.

FHCs have a crucial significance concerning proper vaccinations and covering large populations. As a result, there is a need to identify the vaccine rejection rates in FHCs and to reveal the causes. This study aimed to determine the vaccine rejection rates and affecting factors in the Training Family Health Centers (TFHC) affiliated with a department of family medicine.

MATERIAL AND METHODS

This study was designed as mixed research, using both qualitative and quantitative data. The study was carried out in Atatürk University Faculty of Medicine Department of Family Medicine in June 2019. There are two TFHCs belonging to Department of Family Medicine. TFHC-1 has three family health units, and TFHC-2 has two family health units. Parents of children aged 0-16 with at least one missing vaccination from the 2018 extended immunity program childhood vaccination schedule, who could be reached by phone and who agreed to participate, were included in the study. Parents were accessed through the phone numbers registered in the Family Medicine Information System. The medical records of 749 children who were supposed to be vaccinated in 2018 were examined. It was observed that in 9 children (1.2%), at least one vaccine was missing. An in-depth interview was done with 6 volunteering parents.

Data collection was performed via phone calls using a semi-structured in-depth interview technique. A data collection form was used to determine the socio-demographic characteristics of the parents. Questions included demographic information of the parents (age, educational level, monthly income) and reasons for vaccine rejection. Parents who have monthly income 5000 and under 5000 Turkish Lira were accepted as low income, and have monthly income over 5000 Turkish Lira were accepted as high income.

The interviews were quantitatively assessed about how their structure was performed. Telephone interviews were transcribed verbatim. Thematic content analysis was performed for qualitative data.

The study protocol was approved by the ethics committee of Atatürk University Faculty of Medicine (Protocol Number: B.30.2.ATA.0.01.00/1). Statistical analysis was done with content analysis, and numerical data were presented as numbers, percentages, and standard deviations with the SPSS 23.0 package program (SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age was 30±1.2 years for the parents. All parents (n=6) who refused vaccination were university graduates. Of the parents, 2 (33.3%) had low monthly incomes, while 4 (66.7%) had high monthly income. The general characteristics of the participants are presented in Table 1.

Table 1. General features of the participants

	Interviewed parent	Education of mother/father	Mother/Father profession	Monthly income
P 1	Father	University/University	Academic staff/Academic staff	High
P 2	Mother	University/University	Housewife/Academic staff	High
P 3	Mother	University/University	Academic staff/Academic staff	High
P 4	Mother	University/University	Housewife/Academic staff	High
P 5	Father	University/University	Housewife/Officer	Low
P 6	Father	High school/University	Housewife/Self-employment	Low

P: parent

The rates of vaccination rejections for the each age group are demonstrated in Table 2. According to the medical records of 749 children between 0-16 age who were supposed to be vaccinated in 2018, it was observed that in 9 children (1.2%), at least one vaccine was missing. 5 (2.5%) of the 200 children aged 0-16 registered to the TFHC-1 and 4 (0.7%) of the 549 children aged 0-16 registered to THFC-2 had missing vaccinations. Missing vaccinations were observed in 3 (3.3%) out of 89 children aged 0-2 years registered to the TFHC-1, and 4 (1.32%) of 301 children between the ages of 0-2 registered to the TFHC-2. On the other hand, when the primary school first-grade vaccines were examined, it was found that 1 (1.96%) of 51 children enrolled in the TFHC-1 had missing vaccinations. In TFHC-2, all 147 children (100%) were vaccinated. Eighth-grade vaccines in primary school were examined, and it was seen 1 (1.66%) of the 60 children registered to the TFHC-1 had missing vaccinations, while all 101 children (100%) in the TFHC-2 were vaccinated.

Table 2. The rates of vaccination rejections in the age groups

Age groups	Total children (n)	Total vaccine rejection (n - %)	TFHC-1 (n - %)	TFHC-2 (n - %)
0-2 age	390	7 – 1.7%	3 – 3.30%	4 – 1.32%
1st grade	198	1 – 0.5%	1 – 1.96%	0 – 0%
8th grade	161	1 – 0.6%	1 – 1.66%	0 – 0%
0-16 ages	749	9 – 1.2%	5 – 2.5 %	4 – 0.7%

Of the parents, 83.3% (n=5) stated that families decided to refuse the vaccination by the agreement of both parents, and one child (16.7%) could not be vaccinated because he was afraid of the vaccine. All parents (n=6) mentioned that it was easy to access vaccination and that they were well informed by the healthcare professionals about the significance and side effects of the vaccines:

''*I know that I can easily access all the vaccinations without any payment*'.'

The reasons for not getting vaccinated were examined, and it was seen that four children were not vaccinated due to distrust to the vaccine:

''*I do not trust the vaccines, I am concerned about the content of them.*''

It was observed that 3 of the parents did not want their children to get vaccinated due to complications developed after previous vaccinations. One parent rejected the immunization due to different schedules between countries and changes in the schedules and the resulting insecurity of this change:

''*I do not understand why all countries do not have same vaccine schedule. In our country, the vaccine schedule changes in every year. This situation causes insecurity in our family.*''

One parent thought that the vaccine was not so important because it was not obligatory. On the other hand, one child was not vaccinated because he was afraid of vaccination.

When asked about the sources of information about vaccination, it was seen that all parents (n=6) used social and visual media. Two parents also accessed information about the vaccine from publications, one obtained information from the neighbors, and one attained knowledge by consulting a physician. None of the parents was aware of the Ministry of Health's website containing the vaccination schedule.

Five of the parents said that having an oral or nasal form of vaccines would not affect vaccine rejection decisions. However, the parents who could not apply the vaccine because their child was afraid said that if these forms were found, they could easily vaccinate their child. Two parents stated that they were not allowed to be discharged from the hospital until the child was vaccinated. Hence, they wanted but could not prevent vaccination against the Hepatitis B virus. Two parents stated that there were no anti-vaccination campaigns when their children were born, and one parent explained that they did not get vaccinated at birth.

While one parent thought that the MMR (Measles, Mumps, Rubella) vaccine could cause autism, another parent stated that she would only get the MMR vaccine to her child because she was informed that there was an outbreak of measles in Turkey. All parents (n=6) agreed that they would administer the vaccines if they would be produced in Turkey.

Parents were also asked about the newborn screening tests, breastfeeding, the use of recommended vitamin and mineral supplements, the month of starting complementary feeding, refrain from medications in the event of disease (despite the doctor's suggestion), and the status of Hepatitis B vaccination at birth. All parents interviewed agreed to the breast milk recommendations of the ministry of health and/or the transition to complementary feeding. Only one parent did not comply with the newborn screening tests, and heel prick test was not performed from their child. Although children of four parents were recommended medications by the doctors in times of sickness, they did not use them, especially if they were antibiotics. Two of the six parents did not use vitamin D and iron supplements at all, and one was using them irregularly.

DISCUSSION

In our study, the total vaccine rejection rate in TFHC's affiliated with the university was found

to be 1.2%. Since there is no precise data about vaccine rejection rates in Turkey, it is difficult to compare our findings. However, even when the age groups are examined individually, it can be said that the vaccination rates in the TFHCs are above the targets of the Ministry of Health of the Republic of Turkey (10).

In this study, the monthly income and educational levels of parents who rejected vaccinations were high. TFHC-1 primarily serves academic staff, administrative staff, and students. Thus, they are expected to have a higher socioeconomic level than the general population. Interestingly, the vaccine rejection rate on the THFC-1 was higher than that of the TFHC-2, which is similar to the other FHCs in the city. In a previous study, vaccination rates increased parallel to maternal education; no relationship was found with paternal schooling and socioeconomic level (11). In the study conducted by Topçu et al. in Ankara and Adıyaman in 2019, it was found that the monthly income and educational status of those who rejected the vaccine were lower than those who received the vaccine (12). A study conducted in the USA revealed that vaccine rejection rates were higher in those with a higher socioeconomic status (13). In low- and middle-income countries, anti-vaccination attitudes and low educational levels coexist, while in high-income countries, the reverse is true. Today, the level of vaccination is higher in well-educated and high-income families (14).

When vaccination rejection reasons were examined, it was seen that a child was not vaccinated due to fear of needles. The family stated that they wanted to have the vaccine, but could not get it done because of the child's anxiety. The same family expressed that oral or nasal vaccines would be a suitable solution. In one study, 63% of children reported fear of needles, 8% reported non-compliance, and 5% postponed the vaccine due to fear of needles in the child (15). In our study, the decision of vaccination rejection in the case with fear was given by the parents and the child together.

When the reasons for not getting vaccinated were examined, it was seen that four families rejected the vaccine due to not trusting the vaccine content and one family due to the distrust caused by the different vaccination calendars in different countries and their frequent changes. One of the families rejected vaccination because the ministry of health did not force people for vaccination. Leaving the initiative to the parents may produce an idea that vaccination is not crucial. One parent did not send his child for the heel prick test, and four parents did not use the drugs recommended to their children (especially antibiotics), although they were prescribed by the doctor when they were sick. Considering these findings, it can be concluded that families who refuse vaccines do not trust the health system and health professionals. Increased trust in the healthcare system and healthcare professionals has been previously shown to increase vaccination rates (16-18). Additionally, adding new vaccines to childhood vaccines, rapid developments and changes in the field of vaccines, and the different vaccination programs in different countries may create negative perceptions in parents (14). This suggests that vaccination adherence can be increased by providing more detailed information to families about possible changes in the vaccination schedules.

While one parent absolutely rejected the vaccine because of the thought that the MMR vaccine could cause autism, another parent was informed that there was a measles outbreak in Turkey through the media; thus, he would only allow the child to have the MMR vaccine. There is strong evidence that MMR vaccination is not related to autism (19, 20), and even other vaccines and compounds such as thimerosal and mercury, which are protective agents in vaccines, do not cause an increase in autism spectrum disorders (20). While the Turkish Ministry of Health has a web page titled "Vaccine Content", parents are not aware of this service (21). Families stated that they generally received information about vaccines through social and visual media. On the other hand, anti-vaccine misinformation spreads easier and faster through the media (22), and families with anti-vaccination attitudes are more active on the internet searching for information than other families (23). Although two giant social media companies, Facebook and YouTube, have stated that they will apply sanctions against anti-vaccination pages, there is still much false information on the internet (23, 24). Two parents in our study obtained contradictory information through the media. There are worrisome increases in cases of measles in the European geography, including Turkey. Measles began to reappear in countries where it had been eliminated (25, 26). Furthermore, measles outbreaks primarily affect unvaccinated societies (27).

All parents who participated in our study stated that it was easy to access the vaccine, and they were well informed by the healthcare professionals about the significance and side effects of the vaccines.

CONCLUSION

This study demonstrated that vaccine rejection rates were low in our TFHCs. However, interestingly, those who rejected vaccination had high socioeconomic levels. It was observed that the parents who refused the vaccine did not trust the vaccine's content, and had different and insufficient information about vaccines. It was understood that studies with broader participation should be done on behalf of preventive medicine, and appropriate strategies should be developed against the increasing trend of vaccine rejection.

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RESEARCH ARTICLE

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Changes in Early Childhood Obesity from 2016 to 2019 and Effective Factors

ABSTRACT

Objective: Aim of our study is showing the changes of factors that affecting early childhood obesity from 2016 to 2019 and to ensure that necessary measures are taken about this regard.

Methods: 3 years follow-up information of 388 babies whom born in 2013 and 2016 and registered at the Family Health Centers of Rize (Turkey) included to our study. The family doctors participating in this study examined these babies who were registered to them during their 1st, 3rd, 7th, 9th, 12th, 18th, 24th, 30th, 36th months at the family health centers in accordance with Turkish Health Ministry protocols and recorded their height, weight, head circumference and Body Mass Index (BMI). Descriptive statistical methods were used to evaluate the obtained data.

Results: 388 babies included in study, 177 of them were born in 2013 and 211 of them were born in 2016. Percentage of being overweight or obese was 19.2% in babies born in 2013 and this rate decreased to 18.2% in babies born in 2016. Percentage of being overweight or obese was 16% in girls and 21.2% in boys. We observed that high birth weight (>4000 gr) and excess gestational weight gain (GWG) are risk factors for being overweight or obese at the age of three (p=0.048).

Conclusions: Result of our study showed us that although prevalence of early childhood obesity decreased, but prevalence is still at critical level. We found that GWG and high birth weight are risk factors for early childhood obesity. In future obesity prevention studies, taking these risk factors into account will be beneficial.

Keywords: Obesity, Overweight, Body Mass Index, Child

Erken Çocukluk Çağı Obezitesinde 2016'dan 2019'a Değişiklikler ve Etkili Faktörler

ÖZET

Amaç: Çalışmamızın amacı 2016 yılından 2019 yılına erken çocukluk çağı obezitesine etkili faktörlerin değişimini göstererek bu konuda gerekli önlemlerin alınmasını sağlamaktır.

Gereç ve Yöntem: Retrospektif kohort tipindeki çalışmamıza 2013 ve 2016 yılı doğumlu olan ve Rize ili Aile sağlığı merkezlerine kayıtlı 388 çocuğun 3 yaş izlem bilgileri dahil edilmiştir. Çalışmaya katılan Aile Hekimleri kendilerine kayıtlı olan çocukları Türkiye Cumhuriyeti Sağlık Bakanlığı'nın bebek ve çocuk izlem protokolüne uygun olarak 1, 3, 7, 9, 12, 18, 24, 30 ve 36. aylarında aile sağlığı merkezlerinde izleyerek boy-kilo-baş çevresi ve vücut kitle indekslerini (VKİ) kaydetmişlerdir. Elde edilen verilerin değerlendirilmesinde tanımlayıcı istatistiksel yöntemler kullanıldı.

Bulgular: Çalışmaya 177'si 2013 doğumlu, 211'i 2016 doğumlu toplam 388 çocuk dahil edilmiştir. Fazla kilolu ya da obez olma durumu 2013 yılı doğumlularda %19,2 iken bu oran 2016 doğumlularda %18,2'ye gerilemiştir. Çalışmaya alınan çocuklarda obezite ya da fazla kilolu olma durumu kızlarda %16 iken erkeklerde %21,2 idi. Yüksek doğum ağırlığının (>4000 gr) ve fazla gestasyonel kilo alımının 3 yaş fazla kilolu ya da obez olma durumu için bir risk olduğunu gözlemledik (p=0,048).

Sonuç: Çalışmamızın sonucu bize erken çocukluk çağı obezitesi prevalansının alınan son önlemlerle bir miktar gerilese de hala ciddi seviyede olduğunu gösterdi. Gestasyonel kilo alımı ve yüksek doğum ağırlığının erken çocukluk çağı obezitesi için bir risk olduğunu bulduğumuz çalışmamızdan yola çıkarak ileriye yönelik obezite önleme çalışmalarında bu risklerin göz önüne alınması konusunda faydalı olacaktır.

Anahtar Kelimeler: Obezite, Fazla Kiloluluk, Vücut Kitle İndeksi, Çocuk

INTRODUCTION

Obesity is an important public health problem due to its high prevalence and concomitant morbidity and mortality (1,2). BMI, which is the most commonly used measure to diagnose obesity in childhood is highly correlated with BMI measured in later life and there are correlations changing between 0.3 and 0.9 depending on time interval and age (3,4). The World Health Organization (WHO) currently estimates that 42 million children under the age of 5 are obese. The prevalence of obesity in the WHO European Region, including Turkey has increased 3 times in the last 20 years (5). Among the low and middle income countries, the highest prevalence of overweight in children and associated metabolic disorders was found in the Middle East and Eastern Europe countries (6). In a cross-sectional study conducted by Olaya et al. among seven European countries including Turkey, prevalence of obesity in elementary school children has been shown that Turkey ranked ranked second after Romania (7).

Many factors, including behavioral, genetic and environmental factors, may be relative to childhood obesity. Previous studies have revealed that various prenatal and early life factors, including maternal BMI, maternal cigarette smoking, infant birth weight, GWG and gestational diabetes, are effective in early childhood obesity (8,9).

Current studies show that overweight up to 2 years of age in early childhood can predict overweight/obesity after 10 years (10). Despite all pharmacological and non-pharmacological efforts, treatment of obesity remains difficult and usually fails. Therefore, prevention of obesity is essential and patients can be informed by determining the risk factors of obesity in early life (11).

Although there are studies about early childhood obesity, there are very few studies in recent years showing the change in the prevalence of factors affecting obesity. Risk factors in obese or overweight children at 2016 and risk factors in obese or overweight children at 2019 were evaluated in our study which is the first study showing change of 3 years old childhood obesity from 2016 to 2019 in Turkey. Aim of our study is showing the changes of factors that affecting early childhood obesity from 2016 to 2019 and to ensure that necessary measures are taken about this regard.

MATERIAL AND METHODS

Three years follow-up information of 388 babies whom born in 2013 and 2016 and registered at the Family Health Centers of Rize (Turkey) included to our retrospective cohort study.

The family doctors participating in this study examined these babies who were registered to them during their 1st, 3rd, 7th, 9th, 12th, 18th, 24th, 30th, 36th months at the family health centers in accordance with Turkish Health Ministry protocols and recorded their height, weight, head circumference and BMI.

Baby weight measurements were made with scales sensitive to 0.01 kg. Before taking the measurement, the baby's clothing and diaper, if any, were removed and baby's weight recorded when they were not moving. In children over 2 years of age, height measurement was done by removing shoes while standing. Height measurements were made with a sensitivity of 0.1 cm.

BMI Classification: Body mass index (BMI) was calculated by dividing the child's weight in kilograms by the square of their height (kg/ m2). Reference growth chart of the Centers for Disease Control and Prevention (CDC) 2000 was used to classify the children into one of three categories using their weight status. Children under 85 percentile are classified as having a healthy weight status. Children with a BMI percentile between 85 and 94 were considered overweight and children 95 and above 95 percentile were categorized as obese. The BMI percentiles of all 3 years old children were calculated and categorized according to the reference values suggested by the CDC.

Gestational Weight Gain (GWG): All of mothers participating in the study had attended at least three pregnancy follow-up visits with their family physician (at least one visit in each trimester). Weight of the mothers before pregnancy recorded and weight and height measurements of the last trimester (between 36th and 40th weeks) were made. The weight gain of mothers during pregnancy was calculated. Besides that weight, height and BMI measurements of the mothers made when children were 3 years old. GWG described as the difference between mother's weight a week before birth and mother's weight before pregnancy. Suggested GWG is 12.5-18 kg for underweight women, 11.5-16 kg for normal weight women, 7-11.5 kg for overweight women and 5-9 kg for obese women according to WHO. After that, GWG was divided into three categories. Weight gain is classified as low if it is below the recommendation, classified as enough if it is appropriate to recommendation and it is classified as high if it is above the recommendation.

Neonatal Characteristics: Babies were divided into 3 groups according to their birth weights. While birth weight between 2500-4000 g for a term baby is accepted as "normal", over 4000 g accepted as high and below 2500 g accepted as low birth weight (12).

Ethical Procedure: Ethics committee approval for this study was taken from the Ethics Committee of Recep Tayyip Erdoğan University Faculty of Medicine with protocol number 2020/01. In addition, informed consent forms were obtained from the mothers.

Statistical Analysis: SPSS 23.0 program was used for statistical analysis. Descriptive statistics of the evaluation results given as numbers and percentages for categorical variables, given as mean
and standard deviation for numerical variables. Normal distribution of groups was determined by One Sample Kolmogorov Smirnov test. Student-t Test used for comparison of independent two groups when normal distribution condition is provided and Mann Whitney U used when normal distribution condition is not provided. We accepted $p<0.05$ value as statistically significant.

Inclusion Criteria: Babies whom born in 2013 and 2016 and registered at the Family Health Centers of Rize

Exclusion Criteria: Children who didn't come to their regular control until 36 months of age exluded from the study.

Babies with congenital heart disease, congenital immune system deficiency, malabsorption syndrome and those diagnosed with phenylketonuria were also excluded because these conditions might have an effect on the weight and height percentiles of the babies.

RESULTS

388 babies included in study, 177 of them were born in 2013 and 211 of them were born in 2016. Percentage of being overweight or obese was 19.2% in babies born in 2013 and this rate decreased to 18.2% in babies born in 2016. Percentage of being overweight or obese was 16% in girls and 21.2% in boys. From 2016 to 2019 maternal cigarette smoking percentage was decreased to 6.2% from 13.6% (p=0.022). Mean pregnancy age was 29.3 (± 5.7) in 2013 and this rate was increased to 29.7 (± 6.2) in 2016 (p=0,513) (Table 1).

Table 1. Sociodemographic characteristics of 3 years old children born in 2013 and 2016

	Children born in 2013		**Children born in 2016**		**p**
	n	%	n	%	
Gender					
Female	86	48.6	102	48.3	0.961
Male	91	51.4	109	51.7	
Mother's educational status					
≤8 years	116	65.5	109	51.7	**0.006**
>8 years	61	34.5	102	48.3	
Socioeconomic situation					
Low	18	10.2	14	7.3	0.395
Middle	104	58.8	134	63.5	
High	55	31.1	63	29.9	
Mother smoking					
Yes	24	13.6	13	6.2	**0.022**
No	153	86.4	198	93.8	
Gestational age (mean)	29.3 ± 5.7		29.7 ± 6.2		0.513
Gestational weight gain	12.9 ± 5.1		13.0 ± 4.8		0.723
Mother's BMI	26.8 ± 5.1		26.3 ± 5.4		0.168
Neonatal birth weight	3340.6 ± 515.5		3304 ± 532.8		0.931
Total breast milk intake(month)	17.6 ± 7.6		17.5 ± 7.7		0.927
Childrens' BMI					
Weak - Normal	143	80.8	171	81.8	0.082
Overweight - Obese	34	19.2	38	18.2	

BMI: Body Mass Index

We showed comparison of the variables that have an impact on obesity of children born in 2013 and 2016 at Table 2. We evaluated the gender, neonatal birth weight, GWG, mother BMI, delivery type, total breastfeeding time, first 6 months exclusive breastfeeding, gestational age, socioeconomic level like factors that can affect the obesity. We evaluated overweight and obese babies among themselves according to their birth years and also we evaluated normal and underweight babies among themselves according to their birth years.

Table 2. Evaluation of variables on obesity status of children born in 2013 and 2016

	2013		2016			2013		2016		
	Weak - Normal		Weak – Normal		p	Overweight - Obese		Overweight – Obese		p
	n	%	n	%		n	%	n	%	
Gender					0.992					1.000
Female	72	50.3	86	50.3		14	41.2	16	42.1	
Male	71	49.7	85	49.7		20	58.8	22	57.9	
Mother's educational status										
≤8 years	90	62.9	88	51.5		26	76.5	20	52.6	0.063
>8 years	53	37.1	83	48.5	**0.041**	8	23.5	18	47.4	
Socioeconomic situation										0.406
Low	15	10.5	12	7.0	0.550	3	8.8	2	5.3	
Middle	85	59.4	106	62.0		19	55.9	27	71.1	
High	43	30.1	53	31.0		12	35.3	9	23.7	
Mother smoking										
Yes	18	12.6	11	6.4	0.093	6	17.6	2	5.3	0.138
No	125	87.4	160	93.6		28	82.4	36	94.7	
Way of birth										
C/S	82	57.3	68	39.8	**0.002**	14	41.2	17	44.7	0.947
NSD	61	42.7	103	60.2		20	58.8	21	55.3	
6 months breastfeeding										
Yes	102	71.3	112	66.3	0.338	27	79.4	26	68.4	0.430
No	41	28.7	57	33.7		7	20.6	12	31.6	
Gestational age	29.2 ± 5.7		29.8 ± 5.9		0.339	30.0 ± 5.5		29.3 ± 7.4		0.459
Gestational weight gain	13.1 ± 5.3		13.0 ± 4.5		0.997	12.1 ± 4.2		13.2 ± 5.8		0.639
Inadequate	25	17.6	31	18.1		5	14.7	3	7.9	
Adequate	50	35.2	56	32.7	0.900	16	47.1	20	52.6	0.648
Excessive	67	47.2	84	49.1		13	38.2	15	39.5	
Mother's BMI	26.7 ± 5.1		26.2 ± 5.5		0.244	27.4 ± 4.8		26.5 ± 5.0		0.321
Neonatal birth weight	3321.7 ± 521.3		3253.7 ± 530.0		0.860	3419.9 ± 489.8		3529.1 ± 498.2		0.892
Total breast milk intake (month)	17.9 ± 7.5		17.5 ± 7.8		0.831	16.5 ± 7.9		17.2 ± 7.3		0.818

C/S: Cesarean, NSD: Normal spontaneous delivery, BMI: Body Mass Index

We showed effects of mother BMI, GWG and neonatal birth weight on three years old obesity of children born in 2013 and 2016. We couldn't find significant effect of mother BMI on three years old overweight or obesity of children born in 2013 and 2016 in Table 3 (p=0.990, p=0.753). When we evaluate GWG, obesity rate is higher in babies of mothers who gain enough weight during pregnancy compared to babies of mothers who gain insufficient weight in 2016 (p=0.05). We observed that high birth weight (>4000 gr) is a risk factor for being overweight and obesity at the age of three (p=0.048). But neonatal birth weight was not statistically significant for three years old obesity at the babies born in 2013 (p=0.178). We searched the factors that effective for three years old BMI of all participant children at Table 4. We observed that insufficient GWG has a positive effect on overweight or obesity (p=0.033). Effect of other factors was not statistically significant.

Table 3. Children born in 2013 and 2016; effect of maternal BMI, GWG and neonatal birth weight on obesity at 3 years of age

Children born in 2013	All		Weak - Normal		Overweight - Obese		P
	n	%	n	%	n	%	
Mother's BMI (n=174)							
Normal or low <25	68	39.1	55	80.9	13	19.1	0.990
Overweight 25 – 29.9	65	37.4	53	81.5	12	18.5	
Obese ≥30	41	23.6	33	80.5	8	19.5	
Gestational weight gain (n=176)							
Inadequate	30	17.0	25	83.3	5	16.7	0.439
Adequate	66	37.5	50	75.8	16	24.2	
High	80	45.5	67	83.8	13	16.3	
Neonatal birth weight (n=177)							
Low < 2500	6	3.4	4	66.7	2	33.3	0.178
Normal 2500- 4000	160	90.4	128	80.0	32	20.0	
High > 4000	11	6.2	11	100.0	0	0.0	
Children born in 2016							
Mother's BMI (n=207)							
Normal or low <25	92	44.4	76	82.6	16	17.4	0.753
Overweight 25 – 29.9	75	36.2	62	82.7	13	17.3	
Obese ≥30	40	19.3	31	77.5	9	22.5	
Gestational weight gain (n=209)							
Inadequate	34	16.3	31	91.2	3	8.8	**0.050**
Adequate	76	36.4	56	73.7	20	26.3	
Excessive	99	47.4	84	84.8	15	15.2	
Neonatal birth weight (n=209)							
Low < 2500	13	6.2	13	100.0	0	0.0	**0.048**
Normal 2500- 4000	186	89.0	152	81.7	34	18.3	
High > 4000	10	4.8	6	60.0	4	40.0	

BMI: Body Mass Index

Table 4. Factors affecting the obesity status of all children included in the study

	All		Weak - Normal		Overweight - Obese		P
	n	%	n	%	n	%	
Gender							
Female	188	48.7	158	84.0	30	16.0	0.185
Male	198	51.3	156	78.8	42	21.2	
Mother's educational status							
≤8 years	224	58.0	178	79.5	46	20.5	0.264
>8 years	162	42.0	136	84.0	26	16.0	
Socioeconomic situation							
Low	32	8.3	27	84.4	5	15.6	0.852
Middle	237	61.4	191	80.6	46	11.9	
High	117	30.3	96	82.1	21	17.9	
Mother smoking							
Yes	37	9.6	29	78.4	8	21.6	0.626
No	349	90.4	285	81.7	64	18.3	
Gestational age	29.5 ± 5.9		29.5 ± 5.8		29.6 ± 6.5		0.878
Total breast milk intake (month)	17.5 ± 7.6		17.7 ± 7.6		16.9 ± 7.69		0.595
Mother's BMI							
Normal or low <25	160	42.0	131	81.9	29	18.1	0.827
Overweight 25 – 29.9	140	36.7	115	82.1	25	17.9	
Obese ≥30	81	21.3	64	79.0	17	21.0	
Gestational weight gain							
Inadequate	64	16.6	56	87.5	8	12.5	**0.033**
Adequate	142	36.9	106	74.6	36	25.4	
Excessive	179	46.5	151	84.4	28	15.6	
Neonatal birth weight							
Low < 2500	19	4.9	17	89.5	2	10.5	0.647
Normal 2500- 4000	346	89.6	280	80.9	66	19.1	
High > 4000	21	5.4	17	81.0	4	19.0	

DISCUSSION

We evaluated obesity which is a risk factor for diseases such as diabetes, hypertension and cancer in adulthood, risk factors and necessary measures about this regard by observing changes of three years old children from 2016 to 2019 with retrospective cohort method (3,13). In our study which is the first study showing three years change at this age group in Turkey, we evaluated criteria that can be a risk factor for childhood obesity.

The WHO announced that the prevalence of obesity, which was 31 million in 1990 for children aged 0-5, increased to 42 million in 2016 (14).

There is evidence about decrease in obesity increase rate in children at recent years: rate increased from 0.4 to 0.7 points between 1978 and 2004 years, after that rate of increase slowed to 0.1 points from 2004 to 2016 (15). Percentage of being overweight or obese was 19.2% in babies born in 2013 and this rate decreased to 18.2% in babies born in 2016. Although this decrease was not enough, most important cause of this can be 'Obesity Prevention and Control Program of Turkey' started by Ministry of Health (16).

There are many studies in the literature showing the relationship between maternal obesity and early childhood obesity (17-19). We didn't find a significant relationship between 3 years old childhood obesity and maternal obesity (p=0.827). The reason for this may be the regional feature of the study group. Another reason can be that we don't know the fathers' BMI. It will be more accurate to present the genetic characteristics of the child by knowing the BMI of both the mother and father.

In a study conducted by Werneck AO. et al. (21) it was showed that birth weight was associated with obesity in adolescent period (20). Qiao Y. et al. found that birth weight was effective on childhood obesity in their study that containing participants from 12 different countries. In our study, in accordance with the literature, we found that birth weight over 4000 g was related with obesity at the age of 3 for babies born in 2016 (p=0.048).

In our study we found significant relationship between GWG and obesity at the age of 3 (p<0.033). This was a consistent result with the literatüre (22-24). This result can be explained with that mechanism; high GWG indicates more maternal fat accumulation and possibly maternal abnormal metabolism status (25-27). This altered maternal environment can interact with placental factors that cause increased calorie supply in the fetus (28).

In a study conducted in the USA in 2013 showed a negative relationship between socioeconomic level and childhood obesity (29). In our study, we couldn't find a relationship between socioeconomic level and obesity. The reason for this is when we ask the mothers how their socioeconomic level is; they were marking one of the good, medium or bad options. The absence of household income per capita made the answers given inadequate.

In the literature, there are studies about breast milk preventing early childhood obesity, but its mechanism of action remains uncertain (30-32). One possible explanation for breast milk's benefit; breastfeeding can improve children's ability to control food intake and determine hunger satisfaction (33). On the other hand children who meet the bottle in the early period may not be able to improve their saturation control and may be prone to weight gain (34). In our study, we didn't find a relationship between breastfeeding times and obesity at the age of three. This may be caused by that transition times to supplementary food and daily calorie intake were not calculated in the study group.

Strengths of the study were that we observed children at least 7 times before they reached the age of 3, and all the observation records were conducted were kept in computer. Although there are studies about early childhood obesity, there are very few studies like our study showing the three years change. Besides that another strength of our study is that all mothers participated to our study were observed by the same family doctors at least 4 times during their pregnancies.

That we didn't ask about the nutritional composition of the food given to the babies, did not determine the nutritional values and being a regional study can be considered as limitations. Another limitation can be added that the income status of families cannot be documented.

CONCLUSION

Result of our study showed us that although prevalence of early childhood obesity decreased, but prevalence is still at critical level. We found that GWG and high birth weight are risk factors for early childhood obesity. In future obesity prevention studies, taking these risk factors into account will be beneficial.

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RESEARCH ARTICLE

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Clinical and Magnetic Resonance Imaging Findings of Patients with Acute Carbon Monoxide Poisoning

ABSTRACT

Objective: We aim to evaluate the demographic and clinical characteristics of patients with acute carbon monoxide (CO) poisoning, who had a Glasgow Coma Score (GCS) below 15, and who had cerebral lesions detected in magnetic resonance imaging (MRI).

Methods: The age, gender, causes of CO intoxication, clinical signs, neurological findings, GCS, blood carboxyhemoglobin level (COHb), serum pH, lactate, creatine kinase (CK), creatinine kinase-myocardial band MB (CK-MB), troponin-I level, brain MRI (T1-weighted, T2-weighted, FLAIR and diffusion-weighted imaging), treatment, and mortality status of 327 patients were evaluated retrospectively.

Results: The median age of patients was 31.5 years (IQR=19.5 years), 72.2% of the patients were women. Neurological findings were detected in 34 (10.4%) of the patients. The frequency of dyspnea was significantly higher in patients with neurological findings ($p<0.05$). The COHb and lactate levels of patients with neurological findings were found to be significantly high, the pH level was significantly lower ($p<0.05$). There was no significant relationship between the presence of neurological findings and CK, CK-MB, and troponin-I levels ($p>0.05$). Patients with neurological findings were found to have a significantly longer follow-up period, more frequently received hyperbaric oxygen therapy ($p<0.05$). The rate of hospitalization was 10.7%, the mortality rate was 0.9%. Hospitalization and mortality rates were significantly high in patients with neurological findings ($p <0.05$). Pathological findings were detected in 13 (40.6%) of 32 of patients (except for 2 patients who did not respond to the resuscitation) who had an MRI.

Conclusions: It was determined that acute CO poisoning may lead to acute brain damage, 40.6% would be detected in brain MRIs taken in patients during the acute phase.

Keywords: Carboxyhemoglobin, Emergency Department, Magnetic Resonance Imaging, Mortality

Akut Karbonmonoksit Zehirlenmesi olan Hastalarının Klinik ve Manyetik Rezonans Görüntüleme Bulguları

ÖZET

Amaç: Bu çalışmada akut karbonmonoksit (CO) zehirlenmesi tanısı konulan hastaların demografik ve klinik özellikleri ile Glasgow Koma Skoru (GKS) 15'in altında olan hastaların manyetik rezonans görüntüleme (MRG)'de tespit edilen serebral lezyonları tanımlamayı amaçladık.

Gereç ve Yöntem: 327 hasta yaş, cinsiyet, CO zehirlenme nedenleri, klinik belirtileri, nörolojik bulguları, GKS'ları, karboksihemoglobin (COHb), serum pH, laktat, kreatin kinaz (CK), kreatini kinaz, miyokardiyal band (CK-MB), troponin-I düzeyleri ile beyin MRG (T1 ağırlıklı, T2 ağırlıklı, FLAIR, difüzyon ağırlıklı görüntü) bulguları ve mortalite durumları açısından retrospektif olarak değerlendirildi.

Bulgular: Çalışmamızda hastaların yaş ortancası 31,5 yıl (IQR=19.5 yıl) olup, hastaların %72,2'si kadındı. Hastaların 34 (%10,4)'ünde nörolojik bulgular saptandı Nörolojik bulgusu olan hastaların dispne sıklığı anlamlı olarak yüksekti ($p<0,05$). Çalışmamızda nörolojik bulgusu olan hastaların COHb düzeyi ve laktat düzeyi anlamlı olarak yüksek, pH düzeyi anlamlı olarak düşük saptandı ($p<0,05$). Nörolojik bulgu varlığının CK, CK-MB ve troponin-I düzeyi arasında anlamlı bir ilişki saptanmadı ($p>0,05$). Nörolojik bulgusu olan hastaların, takip süresi anlamlı olarak uzun olduğu, daha sıklıkla hiperbarik oksijen tedavisi aldığı saptandı ($p<0,05$). Çalışmamızda olguların yatış oranı % 10,7, mortalite oranı % 0,9 olarak saptandı. Nörolojik bulgusu olan hastalarda yatış ve mortalite oranları anlamlı olarak yüksek saptandı ($p<0,05$). MRG çekilen 32 olgunun (resistasyona yanıt vermeyen 2 hasta haricinde) 13'ünde (%40,6) patolojik bulgulara rastlandı.

Sonuç: Akut karbonmonoksit zehirlenmelerinin akut beyin hasarına yol açabileceği, klinik bulgu veren bu hastalarda akut dönemde çekilen MRG'sinde %40,6 oranında bulgu vereceği saptandı.

Anahtar Kelimeler: Karboksihemoglobin, Acil Servis, Manyetik Rezonans Görüntüleme, Mortalite

INTRODUCTION

Carbon monoxide (CO) poisoning is one of the most important public health problems in Turkey that can result in death if neglected. CO is a colorless, odorless, tasteless, and non-irritant gas that occurs as a result of carbon-containing fuels not being burned until the end product (1,2). CO poisoning is a clinical condition that usually develops due to the incomplete combustion of fuels used for heating such as stoves and natural gas. Also, exposure to fire and exhaust fumes, smoking, or hookah smoking leads to CO poisoning (1).

The tissues are exposed to hypoxia as the oxygen rate in the tissues of the patient exposed to CO gas decreases. The central nervous system and cardiovascular system are mostly affected by this condition.

There are publications that report that CO poisoning accounts for 34% of all poisonings (1). It was reported that deaths due to CO poisoning are in the first rank among all poisonings, and the mortality rate related to this is between 1-4.3% (3,4). Cardiac disorders (arrhythmia, left ventricular dysfunction) and up to 40% neuropsychological disorders may occur in approximately one-third of moderate and severe poisoning patients (4,5).

Symptoms of CO poisoning patients who are referred to the Emergency Department (ED) range from a mild headache to coma (6). Although the frequency of acute brain injury (ABI) due to CO poisoning has been shown to be around 37% in a study (7), little is known about the lesions developing in the acute period and the clinics that these lesions will cause (8). The diagnosis of ABI can be difficult, especially because it causes changes in the symptoms and findings of patients who use hypnotic drugs and alcohol (9).

Since correct treatment can reduce morbidity in CO poisoning, it is important to diagnose ABI in these patients (9). Magnetic resonance imaging (MRI) is a sensitive imaging method that identifies cerebral lesions in the acute period of CO poisoning (2,9).

In our study, we aimed to examine the demographic and clinical features of patients diagnosed with acute CO intoxication in the ED, and the cerebral lesions detected on MRI in patients with Glasgow Coma Score (GCS) below 15.

MATERIAL AND METHODS

Patients diagnosed with CO intoxication in the ED between December 1, 2015, and December 1, 2018, were evaluated retrospectively after obtaining approval from the hospital ethics board. 479 patients were diagnosed with acute CO intoxication in the ED, and 327 patients who met the criteria were included in the study. Age, gender, causes of CO exposure, symptoms during admission, duration of treatment, hospitalization rate, mortality rate, and GCS were determined. Blood carboxyhemoglobin level (COHb), pH, serum lactate level, creatine kinase (CK), creatine kinase-myocardial band MB (CK-MB), and troponin-I levels, as well as MRI findings and prognoses, examined. Patients over 18 years of age diagnosed with acute CO intoxication after admission to the ED were included in the study. Patients with a lack of information in the patient files, and patients with a history of migraine, multiple sclerosis, Alzheimer's disease, dementia, hemorrhagic or ischemic stroke in the past, traumatic brain damage, and sequelae neurological findings were excluded from the study.

Syncope, loss of consciousness, altered mental status, decrease in GCS into 14 or below, isolated unable to speech or disorder, hearing impairment and vision defect or acute diplopia, and also motor deficits on physical examination were accepted as neurological impairment.

Two different 1.5 Tesla Magnetic Resonance Imaging scanners; (Magnetom®, Aera, Siemens-Erlangen, Germany and Philips Achieva®, Philips Medical Systems, Eindhoven, The Netherlands) with a standard head coil were used for performing the magnetic resonance imaging of patients. The non-contrast conventional brain MRI, protocol constituted the following sequences, axial T1-weighted, axial T2-weighted, axial FLAIR, coronal T2-weighted, sagittal FLAIR, and diffusion-weighted imaging. The patients' images were evaluated on MRI via Extreme Picture Archiving and Communications System (PACS, Ankara, Turkey).

Statistical Analysis: All statistical analyses were performed using the Statistical Package for Social Sciences® (SSPS) software (SPSS for Windows, Version 24, SPSS Inc., USA). The distribution of the data was analyzed using the Kolmogorov-Smirnov test. Quantitative (parametric) variables were presented as median and interquartile range (IQR) deviation, and qualitative (nonparametric) variables were expressed as observed numbers and percentages. Pearson’s Chi-Square test was used to test if differences between dichotomous groups were significant. Fisher’s exact test was used when a table had a cell with an expected frequency of less than 5. Upon determining that quantitative data is non-parametric, a Mann-Whitney U test was used to analyze the data with categorical variables. All analyses were performed within a 95% confidence interval and a p value <0.05 was considered statistically significant.

RESULTS

Of the 34 (10.4%) accepted patients with neurological findings, 82.4% had syncope, and loss of consciousness developed in 29.4%, visual disturbance in 26.5%, impaired speech in 26.5%, hemiparesis in 2%, and cardiopulmonary arrest in 2.9% and GCS of the patients were below 15 in 55.9%.

It was determined that out of the three patients who developed cardiopulmonary arrest, one that was brought as cardiopulmonary arrest responded to resuscitation and an MRI was taken during this process. MRI could not be performed on the other two patients of cardiopulmonary arrest, as they did not respond to resuscitation.

The median age of patients in our study was 31.5 years (IQR=19.5 years), and 72.2% of the patients were women. No relationship was found between the presence of neurological findings and age and gender (p>0.05). It was determined that poisoning developed most frequently from the stove (64.5%). No relationship was found between the cause of poisoning and neurological findings (p>0.05). The most frequently recorded symptoms were dizziness (81%; n = 265) and nausea (66.7%; n = 218). While the frequency of dyspnea development was significantly higher in patients with neurological findings (p<0.05), there was no relationship found between neurological findings and nausea, dizziness, headache, weakness, and chest pain with the presence of neurological findings (p>0.05). In our study, the COHb and lactate levels of patients with neurological findings were found to be significantly high, and the pH level was significantly lower (p<0.05).

There was no significant relationship between the presence of neurological findings and CK, CK-MB, and troponin-I levels (p>0.05). The follow-up period of patients with neurological findings was significantly longer (p<0.05). It was found that 44 (13.5%) of the patients received additional hyperbaric oxygen therapy (HBO2).

The frequency of HBO2 treatment was significantly higher in patients with neurological findings (p<0.05). In our study, the rate of hospitalization was 10.7%, and the mortality rate was 0.9%. Hospitalization and mortality rates were significantly high in patients with neurological findings (p<0.05). The relationship of the presence of neurological findings with clinical, demographic, and laboratory features is presented in Table 1.

Table 1. The relationship between clinical and demographic features and the presence of neurological findings

Clinical, demographic and laboratory findings	Neurological symptoms (+) (n=34)	Neurological symptoms (-) (n=293)	Total (n=327)	P value
Age (year), (IQR)	31.5 (19.5)	33 (20)	31.5 (19.5)	0,681$^{\alpha}$
Gender, n (%)				
Male	14 (41,2)	77 (26,3)	91 (27,8)	0,067$^{\beta}$
Female	20 (58,8)	216 (73,7)	236 (72,2)	
Causes of poisoning, n (%)				
Stove	22 (64,7)	189 (64,5)	211 (64,5)	0,982$^{\beta}$
Natural gas	11 (32,4)	87 (29,7)	98 (30)	0,749$^{\beta}$
Hookah	0	10 (3,4)	10 (3,1)	0,507*
Automobile exhaust	1 (2,9)	7 (2,4)	8 (2,4)	0,589*
Symptoms / Findings, n (%)				
Nausea	18 (52,9)	200 (68,3)	218 (66,7)	0,073$^{\beta}$
Dizziness	24 (70,6)	241 (82,3)	265 (81)	0,101$^{\beta}$
Headache	14 (41,2)	133 (45,4)	147 (45)	0,640$^{\beta}$
Weakness	7 (20,6)	87 (29,7)	94 (28,7)	0,267$^{\beta}$
Dyspnea	7 (20,6)	27 (9,2)	34 (10,4)	0,040$^{\beta}$
Syncope	28 (82,4)	0	28 (8,6)	<0,001*
Loss of consciousness	10 (29,4)	0	10 (3,1)	<0,001*
Chest pain	2 (5,9)	6 (2)	8 (2,4)	0,798*
Visual disturbance	9 (26,5)	0	9 (2,8)	<0,001*
Impaired speech	9 (26,5)	0	9 (2,8)	<0,001*
Cardiopulmonary arrest	3 (8,8)	0	3 (0,9)	0,001*
Hemiparesis	1 (2,9)	0	1 (0,3)	0,104*
GCS, median (IQR)	14 (2)	15 (0)	15 (0)	<0,001$^{\alpha}$
Laboratory findings				
COHb (%), median (IQR)	32,5 (8)	26 (4,5)	26 (5)	<0,001$^{\alpha}$
pH, median (IQR)	7.34 (0,2)	7.33 (0,05)	7,34 (0,03)	0,011$^{\alpha}$
Lactate (mmol/L), median (IQR)	1.6 (0.4)	2,25 (1.2)	1,6 (0,5)	0,004$^{\alpha}$
CK (U\L), median (IQR)	331 (114,3)	289 (129)	300 (124)	0,407$^{\alpha}$
CK-MB (U\L), median (IQR)	26 (8)	25 (10)	26 (9)	0,244$^{\alpha}$
Troponin-I (ng/L), median (IQR)	5 (2)	5 (4)	5 (4)	0,098$^{\alpha}$
Follow-up period (hour), median (IQR)	72 (24)	6,8 (2,8)	7 (2,8)	0,001*
Treatment				
Normobaric oxygen	3 (2.9)	280 (95.6)	283 (86.5)	<0,001*
Hyperbaric oxygen+normobaric oxygen	31 (97,1)	13 (4,4)	44 (13,5)	
Hospitalization (day), n (%)	31 (91.2)	4 (1.4)	35 (10.7)	<0.001*
Mortality, n (%)	3 (8,8)	0	3 (0,9)	0,001*

α: Mann-Whitney U test, β: Pearson's Chi-Square test; *: Fisher's exact test, GCS: Glasgow Coma Score, COHb: carboxyhemoglobin, CK: creatine kinase, CK-MB: creatinine kinase- myocardial band

Pathological findings were observed in 13 (40.6%) of 32 patients with MRI. The incidence of MRI findings in the study group was 4% (n = 13/327). Symmetric hyperintensities in the globus pallidus in 7 (53.8%) patients and asymmetric hyperintensities in the caudate nucleus, putamen, and thalamus in 4 (30.7%) patients in the T2-weighted and FLAIR images. 1 (%7.6) patient restricted diffusion in the caudate nucleus, putamen, and 1 (%7.6) patient restricted diffusion in the globus pallidus in the diffusion-weighted imaging (Figure 1 a,b). In our study, no relation was found between the presence of pathological findings on the MRI and age, gender, cause of poisoning, and symptoms/findings ($p>0.05$). Patients with pathology in their MRI were found to have significantly low GCS and a longer follow-up time ($p<0.05$). All patients received HBO_2 + NBO_2 (normobaric oxygen) therapy and all patients with neurological findings were hospitalized. Pathological findings were seen in the MRI of the patient who responded to cardiopulmonary resuscitation. The relationship between clinical, demographic, and laboratory characteristics of the patients and the presence of pathological findings on MRI are shown in Table 2.

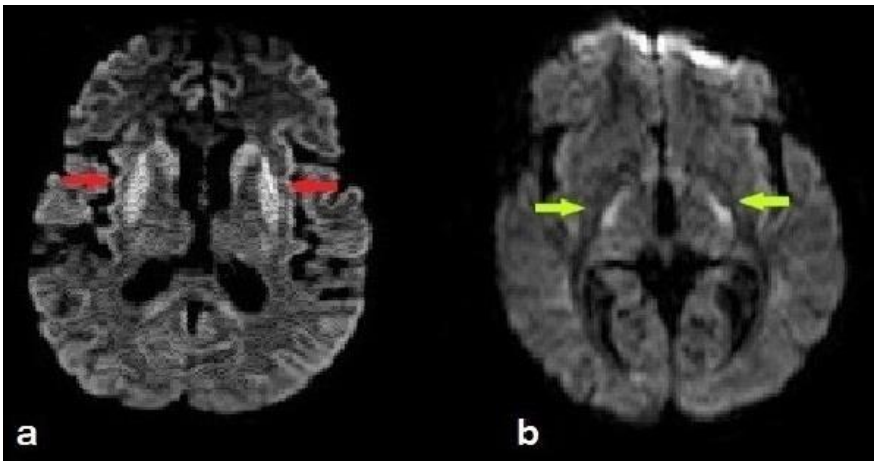

Figure 1 a,b. Axial diffusion-weighted magnetic resonance image (a) shows restricted diffusion in the caudate nucleus and putamen (red arrows), (b) axial diffusion-weighted magnetic resonance image shows restricted diffusion in the globus pallidus (yellow arrows).

Table 2. Relationship between magnetic resonance imaging finding and clinical and demographic characteristics

Clinical, demographic and laboratory findings	MRI (+) (n=13)	MRI (-) (n=19)	P value
Age (year), Median (IQR)	35 (29)	31 (12)	0,209[α]
Gender			
Male	5 (38,5)	9 (47,4)	0,618[β]
Female	8 (61,5)	10 (52,6)	
Causes of poisoning, n (%)			
Stove	7 (53,8)	13 (68,4)	0,473*
Natural gas	6 (46,2)	5 (26,3)	0,283*
Automobile exhaust	0	1 (2,9)	>0,999*
Symptoms / Findings, n (%)			
Nausea	7 (53,8)	11 (57,9)	0,821
Dizziness	11 (84,6)	12 (63,2)	0,249*
Headache	5 (46,2)	7 (36,8)	0,598
Weakness	3 (23,1)	4 (21,1)	>0,999*
Dyspnea	3 (23,1)	2 (10,5)	0,374*
Syncope	12 (92,3)	14 (73,7)	0,361*
Loss of consciousness	3 (23,1)	6 (31,6)	0,704*
Chest pain	2 (15,4)	0	0,157*
Visual disturbance	4 (30,8)	4 (21,1)	0,684
Impaired speech	4 (30,8)	5 (26,3)	>0,999*
Hemiparesis	1 (5,3)	0	>0,999*
Laboratory findings			
COHb (%), median (IQR)	32 (9)	33 (14)	0,495[α]
pH, median (IQR)	7.32 (0,14)	7.33 (0,05)	0,495[α]
Lactate (mmol/L), median (IQR)	1.4 (1.6)	2,3 (1.1)	0,623[α]
CK (U/L), median (IQR)	341 (91,5)	321 (207)	0,791[α]
CK-MB (U/L), median (IQR)	25 (8,5)	27 (8)	0,910[α]
Troponin-I (ng/ml), median	5 (1,5)	6 (3)	0,520[α]
GCS, median (IQR)	13 (2,5)	15 (1)	0,013[α]
Follow-up period (hour), median (IQR)	72 (48)	40,3 (39)	0,001*
Mortality, n (%)	1 (7.7)	0	0,406*

α: Mann-Whitney U test, β: Pearson's Chi-Square test; *: Fisher's exact test, MRI: magnetic resonance imaging, GCS: Glasgow Coma Score, COHb: carboxyhemoglobin, CK: creatine kinase, CK-MB: creatinine kinase-myocardial band

DISCUSSION

ABI, which develops in acute CO intoxications, can develop even within minutes in relation to the CO concentration and contact time of the medium. However, even if this damage did not appear on an MRI at the beginning, these patients were shown to experience highly delayed neuropsychiatric pathologies (2). The affinity of CO to hemoglobin is 200 times higher than that of oxygen. Therefore, the developed hypoxia causes ischemia in the brain and reduces energy production. As a result, edema develops in the cells and free oxygen radicals begin to accumulate. Loss of consciousness caused by an excessive increase in COHb leads to lipid peroxidation and apoptosis (9,10).

In patients with CO poisoning, it was found that there was a 10-26% finding in MRI in the long term, and this rate was reported to be 14 times higher than those that developed acutely (9,11-13). Kim et al. reported that ABI developed in 37.2% of the patients (7). O'Donnell et al. reported that in 63% of unconscious patients, they observed findings in the diffusion-weighted MRI examination (13). Jeon et al. stated that ABI developed in 26.9% of the patients and this rate was higher in unconscious patients (8). In our study, neurological findings were detected in 10.4% of the patients, and MRI findings were detected in 40.6% of these patients. The main reason for the low frequency of neurological findings in our study may be due to the evaluation of patients in the acute process. The frequency of lesions in patients with MRI is consistent with the literature.

CO poisonings are among the pathologies that can be seen in all age groups, and studies reported that it is mostly observed in the female population between the ages of 35-41 and at the rate of 57-68% (1,7,14,15). Stearns et al. reported that female patients showed lower levels of symptoms in CO intoxications depending on physiological factors between genders (15). Kim et al. could not find a relationship between ABI development and age and gender (7). In our study, the median age of patients with acute CO poisoning was 31.5 years and 72.2% were females which is consistent with the literature. No relationship was found between the neurological findings and MRI characteristics and age and gender. We think that the results found in our country are due to the fact that the female population is not sufficiently involved in business life and the national average age is young. We believe that neurological findings are related to exposure time and CO concentration in the environment rather than demographic factors such as age and gender, which is why there is no difference between the groups. In addition, the fact that suicide attempts are more frequent in women may have contributed to this process.

In our study, no relationship was found between the neurological and MRI findings of the cause of poisoning in patients. We think that individuals are exposed to a higher rate of neurological involvement due to the long-term exposure due to both sleeping and CO being odorless and that patients who smoke hookahs are less affected by CO as it leaves the environment in a shorter time. However, we believe that the difference is not significant in relation to the small number of patients who are poisoned by hookah.

The symptoms that develop when the COHb level is 15–30% are not specific. Headache, dizziness, nausea, fatigue, and a decrease in dexterity are the most common symptoms (10). Hassan et al. stated that the most common symptoms include headache, nausea/vomiting, and weakness (16). In the study conducted by Genç and Aygün, the most common symptoms reported were dizziness, nausea/vomiting, weakness, and headache (17). Consistent with the literature, the most common symptoms in our study were nausea, dizziness, and headache.

CO intoxications are clinical dose-dependent and the clinical deterioration occurs as the COHb level increases. In severe poisonings, loss of consciousness, chest pain, cardiovascular diseases, delayed neurological sequelae, coma, and death can be seen (18). It has been reported that there is no clear relationship between exposure time and ABI (19). Kim et al. reported that the COHb level of patients who developed ABI was higher than the group without ABI (7). Hassan et al. stated that COHb levels were high in patients with neurological disorders (16). In a study, it was stated that the COHb level is high in patients who developed syncope (20). In our study, while the COHb levels of patients with neurological findings were significantly high, no relationship was found between MRI findings and COHb levels. We think that neurological findings develop more frequently due to the increase in the level of hypoxia, edema, and free radicals as the COHb level increases. It is important to remember that factors such as exposure amount, COHb intensity of the environment, pre-hospital duration and amount of oxygen delivered, and the anxiety status of patients may change the presence of neurological symptoms and MRI findings.

Although studies reported that there is a relationship between the development of neurological findings, pH, and lactate levels, it has been stated that this relationship is not clinically important (21,22). Yildiz et al. reported that syncope development was unrelated to CO and lactate levels, and those who developed syncope had high troponin levels (1). Kaya et al. reported that while the CO levels of patients who are troponin positive in CO poisoning is high; they stated that CK and CK-MB levels were similar to troponin negatives (14). Hassan et al. found that patients with neurological findings had high

troponin, CK, and CK-MB levels, and low pH levels (16). Kim et al. reported that patients with neuropsychiatric disorders had high troponin levels, while lactate levels were similar to those that did not (12). In our study, the presence of neurological findings and MRI findings revealed a high lactate level and a low pH level. There was no relationship between CK, CK-MB, and troponin-I levels between the groups. This may be due to the low resistance of axons to COHb. The axon damage can be related to axons being affected before other organ systems.

In a study, it was stated that while patients with neuropsychiatric disorders in the later periods had low GCS, there was no relationship with the symptoms (12). The prominence of neurological findings has been linked to the sensitivity of neurons to CO (2). In our study, there was no relationship between neurological findings and non-specific symptoms (nausea, dizziness, headache, and chest pain); however, patients with neurological findings had lower GCS and higher dyspnea frequency. We believe that nonspecific symptoms develop even at low COHb levels since neurons are more sensitive to CO than other cells. We also believe that developing hypoxia causes many nonspecific symptoms. We believe that CO increases the central effectiveness and therefore, the frequency of dyspnea increases in patients with neurological symptoms.

In the studies, it was stated that the most common finding in MRI due to CO poisoning was in the globus pallidus, followed by the caudate nucleus, putamen, and thalamus. Frequent lesions in these areas have been linked to their susceptibility to hypoxia (2). It has been reported that lesions in globus pallidus generally develop in a short time (23). In our study, the most common lesions were found in the globus pallidus which is consistent with the literature. This may be due to the fact that some regions have higher oxygen requirements and are more sensitive to ischemia.

Yildiz et al. stated that 91.8% of the patients received NBO_2, and 8.2% received HBO_2 + NBO_2 in their study (1). Thom et al. reported that HBO_2 reduced the delayed neurological sequel from 23% to zero in their study (24). Ducassé et al. reported that patients who received HBO_2 had less electroencephalography and brain flow abnormalities (25). Moon and DeLong reported in their study that although neurological sequelae develop in patients given HBO_2, it develops less compared to patients given only NBO_2 (26). In our study, it was found that patients with neurological findings and lesions detected on MRI received HBO_2 more frequently. This may be due to the fact that the development of neurological findings is related to high COHb level, and both high COHb level and the presence of neurological findings are criteria for HBO_2.

Yildiz et al. stated that 2.2% of the patients were hospitalized in their study (1). Chang et al. stated in their study that 15% of patients needed intensive care and 30.8% of them were treated by hospitalization (6). In our study, 10.7% of the patients were admitted and the frequency of hospitalization and follow-up were longer in patients with neurological findings and lesions detected on MRI. We believe that patients with neurological findings are hospitalized for treatment due to the requirement of longer treatment and the fact that HBO_2 treatment consists of several sessions.

In studies conducted, the mortality rates in CO intoxications have been reported to be between 1-3% (4,18). In a study, it was stated that the frequency of ABI is high in patients with mortality (14). In our study, the mortality rate was 0.8%. We believe that one of the main causes of cardiopulmonary arrest in patients is the cardiac adverse effects at high COHb levels as in ABI.

Jeon et al. reported that the diffusion-weighted MRI imaging showed 75.2% sensitivity and 90.2% specificity in showing ABI (8). In our study, the sensitivity was 76.5% and specificity was 85.3% for the 29.5% cut-off value for neurological findings, and the sensitivity was 76.9% and specificity was 88.5% for the cut-off value of 30.5 for the MRI findings. We believe that high sensitivity and specificity support that MRI is highly diagnostic.

Limitations

As our study is retrospective, we believe that some data are insufficient. Again, information on factors affecting neurological findings such as exposure amount, duration, and the COHb density of the environment; pre-hospital duration; and the amount and duration of oxygen delivered are limited.

Conclusion

It was determined that acute CO poisoning may lead to acute brain damage, and 40.6% would be detected in brain MRIs taken in patients during the acute phase.

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RESEARCH ARTICLE

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Prevalence of Gastroenteritis Caused by Rotavirus in the Children of Southeastern Anatolia

ABSTRACT

Objective: Acute gastroenteritis is an important cause for morbidity and mortality in the children. Rotavirus is an important viral agent in the etiology of childhood gastroenteritis globally. Rotavirus may vary depending on the climate and geographical territory. The aim of the present study was to search for the prevalence of rotavirus in pediatric patients who have referred due to acute gastroenteritis in Sanlıurfa province of South-Eastern Anatolia.

Methods: Stool sample records of 5,777 cases who have referred to Harran University Hospital because of gastroenteritis between March 2016 and March 2018 were evaluated according to the age, season and month.

Results: Rotavirus antigens were detected in 532 (9.2%) stool samples. The cases with positive viral antigen were most common in 13 to 24-month age group by 36.8%. The most common period was fall with a rate of 35.3%, and the most common month was October by 15.6%.

Conclusions: Rotavirus gastroenteritis is observed with a prevalence rate of 9.2% in Sanliurfa province of South-eastern Anatolia. Rotavirus, the most common agent for gastroenteritis in pediatric patients below 2 years of age, between 13 and 24 months in particular, should be searched during October in fall season.

Keywords: Acute Gastroenteritis, Child, Rotavirus

Güneydoğu Anadolu Bölgesi'nde Çocuk Gastroenteritlerinde Rotavirus Sıklığı

ÖZET

Amaç: Akut gastroenteritler çocuklarda morbidite ve mortalitenin önemli nedenlerindendir. Rotavirüs gastroenteritleri tüm dünyada çocukluk döneminde görülen gastroenteritlerin etyolojisinde yer alan viral etkenler arasında önemli bir yere sahiptir.

Gereç ve Yöntem: Bu çalışma ile hastanemize akut gastroenterit ile başvuran çocuk hastalarda rotavirüs sıklığının araştırılması amaçlanmıştır.

Bulgular: Dışkı örneklerinin 532'sinde (%9,2) rotavirüs antijenleri belirlenmiştir. Viral antijen pozitif olgular en sık 13-24 aylık yaş grubunda ve zaman olarak Ekim ayı ile sonbahar mevsimde görülmüştür.

Sonuç: Mortalite ve morbiditeye neden olan gastroenteritler içinde rotavirus insidansı önemli bir yere sahiptir. İlimizde %9,2 oranında görülmektedir. İki yaş altı çocuklarda ve özellikle 13-24 aylık bebeklerde en yaygın gastroenterit etkeni olan rotavirüs özellikle sonbahar ve kış mevsimlerinde rutin olarak araştırılmalıdır.

Anahtar Kelimeler: Akut Gastroenterit, Çocuk, Rotavirus

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INTRODUCTION

Acute gastroenteritis (AGE) is the most important cause for morbidity and mortality globally and especially in developing countries following lower respiratory tract infections. Rotaviruses are the leading cause for diarrhea, which is observed in the babies and the children below 5 years of age, and for severe gastroenteritis, which causes hospitalization and infant deaths (1). The infection causes mortality in developing countries where treatment options are limited, and morbidity as well as economic losses in developed countries (1, 2). The cause for AGE may be viral, bacterial, parasitic and fungal. Many seem to be related to water resources, sewage systems and personal hygiene. It is mostly spread through fecal-oral route. Rotavirus is the most common viral cause (3). The increase of infection in colder months may be associated with aerosol spread; the spread through aerosol route was shown in animal experiments (4). Rotavirus is a double- stranded, segmented RNA virus from Reoviridaea family. Incubation period is approximately 1 to 4 days (5). Approximately 440,000 children die because of rotavirus gastroenteritis, 2 millions of children are admitted to the hospital and 25 millions of children refer to pediatric polyclinic (6).

Clinical presentation of rotavirus varies from an asymptomatic infection to severe diarrhea causing dehydration and death. Infections appear with vomiting, watery diarrhea, and fever for several days.

The infection may be diagnosed by fresh stool samples during acute period. The most common methods used for diagnosis include ELISA, latex agglutination and immunochromatographic methods. Sensitivity of these tests varies between 70% and 100% (7).

The present study was planned to detect the incidence of gastroenteritis caused by rotavirus in pediatric patients between 0 and 17 years of age who have referred to Research and Practice Hospital of Medical Faculty within Harran University, and to detect seasonal and age distribution.

MATERIAL AND METHODS

The study was conducted retrospectively on the children between 0 and 17 years of age who have referred because of acute gastroenteritis between March 2016 and March 2018 after approval of local ethical committee. All patients who were examined in the polyclinic, the patients who were admitted from emergency service because of gastroenteritis, and those who provided stool sample in the clinic were enrolled into the study. Data of the patients who had rotavirus antigen test were reviewed retrospectively.

The adequate tests accepted for the study included immunochromatographic method to analyse rotavirus.

Statistical Evaluation: Descriptive statistical method was used for data evaluation. Furthermore, chi-square test was used to compare binary group data.

RESULTS

Among 5,777 patients who were examined for acute gastroenteritis, 2,485 (43%) were female and 3,292 (57%) were male; rotavirus antigen was negative in 5,245 (90.2%) patients, and positive in 532 (9.2%) patients. The positive cases included 296 (55.6%) males and 130 (44.4%) females. Rotavirus was detected more in male gender (Table 1).

Table 1. Distribution of cases according to gender

Sex	Positive	Negative	Total
Female	236	2249	2485
Male	296	2996	3292

Majority of the cases were detected in October (n: 97, 15.6%), March (n: 29, 14%), December (n: 51, 13.9%), January (n: 47, 13.6%) months, mostly in fall (35.3%), followed by winter (27.6%), spring (18.6%) and summer (18.4%). July (n: 30, 3.9%), June (n:22, 4.9%) and September (n: 37, 5.4%) were the months with least rotavirus positivity (Table 2).

Table 2. Distribution of cases according to months

Monhts	Positive	Negative	Total	Ratio %
January	47	297	344	13.6
February	49	320	369	13.2
March	29	178	207	14
April	36	236	272	13.2
May	34	349	383	8.8
June	35	675	710	4.9
July	30	722	752	3.9
August	33	522	555	5.9
September	37	649	686	5.4
October	97	521	618	15.6
November	54	462	516	10.4
December	51	314	365	13.9
Total	532	5245	5777	9.2

One hundred and ninety-six patients whom rotavirus was detected were infants between 13 and 24 months of age. One hundred and fifty-three patients (28.7%) were within first 12 months of age, followed by 102 (19.1%) cases between 25 and 36 months of age, and 55 (10.3%) cases between 37 and 48 months of age. The cases significantly reduced in further ages, and no case was detected after 10 years of age (Figure 2).

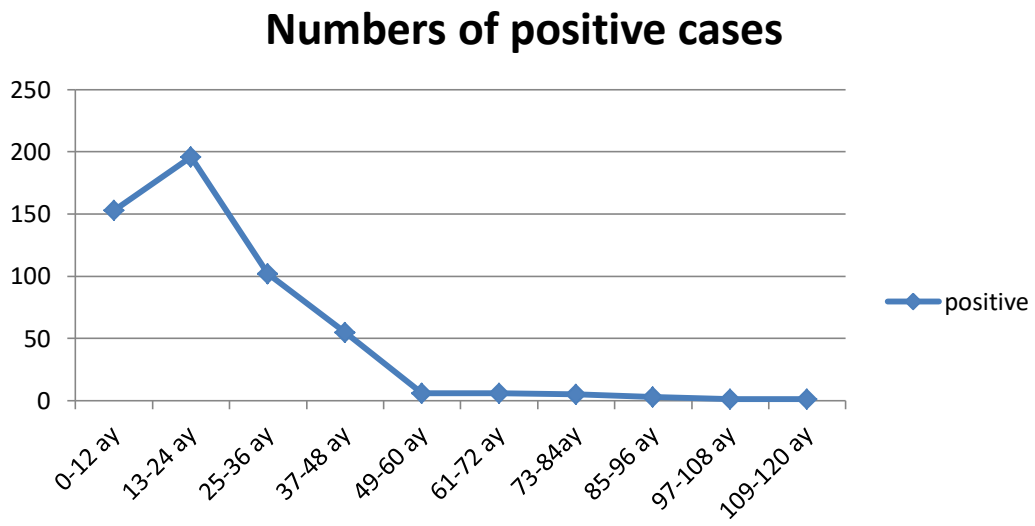

Figure 1. Distribution of gastroenteritis cases according to age

DISCUSSION

Rotavirus is the most important cause for childhood gastroenteritis. The disease causes diarrhoea-induced hospitalization, severe morbidity, mortality and significant medical costs in our country and all over the world. Although similar incidence rates are detected in developed and developing countries, mortality due to rotavirus infection is higher in developing countries (8, 9).

The infection is spread through fecal-oral route, it is common below 2 years of age and progresses severer. The disease causes fever, vomiting, watery diarrhoea without blood and mucus, and severe dehydration following an incubation period for 1 to 4 days (10). Although medical history and clinical presentation guide the clinician for diagnosis of viral gastroenteritis, laboratory tests are needed for final diagnosis. The methods that may be used to analyze rotavirus in the stool samples during acute period include electron microscopy, enzyme immunoassay, immunochromatography or antigen detection through latex agglutination or assertion of the virus in the stool by culture (10, 11, 12). Electron microscopy is a rapid method which is useful to detected rotavirus in the stool; however, it is not practical (13). Majority of the studies that analyse positivity of rotavirus were conducted through immunochromatographic and ELISA methods. These are preferred antigen detection tests in the laboratories due to resulting in shorter time, high specificity, and compliant results (14). The samples were analyzed through immunochromatographic method in the present study.

According to the data of World Health Organization (WHO) which was updated in 2011, incidence of rotavirus infection was reported as 20% to 40% in European countries, 5% to 25% in America, 30% to 50% in Asian countries, 10% to 65% in African countries (15). The studies conducted in their countries report that rotavirus rate varies between 11% and 71% among viral gastroenteritis (16, 17) whereas the studies conducted in our country report the rotavirus incidence between 9.9% and 39.8% (18, 19, 20). Prevalence of rotavirus antigen was detected 9.2% in the present study. This study which was performed through immunochromatographic method suggested that the prevalence of rotavirus infection is below Turkey average.

Although rotavirus infection may be seen in any age, symptomatic infections mostly appear in the children below 2 years of age (21). Breastfeeding for the first 6 months reduce the incidence of diarrhoea (22). Recurrent infections are milder and asymptomatic due to partial immunity created by rotavirus after 24 months of age. Rotavirus is most commonly detected between 0 and 24 months of age in our country. In the studies which have focused on the cases between 0 and 5 years of age, the rate of the cases younger than 12 months of age was 26.3% to 65.4%; the rate of the cases within first 2 years was 46% to 88.9% (18, 23). A previous study conducted in Izmir reported that 80.7% of 366 rotavirus cases were within first 2 years, 46% were between 6 and 23 months of age, and 48% were within first 12 months of age (18). Gul et al. reported in their study conducted in Kahramanmaras that 26.3% of their cases were within first 12 months of age, and 71% were within first 2 years (11). From the view of wider age groups, the rate of the cases within first 2 years of age varied between 54.9% and 72% (24, 25). Incidence of rotavirus within first 2 years was detected 56% in Istanbul, 70.3% in Kayseri, and 69% in Bursa (26, 27, 28). Rotavirus gastroenteritis was most common in the children between 13 and 24 months of age by a rate of 36.8% in the present study. This was followed by the infants within first 12 months of age by a rate of 28.7%. The cases within first 2 years of life were more than half of

the cases (65.5%). Our findings were consistent with the literature. The prevalence gradually decreased in further ages, and there was not any case after 10 years of age. Rotavirus was most commonly detected between 0 and 24 months of age, followed by 24 to 69 months of age.

Rotavirus-induced diarrhoea is affected by the region, season and climate. Rotavirus is detected every season of the year in tropical countries; it is more common in dry seasons in some countries (29). Although seasonal variations are observed depending on the climate conditions of the study region in our country, it is more common in the winter and spring in many studies (30, 31, 32). It usually appears during fall, winter and spring seasons in mild climate conditions (33). In the present study, the infection was most common in October (15.6%) followed by March (14%), December (13.9%) and January (13.6%); the most common seasons were fall (35.3%) and winter (27.6%). The infection was least common in July and in summer. In a previous study in this region, the most common infectious agent rotavirus was fund (34).

Limitation of the present study was the possibility of false positive results by immunochromatographic tests in the newborns and gastroenteritis in the patients with an underlying disease. Exclusion of misleading by reference methods may enable to obtain more accurate data. However, use of expensive methods for scanning is not a cost-efficient approach.

Consequently, incidence and importance of rotavirus in gastroenteritis cases should be kept in mind within the first two years of age. Detection of a positive rotavirus antigen would reduce the use of unnecessary antibiotics; would allow to predict the clinical presentation of the patient, and to determine a therapeutic approach. It is important to recognize the fact that rotavirus gastroenteritis is most common in October and during fall in our country. We believe that rotavirus infection would be reduced through vaccination programs in the early period.

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RESEARCH ARTICLE

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Evaluation of Demographic Factors Affecting Peripapillary Nerve Fiber Thickness by Optical Coherence Tomography in Diabetic Patients

ABSTRACT

Objective: To investigate the demographic factors affecting the peripapillary nerve fiber thickness(PNFL) measured with optical coherence tomography(OCT) in diabetic patients.

Methods: A total of 207 eyes of 104 diabetic patients (92 eyes of 46 males, 115 eyes of 58 female) who were followed-up between 2009-2013 were included. PNFL was measured with OCT in the superior, inferior, temporal and nasal quadrants and compared with demographic factors.

Results: PNFL was found to be thinner in superior and inferior at the age of 60 years and above compared to under 60 years (p=0.004, p=0.001). There is a significant relationship between gender and the average PNFL only in inferior quadrants(p=0.006). There is no relationship between hypertension and the mean PNFL in 4 quadrants(p>0.05). Superior PNFL was decreased in eyes with glaucoma compared to those without glaucoma(p=0.019). The mean PNFL in superior, inferior and nasal patients with diabetes duration of more than 15 years decreased compared to those with 15 years or less (p=0.048, p=0.020, p=0.020). Temporal PNFL was decreased in eyes without retinopathy compared to eyes with proliferative diabetic retinopathy(PDR) and non-PDR(p=0.025). Temporal PNFL was increased both in patients with diabetic macular edema(DME) and the patients treated with panretinal photocoagulation (p=0.001, p=0.001). No correlation was found between the mean PNFL in four quadrants with focal laser treatment(p>0.05).

Conclusions: Age, gender, duration of diabetes, glaucoma, DME, PDR, non-PDR have an effect on PNFL, but HT and focal laser have not. In addition, the duration of diabetes and the presence of diabetic retinopathy(DR) should be taken into account when evaluating the progression of PNFL defects in patients with both glaucoma and diabetes.

Keywords: Diabetes Mellitus, Peripapillary Nerve Fiber Thickness, Optical Coherence Tomography, Demographic Factors

Diyabetik Hastalarda Peripapiller Sinir Lifi Kalınlığını Etkileyen Demografik Faktörlerin Optik Koherens Tomografi ile Değerlendirilmesi

ÖZET

Amaç: Diyabetik hastalarda optik koherens tomografi (OKT) ile ölçülen peripapiller sinir lifi kalınlığını (PLSK) etkileyen demografik faktörleri araştırmaktır.

Gereç ve Yöntem: Bu çalışmaya 2009-2013 yılları arasında izlenen 104 diyabetik hastanın (46 erkek hastanın 92 gözü, 58 kadın hastanın 115 gözü) toplam 207 gözü dahil edildi. PLSK, OCT ile üst, alt, temporal ve nazal kadranlarda ölçüldü ve demografik faktörlerle karşılaştırıldı.

Bulgular: 60 yaş ve üzerinde ortalama PSLK, 60 yaş altına göre üst ve alt kadranda daha ince olduğu görüldü(p=0,004, p=0,001). Cinsiyet ile ortalama PSLK arasında sadece alt kadranlarda anlamlı bir ilişki vardır (p = 0,006). Dört kadranda da hipertansiyon(HT) ile ortalama PSLK arasında ilişki yoktur(p>0.05). Glokomlu gözlerde, glokomu olmayanlara göre üst kadranda ortalama PLSK azalmaktadır(p=0.019). 15 yıldan fazla diyabet süresi olan hastalarda üst, alt ve nazal kadranlarda ortalama PLSK, 15 yıl veya daha az olanlara göre azaldığı görüldü(p=0,048, p=0,020, p=0,020). Retinopatisi olmayan gözlerde ortalama temporal PLSK, proliferatif diyabetik retinopatili (PDR) ve non-PDR olan gözlerle karşılaştırıldığında azalmıştı(p=0,025). Temporal PLSK hem diyabetik maküla ödemi (DMÖ) olan hem de panretinal fotokoagülasyon uygulanan hastalarda artmıştı (p=0,001,p=0,001). Fokal lazer tedavisi uygulanan hastalarla dört kadrandaki ortalama PLSK arasında korelasyon bulunmadı (p>0.05).

Sonuç: Yaş, cinsiyet, diyabet süresi, glokom varlığı, DMÖ, PDR-nonPDR gibi faktörlerin PSLK üzerine etkisinin olduğu fakat HT, fokal lazer gibi faktörlerin PSLK üzerine etkisi yoktur. Ayrıca hem glokomu hem de diyabeti bulunan olgularda, retina sinir lifi defektlerinin progresyonunu değerlendirirken diyabet süresi ve diyabetik retinopati mevcudiyetinin dikkate alınması gerekir.

Anahtar Kelimeler: Diyabetes Mellitus, Peripapiller Sinir Lifi Kalınlığı, Optik Koherens Tomografi, Demografik Faktörler

INTRODUCTION

Diabetes mellitus, which is common all over the world and characterized by abnormal insulin secretion and increased blood glucose levels, is a chronic disease affecting the circulatory and nervous system, kidney and eye, and causing microvascular events (1,2). Clinically, the most important effect of microangiopathy associated with diabetes is on the retina and choroid, however, the pathogenesis of diabetes, especially its effects on the ocular circulation, has not been fully elucidated (3). Circulatory disorders seen in diabetes occur with the increase in the resistance of the retinal vascular bed to blood flow. In most diabetic patients, in addition to characteristic findings in the blood vessels, changes also occur in the blood structure. As a result of these disorders, changes occur in the flow rate of the blood (4).Ocular blood flow velocities in patients with diabetic retinopathy have been reported to be increased by some researchers (5) and decreased by others (6,7).

RNFL is located in the inner retina just below the internal limiting membrane (1-3).The fibers in this layer consisting of 1.0-1.3 million axons of retinal ganglion cells combine in the optic disc and form the optic nerve (1).Today, damages in RNFL can be detected in the early period with OCT and other RNFL imaging methods (2).OCT is a technique in which high resolution tomographic sectional images of the retina and optic nerve are obtained in a non-contact, non-invasive manner using light at a wavelength of ~ 800 nm (5).Tomographic cross-sectional images of the optic disc and retina are obtained by making use of the back reflection of infrared light from tissue layers similar to the B-mode ultrasound principle (4,5). In this study, we evaluated the measurements of PNFL with OCT, which is used extensively in our clinic, in order to investigate the factors that affect PNFL in diabetic patients. The relationship between demographic factors such as age, gender, systemic hypertension (HT), duration of diabetes, diabetic retinopathy level, diabetic macular edema, presence of glaucoma, panretinal photocoagulation and laser treatment and PNFL were examined in patients with DM in this present study.

MATERIAL AND METHODS

A total of 207 eyes of 104 diabetic patients, including 92 eyes of 46 male patients and 115 eyes of 58 female patients, who were followed up and treated in Düzce University Medical Faculty Ophthalmology Outpatient Clinic between July 2009 and January 2013 were included in this retrospective study. One eye of 1 patient was excluded due to phthisis bulbi. Patients without glaucoma (n = 59) were selected from diabetic cases with intraocular pressure of 21 mmHg and below and with normal disc appearance. Eyes with glaucoma (n = 45) were selected from patients with diabetes who were diagnosed with glaucoma during examination at our clinic, whose intraocular pressure (IOP) was measured high, and who were previously followed and treated with a diagnosis of glaucoma. Goldman applanation tonometer was used to measure IOP. All glaucoma cases included in the study were selected from those who came for control at least three times. Patients with very large and very small optic disc were excluded in the study. Patients with microaneurysms, dot or line-shaped intraretinal hemorrhages, hard exudates, diffuse hemorrhage, venous pilling, and intraretinal microaneurysm were divided into nonproliferative DR; neovascularization in the disc, retinal neovascularization, preretinal or intra-vitreous hemorrhage, fibrovascular proliferation, iris and iridocorneal neovascularization patients were divided into proliferative DR.

Information such as demographic characteristics of the patients, presence of hypertension, presence of glaucoma, duration of diabetes, diabetic retinopathy level, diabetic macular edema, and laser photocoagulation therapy were obtained from the patients' hospital records. Following the routine ophthalmologic examination in all cases, PSLK measurements were made by two ophthalmologists (NA, MT) with the OCT device. Nerve fiber thicknesses of the nasal, temporal, superior and inferior quadrants for all eyes were determined as micron (μ). A high resolution OCT device (TOPCON SD-Optical Coherence Tomography) was used for measurement. The factors whose effects on PNFL were investigated in patients with DM were age, gender, HT, diabetes duration, DR's stage, retinopathy, DME, panretinal photocoagulation and focal laser treatment. The effect of age factor on PNFL was examined by forming two groups: over 60 and under 60, and the duration of diabetes over 15 years and under 15 years. This study was approved by the Düzce University Medical Faculty non-invasive health research ethics committee (2012/301) and all patients were informed about the study, informed consent form and ethical approval were obtained.

Statistical Analysis: Descriptive statistics (mean, standard deviation, minimum, maximum, percentage values) of all data in the study were calculated. Kalmagarov-Smirnov test was used to examine the variables in the continuous nature with the assumption of normality. In this respect, Mann-Whitney U and Kruskal-Wallis tests were used for comparisons between groups according to the number of groups. While evaluating the findings obtained in the study, an appropriate computer program (SPSS 19) was used for statistical analysis. A $p < 0.05$ was considered statistically significant.

RESULT

A total of 104 (60 [n:119 eyes] female, 44 [n:88 eyes] male) patients who diagnosed diabetes mellitus were included in this present study. In

addition, 50 (n = 99 eyes) were under the age of 60 and 54 (n = 108 eyes) were 60 and over of the 104 cases.

The PSLK was thinner in the superior and inferior quadrants in patients aged 60 and over than those under 60 years of age. There is a statistically significant correlation in the superior and inferior quadrants when age and the average PSLK in 4 quadrants are evaluated (p = 0.004, p = 0.001). Average PSLK in women was found to be thicker than men. When gender and average PSLK in 4 quadrants are evaluated. There is a statistically significant relationship in the inferior quadrant (p = 0.006) (Table 1).

Table 1. Average PFNL change by age and gender

PFNL	Age		Gender		P	
	<60(n=99) mean±SD	≥60(n=108) mean±SD	female(n=119) mean±SD	male (n=88) mean±SD	*p	**p
superior	106.93±22.3	94.87±33.4	103.04±27.9	97.38±30.7	0.004	0.131
inferior	112.84±23.7	99.31±29.0	109.77±25.0	100.38±29.6	0.001	0.006
temporal	66.36±17.7	63.01±22.6	67.01±18.2	61.37±22.8	0.119	0.277
nasal	75.31±23.2	70.75±29.6	75.99±25.5	68.79±28.1	0.132	0.087

PFNL: peripapillary nerve fiber thickness, SD: Standard deviation, n: number of participants

While 71 of 104 diabetic patients (n = 141 eyes) had HT, 33 patients (n = 66 eyes) did not have HT. There is no significant relationship between the presence of systemic HT and the average PSLK in 4 quadrants (p> 0.05). In a study of 207 eyes of 104 diabetic patients, 114 eyes with glaucoma and 93 without glaucoma were examined. In eyes with glaucoma, the superior mean PSLK was significantly decreased compared to eyes without glaucoma (p = 0.019) (Table 2).

Table 2. Average PFNL change according to the presence of systemic hypertension and glaucoma

PFNL	HT(+)(n=141) mean±SD	HT(-) (n=66) mean±SD	Glaucoma (+) (n=114) mean±SD	Glaucoma (-) (n=93) mean±SD	P*	P**
superior	100.72±29.1	100.47±29.5	109.50±26.8	103.00±29.2	0.916	0.019
inferior	106.91±28.2	103.36±25.5	112.50±28.2	108.00±27.4	0.081	0.133
temporal	65.25±20.8	63.24±19.7	66.50±21.9	65.00±20.4	0.445	0.058
nasal	72.09±24.4	74.73±31.4	74.00±26.1	72.00±26.8	0.877	0.453

PFNL: peripapillary nerve fiber thickness, HT: hypertension SD: Standard deviation, n: number of participants

The mean duration of diabetes in 104 diabetic patients was found to be 12.4 ± 7.6 (0.08-30) years. When the average PSLK change in 4 quadrants in 148 eyes with a diabetes duration of 15 years or less and 59 eyes with a diabetes duration of 15 years was evaluated. The mean PSLK in the superior, inferior, and nasal quadrants in 59 eyes over 15 years was significantly reduced compared to those with 15 years or less (p = 0.048, p = 0.020, p = 0.020). 62 of 207 eyes have DME and 145 eyes have no DME. When the mean PSLK change in 4 quadrants was evaluated according to the presence of DME, the PSLK in the temporal quadrant increased significantly in DME eyes (p = 0.001) (Table 3).

Table 3. Change in PNFL according to DM duration and DME

PFNL	≤15 year (n=148) mean±SD	>15 year (n=59) mean±SD	DME(+) (n=62) mean±SD	DME(-) (n=145) mean±SD	P*	P**
superior	109.00±27.5	104.00±29.2	99.88±28.9	100.96±29.3	0.048	0.512
inferior	112.00±28.4	105.00±27.4	111.11±25.4	103.50±27.9	0.020	0.442
temporal	65.00±22.6	65.00±20.4	73.46±18.7	60.82±20.0	0.758	0.000
nasal	75.00±24.3	69.00±26.8	74.76±26.4	72.15±27.0	0.020	0.884

PFNL: peripapillary nerve fiber thickness, SD: Standard deviation, DME: diabetic macular edema, DM: diabetes mellitus, n: number of participants

While 27 of 207 eyes had PDR and 88 had NPDR, 92 eyes had no retinopathy. When the mean PSLK change in 4 quadrants was evaluated according to the presence of DR, it was found that the PSLK in the temporal quadrant was significantly decreased in eyes without retinopathy compared to eyes with PDR and NPDR (p = 0.025). There is no significant relationship between the PSLK in the temporal quadrant in eyes with PDR and non-PDR (p = 0.349) (Table 4). Focal laser was applied to 14 of 207 eyes, panretinal photocoagulation was applied to 72 eyes, but no laser treatment was applied to 121 eyes. When the average PSLK change in 4 quadrants is evaluated in patients who underwent focal laser or panretinal photocoagulation, in eyes with focal laser applied, the mean PSLK in the superior quadrant is 99.50 ± 35.3, inferior 110.57 ± 15.3, temporal 64.86 ± 23.4

and nasal 78.29 ± 33.8 µm. In eyes with panretinal photocoagulation, the mean PSLK in the superior quadrant is 97.78 ± 33.4, inferior 105.78 ± 32.0, temporal 70.50 ± 23.1 and nasal 73.92 ± 32.8 µm. The PSLC significantly increased in the temporal quadrant in eyes with panretinal photocoagulation (p = 0.001). There is no significant relationship between focal laser eyes and PSLK in four quadrants (p> 0.05).

Table 4. PNFL change according to the presence of DR

PFNL	PDR(+) (n=27) mean±SD	Non-PDR(+) (n=88) mean±SD	retinopathy(-) (n=92) mean±SD	P
superior	96.07±33.8	99.35±29.5	103.21±27.4	0.188
inferior	95.93±41.2	108.11±24.3	106.45±24.8	0.176
temporal	62.44±26.7	69.43±19.7	60.64±18.2	0.025
nasal	70.48±40.1	72.92±25.9	73.66±22.8	0.579

PFNL: peripapillary nerve fiber thickness, SD: Standard deviation,DR:diabetic retinopathy,PDR: Proliferative diabetic retinopathy, n: number of participants

DISCUSSION

Clinically, the most important effect of diabetic microangiopathy is on the retina and choroid. In addition to characteristic findings in the blood vessels, changes occur in the flow rate of the blood in most diabetic patients (4). It has been stated in previous studies that thinning, defects or both may occur in RNFL in patients with DM (9, 10). Chiara et al. showed that defects are common in RNFL in patients with early diabetic retinopathy, and that advanced age, stages of diabetic retinopathy and systemic hypertension are risk factors for these defects (10). Conceiçao et al. showed that retinal thickness increased in type 2 diabetics with mild nonproliferative retinopathy in their 3-year follow-up (11). Similarly, Lopes de Faria et al thought that there was nerve fiber loss only in the upper quadrant, which was probably due to low perfusion in 12 patients with type 1 DM (12).

The age factor affecting PNFL differs in various studies (10,13). In a study conducted by Lee et al in a patient group with a mean age of 42.90 ± 16.15 (302 eyes, 155 patients, age range 20-79), RNFL thickness decreases by 2.1 µm per decade (p <0.001) (13). In our study, PNFL was found to be significantly thinner in the superior and inferior quadrants in patients aged 60 and over (p = 0.004, p = 0.001). In a study conducted by Nakatani et al., it was observed that gender had no effect on PNFL (14). However, in our study, PNFL was found to be thicker in the inferior quadrant in women (p = 0.006).

Before the onset of small vessel damage, increased blood pressure in the early period in HT patients may result in increased blood flow or greater hydrostatic resistance developed against the occlusion of small vessels. With this result, it can protect ganglion cells and their axons from damage (14). Later, when small vessel damage occurs and resistance to flow increases, a positive relationship can be detected between optic nerve damage and HT.

Tielsch et al. results obtained in his study support this hypothesis (15). The protective effect of HT is observed among those younger than 60 years old, and the adverse effect is observed among those aged 70 years and over. As a result, Tielsch et al. demonstrated that ocular perfusion pressure is associated with a higher risk of primary open angle glaucoma. At the same time, they stated that other parameters of HT may cause a moderate risk increase (15). Cheung et al. showed that parameters such as age, IOP, axial length had an effect on retinal nerve fiber thickness measured by spectral domain-OCT, but parameters such as systemic blood pressure had little effect in their study on 542 eyes without glaucoma (16). In our study, no statistically significant difference was found between PNFL in all 4 quadrants and systemic HT (p> 0.05). In order to understand more confidently to what extent PNFL can be affected by hypertension, larger series and studies with untreated HT patients are needed.

Glaucoma is a multifactorial disease characterized by visual impairment, optic neuropathy and loss of retinal ganglion cells (8). Retinal ganglion cells; the retinal nerve fiber layer consisting of ganglion cell axons, the ganglion cell layer (GCL), and the inner-plexiform layer consisting of ganglion cell dendrites. These three layers are called ganglion cell complex (GCC). This layer becomes thinner due to ganglion cell death in glaucoma (16).

In the longitudinal OCT study of Schuman et al., the mean RNFL thickness was 95.9 ± 10.09 µm in the normal group (n = 107), 80.3 ± 18.4 µm in the early glaucoma group (n = 64), and 50.7± 13.6 µm in the advanced glaucoma group (n = 18)(17). Towsend et al. obtained significant results in their study on measuring optic nerve head and retinal nerve fiber analysis with OCT in glaucoma patients (18). In a study by Leung et al. found that optic nerve head and RNFL measurement with OCT are useful in diagnosing glaucoma in the early period (19). One issue that needs to be addressed in the study is that the effect of disc surface area on nerve fiber thickness measurement is neglected. While RNFL was examined with OCT, in our study, as in all other studies, a standard diameter circle was scanned. The disadvantage of using a

standard diameter is that the measurement is made closer to the disc edge in cases with large optic disc surface area, whereas in cases with small disc surface area, this measurement is made further. It is known that the closer the thickness of the retinal nerve fiber layer is measured to the edge of the disc, the thicker it will be. In addition, it has been reported that the number of nerve fibers may be higher in eyes with large optic disc (19).

Chihara et al. showed in their study with scanning laser ophthalmoscope (SLO) that significant RNFL defects were observed in diabetic patients, similar to defects in glaucoma, but the c / d ratio did not increase (20). In this study, it is reported that diabetes-related RNFL loss in DM patients can be differentiated from normal tension glaucoma by not increasing the c / d ratio. It was also shown in the study by Klein et al. that they followed diabetic patients for four years and that the c / d ratio did not increase (21).

In the study of Takahashi and Chihara on 38 eyes with diabetes and glaucoma, they showed that RNFL thickness was thinning in all four quadrants ($p < 0.01$) (22). In our study, it was observed that eyes with glaucoma in 207 eyes with diabetes were significantly thinner ($p = 0.019$). Therefore, complete evaluation of the structural damage of the RNFL, GCC and optic nerve is extremely important in the early diagnosis and follow-up of glaucomatous optic neuropathy. It is natural that the thickness of the nerve fiber layer in eyes with glaucoma is thinner than in normal eyes(22). The reason for this is the damage to the optic disc / nerve fiber layer in the glaucoma group included in the study, and the differences in nerve fiber layer thickness in eyes with glaucoma and normal eyes have been emphasized in many studies (22, 23).

It is accepted by all ophthalmologists that the duration of diabetes is one of the most important risk factors for the development and severity of DR (24-26). It can be stated that the increase in diabetes duration results in the proliferation of ischemic areas in the retina in parallel with the increasing microangiopathy and thus causes thinning in RNFL. Sugimoto et al. performed with OCT in Type 2 DM patients without DR that they reported a statistically significant decrease in the superior quadrant compared to the control group (27). In addition, diabetes duration of Type 2 DM patients was 94.80 ± 87.60 months in this study. Lopes et al. in their study using scanning laser polarimetry (NFA-GDx) in Type 1 DM patients without diabetic retinopathy, they also found a statistically significant decrease in the superior quadrant compared to the control group, And also, type 1 DM patients without retinopathy and those with a diabetes duration of at least 10 years were included in this study (12). Another study, Chihara et al. showed that RNFL defects were significantly higher in Type 1 and Type 2 DM patients without retinopathy compared to the control group. And also, among Type 1 and Type 2 DM patients without retinopathy, those with a diabetes duration of at least 10 years were included in the study(28). Ido et al. examined with NFA-1 in type 2 DM patients that they showed that RNFL thickness was inversely proportional to the duration of diabetes (29).

In our study, the mean PNFL in the superior, inferior and nasal quadrants was significantly decreased in patients with diabetes duration of more than 15 years ($p = 0.048$, $p = 0.020$, $p = 0.020$). Accordingly, it can be said that the thinning of the temporal quadrant in DM develops more slowly than the other quadrants and the temporal quadrant is the most resistant to the effect of diabetes on RNFL. In many studies examining RNFL defects in DM patients with NPDR, the negative effect of diabetes on RNFL has been clearly shown (19, 20, 29, 30, 31). Another study, Lopes et al. examined with NFA-GDx in Type 1 DM patients without diabetic retinopathy that they reported that there was a statistically significant decrease in the superior quadrant compared to the control group, and no thinning in the temporal quadrant (12). Sugimoto et al. stated that there was a statistically significant decrease in the superior quadrant compared to the control group, and there was no defect in the temporal quadrant (27). Another study, Chihara et al. showed that RNFL defects were significantly higher in Type 1 and Type 2 DM patients without retinopathy than in the control group (28). Barber et al. reported that neurodegeneration is an important component of DR by showing neural cell apoptosis in inner plexiform, inner nuclear layer and ganglion cells in diabetic guinea pigs and post mortem diabetic human eyes. In addition, DM triggers apoptosis in neuronal cells from the first month, even in the absence of DR in guinea pigs (31). In the light of this information, it can be said that the thinning of RNFL in DM occurs as a result of developing blood flow disorders and ischemia rather than apoptosis. Similar results was found in our study as published literature. And also, there is no publication in the literature showing the effect of DME on PNFL.

Although panretinal photocoagulation has been proven to be an effective treatment strategy for severe DR, the intensity of the laser used is decided by the physician (31,32). It has been reported that this high intensity laser beam can cause the destruction of the entire retinal layer, including ganglion cells. Ganglion cell damage results in loss of RNFL and a decrease in PSLK (29,31,32). Kim et al. resulted that the panretinal photocoagulation used in DR treatment caused a decrease in PNFL in the treatment group, but this decrease was not found to be statistically significant compared to the control group on 282 eyes consisting of treatment (n = 118 eyes) and control group (n = 164 eyes) (32). In addition, they showed

that while the blood HbA1c level was high, the decrease in PNFL was more pronounced.

There are no reports in the literature showing the effect of focal laser on PNFL. Another study performed with OCT showed a similar decrease in RNFL thickness after laser photocoagulation, however, they showed that hyperpigmented lesions affected the measurements by causing unreliable results (16,33,34). Apple et al. drew our attention to another point that the effects of repeated treatments on RNFL should be taken into account when recurrent laser treatments are planned. If it is necessary to avoid RNFL damage, repetitive laser treatments should be applied within the first few hours after the first laser treatment (33). It is thought that retinal thickening due to edema observed in the early period after laser application protects the ganglion cells against the effects of laser treatment. Retinal damage increases as the retina becomes thinner during late treatments (24,33).

CONCLUSION

In this present study, it was observed that factors such as age, gender, duration of diabetes, presence of glaucoma, panretinal photocoagulation, DME, PDR or non-PDR had an effect on PNFL, but factors such as systemic HT and focal laser did not have a significant effect on PNFL. In DR, damage occurs in retinal neurons together with microcirculation disorders. In order to understand the pathogenesis and treatment of DR, changes in retinal neurons and glial cells should be taken into consideration together with vascular pathologies. This study also suggests that the duration of diabetes and the presence of DR should be taken into account when assessing the progression of RNFL defects in patients with both glaucoma and diabetes. When thinning in RNFL is observed in cases with glaucoma and diabetes, it should be considered that this thinning may be related to glaucoma or the development of DR.

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RESEARCH ARTICLE

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A 20-Year Retrospective Analysis of Skin Cancers: Comparison of the First and Second Decades

ABSTRACT

Objective: The incidence of skin cancer increases day by day depending on environmental factors. Developing diagnostic and pathological methods provide correct typing of skin cancers.

Methods: This retrospective analysis included patients who presented to and were scheduled for treatment at Sivas Cumhuriyet University Plastic Reconstructive and Aesthetic Surgery Clinic between January 1, 2000 and December 31, 2019 due to skin cancer and carcinoma in situ. The results were divided two groups as first ten years and second ten years. The groups were compared among themself in terms of cancer type, age, gender and localization.

Results: 619 cases of 652 skin cancer and in situ carcinoma results were detected. When the groups were compared in terms of tumor types detected, there was a significant increase in MM, Bowen's disease, and rare NMSC subtypes other than SCC and BCC in the second decade ($p<0.001$). Comparison of NMSC and MSC rates between the groups showed that the incidence of MSC had increased significantly from 5.2% to 10% in the past 10 years ($p<0,05$).

Conclusions: Rare Non-melanocytic skin cancer group includes many types of carcinoma, there are various treatment protocols. Furthermore, many members of this group are known to be more aggressive than Basal cell carcinoma and squamous cell carcinoma. There are no consensus especially for approaches targeting lymph nodes. Closely following is necessary for early detection of recurrences and metastases.

Keywords: Skin Cancer, Non-Melanocytic Skin Cancer, Melanocytic Skin Cancer, Merkel Cell Carcinoma, Malignant Eccrine Poroma, Malignant Nodular Hidradenoma

Cilt Kanserlerinin 20 Yıllık Retrospektif Analizi: Birinci 10 Yıl İle İkinci 10 Yılın Karşılaştırılması

ÖZET

Amaç: Çevresel faktörlere bağlı olarak cilt kanserlerinin insidansı gün geçtikçe artmaktadır. Gelişen tanısal ve patolojik metotlar kanserlerin daha doğru tiplendirilmesine yardımcı olmaktadır.

Gereç ve Yöntem: Çalışmamızda cilt kanserleri ve in situ karsinom nedeniyle 1 Ocak 2000-31 Aralık 2019 tarihleri arasında kliniğimizde tedavi amacıyla başvuran ve tedavisi planlanan hastalar dahil edildi. Hastalar ilk on yıl ikinci on yıl olarak iki gruba ayrıldı. Gruplar; kanser tipi, yaş, cinsiyet ve lokalizasyon açısından karşılaştırıldı.

Bulgular: 619 vakaya ait 652 cilt kanseri ve insitu karsinom tespit edildi. Gruplar karşılaştırıldığında ikinci on yılda malign melanoma, Bowen hastalığında ve nadir gözlenen Non Melanositik Cilt Kanseri (NMCK)'nin alt tiplerinde anlamlı bir artış olduğu gözlendi ($p<0,001$). NMCK ve Melanositik Cilt Kanseri (MCK) karşılaştırıldığında MCK insidansının son 10 yılda %5.2 den % 10 a yükselmesi istatistiksel açıdan anlamlı idi ($p<0,05$).

Sonuç: Nadir gözlenen NMCK'ler çeşitli tedavi protokolleri olan pek çok karsinom tiplerini içermektedir. Ayrıca bu grubun pek çok üyesinin Bazal Hücreli Kanser ve Skuamöz Hücreli Kanserden daha agresif seyrettikleri bilinmektedir. Özellikle lenf nodlarına karşı yaklaşım hakkında ortak bir konsensüs bulunmamaktadır. Rekürens ve metastazların erken tespit edilebilmesi için yakın takip gereklidir.

Anahtar Kelimeler: Deri Kanseri, Melanositik Olmayan Deri Kanseri, Melanositik Deri Kanseri, Merkel Hücreli Karsinom, Malign Ekrin Poroma, Malign Nodüler Hidradenom

INTRODUCTION

Non-melanocytic skin cancers (NMSC) are the 5th most common type of cancer, while melanomas rank 19th (1). Malignant melanoma (MM) accounts for only 2% of all skin cancers but is the most common cause of skin cancer-related deaths (2). Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the most common types of NMSC, while other rarer subtypes such as Merkel cell carcinoma (MCC), Porocarcinoma (PC), and Hidradenocarcinoma account for less than 1% of cases (3). According to Turkish Cancer Statistics data (2015), the number of newly reported cases of melanocytic skin cancer increased from 330 in 2011 to 618 in 2015. For NMSCs, 4,450 new cases were reported in 2011 and this figure jumped to 8,800 in 2015 (4). The aim of this study was to determine changes in the incidence and distribution of skin cancers between the first and second decades of a 20-year period.

MATERIAL AND METHODS

This retrospective analysis included patients who presented to and were scheduled for treatment at Sivas Cumhuriyet University Plastic Reconstructive and Aesthetic Surgery Clinic between January 1, 2000 and December 31, 2019 due to skin cancer and carcinoma in situ. The patients were divided into two groups: those who presented between January 1, 2000 and December 31, 2009 comprised Group 1 and those who presented between January 1, 2010 and December 31, 2019 comprised Group 2. Both groups were evaluated in terms of age, sex, tumor type, number of cases, localization, reconstruction method and increase in tumor type. Patients whose patient files and pathology results were not reached, these were excluded from the study. Ethical approval for the study was obtained from the Cumhuriyet University Ethics Committee. (Decision no:2020-01/41).

Statistical Analysis: The collected data were uploaded to the SPSS (version 23.0) software package and tested for normal distribution using the Kolmogorov–Smirnov test. Data analyses included descriptive statistics (frequency, percent, etc.), as well as chi-square test in 2x2 and multicell tables for discrete qualitative data and Mann–Whitney U test for measured data because they did not meet parametric test assumptions. The type I error level was 0.05.

RESULTS

Data pertaining to 619 patients were accessed and a total of 652 skin cancers and in situ carcinomas were identified. Of this patient group, 40.9% (n=253) were in Group 1 and 59.1% (n=366) were in Group 2. When all lesions were evaluated, 61.4% (n=393) of the cancers were BCC, 27.5% (n=176) were SCC, 7.97% (n=51) were MM, and 3.13% (n=20) were other NMSC subtypes. NMSC accounted for 90.3% (n=589) of all lesions, MSC for 7.8% (n=51), and the prevalence of Bowen's disease was 1.8% (n=12). (Table 1 and 2).

Table 1. Distributions of Subtypes of Carcinomas and Anatomical Location

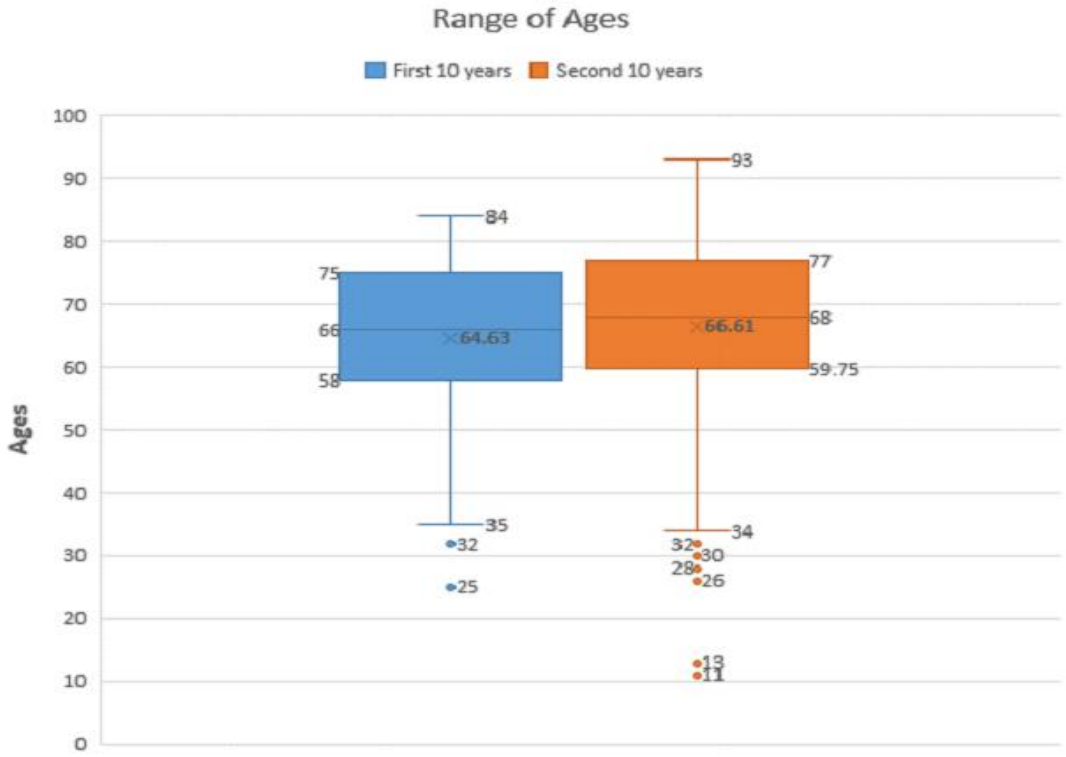
	Basal Cell Carsinoma		Squamous Cell Carsinoma		Malignat Melanoma		Bowen Diasases		Others		TOTAL
Groups	I	II	I	II	I	II	I	II	I	II	
Scalp	4	30	5	10	2	3	0	1	0	0	55
Forehead	26	17	3	2	2	4	0	0	0	1	55
Nose	50	66	2	13	1	0	0	0	0	2	134
Ear	5	6	1	2	0	0	0	0	0	1	15
Periorbital area	53	47	2	7	1	1	0	0	0	2	113
Lower lip	2	2	34	34	2	2	0	1	0	1	78
Upper lip	5	6	4	6	0	0	0	1	0	0	22
Cheek	25	31	6	10	2	4	0	2	0	0	80
Lower extremite	2	3	12	5	1	13	0	1	0	4	41
Upper extremite	0	1	6	7	1	6	1	3	0	3	28
Trunk	1	5	2	0	2	3	0	2	2	4	21
Neck	2	4	2	1	0	1	0	0	0	0	10
Total	175	218	79	97	14	37	1	11	2	18	652

Table 2. Uncommon Types of NMSC

Uncommon Types of NMSC	Group 1	Group 2
Dermatofibrosarcoma Protuberans	0	5
Basosquamous Cell Carsinoma	0	1
Spindle Cell Carcinoma	0	2
Sebaceous Carcinoma	0	1
Merkel Cell Carsinoma	2	1
Caposi Sarkoma	0	1
Verrucous Carcinoma	0	1
Malignant Nodular Hidradenoma	0	1
Epithelioid sarcoma	0	1
Malignant Eccrine Poroma	0	2
Total	2	16

The study sample comprised 39.1% female (n=242) and 60.9% male (n=377) patients. Analysis of sex distribution by group showed that Group 1 included 153 males (60.5%) and 100 females (39.5%), while Group 2 included 224 (61.2%) males and 142 (38.8%) females. Mean age was 65.9 ± 13.6 (11–93) years in the entire patient group, 64.7 ± 12.1 (25–84) years in Group 1, and 66.4 ± 14.1 (11–93) years in Group 2. (Graphic1)

When the two groups were compared based on the median age of patients diagnosed with the different cancer types, there were no significant age differences except for BCC ($p<0.05$) (Table 3).



Graphic 1. Range of ages

Table 3. Statistical analysis of age and tumour subtypes

	Mean Ranks For Ages	Median ± SD (min-max)	Results
BCC			
The first ten years (n:74)	112.41	67 ± 12.787	p:0.005*
The second ten years (n:193)	142.28	(26-93)	
SCC			
The first ten years (n:46)	72.23	69 ± 11.744	p:0.884
The second ten years (n:96)	71.15	(25-90)	
MM			
The first ten years (n:6)	25.50	62 ± 20.465	p:0.461
The second ten years (n:37)	21.43	(11-90)	
Bowen			
The first ten years (n:1)	5.00	65 ± 14.514	p:0.751
The second ten years (n:10)	6.10	(34-85)	
Other			
The first ten years (n:2)	13.00	67 ± 14.902	p:0.528
The second ten years (n:18)	10.22	(33-87)	

*$p<0.05$; Mann Whitney U test was used.

When the first and second decades were compared in terms of the types of cancers detected, there was no significant difference for male patients (p>0.05). However, there was a significant increase in other rare NMSCs in female patients (p<0.05). Comparison of MSC and NMSC subgroups revealed that the incidence of MSC had increased from 27.8% (n=5) to 72.2% (n=13) in females and from 27.3% (n=9) to 72.7% (n=24) in males, but these differences were not statistically significant (p>0.05).

The most common type of skin tumor in Group 1 was BCC (n=175, 64.6%), followed by SCC (n=79, 29.2%). The incidence of MM was 5.2% (n=14). Bowen's disease was detected in only one patient, while other NMSCs accounted for 0.7% of the lesions (n=2). MCC was detected in two patients who had an NMSC other than SCC or BCC. Among the NMSCs, 68.3% (n=175) were BCC, 30.8% (n=79) were SCC, and 0.8% (n=2) were other rare NMSC subtypes. Lesions in non-head and neck locations accounted for 11.1% (n=30).

Similarly, the most common skin cancers in Group 2 were BCC (57.2%, n=218) and SCC (25.5%, n=97). MM was detected in 9.7% (n=37) and Bowen's disease in 2.9% (n=11) of the patients. Other NMSC subtypes were detected in a total of 16 lesions (4.7%). In the past 10 years there were 333 cases of NMSC (90%) and 37 cases of MSC (10%). Of the NMSCs, 65.4% (n=218) were BCC, 29.1% (n=97) were SCC, and 5.4% (n=18) were other rare NMSC subtypes. Sixty lesions (15.7%) occurred in non-head and neck localizations.

When the groups were compared in terms of tumor types detected, there was a significant increasement in MM, Bowen's disease, and rare NMSC subtypes other than SCC and BCC in the second decade (p<0.001). Comparison of NMSC and MSC rates between the groups showed that the incidence of MSC had increased significantly from 5.2% to 10% in the past 10 years (p<0.05) (Table 4). In terms of tumor location, there was a significant increase in tumors located on the scalp and decrease in those located on the forehead and periorbital region (p<0.05) (Table 4).

Table 4. Statistical analysis of groups

	Group 1 n (%)	Group 2 n (%)	Results
Sex			
Female	100 (39.5)	142 (38.8)	X^2: 0.033
Male	153 (60.5)	224 (61.2)	p:0.867
Total	253	366	
Types of Carsinomas			
BCC	175 (66.6)	218 (57.2)	
SCC	79 (29.2)	97 (25.5)	
MM	14 (5.2)**	37 (9.7)**	X^2: 20.064
Bowen	1 (0.4)**	11 (2.9)**	p<0.001**
Others	2 (0.7)**	18 (4.7)**	
Total	271	381	
Distributions of Carcinomas			
NMSC	256 (94.8)	333 (90.0)	X^2: 4.934
MSC	14 (5.2)	37 (10.0)	p:0.026*
Total	271	370	
Anatomic Distributions of Carcinomas			
Scalp	11 (4.1)**	44 (11.5)**	
Forehead	31 (11.4)**	24 (6.3)**	
Nose	53 (19.6)	81 (21.3)	
Ear	6 (2.2)	9 (2.4)	
Periorbital region	56 (20.7)**	57 (15.0)**	X^2: 23.609
Lower lip	38 (14.0)	40 (10.5)	p:0.014**
Upper lip	9 (3.3)	13 (3.4)	
Cheek	33 (12.2)	47 (12.3)	
Lower Extremite	15 (5.5)	26 (6.8)	
Uppeer Extremite	8 (3)	20 (5.2)	
Trunk	7 (2.6)	14 (3.7)	
Neck	4 (1.5)	6 (1.6)	
Total	271	381	
Region			
Head and neck	241 (88.9)	321 (84.3)	X^2: 2.913
Other	30 (11.1)	60 (15.7)	p:0.088
Total	271	381	

*p<0.05 **Chi square test was used; Bonferroni test was used for subgroups.

Recurrences accounted for 5.1% (n=33) of all lesions. Reconstruction techniques used were primary repair in 21.2% (n=138), graft in 34.4% (n=224), and flap in 42.8% (n=279) of the lesions. Distant flaps were used in 5.39% (n=15) of flap reconstructions, while the rest utilized local flaps. Tumor-related amputation was performed in 1.4% (n=9) of the patients. Two patients refused surgery and were referred for radiotherapy.

DISCUSSION

Skin cancers are among the most common cancers. The most frequent type of skin cancer is BCC, which is more benign than other types. SCC and other rare NMSC subtypes tend to be more aggressive. Although MMs are responsible for most skin cancer-related deaths, high rates of recurrence and metastasis have also been reported for NMSCs such as MCC, Porocarcinoma, and sebaceous carcinoma. These tumors reportedly account for less than 1% of NMSCs (5), but their incidence in the second decade of our series was 4.7%, which is substantially higher than rates reported in the literature.

Merkel cell carcinoma is an aggressive neuroendocrine skin tumor (6). The number of patients diagnosed increases each year, which is believed to be due in part to the advanced methods used for the diagnosis of this tumor (7). Although 75% of cases are diagnosed as local disease, recurrence rates are high, at 30% (7,9). Even in localized disease, lymph node involvement can occur in 25% of cases (10). One of the most important prognostic factors is lymph node involvement (8,11-13). However, there is no consensus on elective lymph node dissection. Involvement is detected in about 30% of patients who undergo sentinel lymph node biopsy (SLNB) (6). Like other neuroendocrine tumors, it is radiosensitive (14). A total of three MCCs were identified in our series. Of the two patients with tumors located on the back, axillary single node metastasis was detected in one patient and involvement of four inguinal lymph nodes was detected in the other patient. No lymph node involvement was detected in the one patient in the second decade.

Hidradenocarcinoma has an incidence of less than 0.001% (15,16). Because it is so rare, the treatment protocols used are a subject of debate. It has local recurrence rates up to 50% and metastasis rates of around 60% despite wide excision, which is the generally accepted treatment method (17,18,19). As dermal lymphatic invasion, nerve sheath involvement, deep structure infiltration, positive resection margins, highly anaplastic morphology, and extracapsular lymph node spread are associated with high recurrence rates, these patients have been recommended adjuvant radiotherapy (20,21). Furthermore, successful outcomes have been reported regarding preoperative radiotherapy (22). Although some authors recommend prophylactic lymph node dissection because of high lymphatic involvement (23,24), it has also been emphasized that SLNB provides tumor-free survival, even if the number of the cases is limited (25-27). Due to high recurrence and metastasis rates, antihormone therapy to prevent spread has also been proposed as beneficial for the treatment of these tumors in receptor-positive cases (27). A 67-year-old woman in our series had a MNH on her lower lip. No lymphatic involvement or distant metastasis was detected at the time of diagnosis. The patient underwent wide excision and is currently in her second postoperative year of follow-up with no recurrence or metastasis.

Porocarcinoma accounts for 0.005–0.01% of skin tumors (28,29). Metastatic disease is present in 22.3% of patients at the time of diagnosis (30). It is an aggressive tumor with recurrence and metastasis rates of about 20% despite curative surgery (29,30). The generally accepted treatment is surgical excision. Poor prognostic factors include lymphovascular invasion, high mitosis, tumor thickness over 7 mm, irregular tumor margins, and poor differentiation (32,33). In addition, tumor location is also an important factor for prognosis. Primary lesions in the upper and lower extremities, trunk, hips, and genital area are associated with higher risk of lymph node metastasis than tumors located in the head and neck region. SLNB is recommended for patients in the high-risk group (29). Lymph node positivity is reported to increase to 50% for tumors that are poorly differentiated (34,35). Despite reports that response to radiotherapy and chemotherapy was poor (36) and radiotherapy had no effect on survival, radiotherapy can be used for patients with positive surgical margins and those not eligible for surgery (37). There were two cases of MEP in our series. One was located on the lower eyelid of a 75-year-old patient, while the other was located in the gluteal region of an 83-year-old patient, both of whom were women. No lymphatic involvement or distant metastasis was detected at the time of diagnosis in the patient with the eyelid tumor. She underwent wide excision and has been under follow-up for 1.5 years. The tumor located in the gluteal region was reported to be carcinoma in situ.

Dermatofibrosarcoma protuberance (DFSP) is a soft tissue sarcoma with an incidence of four per million (38). It typically grows slowly and has less than 5% likelihood of regional or distant metastasis unless it transforms into a high-grade fibrosarcoma (39,40). Histopathologically, 3–20% of DFSPs contain fibrosarcomatous changes, and this finding is described as an independent risk factor for recurrence and distant metastases (39,41,42). Other risk factors for recurrence are a clean resection margin narrower than one millimeter or a positive surgical margin and tumor

size. Recurrence is more common with tumors larger than five centimeters (41). Most distant metastases are found in the lungs, but they are also known to metastasize to the bone, soft tissue, liver, kidneys, gastrointestinal tract, and lymph nodes (38). While metastasis was not observed in any of our cases, one of our patients presented with a fifth relapse.

Epithelioid sarcoma (ES) is a rare type of sarcoma with a reported incidence of 0.02–0.05 per 100,000 (43,44). There are two types of ES, proximal and conventional. The conventional type usually occurs in distal locations in the upper extremities, and is seen in adolescents and young men (45). The proximal type is less common, located on the trunk, and has poorer prognosis (46). It also occurs very rarely in the perineum, penis, and vulva (47,48). Treatment planning is based entirely on the presence or absence of lymphatic involvement and distant metastasis. Lymphatic involvement has been reported at rates of 10–80% (49-52). Preoperative evaluation of lymphatic involvement is important due to the high risk. Therefore, many authors recommend SLNB for accurate staging (50,52,53). Pre- or postoperative radiotherapy reduces local recurrence rates and is recommended as an adjunct to radical surgical treatment (50,53). In our patient, the tumor was located in the perineal region and the patient underwent wide excision, bilateral groin dissection, and chemoradiotherapy. While receiving radiotherapy, metastasis developed on the skin of the vulva at postoperative five months. The vulvar metastasis was controlled with wide surgical excision. However, the patient died one and a half years later due to distant metastasis and recurrence.

Sebaceous carcinoma is an aggressive adnexal tumor with two types, ocular (OSC) and extraocular (EOSC). The ocular type is more common but more aggressive than the extraocular type (54). As few cases of EOSC have been described, a definite consensus regarding treatment has yet to be reached, and there are conflicting views in the literature. The generally accepted treatment is wide tumor resection (55). Different figures have been reported regarding its lymphatic involvement and metastasis rates. Lymphatic metastasis rates of 1.3–16% and non-lymph node metastasis rates of 0.4–10% have been reported (55,56). Due to these different rates, there are different attitudes regarding the use of sentinel lymph nodes. Some authors report that subclinical nodal spread is rare for EOSC and few SLNBs are positive (57-59), while others argue that EOSC is a locally aggressive tumor with a high likelihood of regional nodal metastasis and that regional nodal dissection together with a wide local excision should be considered optimal (55). For optimal treatment, SLNB may be helpful in determining subclinical lymphatic involvement in high-risk patients, particularly those with tumors thicker than two millimeters, tumors with a Clark stage over 4, lymphovascular invasion, perineural invasion, bone infiltration, and anaplasia or poorly differentiated tumors (55,60). Although the role of adjuvant radiotherapy is controversial, radiotherapy can be given after complete tumor resection either alone or in combination with chemotherapy (55). Primary radiotherapy alone is not recommended due to high recurrence rates (56,58,60). It can be used in patients who refuse surgery or cannot undergo surgery due to comorbidities, and there are also publications that recommend its postoperative use after resection (55). Our patient was an 85-year-old man with nasally located cancer. Although his cervical lymph nodes were positive at the time of diagnosis, he did not consent to neck dissection and was lost to follow-up.

Detection of spindle cells in pathologic examination is suggestive of spindle squamous cell carcinoma, spindle-cell melanoma, pleomorphic undifferentiated sarcoma, and leiomyosarcoma in diagnosis (61). Spindle and basal cells may also be found in the sarcomatous type of BCC (62). In fact, it has been emphasized that basal cells may be overlooked in some cases (62-65). This subtype exhibits aggressive behavior and has metastatic potential (62). The spindle cell variant of SCC is rare. While it can be seen in sun-exposed regions and radiotherapy areas (66). It is a poorly differentiated form of SCC (61) and progresses more aggressively (62). The spindle variant of MM is in the vertical growth phase. Like the SCC variant, it occurs in sun-exposed areas (62). It is detected as widespread metastatic disease (67,68). In our series, spindle cell carcinoma was detected in two patients, both patients were over 70 years of age and the tumors were located on the face. The pathology department reported them as spindle cell carcinomas, with no subtyping.

In this study, the quantitative increase observed in MM, Bowen's disease, and rare types of NMSC in the second decade was statistically significant. The increase in Bowen's disease may be considered a result of early diagnosis.

The number of patients with MM is increasing daily worldwide (69) and our country (70). The increase in our series is consistent with the literature. This increase has also been observed in the pediatric age group (71). Pediatric malignant melanoma (PMM) accounts for 1–4% of all cases of melanoma (72). Although prognosis is more favorable in the pediatric age group (72-74), MM is a deadly disease and should be treated aggressively. Diagnosing PMM can be difficult, even for experienced physicians. Misdiagnosis in this age group has been reported at around 40% (75,76). Nodular PMMs may exhibit a pyogenic granuloma-like morphology (76,77). In the pediatric age group, PMM should not be overlooked in the differential diagnosis of pigment-free lesions with benign morphology. The treatment protocol is the same as

the protocol for adults. However, sentinel lymph node involvement occurs at a higher rate than in adults (72). Two of the MM patients in the second decade were in the pediatric age group and MM was detected incidentally. One patient was 13 years old and presented with a long-standing unpigmented granulomatous lesion on the front of the thigh. The result of incision biopsy was reported as PMM. Sentinel sampling was performed in this case because Breslow's depth was 6 mm. SLNB was positive and the patient underwent lymph node dissection. MM involvement was not observed in any of the nodes dissected after the sentinel lymph node. The other patient presented because of a nail change and excisional biopsy was performed upon observation of irregular pigmented lesions on the anterior surface of the tibia. The pathology result was reported as superficial spreading MM. The Breslow's depth of the tumor was 0.5 mm. Both of patients are in the second year of postoperative follow-up with no recurrence or metastasis. Although there were a small number of pediatric patients in our study, pediatric patients represented 3.9% of all cases of MM detected in 20 years.

The most important limitation in our study is that the hospital in which we are working has a patient profile limited with local region and it is a single center study. Although small skin cancers are treated in state hospitals in our region, metastic tumors such as SCC, MM, big size tumors and rare forms are consulted and this contributes positively to our work.

The pathological differential diagnosis of rare NMSC subtypes such as MCC, MNH, MEP and sebaceous carcinoma includes BCC and SCC. Different immunohistochemical dyes are used for differential diagnosis (79-82). This increase may be due to an increase in the number of cases or it may be related to more accurate diagnosis with advanced detection methods and staining techniques. As this group includes many types of carcinoma, there are various treatment protocols. Furthermore, many members of this group are known to be more aggressive than SCC and BCC. However, for many types of cancer there are a limited number of cases in the literature and no clear consensus regarding treatment. This creates as limitation, especially for approaches targeting lymph nodes. Treatment protocols are based on case reports and a few case series. It should be kept in mind that without the correct approach and follow-up planning, morbidity and mortality will be higher, especially in patients with aggressive types. This increases the importance of closely following patients for early detection of recurrences and metastases.

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RESEARCH ARTICLE

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Robotic Gynecologic Surgery: What it Means for Women

ABSTRACT

Objective: The aim of this study is to improve the understanding of the experiences of women undergoing robotic-assisted gynecologic surgery.

Methods: A qualitative descriptive phenomenologic approach was used. We conducted phone interviews with women who had undergone a gynecologic procedure via robotic-assisted surgery in a gynecology clinic of a university hospital (n=19). Semi-structured interviews were conducted with women, and data were analyzed using Colaizzi's methods.

Results: Two major themes were identified. These two themes concerned: (1) Ambivalent Feelings on Robotic Surgery, and (2) Robotic Surgery was a Piece of Cake.

Conclusions: Because of the newness of this procedure, the women in this study indicated that they had concerns and lacked information about robotic-assisted gynecologic surgery but that their decision was influenced by the confidence they had in their physicians. The women indicated that they had confidence in the robotic technique and recovered quickly physically.

Keywords: Qualitative Research, Patient Education, Patient Experience, Phenomenology, Robotic Gynecologic Surgery

Jinekolojik Robotik Cerrahi: Kadınlar İçin Anlamı

ÖZET

Amaç: Bu çalışma ile, jinekolojik robotik cerrahi ile ameliyat olan kadınların robotik cerrahi ile ameliyat olma kararı, bu ameliyat şeklinin kadına ne hissettirdiği ve ameliyat sonrası deneyimlerini derinlemesine incelemek amaçlanmıştır.

Gereç ve Yöntem: Çalışmada nitel fenomenolojik yaklaşım kullanılmıştır. Araştırma kapsamında jinekolojik robotik cerrahi operasyonu geçiren 19 kadın ile görüşülmüştür. Kadınlar ile telefon görüşmesi yapılmış ve veriler yarı yapılandırılmış görüşme formu ile toplanmıştır. Görüşmeler sonucu elde edilen verilerin değerlendirmesinde Colaizzi'nin fenomenolojik yorumlama metodu kullanılmıştır.

Bulgular: Çalışmada (1) Robotik Cerrahiye İlişkin Ambivalans Duygular ve (2) Robotik Cerrahi Çok Kolaydı olmak üzere iki ana tema tanımlanmıştır.

Sonuç: Kadınlar, robotik cerrahinin yeni bir uygulama olması ve daha önce duymamış olmaları nedeniyle kaygı ve anksiyete yaşadıklarını ifade etmiştir. Ancak kadınların tamamı doktorlarına duydukları güvenin bu kaygıyı azalttığını ve robotik cerrahi ile operasyonu kabul etmelerinde etkili olduğunu belirtmiştir. Kadınlar, robotik cerrahi sonrası kendilerini fiziksel olarak çok iyi hissettiklerini ve güven duyduklarını bildirmiştir.

Anahtar Kelimeler: Nitel Araştırma, Hasta Eğitimi, Hasta Deneyimi, Fenomenoloji, Robotik Jinekolojik Cerrahi

INTRODUCTION

The newest computer-assisted laparoscopic surgery (robotic-assisted surgery) is a popular option for minimally invasive surgical procedures. Robotic-assisted surgery provides advantages for patient and also health care professions (1). These advantages have led to more widespread use of robotic-assisted surgery in several specialties (2).

One of the most common fields of using robotic-assisted surgery is in gynecology (3). In many parts of the developed world, an increasing number of women are offered robotic-assisted surgery in gynecology as treatment for hysterectomy, myomectomy, tubal reanastomosis, ovarian transposition, gynecologic oncology procedures, and pelvic reconstructive surgery (4-6). Robotic-assisted surgery in gynecology is advantageous because of shortened operative times, reduced blood loss and transfusion rates, lessened hospital stay, decreased risk for complications, and an earlier return to a regular diet in the postoperative period (3,7,8).

Current literature suggests that robotic-assisted surgery in gynecology has advantageous for patients. Healthcare professions are also aware of these advantages and use robotic surgery for the benefit of their patients (9-11). Yet, healthcare professionals should work harder to understand how the decision to undergo robotic-assisted surgery makes patients feel, as it is an important part of informing patients about the methods of the surgery. There is a gap in the literature regarding the opinions, experiences, and attitudes of women who are considering robotic surgery as an option/who have undergone robotic surgery (12). Because of the short length of hospital stay and limited contact in the outpatient clinic, healthcare professionals have only brief contact with these women (13).

How women feel about robotic-assisted gynecologic surgery has not previously been explored. Knowledge of women's experiences and feelings about the gynecologic diseases and their surgical treatment could better inform healthcare professionals, especially nurses, who spend significant amounts of time with patients (13). A deep understanding of patients' thoughts and feelings about robotic-assisted surgery during the pre-operation period is necessary in order to properly educate patients. More information on this topic could allow healthcare providers to offer more support to patients in giving appropriate information about treatment, providing relevant education concerning the surgery, and planning proper postoperative care.

This study aims to give voice women's feelings about undergoing robotic-assisted gynecologic surgery, the decision-making process involved, the implications of this type of surgery, and the post-surgery experiences of women diagnosed with different gynecologic medical diseases/problems.

MATERIAL AND METHODS

A qualitative descriptive phenomenologic approach was used in this study. Phenomenology, a frequently used approach in qualitative research, focuses on the experience of individuals as the main method of understanding the broader meaning of people's life experiences (14). Phenomenologists assert that reality is not a fixed entity, and that it changes and develops according to people's experiences and the social context within which they find themselves (14).

Sample and Setting: This study was performed with women who had undergone robotic-assisted gynecologic surgery and have discharged from the gynecology clinic of a university hospital in Ankara, Turkey. In this gynecology clinic, 25 women had undergone robotic-assisted gynecologic surgery, the first cases of using such a surgery to treat malignant and benign diseases until the data collection. The study was started in September 2012 and completed in January 2013. Participants were recruited until the data saturation limit was reached, that is, when no new information was obtained. During the study period, 19 women undergone robotic-assisted gynecologic surgery were interviewed.

Criteria for inclusion in the study were as follows: (a) having undergone robotic-assisted gynecologic surgery for various gynecologic conditions such as gynecologic cancer, endometrial hyperplasia, abnormal uterine bleeding, myoma, and prolapsed pelvic organs; (b) being willing to participate in the study, and (c) having sufficient Turkish language proficiency. Women needing adjuvant treatment were excluded from the study. This study was approved by the local ethics committee of the hospital (Approval Number: 1539-282).

Data Collection: Data were obtained through audiotape-recorded telephone interviews. Consent and all data collection occurred in two phases.

In the first phase of data collection, potentially eligible women were identified using the patient registration system. A list of the women who had undergone robotic-assisted surgery was prepared. Patients' contact information was then found in the medical records, and an informational letter explaining the purpose and procedures of the study was sent to the women who had met the study's criteria.

In the second phase, a few weeks after being informed with letter the women were called by the principal investigator (PI-GK) while they were own home. The phone interviews were conducted by PI in a quiet, private room at hospital. The door of the room was locked to ensure confidentiality and

privacy during the phone interviews. PI introduced the study to the women and inquired about their interest. If women were interested in participating, they were provided sufficient time for questions and all questions answered by the PI. It also was explained that participation in the study is voluntary and they could refuse to participate or withdraw from the study at any time without any negative consequences on the services received from the hospital. Verbal consent was obtained for participation in the study from interested women. The women were then asked questions meant to prompt responses concerning their feelings and experiences regarding robotic-assisted surgery. All responses of the women were recorded during the phone interviews. Permission was also obtained to make audiotape recordings. Each interview lasted about 45-60 minutes. All the data including audiotape recordings and transcriptions were kept in a locked cabinet at a PI's office.

We designed the semi-structured interview guide that facilitated the in-depth interviews (Table 1). A pilot study with two women was conducted before the formal study. The PI performing the interviews had received previous training on qualitative study methods and their implementation. PI (GK) and the co-authors (AA, MS) in the data analysis were not responsible for the care or treatment of the women.

Table 1. Interview guide.

1. What did you think when you were told that you would be operated on using robotic surgery, and how did you feel about it?
2. What influenced your decision to undergo robotic surgery?
3. How did your surgery being performed by robotic surgery make you feel? Can you describe your emotions and what you felt after the surgery?
4. Could you compare your previous experience of surgery, if any, with your current experience?
5. Did you need postoperative help and support? Can you explain what issues you needed help and support for?
6. Would you prefer robotic surgery if you had to undergo surgery again?
7. Is there anything you would like to add regarding your experience?

Data Analysis: All audiotape-recorded interviews were transcribed verbatim and managed using Microsoft Word by the principal investigator (GK). Analysis of interview transcriptions was based on Colaizzi's phenomenologic methodology: (a) Reading and rereading the participants' descriptions of the phenomena to acquire a feeling for their experience and make sense of their account. (b) Extracting significant statements that pertain directly to the phenomenon. (c) Formulating meanings for these significant statements. (d) Categorizing the formulated meanings into common thematic clusters and validating these clusters. (e) Providing an exhaustive description of the phenomenon by integrating these findings. (f) Validating the findings by returning to participants to ask how the researcher's story matches with their own. (g) Incorporating any changes offered by the participants into the final description of the phenomenon (15).

During the analysis, in order to become familiar with the data, researchers (GK, AA) began by separately reading through the data multiple times. Significant statements and phrases that pertained to the study objectives were identified. Meanings were formulated from these significant statements and phrases. The two researchers recorded notes of their first reactions to the initial analysis process and created multiple codebooks, with the codes identifying from the separate texts. The formulated codes were then organized into clusters of themes. In the last stage of data analysis, researchers discussed the wording of themes and categories until unanimous agreement was reached. The final analysis revealed two major themes.

To maintain the credibility of data analysis, the transcripts were examined repeatedly by each researcher in order to include them into the data. Two researchers worked independently to identify the major categories of the transcripts. The coding was compared. Between the coding of the two researchers, which mainly related to the choice of words, were minor differences. Differences were discussed until a final agreement was reached. To achieve final validation (15), two participants were selected randomly and contacted again to read the descriptions; they agreed that the analyses had accurately represented their personal experiences. To preserve confidentiality, each participant was described the letter "P" and assigned a number (P1, P2, P3, etc.).

RESULTS

Characteristics of participants in this study are shown in Table 2. Participants' median age was 51.5 years (min=42; max=71). Most of the participants (57.9%) graduated primary school and 63.2% being unemployed. 57.9% of the participants had gynecologic cancers.

Table 2. Characteristics of participants.

Age, Median (min-max), years	51.5 (42-71)	
	n	**%**
Education Status		
Primary school/Elementary school	11	57.9
Secondary school / High school	5	26.3
College – graduate	3	15.8
Work status		
Not working	12	63.2
Working	3	15.8
Retired	4	21.0
Diagnosis		
Benign gynecologic diseases	8	42.1
Malignant gynecologic diseases	11	57.9

Analysis of the data resulted in the following two main themes: (1) "Ambivalent Feelings on Robotic Surgery", and (2) "Robotic Surgery was a Piece of Cake". Themes and categories of the study are shown in Figure 1.

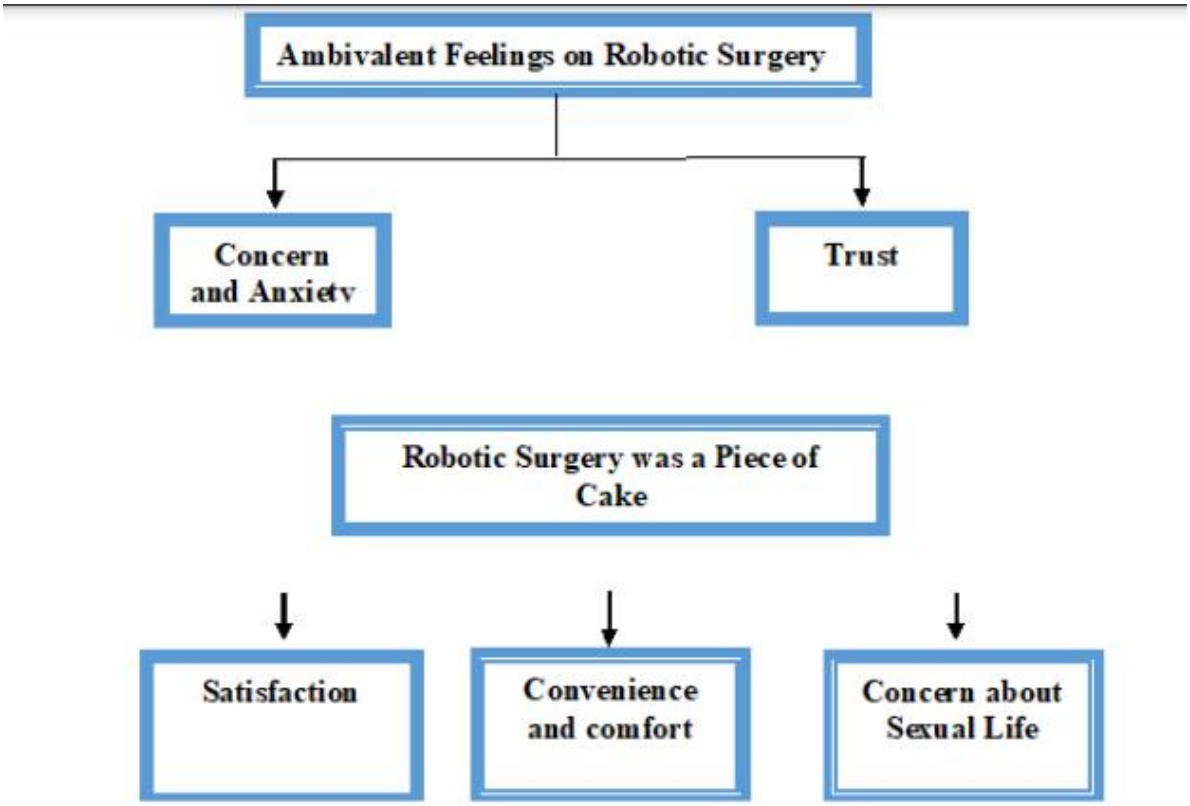

Figure 1. Themes and Categories of the Study

Theme 1. Ambivalent Feelings on Robotic Surgery: All the patients in the study arrived to the gynecologic outpatient department with symptoms of bleeding and pain. Patients stated that they experienced intense fear when they first heard that they had to undergo robotic surgery after examination. However, they also stated that they put their physician trust in.

Concern and anxiety about robotic surgery. Most of the patients in the study stated that they experienced concern and anxiety when they first heard they would undergo robotic surgery. Their reasons for such concern were related to the fact that robotic surgery is a new practice and that they therefore knew little about it.

One patient said: I was worried when I first heard that my surgery would be performed with a robotic technique; I got anxious. I thought, this is a new technology. Has it ever been used before? Or am I the first? (P2).

Three patients said that their worries continued due to the fact that the surgeon performs the surgery in a section (console) away from the patient and their fear that he/she may not be able to intervene easily if any mistake/problem occurred during the surgery. The loss of tactile feedback for surgeons was also a concern.

One patient expressed her concern about robotic surgery: My doctor would perform my surgery somewhere far away from me, what if the doctor's hand slipped while pressing the keys and another of my organs suffered damage? (P12).

Some of the patients stated that they have heard about robotic surgery for the first time. They had concerns because of not having any knowledge about robotic surgery. However, all the patients stated that their anxiety decreased after their physicians provided preliminary information regarding robotic surgery.

One patient made the following comments: It (robotic surgery) was something I had never heard of before. … I had worries and concerns such as: Will my doctor not touch me during my surgery? Will the robot operate on me from the beginning to the end? ..... Will my life be in danger? (P5).

Another patient stated that: My doctor explained to me with pictures how my surgery would be performed with the robotic technique. After the explanation, my concern regarding the surgery decreased slightly (P16).

One patient experienced surprise and fear when she saw the arms and parts of the robot at the operating theater.

I was surprised when I saw the robotic device (da Vinci Robotic System) that would be used in my surgery in the operating theater, I felt like I was in a space base. I was a little frightened.

But I was also thinking how technology had progressed (P4).

Trust in physician and decision to undergo robotic gynecologic surgery. All of the patients said that they had learned about the advantages of the robotic technique after preliminary explanation and information was provided by their physicians before the surgery. The patients were convinced that they got the most up-to-date treatment available and thankful for that after information by their physicians. All of the patients stated that they had faith in their physicians. These had affected their acceptance of undergoing surgery with the robotic technique.

One patient stated that: My doctor explained to me how he would operate with the robot and even showed pictures. At that moment, I felt surgery with the robot was safer. I was very confident in my doctor. I thought that I would not have much pain if I underwent surgery with the robot and therefore decided to have surgery with the robotic technique (P1).

Another patient made the following case: When my doctor told me about the surgery with the robot and its benefits, I thought of my health first. I am diabetic, and my wounds heal with difficulty. With the robot, the wound is small and the healing quicker. I therefore decided to undergo surgery with the robot in order to avoid any difficulties with the surgery (P7).

Another patient expressed her decision to undergo robotic surgery: My doctor explained the robotic surgery to me and said that he would operate the robotic device. I was very confident in my doctor….. I therefore accepted my surgery to be performed with the robotic technique (P17).

Theme 2. Robotic Surgery was a Piece of Cake

Satisfaction of having robotic gynecologic surgery. The patients stated that before the robotic surgery, they thought that they may experience problems such as pain, bleeding, and the inability to perform daily tasks after the surgery. However, after the robotic surgery, most patients reported that they felt physically very well, as if they had not undergone surgery at all. Due to the lack of pain or presence of pain at a minimum level after surgery (13 patients), early ambulation (14 patients), a very small incision site (15 patients), and lack of bleeding (12 patients), they stated they were very satisfied with having undergone robotic surgery.

One patient noted that: There was a small incision on my abdomen after the surgery. I felt so well that…I wondered whether I had actually undergone surgery (P2).

Another patient said: I had almost no pain after the surgery, no bleeding. I was very comfortable. It almost looked like I had not undergone any surgery; I can say that I did not even have a scar on my abdomen. I thought that it was quite good to have my surgery done with a robot. I am very pleased (P8).

After discharge from the hospital, the patients were in doubt about normal bodily functions. The patients attributed positive outcomes to the robotic surgery. Seventeen of the patients stated they did not need any support to take care of their daily activities after robotic surgery.

One of them said: I was very comfortable after the surgery, and I got up right away the next day. The other patient in the room had a lot of pain, a lot of stitches on her abdomen, and they were changing the dressing every day. I had four holes, and I did not have any pain. I am very satisfied (P6).

Two of the patients interviewed within the scope of the study stated that they needed support for a few days due to gas, distension, and groin pain after surgery.

One patient stated that: I had gas pain and bloating after surgery, and I could not do a lot of housework because of these troubles (P18).

Another patient said: I had pain in my groin for a few weeks after surgery, and there was pain when urinating ... My sibling, therefore, helped me with my daily needs for the next few days after the surgery (P14).

Convenience and comfort after robotic gynecologic surgery. Due to the rapid recovery after robotic surgery (16 patients), short duration of hospitalization (17 patients), and a quick return to normal life (15 patients), almost all of the patients were satisfied with the surgery and said they would prefer robotic surgery if they had to undergo it again. Four patients said that the surgery had an aesthetic advantage because the incision was very small.

I had a cesarean delivery, and there were quite a lot of stitches on my stomach, and the scar is still there. My abdomen was cut less in this surgery; here were three holes. They improved immediately; you cannot even really see the scar. Surgery with the robot was more comfortable than the other one (P19).

Another patient said that: My pain was very light, and I almost had no incision in my abdomen and no bleeding. It is really very comfortable and an ideal surgery method for women in terms of aesthetics (P16).

When the patients looked back, they were surprised how little bleeding, pain they experienced postoperatively.

One patient stated her experience: Surgery with the robot was really very different, very comfortable compared to my previous surgeries, and there is less blood loss. The risk of infection is less. There is a small scar, and it is not important (P11).

Overall, recovery after the robotic surgery was experienced as easy and rapid by the patients. One patient expressed nervousness that she would

be unable to take care of her roles and responsibilities immediately after the surgery. However, she stated that she had recovered much more quickly than she had hoped and had returned to her duties and responsibilities within a very short time.

I was so nervous that I would not be able to return to my duties in a short time and fulfill my children's needs. However, I got up just one day after my robotic surgery. … I started working soon. The surgery with the robotic technique was very good (P10).

Concern about sexual life after surgery. Independently from robotic surgery, all of the patients stated that before the surgery, they worried that their sexual life would be negatively affected, as they would be undergoing surgery for a gynecologic problem. However, most of the patients expressed that they experienced no such problems after surgery. Three patients did say that they avoided having intercourse with their spouses after the surgery, thinking that they may feel pain.

One of these patients stated that: We did not have any problems during my first sexual intercourse with my husband after the surgery, but I had not been with my husband for a long time previously because we had thought that something could happen to me (P3).

Another patient said that: I did not have sexual intercourse with my husband for 4-5 months after the surgery. My spouse was afraid because he thought that I would become ill or could get hurt. Later, when we had sexual intercourse, I did not experience any discomfort (P9).

Some of the patients stated that due to surgical menopause, they suffered from symptoms such as vaginal dryness, hot flashes, sweating, and nervousness. One patient stated that she experienced pain during sexual intercourse due to vaginal dryness, while another patient stated that she experienced emotional problems related to the loss of a sexual organ:

I felt psychologically uncomfortable because my womb was removed. I felt like I was not a woman anymore. I was empty inside, and I would not experience menstruation any longer. I was reluctant to have intercourse; I think my husband was uncomfortable about this situation and could not tell me. I did not have sexual intercourse with my husband for a long time because I thought I could experience pain or get hurt (P13).

Another patient stated that: We did not experience any problems with sexuality after the surgery. However, there was a decrease in nervousness, hot flashes, and lubrication because I had menopause. That made me feels uncomfortable during intercourse (P15).

DISCUSSION

After the approval of robotic surgery in gynecology by the FDA in 2005, it has been widely adopted at various centers in the USA and is being increasingly performed worldwide. Most of the patients in this study expressed concern and fear when they first heard about robotic surgery. They felt disbelief and surprise when they were informed that they would undergo surgery performed by a robot. Some of the patients were anxious about the success of the surgery because they believed that the doctor would not be present in the operating room during the surgery. However, after being informed of the details of the surgery by their doctors, all of the patients expressed relief and made the decision to undergo surgery. Similarly, in another qualitative study, women who underwent robotic surgery stated that they had little knowledge about the procedure but had faith in the robotic surgeons (13). Due to lack of knowledge, such patients may experience anxiety about undergoing surgery performed by a robot. The same study also reported that healthcare attitudes might affect patients' decision to undergo robotic surgery (13). These findings reinforce the importance of providing preoperative education and healthcare approach when informing patients about robotic surgery. Because may patients are hearing about the surgery for the first time, it is necessary that medical health professionals give adequate information to patients in order to relieve their concerns.

Although some studies show that robotic surgery does not seem to have significant advantages over conventional laparoscopic surgery for the treatment of benign gynecological diseases (16), more surgeons are adopting the use of robotic surgery in laparoscopy due to the fact that it is minimally invasive (16). Robotic surgery in gynecology is highly feasible (17) because it allows surgeons to be more precise, which is particularly important in more complex surgeries (16,18). Moreover, operations by robotic surgery are usually shorter, depending on the surgeon's experience (16). In addition to the advantages of robotic surgery for the surgeon, it also has advantages for the patients. In a systematic review, it was reported that robotic surgery shortened the length of hospital stays and, when compared to open and laparoscopic surgeries, reduced the amount of postoperative blood loss (17). Some of the other benefits of robotic surgery include smaller incisions, lower morbidity rates, less postoperative pain and scarring, less risk of infection, and a shorter return to normal daily life (16,19,20). Most of the patients in this study stated that they felt physically well after the surgery, or that they felt as if they had not undergone surgery at all. All of the women were extremely satisfied by the surgery because they were able to walk shortly after, experienced little pain, and little bleeding or scarring. Despite patients' concerns prior to their decision to undergo surgery, all were satisfied with the robotic technique. Similarly, a previous study shows that women who had undergone robotic surgery were

very surprised by the little amount of postoperative blood, though some of them thought that less bleeding may be abnormal (13).

The patients in this study rated their overall surgery experience as comfortable and easy and expressed satisfaction with a shorter hospital stay and a quicker return to normal life. Almost all of them stated that if there was a need in the future, they would definitely prefer to have surgery by the same technique.

CONCLUSIONS

Although there is concern about the cost and training requirements for robotic surgery (17, 20), it has the potential to make the patient experience an easier one. All patients spoke positively about the robotic surgery technique and claimed that it eased their concerns about undergoing surgery. The only concerns the patients expressed were those stemming from the lack of knowledge about the surgery. Therefore, it is vital that patients are provided with the necessary information in order to make their experience a more comfortable one. In order to make the transition from the decision-making process to the postoperative period a smooth one, patients should be able to place trust in their healthcare professionals. The findings of this study reinforce the importance of preoperative patient education about the procedures of robotic surgery and the need for more support for patients from their healthcare providers. Healthcare providers, as very crucial responsibility, should inform patients and educate them before the robotic procedure in order to give robotic surgery advantages to the patients.

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RESEARCH ARTICLE

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Evaluation of Langerhans Cell Density in Oral Lichen Planus and Squamous Cell Carcinoma

ABSTRACT

Objective: Oral mucosa exposed to many external factors. It has been suggested that oral pathologies may be related to cell-mediated immunity. Dendritic cells are antigen presenting cells that initiate adaptive cellular response. Langerhans cells(LCs), an important member of this group. Oral lichen planus(OLP) is a common chronic mucocutaneous inflammatory disease of unknown etiology. The most common malignancy in the oral cavity is oral squamous cell carcinoma(OSCC). In this study, we aimed to understand the role of LCs in OLP and OSCC which has an important role in mucosal defense.

Methods: A total of 74 biopsies taken from Dentistry Department between 2013-2016 were included into the study. The 74 cases;36 OLP, 28 OSCC and 10 normal mucosa as a control group were retrospectively re-evaluated. After selecting appropriate blocks, to evaluate Langerhans cells Langerin was applied immunohistochemically. Basal and suprabasal located immune positive Langerhans cells were counted in 1mm^2 areas in each case.

Results: In our study, female (60%) predominancy in OLPs, male predominancy(58%) in OSCCs were reported. Age distribution mean was 53±12 in OLPs and 61±21 in OSCCs. OLP was localized in the buccal mucosa in 86% of patients, whereas this rate was only 11%in OSCC cases. LCs density was 87(57-105) in the control group, 104(84-143) in OLPs, and 82(48-128) in OSCCs.

Conclusions: LC density was found significantly higher in OLPs compared to control group and OSCCs.In literature, variable results were published. Determining the density of Langerhans cells in these diseases can be a guide in terms of the pathogenesis of the disease and the improvement of treatment options.

Keywords: Oral, Squamous Cell Carcinoma, Lichen Planus, Langerhans Cell

Oral Liken Planus ve Skuamöz Hücreli Karsinom Olgularında Langerhans Hücre Yoğunluğunun Değerlendirilmesi

ÖZET

Amaç: Oral mukoza pek çok etken tarafından hasara uğratılabilmektedir. Oral patolojilerin hücre aracılı immünite ile ilişki olabileceği öne sürülmüş ve bu konuda çok çeşitli araştırmalar yapılmıştır. Dendritik hücreler, adaptif hücresel cevabı başlatan antijen sunucu hücrelerdir. Bu grubun önemli bir üyesi olan Langerhans hücreleri(LH), tüm stratifiye epitellerde özellikle de skuamöz epitelin orta ve üst kısmında yerleşir. Oral liken planus(OLP) sık görülen, etyolojisi net bilinmeyen kronik mukokutanöz inflamatuar bir hastalıktır. Oral kavitede en sık rastlanan malignite oral skuamöz hücreli karsinomdur(OSHK). Çalışmamızda mukozal savunmada önemli rolü olan Langerhans hücrelerinin OLP ve OSHK'da dağılımını inceleyerek lokal immün cevaptaki rolü hakkında fikir sahibi olmayı amaçladık.

Gereç ve Yöntem: 2013-2016 yılları arasında Diş Hekimliği Fakültesi tarafından gönderilen, 36 adet OLP, 28 adet OSHK ve kontrol grubu olarak 10 adet normal mukoza olmak üzere toplam 74 hasta retrospektif olarak yeniden değerlendirilmiş, uygun bloklar seçilerek immunhistokimyasal olarak Langerin antikoru uygulanmıştır. Her olguda 1mm^2'lik alanlarda bazal ve suprabazal yerleşimli LH'leri sayılmıştır.

Bulgular: Çalışmamızda OLP olgularında kadın(%60),OSHK olgularında erkek hakimiyeti(%58) izlendi. Yaş dağılımı OLP'larda 53±12 iken OSHK'da 61±21 idi. OLP hastaların %86'sında yanak mukozasında yerleşimli iken OSHK olgularında bu oran sadece %11'di. Langerhans hücre yoğunluğu kontrol grubunda 87(57-105), OLP'da 104(84-143), OSHK'da 82(48-128)'du.

Sonuç: Çalışmamızda LH'lerinde sayısal olarak OLP'lerde kontrol ve OSHK olgularına göre istatiksel olarak anlamlı artış izlenmiştir. Literatürde bu durumlarla ilgili çeşitli farklı sonuçlara rastlamak mümkündür. Langerhans hücrelerinin; bu hastalıklardaki yoğunluğunun belirlenmesi, hastalığın patogenezi ve tedavi seçeneklerinin geliştirilebilmesi açısından yol gösterici olabilir.

Anahtar Kelimeler: Oral, Skuamöz Hücreli Karsinom, Liken Planus,Langerhans Hücresi

INTRODUCTION

Oral cavity is a gate of human body. The immune system and microbial flora have balanced contribution that helps to maintain homeostasis of the mucosa (1). Many physical traumas, microbiologic factors, poor oral hygiene, caries, prosthesis and other factors such as nicotine chewing, smoking and alcohol consumption may cause damage on oral mucosa (2) The literature have shown probable relation of oral pathologies with cell-mediated immunity (3).

Dendritic cells are antigen presenting cells that initiate adaptive cellular response (4). Langerhans cells (LCs) are an important member of dendritic cell family presenting antigen to T lymphocytes (4,5). They are playing a role in immunologic response as a defender (6) . After being captured by LCs, antigens are transported to lymph nodes and presented to CD4 -T helper lymphocytes. This process is followed by activation of CD8 -T supressor lymphocytes (7). In oral mucosa, LCs are commonly located in the basal and suprabasal layer of the squamous epithelium (8).

Lichen planus is an immune mediated chronic inflammatory disease generally affects oral mucosa followed by skin, genital mucosa, scalp and nails (9). Oral lichen planus (OLP) is a quite common disease of mucocutaneous region, ranging from 0.5 to 2% frequency (10).

The disease is characterized by degeneration of basal keratinocytes. The process of degeneration is thought to be triggered by antigens caused by trauma, infections, restorative materials...etc (9). The antigens are trapped within epidermis by a plexus of interdigitating LCs, followed by presentation of antigens to T lymphocytes (5). Additionally, Langerhans and mast cells are held responsible for local response and induce lymphocyte migration to subepithelial region (4, 9).

OSCC is the most common carcinoma of oral cavity caused by many etiological factors such as smoking, alcohol, viral agents (HPV...etc). It constitutes approximately 95 % of oral malignancies (11).

Although WHO classified OLP as a precancerous lesion, its' potential transformation to OSCC is still controversial (9,12).

LCs are one of the suggested elements of tumor progression via inapproptiate tumor antigen presentation (5).

MATERIAL AND METHODS

The study was performed at Bezmialem Vakıf University Hospital. It was approved by institutional ethical board with permission number: 5/30 (09.03.2016). The 74 patients sent from Dentistry Clinic to our department between January 2013 to January 2016 were included. Paraffin embedded blocks of 74 patients- 36 OLP, 28 OSCC and 10 normal mucosa as a control group were retrieved from the archieves and appropriate blocks were chosen. After reviewing the slides, 3-micron thick slices were cut and immunohistochemistry was performed by automated Ventana Benchmark XT system, using Langerin protein mouse monoclonal antibody (Cell Marque, Clone 12D6). Appropriate positive control sections were included. After applying Langerin immune stain, positive LCs showed cytoplasmic brown colour. The prepared specimens were evaluated by light microscope and images were captured by digital camera (Nikon Eclipse Ci microscope, Japan). In each case immunohistochemically positive for LCs were counted in areas of $1mm^2$ under x40 magnification by two pathologists. The most stained (hot point), basal and suprabasal areas were chosen for manual counting. Moreover age, gender and localisation were evaluated.

Statistical Analyses: Continuous variables are expressed as mean±SD or median (interquartile range) when appropriate. Categorical variables are expressed as percentages. To compare nonparametric continuous variables, the Kruskal Wallis-test was used. To compare categorical variables, the Chi-square-test was used. The Spearman correlation coefficient were used to determine parametric and nonparametric measure of statistical dependence between two variables. A two-tailed p-values of less than 0.05 were considered to indicate statistical significance. The statistical analyses were performed using software (SPSS 15.0, SPSS Inc, Chicago, Ill).

RESULT

In our study, most of the control biopsies (7/10) and OLPs (31/36) were excised from buccal mucosa. OSCCs were especially located on the tongue (20/28). The gender distribution indicated that control and OLP groups were predominantly female, 60% and 72% respectively, whereas only 42% of OSCCs were female. The age median was 46±17 for control group, 53 ± 12 for OLPs and 61 ± 21 in OSCCs. Langerhans cells were predominantly located in basal and parabasal layers in all groups (Figure 1 ,2, 3). LC density was 87 (57-105) in the control group, 104 (84-143) in OLPs, and 82 (48-128) in OSCCs (Table 1).

Table 1. Langerin positive LCs distribution in groups

(n)	Control (n=10)	OLP (n=36)	OSCC (n=28)
LCs/1 mm^2	87 (57-105)	104 (84-143)	82 (48-128)

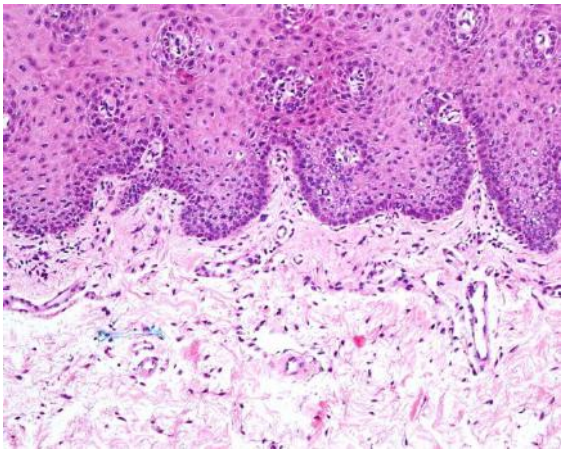

Figure 1a. Control mucosa; Vascularized control tissue from the oral mucosa (HEx100)

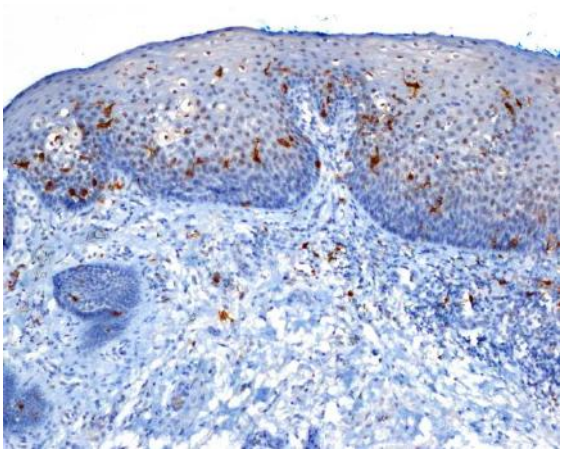

Figure 1b. Control mucosa; Langerin positivity in the control tissue (x100)

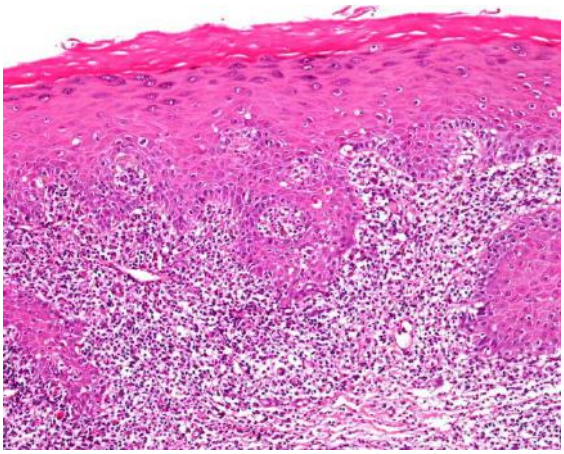

Figure 2a. OLP; Typical histomorphological features of LP (HEx100)

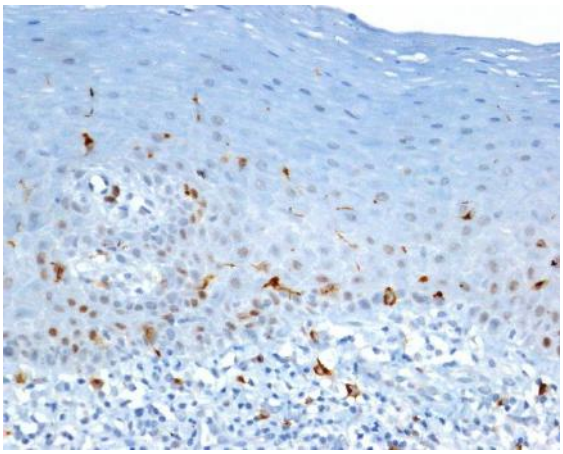

Figure 2b. OLP ; Langerin positivity in OLP (x200)

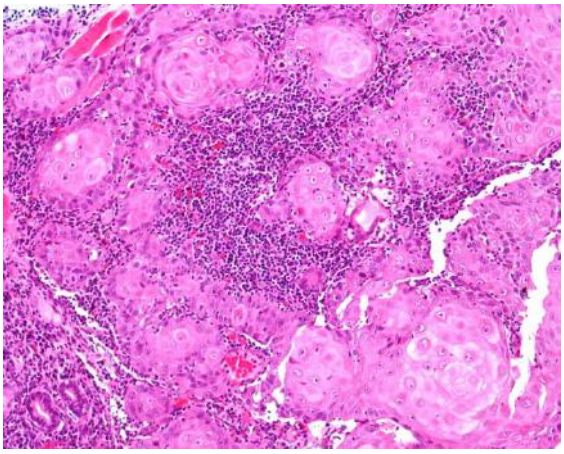

Figure 3a: OSCC; Well-differentiated oral squamous cell carcinoma (HEx200)

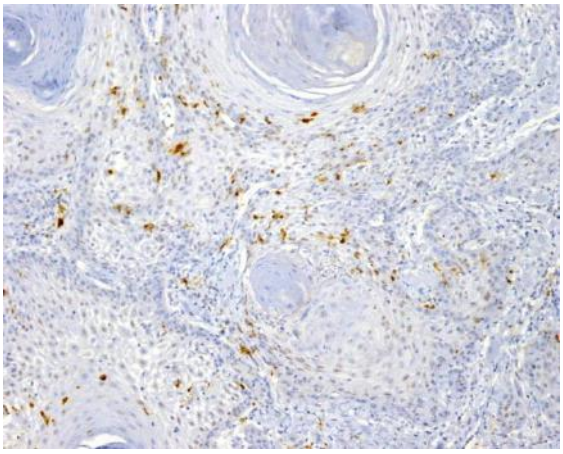

Figure 3b: OSCC; Langerin positivity in well differentiated oral squamous cell carcinoma (x100)

LC density was found significantly higher in OLPs compared to control group and OSCCs. ($p = 0.026$).

According to tumor differentiation; 11 of the patients were well-differentiated, 7 of them were moderately differentiated, and 5 of them were poorly differentiated. 1 of OSCC was basaloid type and 4 of them could not be graded. We have limited OSCC patients for grade groups, statistically there was no correlation between tumor grade and Langerhans cell density for well-differentiated and poorly differentiated tumors In moderately differentiated OSCCs. LC density was significantly higher than other groups. ($p = 0.045$).

Table 2. Langerin positive LCs distribution in OSCC groups

(n)	Well (n=11)	Moderately (n=7)	Poor (n=5)
LHS/1 mm^2	64 (48-94)	130 (86-135)	15 (0-128)

DISCUSSION

LCs were first described in 1868, since then many researchers studied their role on immune system and relationship between diseases (5,13). Oral mucosa was the first described part of the body LCs residing (14). In literature addition to their contribution to self tolerance against commensal microoorganisms, their response to inflammatory conditions (Candida, lichen planus, lichenoid drug reactions, human immunodeficiency virus infection and hairy leukoplakia) and anti-tumor immunity were reported (5).

OLP is a common mucocutaneous disorder. Although the exact pathogenesis has not been clarified yet, considerable number of studies associated the disease with cell-mediated immunity (15). OLP is commonly seen in the fifth decade and female/male ratio is approximately 2-3:1 (16). Our findings were consistent with this data.

There were different methods of evaluation of LCs in literature (17). We preferred $1mm^2$ area to evaluate the Langerin positive LCs, because in our opinion it is easy to applicate and take more reliable results.

In our study the number of LCs in OLPs were significantly higher than control group and OSCCs. Our data correlated with the literature as Maloth et al emphasized in their study. They hypothesized the increase may be related to the change in the regulation of locale immune reaction (3). In epithelial damage mostly epithelial-stromal border is affected where keratinocytic apoptosis seen (7). Kumar et al suggested that LCs have pivotal role as taking antigens from apoptotic cells. This adaptive immune response could explain the increase of LCs (17).

As the other carcinomas, OSCCs has multiple steps as following: initiation, promotion and progression. During this steps immunologic factors have important roles. LCs are proposed as one of the factor responsible for host's inadequate presentation of tumor antigens (13). In literature many studies have showed increase of LCs in OSCCs (4). In our study, LC counts were similar to normal mucosa without considering grade of the tumor. Overall OSCCs had no statistically significant difference for Langerin expression. When grouped according to tumor differentiation, moderately differentiated had significantly higher Langerhans cell density than other groups ($p = 0.045$).

Many studies have showed increase of LCs in OSCC (3, 18, 19, 20). One of them was Maloth et al study where LCs were significantly high. Like previous studies they associated the increase with presentation of tumor antigens by LCs (3).

However, gradual decrease in LCs density from well differentiated to poorly differentiated carcinomas was reported. This was explained by immune suppression caused as a result of anaplastic tumor cell induction. Immune suppression has been implicated in the apoptosis of LCs (3).

On contrary there are also studies showing LCs decrease compared to normal mucosa in OSCCs (4, 21). It has been suggested that this situation may occur as a result of accompanying immune suppressive conditions such as smoking, tobacco chewing, alcohol consumption…etc (22). Unfortunately we didn't have detailed history of patients to compare.

CONCLUSION

Immune system plays an important role in the formation, limitation and progression of diseases. LCs have pivotal role in this system. Our findings for LP are compatible with the literature. OSCCs have controversial results for the number of LCs in different studies. The restriction of our study was to have limited number of patients with limited histories. We need more patients with detailed history to gather more reliable data which would help us to show importance of immune response and discover strategies to enhance immune activity for determining prognosis and regulating treatment.

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RESEARCH ARTICLE

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Risk Factors for Diabetic Polyneuropathy

ABSTRACT

Objective: Diabetes Mellitus is one of the most common metabolic diseases. The most frequent complication of DM is diabetic polyneuropathy. Diabetic polyneuropathy is related to high mortality, morbidity, hospitalization rate and serious level of economic burden. We aimed in this study to determine the risk factors that affect DPN pathology.

Methods: Patients with abnormalities in the nerve conduction study constituted the polyneuropathy group, and patients without abnormalities formed the control group. When the laboratory values of the patients were analyzed, blood tests of 168 of 202 patients were reached. 117 of these patients had PNP and 51 did not have PNP.

Results: In patients with PNP, glycolyzed hba1c ratio and fasting blood sugar were significantly higher than patients without PNP (p<.001).

While HDL rate was lower in patients with PNP than those without PNP (p<0.01), TG/HDL ratio was higher (p<0.05). In patients with PNP, glycolyzed urea (p<0.001) and creatinine (p<0.01) were significantly higher than those without PNP. The serum level of 25(OH) vitamin D was significantly lower in patients with PNP than in patients without PNP (p<0.05). Ferritin was significantly higher in patients with PNP than patients without (p<0 .01).

Conclusions: Knowing and preventing risk factors for diabetic polyneuropathy, we can take a new direction to our treatment approaches and take early measures. Fasting blood sugar and hba1c control, regulation of lipid profile, monitoring of vitamin d and ferritin levels are particularly necessary for protection of polyneuropathy.

Keywords: Diabetic Polyneuropathy, HbA1c, Ferritin, Trigliceride/HDL (Atherogenix Index), 25(OH) Vitamin D

Diyabetik Polinöropati Risk Faktörleri

ÖZET

Amaç: Diyabet Mellitus(DM) en yaygın metabolik hastalıklardan biridir. DM' nin en sık görülen komplikasyonu diyabetik polinöropatidir. Diyabetik polinöropati yüksek mortalite, morbidite, hastaneye yatış oranı ve ciddi ekonomik yük ile ilişkilidir. Biz çalışmada DPN patolojisini etkileyen risk faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: Sinir iletim çalışmasında anormalliği olan hastalar polinöropati grubunu, anormalliği olmayan hastalar kontrol grubunu oluşturdu. Hastaların laboratuvar değerleri incelendiğinde 202 hastanın 168'inin kan testlerine ulaşıldı. Bu hastaların 117'sinde PNP varken, 51'inde PNP yoktu.

Bulgular: PNP olan hastalarda glikolize hba1c oranı, açlık kan şekeri PNP olmayan hastalara göre anlamlı olarak yüksek bulundu (p<.001). PNP' si olan hastalarda HDL oranı PNP'si olamayan hastalara göre düşük saptanırken (p<0.01), TG/HDL oranı daha yüksek saptandı (p<0.05). PNP olan hastalarda glikolize üre (p<0.001) ve kreatinin (p<0.01), PNP olmayan hastalara göre anlamlı olarak yüksek saptandı. PNP olan hastalarda 25(OH) vitamin D düzeyi, PNP olmayan hastalara göre anlamlı olarak düşüktü (p<0.05). PNP olan hastalarda ferritin, olmayan hastalara göre anlamlı olarak daha yüksek saptandı (p<0.01).

Sonuç: Diyabetik polinöropati açısından risk faktörlerinin bilinmesi ve önlenmesi ile tedavi yaklaşımlarımıza yeni bir yön vererek, erken önlemler alabiriz. AKŞ; hba1c kontrolü, lipid profilinin düzenlenmesi, vitamin d ve ferritin düzeylerinin takibi özellikle korunma açısından önemlidir.

Anahtar Kelimeler: Diyabetik Polinöropati, HbA1c, Ferritin, Trigliserid/HDL İndeksi (Aterojenik İndeks), Vitamin D

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INTRODUCTION

Diabetes Mellitus is one of the most common metabolic diseases worldwide seen. The most frequent complication of DM is diabetic neuropathy, especially diabetic polyneuropathy (1). Diabetic polyneuropathy is related to high mortality, morbidity, hospitalization rate and serious level of economic burden (2,3). American Diabetes Association suggests to search for diabetic neuropathy at the time of diagnosis of type 2 DM and five years after the diagnosis of type 1 DM (3,4). EMG, nerve conduction studies can provide evidence before neuropathic symptoms evolve (5).

Diabetic peripheric neuropathy (DPN) is a late phase microvascular complication that evolve in 50% of the patients (6). DPN is related to irreversible structural and functional changes due to demyelinisation, axonal atrophy and decline in regeneration of neurons (7). Although the cause is not fully understood, this event can be explained by endothelial dysfunction, disturbed endoneuronal blood flow, hypoxia and ischemia development in the neurons due to chronic hyperglycemia (6).

Atherosclerosis has also important effect on microvascular and macrovascular complications seen in diabetic patients. Also oxidative stress and inflammation caused by advanced glyco-oxidation end products are also known to contribute to these complications (8,9).

In studies conducted, age, male gender, duration of diabetes, diabetic control are shown to be risk factors for DPN (10). Elevation of fasting blood sugar and HbA1c levels and low vitamin D values have been reported in many studies to be risk factors for development of DPN (9-14).

Risk factors for atherosclerosis; hypertension, smoking, changes in the lipid profile are also shown in studies to be risk factors for DPN. However, there are difference results between the studies (10). We aimed in this study to determine the risk factors that affect DPN pathology. By this way we can take early measures and give a new direction to our treatment approaches.

MATERIAL AND METHODS

Demographic data; including duration of illness and medications of patients with DM diagnosis who applied to Electrophysiology laboratory of Zonguldak Bülent Ecevit University Health Practice and Research Hospital, in between 2016-2019 were recorded retrospectively.

From patients' files glycolyzed HgA1c, fasting blood sugar, TSH, free T4, free T3, lipid profile including serum cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), liver and kidney function tests, 25 (OH) vitamin D serum levels, vitamin b12, folate, ferritin levels were recorded. Electrolyte values, (calcium, magnesium, phosphorus, chlorine, sodium, potassium), hemoglobin, hematocrit, platelet levels were recorded.

Patients underwent standard electrophysiological study. All of the physiological studies were performed with 2 channeled Medelec EMG device. In all of the recordings, superficial electrodes were used. In motor conduction studies, the median, ulnar, peroneal and tibial nerves were stimulated, and compound muscle action potentials (CMAPs), distal latency (DL) and nerve conduction velocities (NCVs) were recorded. Sensory responses were obtained with orthodromic methods. In sensory conduction studies, the median, ulnar and sural nerves were stimulated, and sensory conduction velocities (SCVs), sensory response peak latencies and sensory action potentials (SAPs) were recorded.

Nerve conduction velocities were accepted as abnormal values below 50 m/s in the upper limb and below 40 m/s in the lower limb. Median nerve SAP amplitude below 12 μV, CMAP amplitude below 5 mV and motor DL values above 4.0 ms were accepted as abnormal values. Ulnar nerve SAP amplitude values below 8 μV, CMAP amplitude below 5 mV and motor distal latency above 4.0 ms were accepted as abnormal values.

Posterior tibial nerve CMAP amplitude values below 4 mV, peroneal nerve CMAP amplitude below 2 mV, and sural nerve SAP amplitude below 10 μV were considered as abnormal values.

In cases suggesting polyneuropathy, the presence of polyneuropathy was evaluated according to presence of electrophysiological multiple nerve involvement and presence of pathological findings (decrease in SNAP amplitude, slowing in SNCV, lengthening in DL, decrease in CMAP amplitude).

Patients with abnormalities in the nerve conduction study constituted the polyneuropathy group, and patients without abnormalities formed the control group.

Ethics committee approval was received for this study from the ethics committee of Bulent Ecevit University School of Medicine (Decision No: 2019/09).

Statistical Analysis: Statistical analysis of the research is performed with SPSS 19.0 package program. Descriptive statistics of continuous variables in the study are shown with mean, standard deviation, median, minimum and maximum values; descriptive statistics of categoric variables are shown with frequency and percentage. Independent sampling t-test analysis is used in two groups comparisons of the normally distributed variables. Mann Whitney U test was used in two groups comparisons of the variables those which aren't normally distributed and Chi-square tests were used for categorical variables. For all of the statistical analysis of the research p value under 0,05 was accepted as significant

RESULTS

While polyneuropathy was observed in 131 of 202 patients included in our study, polyneuropathy was not observed in 71 patients. Out of the patients with polyneuropathy, 68 were female and 63 were male, 41 of the patients without polyneuropathy were female and 30 were male. The average age of patients without PNP was determined as 57.48; the mean age of patients with PNP was determined as 64.34. The average age of those with PNP was significantly higher than those without PNP ($p < 0.001$) (Table 1). The mean diabetes duration was found to be 14.30±10.78 in patients with PNP and the diabetes duration was found to be 12.42±5.69 in patients without PNP. Electrophysiological examination revealed 103 sensory-predominant sensorimotor (78.6%), 21 sensory (16%), 4 motor (3.1%), 3 motor-predominat sensorimotor (2.3%) polyneuropathy in 131 patients. 80 patients had axonal (61.1%), 2 had demyelinating (1.5%), and 49 had mixed type (37.4%) polyneuropathy.

Table 1. Demographical parameters of patients with and without diabetic polyneuropathy

	N=202	Male	Female	Age
With DPNP	131	63	68	64.34
Without DPNP	71	41	30	57.48

DPNP: Diabetic polyneuropathy

When the laboratuary values of the patients were analyzed, blood tests of 168 of 202 patients were reached. 117 of these patients had PNP and 51 did not have PNP. In patients with PNP, glycolyzed hba1c ratio and fasting blood sugar were significantly higher than patients without PNP. ($p<.001$) While HDL rate was lower in patients with PNP than those without PNP ($p < 0.01$), TG / HDL ratio was higher ($p < 0.05$). In patients with PNP, glycolyzed urea ($p < 0.001$) and creatinine ($p < 0.01$) were significantly higher than those without PNP. The serum level of 25 (OH) vitamin D was significantly lower in patients with PNP than in patients without PNP ($p < 0.05$). Ferritin was significantly higher in patients with PNP than patients without ($P < 0.01$).

Table 2. Laboratory characteristics of patients with and without diabetic polyneuropathy

	With DPNP	Without DPNP	P value
HbA1c(%)	8.81 ± 12.02	8.39 ± 2.07	**<0.001**
Fasting blood glucose(mg/dl)	149.02 ± 74.001	188.48 ± 85.676	**<0.001**
Total cholesterol (mg/dl)	199.14 ± 52.339	194.21 ± 61.583	0.198
LDL-cholesterol (mg/dl)	119.21 ± 37.869	115.52 ± 49.113	0.361
Triglycerides(mg/dl)	157.98 ± 49.11	189.50 ± 81.69	0.307
HDL-cholesterol (mg/dl)	55.9 ± 24.23	47.08 ± 31.05	**0.001**
Trigliserit/HDL (AIP)	3.35 ± 2.41	4.69 ± 4.82	**0.035**
Cholesterol/HDL	4.00 ± 1.41	4.47 ± 1.47	0.099
25(OH) Vitamin D	24.7 ± 13.37	18.44 ± 9.26	**0.009**
Ferritin	44.27±32.87	78.90 ±67.81	**<0.01**
Ure	34.6 ± 14.94	48.22 ± 33.12	**<0.001**
Creatinin	1.45 ± 4.70	1.61 ± 5.07	**0.001**
Calsiyum	9.62 ± 0.5	9.44 ± 0.9	0.326
Magnesium	1.94 ± 0.295	1.93 ± 0.292	0.923
Potassium	4.49 ± 0.38	4.56 ± 0.56	0.148
Sodium	131.82 ± 31.94	131.82 ± 31.94	0.405

DNPN: Diabetic Polyneuropathy; LDL: low-density lipoprotein; HDL: high-density lipoprotein, AIP: atherogenic index of plasma

DISCUSSION

Diabetic Neuropathy is considered as one of the most common microvascular complications of both type 1 and 2 DM (13). The relationship between diabetes mellitus and neuropathy is clear.

As the duration of diabetes extends, the incidence of neuropathy increases and affects more than 50% of patients (15).

In our research, diabetic PNP was detected in 131 of 200 patients. The most common form of diabetic polyneuropathy is distal, symmetrical, sensory-predominant sensorimotor and axonal involvement (13,16). In our study, the frequency of sensory-predominant sensorimotor axonal type polyneuropathy was high. In our study, similar to the studies performed, the frequency of diabetic polyneuropathy was increasing with age (15,17,18). We think that DPN should be investigated and screened especially in elderly diabetic patients. Patients with polyneuropathy were mostly female patients, but difference was not statistically

significant. Booya et al and Tamer et al showed neuropathy more commonly in diabetic male patients (19,20). However Kaplan et al, Barbaros et al and Perkins et al did not show a significant difference between sex, similar to our study (10,21,22). In our study, there was a significant relationship between increased fasting blood sugar and hb a1c levels and diabetic PNP. Studies have shown that diabetic PNP progression and severity are closely related to glycemic control.

The level of glycosylated hemoglobin (HbA1c) is a good indicator of blood glucose control over the past three months and is considered the "gold standard" in the evaluation of long-term glycemic control in diabetic patients (9,12,13). [Diabetic peripheral neuropathy is thought to develop due to oxidative stress and inflammation due to nerve dysfunction and cell death. Hyperglycemia causes dysregulation of the metabolic pathway, causing imbalance in the mitochondrial redox state and releasing mitochondrial and cytosolic reactive oxygen particles. This causes axonal injury and neuropathy in the peripheral nerves (23,24). We suggest that keeping glucose levels, especially HbA1c under control is an important factor in preventing diabetic polynoropathy.

Atherosclerosis also has an important effect on microvascular and macrovascular complications in diabetic patients, for which dyslipidemia is a risk factor (25). In studies, especially increase in TG and decrease in HDL levels were held responsible. Atherogenic index of plasma (AIP) is calculated as the the ratio between the triglyceride value and high density lipoprotein value (mg/dL). (TG/ HDL-C) AIP is a major risk factor for cardiovascular diseases and metabolic syndrome (26). The high TG / HDL ratio causes endothelial dysfunction, impaired endoneuronal blood flow, nerve hypoxia and ischemia, and consequently neuropathy. Miric et al. showed that AIP was higher in patients with 2 DM patients who developed neuropathy (6). In their study, Li et al. stated that the incidence of diabetic neuropathy and metabolic syndrome is higher in patients with elevated AIP (27). In our study, the risk of developing diabetic PNP was higher in patients with low HDL and high AIP index. This study is the first study to show the relationship between serum atherogenicity index and diabetic polyneuropathy.

In studies conducted, Vitamin D levels are observed to be low in DM patients (14,28). Studies showed that Vitamin D deficiency has an effect and an important role in the development and severity of DPN (1,14). In our study, 25 (OH) vitamin D serum levels were significantly lower in patients with PNP than in patients without PNP. 25 (OH) vitamin D is the major circulating form of Vitamin D. There are several studies on how low vitamin D levels cause DPN. Vitamin D, especially the D3 form, has been shown to reduce demyelination in animal studies (1, 29). Demyelination increases in nerves with low vitamin D. In animal studies, it has been shown that low vitamin D causes a decrease in nerve growth factor (neurotropin) level, disrupts neuronal calcium homeostasis and accordingly increases nerve damage (30). As a result, vitamin D deficiency impairs nociceptor functions, increases nerve damage, and lowers the pain threshold. In order to prevent PNP development in patients with diabetes, vitamin D values should be followed and supplemented in their deficiency.

In our study, hemoglobine, platelet, white blood cells (WBC) values were determined as normal. Serum ferritin level was found to be significantly higher in patients with diabetic polyneuropathy. In studies performed, high ferritin levels were found to be related to increased triglyceride and glucose levels (31). Elevated ferritin level is associated with type 2 diabetes; however, the mechanism underlying this relationship is uncertain (32). In a study by El-Tagui et al; with patients with beta thalassemia, peripheral neuropathy especially with motor impairment was observed in patients with high ferritin levels (33). They thought that this might be due to the increase in iron oxidative stress to the height of the iron. In the study conducted by Bayhan et al, neuropathy was not observed in patients with high ferritin levels (34). Although sensory nerves were not affected, motor nerve studies revealed only prolongation of peroneal nerve latency. Studies are needed regarding the relationship between elevated ferritin levels and polyneuropathy.

CONCLUSISON

Diabetic polyneuropathy is associated with high mortality, morbidity, hospitalization rate and serious economic burden. Knowing and preventing risk factors for diabetic polyneuropathy, we can take a new direction to our treatment approaches and take early measures. Fasting blood sugar and hba1c control, regulation of lipid profile, monitoring of vitamin d and ferritin levels are particularly necessary for protection of polyneuropathy.

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RESEARCH ARTICLE

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Evaluation of Anxiety and Depression Levels in Children with Chest Pain Using a Standardized Scale

ABSTRACT

Objective: Chest pain in children may be caused by psychogenic disorders. We aimed to evaluate the relationship between chest pain and the levels of anxiety and depression in children.

Methods: Children admitted to a pediatric cardiology unit with the complaint of chest pain and healthy controls were included. History of the cases, physical examination findings, and the results of biochemical tests, electrocardiogram, 24-h Holter monitoring and echocardiographic examination were recorded. The group with chest pain and the control group were compared using the Revised Child Anxiety and Depression Scale-Child Version.

Results: A total of 100 children with chest pain [46 (46.0%) boys and 54 (54.0%) girls; mean age, 12.5 years] and 55 healthy controls [25 (45.5%) boys and 30 (54.5%) girls; mean age, 13.1 years] were included into the study. The psychiatric scale was applied to children aged 8-18 years (93 cases with chest pain and 54 control subjects). The scores of all the subscales were statistically higher in the group with chest pain than in the control group (generalized anxiety disorder: 7.39±3.4 versus 5.48±2.6, P=0.001; major depressive disorder: 8.84±6.1 versus 6.27±4.7, P=0.009; panic disorder: 9.07±6.1 versus 4.92±4.7, P=0.000; separation anxiety disorder: 5.53±3.7 versus 3.77±3.3, P=0.005; obsessive-compulsive disorder: 6.48±3.6 versus 4.74±3.3, P=0.005; social anxiety disorder: 10.1±5.5 versus 7.81±4.9, P=0.010).

Conclusions: There seems to be an association between increased levels of anxiety and depression disorders and chest pain in children. A comprehensive psychiatric assessment should be carried out in pediatric chest pain cases in addition to some basic cardiac evaluations.

Keywords: Anxiety, Chest Pain, Children, Depression.

Göğüs Ağrısı Olan Çocuklarda Standart Bir Ölçek Kullanılarak Anksiyete ve Depresyon Düzeylerinin Araştırılması

ÖZET

Amaç: Çocukluk çağında görülen göğüs ağrıları psikojenik kökenli olabilir. Bu çalışmada çocuklarda görülen göğüs ağrısı ile anksiyete ve depresyon düzeyleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Pediatrik kardiyoloji bölümüne göğüs ağrısı şikayeti ile başvuran olgular ve kontrol grubunu oluşturan sağlıklı çocuklar çalışmaya dahil edildi. Hastaların hikayesi, fizik muayene bulguları ile biyokimyasal testlerin, elektrokardiyografik incelemenin, 24-saatlik Holter monitörizasyonunun ve ekokardiyografik incelemenin sonuçları kaydedildi. Göğüs ağrısı olan grup ile kontrol grubu, Çocuk Anksiyete ve Depresyon Ölçeği-Yenilenmiş ölçeği kullanılarak karşılaştırıldı.

Bulgular: Göğüs ağrısı olan toplam 100 çocuk [46 (%46,0) erkek ve 54 (%54,0) kız; ortalama yaş: 12,5 yıl] ve 55 sağlıklı kontrol [25 (%45,5) erkek ve 30 (%54,5) kız; ortalama yaş: 13,1 yıl] çalışmaya dahil edildi. Psikiyatrik ölçek ile değerlendirme 8-18 yaş arasındaki çocuklara (göğüs ağrısı grubundaki 93 hastaya ve kontrol grubundaki 54 olguya) uygulandı. Göğüs ağrısı grubunda tüm alt ölçek skorları, kontrol grubuna göre anlamlı olarak daha yüksek bulundu (yaygın anksiyete bozukluğu: 7.39±3.4 ve 5.48±2.6, P=0.001; majör depresif bozukluk: 8.84±6.1 ve 6.27±4.7, P=0.009; panik bozukluk: 9.07±6.1 ve 4.92±4.7, P=0.000; ayrılık anksiyetesi bozukluğu: 5.53±3.7 ve 3.77±3.3, P=0.005; obsesif-kompülsif bozukluk: 6.48±3.6 ve 4.74±3.3, P=0.005; sosyal anksiyete bozukluğu: 10.1±5.5 ve 7.81±4.9, P=0.010).

Sonuç: Bu sonuçlar, çocukluk çağında artmış anksiyete ve depresyon düzeyleri ile göğüs ağrısı arasındaki ilişkinin varlığına işaret etmektedir. Göğüs ağrısı olan çocuklarda bazı temel kardiyak incelemelere ek olarak kapsamlı bir psikiyatrik değerlendirme yapılması uygundur.

Anahtar Kelimeler: Anksiyete, Göğüs Ağrısı, Çocuk, Depresyon

INTRODUCTION

Chest pain in children and adolescents is a common cause of admission to emergency, general pediatrics and pediatric cardiology departments. In contrast to adult population, chest pain secondary to cardiac causes is rare during childhood. In the routine clinical practice, however, further evaluations directed at identifying some severe and potentially fatal cardiac disorders may be carried out unnecessarily in a considerable ratio of children with non-cardiac etiologies (1).

Chest pain with cardiac causes accounts for 0.5-5% of all chest pain cases in children (1,2). The majority of pediatric chest pain occurs idiopathically or is related to non-cardiac causes such as musculoskeletal, pulmonary, gastrointestinal or psychogenic disorders. These non-cardiac causes are usually benign in nature and are self-limiting (3).

A detailed history, physical examination and electrocardiographic evaluation will enable an easy exclusion of cardiac causes in most of the affected children, and no further examination will be needed. However, in routine practice, almost all of these children are referred to a pediatric cardiology unit which increases the anxiety levels of both the children and the parents. We aimed to evaluate the association between the levels of various anxiety and depression disorders and chest pain in children using a standardized psychiatric scale.

MATERIAL AND METHODS

Study Groups: This study included 100 children who admitted to a pediatric cardiology unit between September 2019 and January 2020 and 55 healthy controls without a known chronic disease. The Revised Child Anxiety and Depression Scale-Child Version (RCADS-CV) was applied to 93 cases with chest pain, and to 54 children in the control group.

Firstly, the etiology of the pain was evaluated. Pain characteristics including the presence of palpitations, relationship of the pain with exercise and symptoms of gastrointestinal reflux were recorded in the group with chest pain, and the scores of RCADS-CV subscales were compared between the patient and control groups.

Written informed consent from the parents and written assent from the children/adolescents were obtained before beginning the evaluation. The Local Ethical Committee of our Institute gave approval for the study, which was performed in accordance with the Declaration of Helsinki (Protocol number of ethical approval: 158; 22.05.2020).

Electrocardiographic Examination: A resting, lying 12-lead electrocardiogram (ECG) using Nihon Kohden ECG machine (speed, 25 mm/sec; acquisition sensitivity, 10 mm/mV ± 2%) was carried out in all the cases with chest pain, and the heart rate, QTc, and P-R intervals were recorded.

Echocardiographic Examination: Echocardiographic examination was performed in all the cases in the patient group. It was carried out by a pediatric cardiologist using Philips Affiniti 70C Ultrsasound Machine (Philips Healthcare, Andover, USA). The ejection fraction, shortening fraction, left ventricular end-diastolic diameter, interventricular septum and left ventricular posterior wall thickness were measured by M-mode echocardiography in all the patients. Left and right ventricular outflow obstructions were evaluated using long- and short-axis images.

Electrocardiographic Holter Monitoring: When 24-h Holter monitoring was thought to be indicated, Holter monitor electrodes were placed by a nurse in the pediatric cardiology department. Holter rhythms were recorded by Biomedical Instruments Holter Recorder.

Evaluation of Anxiety and Depression Levels: The RCADS-CV includes 47 items, and consists of six subscales (generalized anxiety, major depression, panic disorder, separation anxiety, obsessive compulsive disorder and social anxiety disorder). The inter-scale reliability of RCADS-CV is excellent with a Cronbach's alpha reliability coefficient of 0.95, and coefficients for RCADS-CV subscales range from 0.75 to 0.86, demonstrating good internal consistency (4). The mean ± standard deviation scores of each subscale in various groups were calculated and compared.

Statistical Analysis: The Statistical Package for the Social Sciences 22.0 (IBM SPSS 22) program was used for the statistical analysis. Continuous variables were presented as the mean ± standard deviation, whereas categorical variables were presented as the number (percentages) of cases. In the comparison of numerical variables, Student's t test and ANOVA test were used. A *P* value <0.05 was considered as statistically significant.

RESULTS

Among the 100 children with chest pain, 46 (46.0%) were male and 54 (54.0%) were female. In the control group with 54 children, 25 (45.5%) were male and 30 (54.5%) were female. As RCADS-CV is applicable only to children older than 8 years, it was carried out in 93 cases with chest pain and 54 healthy controls.

Table 1 shows the underlying disorders linked to chest pain and the characteristics of pain in the patient group. Altogether, 58 (58%) cases described the pain as sharp, 19 (19%) as squeezing, whereas 23 (23%) patients could not define the character of the pain. The history of 10 children (10%) revealed the presence of chronic chest pain. Six (6%) cases were found to have an underlying cardiac disorder including minimal mitral insufficiency + mild mitral valve prolapse (n=2), hypertrophic cardiomyopathy (n=1), restrictive

cardiomyopathy (n=1), mitral valve prolapse (n=1), grade 1 pulmonary insufficiency + trace aortic insufficiency (n=1). Electrocardiographic examination revealed mild abnormalities (including sinus arrhythmia, sinus tachycardia and right bundle branch block) in 8 (8%) cases. Holter monitoring was carried out in 12 patients, and displayed no rhythm disorder which may cause chest pain in any of the cases.

Table 1. Underlying disorders and pain characteristics in cases with chest pain (n = 100).

	Pain description n (%)			Pain with exercise n (%)	Palpitations n (%)	GER n (%)
	Sharp	**Squeezing**	**Undefined**			
Idiopathic (n=62)	37 (59.6)	12 (19.3)	13 (20.9)	21 (33.8)	40 (64.5)	18 (29.0)
Musculoskeletal (n=15)	7 (46.7)	2 (13.3)	6 (40.0)	10 (66.7)	8 (53.3)	4 (26.7)
Psychogenic (n=8)	5 (62.5)	2 (25.0)	1 (12.5)	4 (50.0)	4 (50.0)	4 (50.0)
Cardiac (n=6)	3 (50.0)	2 (33.3)	1 (16.7)	5 (83.3)	5 (83.3)	4 (66.7)
Gastrointestinal (n=5)	3 (60.0)	1 (20.0)	1 (20.0)	1 (20.0)	5 (100.0)	2 (40.0)
Respiratory (n=3)	3 (100.0)	0	0	2 (66.7)	2 (66.7)	0
Other (n=1)	0	0	1 (100.0)	0	1 (100.0)	0
Total number (%)	58 (58.0)	19 (19.0)	23(23.0)	43 (43.0)	65 (65.0)	36 (36.0)

GER = gastroesophageal reflux.

Gastrointestinal disorders were identified in 5 (5%) cases. They included gastritis (n=2), inflammatory bowel disorder (n=1), Celiac disease (n=1) and constipation (n=1). However, detailed history suggested mild gastrointestinal reflux in 32 (32%) cases. In the comparison of anxiety and depression levels using the RCADS-CV, scores of the patient group were found to be statistically higher than those of the control group in all the subscales (Table 2).

Table 2. Anxiety and depression scores in patient and control groups.

	Chest pain (n = 93)	Control (n = 54)		
	Mean ± SD	Mean ± SD	***t***	***P***
Generalized anxiety disorder	7.39 ± 3.4	5.48 ± 2.6	3.485	0.001*
Major depressive disorder	8.84 ± 6.1	6.27 ± 4.7	2.643	0.009*
Panic disorder	9.07 ± 6.1	4.92 ± 4.7	4.292	0.000*
Separation anxiety disorder	5.53 ± 3.7	3.77 ± 3.3	2.881	0.005*
Obsessive compulsive disorder	6.48 ± 3.6	4.74 ± 3.3	2.886	0.005*
Social anxiety disorder	10.10 ± 5.5	7.81 ± 4.9	2.606	0.010*

SD = standard deviation.
*Significant at P < 0.05.

In the comparison of male and female subjects with chest pain, girls had statistically higher mean scores of major depression, panic disorder, obsessive compulsive disorder and social anxiety disorder, whereas scores of generalized anxiety disorder and separation disorder were not significantly different between girls and boys with chest pain (Table 3).

Table 3. Anxiety and depression scores according to sex in cases with chest pain.

	Male (n = 43)	Female (n = 50)		
	Mean ± SD	Mean ± SD	***t***	***P***
Generalized anxiety disorder	6.83 ± 3.2	7.88 ± 3.6	-1.149	0.151
Major depressive disorder	7.23 ± 5.3	10.20 ± 6.5	-2.402	0.018*
Panic disorder	6.79 ± 4.9	11.00 ± 6.3	-3.554	0.001*
Separation anxiety disorder	5.46 ± 3.2	5.60 ± 4.1	-0.174	0.862
Obsessive compulsive disorder	5.62 ± 3.0	7.22 ± 3.8	-2.166	0.033*
Social anxiety disorder	8.37 ± 4.8	11.70 ± 5.7	-3.055	0.003*

SD = standard deviation.
*Significant at P < 0.05.

When children with chest pain were stratified into two groups according to their age, cases aged 12 years or older were observed to have significantly higher scores in the subscales of generalized anxiety disorder, major depression, panic disorder, whereas the mean score of separation anxiety was higher in children younger than 12 years.

No difference was observed regarding the scores of obsessive compulsive disorder and social anxiety between the two groups (Table 4).

Table 4. Anxiety and depression scores according to age in cases with chest pain.

	≥12 years (n = 57)	<12 years (n = 36)		
	Mean ± SD	Mean ± SD	***t***	***P***
Generalized anxiety disorder	8.12 ± 3.4	6.25 ± 3.2	2.606	0.011*
Major depressive disorder	10.10 ± 6.4	6.80 ± 5.1	2.617	0.010*
Panic disorder	10.80 ± 6.0	6.22 ± 5.0	3.843	0.000*
Separation anxiety disorder	4.71 ± 2.9	6.83 ± 4.3	-2.771	0.007*
Obsessive compulsive disorder	7.00 ± 3.7	5.66 ± 3.2	1.757	0.082
Social anxiety disorder	10.50 ± 6.0	9.61 ± 4.7	0.800	0.426

SD = standard deviation.
*Significant at P < 0.05.

Among the children with chest pain, those reporting palpitations among the admission complaints had higher scores of panic disorder than the cases without palpitation, whereas no difference was observed regarding the scores of other subscales (Table 5).

Table 5. Anxiety and depression scores according to the presence or absence of palpitations in cases with chest pain.

	Palpitations (n = 60)	No palpitations (n = 33)		
	Mean ± SD	Mean ± SD	***t***	***P***
Generalized anxiety disorder	7.66 ± 3.5	6.90 ± 3.4	1.004	0.318
Major depressive disorder	9.63 ± 6.4	7.42 ± 5.5	1.667	0.099
Panic disorder	10.40 ± 6.6	6.60 ± 4.0	3.020	0.003*
Separation anxiety disorder	5.05 ± 3.8	6.42 ± 3.2	-1.727	0.088
Obsessive compulsive disorder	6.86 ± 3.7	5.78 ± 3.2	1.388	0.169
Social anxiety disorder	10.50 ± 5.3	9.60 ± 6.0	0.753	0.454

SD = standard deviation.
*Significant at P < 0.05.

DISCUSSION

The findings of this study suggest that chest pain in children and adolescents is associated with increased levels of anxiety and depression disorders. In the modern era, psychiatric disorders in children are considered to occur more frequently due to some conditions such as weakened family ties by technology, competition at school, expectations of success from the social environment, putting too much pressure on children and less natural living environments (5,6).

Chest pain is the second most common cause of admission to pediatric cardiology clinics after heart murmurs. The etiology of chest pain in pediatrics is broad, and only a minority of the cases are due to an underlying cardiac pathology (1-3,5-7). In the present study, 6% of the children with chest pain had a cardiac disorder demonstrated by echocardiographic examination (1-3,5), a finding consistent with the literature.

The character of chest pain in children has been mostly reported as sharp in nature (5,7). Among our cases, 58% had sharp pain. In addition, 7-45% of children with chest pain may have the pain for longer than 6 months (8,9). The percentage of chronic chest pain was 10% among our patients. Chest pain especially of musculoskeletal origin tends to recur in children with rapid growth and development.

An electrocardiographic examination is recommended in all children with chest pain. It is cheap and is easily obtained at almost every primary health facility. In addition, primary care physicians can be reassured that most cardiac pathologies can be reliably excluded when the patient's history, physical examination, and ECG are normal.

In the study of Selbst et al. including 191 children with chest pain, 16% of the cases were found to have an abnormality on ECG examination (8). We identified mild ECG abnormalities in 8% of our patients with chest pain, however, the majority of these abnormalities were thought not be related to chest pain. Among the abnormal electrocardiographic findings suggesting a cardiac cause for chest pain are ventricular hypertrophy, high-grade atrioventricular block, pathologic ST segment or T-wave changes, ventricular or atrial ectopy, low QRS voltages, PR-segment depression, or a prolonged QTc >470 ms (10).

Approximately 1-8% of pediatric chest pain cases can be attributed to gastrointestinal disorders including gastroesophageal reflux, esophagitis, gastritis, peptic ulcer and constipation (4,11). Gastroesophageal reflux can cause retrosternal chest pain which may be aggravated by eating or by lying down in supine position. We identified a gastrointestinal disorder that may be associated with chest pain in 5% of the cases although a detailed history revealed the presence of mild gastrointestinal reflux in 32 (32%) cases.

We found the mean scores of all the subscales constituting RCADS-CV to be significantly higher in children with chest pain than in the control group. Similarly, in a recent study including 76 children aged 8-18 years who had chest pain without a cardiac etiology or any other organic cause of chest pain, Kenar et al. have demonstrated non-cardiac chest pain in children and adolescents to be associated with increased levels of anxiety (6).

Chest pain may be a presenting symptom of some psychiatric disorders. However, in the majority of the affected cases, it may not be easy to differentiate whether the anxiety disorder causes the pain or chest pain is the cause of elevated anxiety levels. Chest pain may not solely cause increased anxiety levels in the affected children, but also cause their parents to become stressful. We are in the opinion that although non-cardiac chest pain may have significantly contributed to higher anxiety scores in our patients, referral to a pediatric cardiology unit may also have increased their anxiety levels. In fact, most of the cardiac pathologies associated with chest pain can be reliably excluded with the history, physical examination and an ECG by a primary care physician or a pediatrician. Informing and reassuring the child and the parents will decrease their anxiety levels considerably in most instances.

We found the scores of the subscales major depression, panic disorder, obsessive compulsive disorder and social phobia higher in girls with chest pain than in boys. Selbst et al. have also found psychogenic chest pain to be more common in girls than in boys (9), whereas Irdem et al. have reported a higher prevalence of psychosomatic symptoms in girls although the difference was statistically not significant (5). In fact, almost all anxiety subtypes and depression disorders have been reported to be more common in girls in the general population (12,13).

In a clinical study, children and adolescents with non-cardiac chest pain aged 7-18 years have been found to show higher levels of anxiety, anxiety sensitivity and physiological arousal than children with benign cardiac murmurs (14). Another study including children and adolescents with non-cardiac chest pain revealed a high frequency (56%) of anxiety disorders in cases with chest pain although they had rarely depressive symptoms (15). Garber et al. have reported that 10% of 540 students with a grade range of 2-12 were bothered by chest pain within the last 2 weeks (16). In another study, 4% of high school students reported experiencing chest pain at least weekly throughout the past 12 months (17). In the study of Tunaoglu et al., a psychiatric interview was conducted to 74 children with chest pain, and 55 (74.3%) were found to have a pathologic symptomatology including anxiety, conversion disorder, depression, somatization disorder, avoidance disorder and behaviour disorders (18).

We found the anxiety and depression scores in the subscales of generalized anxiety disorder, major depression and panic disorder to be statistically higher in children aged 12 years or older than those younger than 12 years. Epidemiologic data indicate that the frequency of anxiety and depression disorders shows a tendency to increase following the onset of puberty (12,19). Our finding of significantly higher anxiety and depression scores in half of the subscales in children aged 12 years or older may at least partially be explained by physiological changes related to puberty.

The sensation of palpitations may activate the sympathetic nervous system, and cause panic disorders. Among the patients with chest pain, we found higher scores of panic disorder in children with palpitations, whereas there was no difference regarding other subscales between patients with and without palpitations.

Although we included a moderate number of children with chest pain and used a standardized scale to evaluate the anxiety and depression levels in affected cases, our study has some limitations. Firstly, it is a cross-sectional study, and we cannot establish a cause-and-effect relationship. Longitudinal studies are needed to conclude precisely whether anxiety and depression disorders cause chest pain or chest pain itself increases anxiety and depression levels. Secondly, we used self-evaluation scales for the determination of anxiety and depression levels. Some structured clinical interviews would probably enable a more accurate assessment in subjects with chest pain. Lastly, cases included in our study were seen in a tertiary health care center and therefore do not reflect the community.

In conclusion, chest pain in children and adolescents seems to be associated with increased levels of anxiety and depression. A comprehensive psychiatric evaluation may help to identify a possible underlying disorder in pediatric chest pain cases. Psychogenic disorders may constitute a higher percentage of “idiopathic” non-cardiac chest pain than previously thought. Large-scale studies may enable to assess the contribution of increased anxiety levels to chest pain, particularly in adolescents.

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RESEARCH ARTICLE

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Knowledge and Attitudes of Resident Physicians about Adverse Drug Reactions

ABSTRACT

Objective: WHO reported to all healthcare providers in its universal message that thousands of patients' lives could be saved by reporting adverse drug reactions (ADRs). In this study, we aimed to evaluate the knowledge levels and attitudes of the resident physicians about ADRs and pharmacovigilance in our university hospital.

Methods: This prospective study was performed by a questionnaire form consisted of 14 questions on 88 resident physicians who accepted to participate the study in Harran University Hospital. The study was started after takening the approval of Harran University Faculty of Medicine Ethics Committee. The results of the questionnaire were evaluated by using SPSS 18.0 package program by frequency and percentage tests.

Results: The exact definition of ADRs is correctly marked by 51.1% of doctors. Most of the physicians (69.3%) stated that they had never do ADR reporting. The rate of the participants who think that it is not the responsibility of the healthcare professionals to make ADR reporting is 9.1%. It was observed that only 6.8% of the physicians received professional information or training on ADR reporting. It was expressed by 72.7% of physicians that ADR is a serious problem in Turkey.

Conclusions: This study showed that the level of knowledge and attitude of resident physicians working in our hospital about ADR reporting was not sufficient. We believe that it is important to raise awareness among the healthcare professionals about the ADR reporting and the situation can be improved by effective and periodical training methods.

Keywords: Adverse Drug Reaction, Attitude, Knowledge, Physician.

Asistan Hekimlerin Olumsuz İlaç Reaksiyonları Konusundaki Bilgi ve Tutumları

ÖZET

Amaç: DSÖ, evrensel mesajında tüm sağlık hizmeti sağlayıcılarına, Advers İlaç Reaksiyonlarının (AİR) raporlanması sayesinde binlerce hastanın hayatının kurtarılabileceğini bildirmiştir. Bu çalışmada üniversite hastanemizdeki asistan hekimlerin AİR ve farmakovijilans konusundaki bilgi düzeylerini ve tutumlarını değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu prospektif çalışma, Harran Üniversitesi Hastanesi'nde çalışmaya katılmayı kabul eden 88 asistan hekim üzerinde 14 sorudan oluşan bir anket formuyla gerçekleştirildi. Çalışmaya Harran Üniversitesi Tıp Fakültesi Etik Kurulu onayının alınmasından sonra başlandı. Anketin sonuçları SPSS 18.0 paket programı kullanılarak frekans ve yüzde testleri ile değerlendirildi.

Bulgular: AİR'lerin kesin tanımı doktorların %51,1'i tarafından doğru bir şekilde işaretlenmiştir. Hekimlerin çoğu (%69,3) hiçbir zaman AİR raporlaması yapmadığını belirtmiştir. AİR raporlaması yapmanın sağlık profesyonellerinin sorumluluğu olmadığını düşünen katılımcıların oranı %9,1'dir. Hekimlerin sadece %6,8'inin AİR raporlaması hakkında mesleki bilgi veya eğitim aldığı gözlemlenmiştir. Hekimlerin %72,7'si Türkiye'de AİR'in ciddi bir sorun olduğunu düşünmektedir.

Sonuç: Bu çalışma hastanemizde çalışan asistanların AİR raporlaması konusundaki bilgi ve tutum düzeylerinin yeterli olmadığını göstermiştir. AİR'lerin raporlanması konusunda sağlık uzmanları arasında farkındalığın artırılmasının önemli olduğuna ve durumun etkili ve periyodik eğitim yöntemleriyle iyileştirilebileceğine inanıyoruz.

Anahtar Kelimeler: Advres İlaç Reaksiyonu, Tutum, Bilgi, Hekim

INTRODUCTION

A side effect is described as any undesirable effect of a pharmaceutical product at normally doses, related to the pharmacological properties of the drug. Any symptoms or disease, including an abnormal laboratory finding related to the use of drugs or not, may be considered an adverse event (1, 2).

ADRs are harmful, undesirable reactions that occur at doses, normally used against drugs and classified as serious and non-serious. Especially in elderly, inappropriate drug prescribing is one of the most common reasons for the development of ADRs (3).

WHO reported to all healthcare providers in its universal message that thousands of patients' lives could be saved by reporting ADRs (2).

In clinical trials, products can be explored in a limited number of selected populations. But, after the release of drugs, up to millions of people will be used and people with different diseases will be exposed to these new products. Additionally, some special groups like children elderly and pregnant women are excluded from clinical trials, since it's thought not to be ethical. Whether drugs are safe in these groups cannot be established until they are released (4, 5). For this reason, rare side effects, side effects that can be seen as a result of chronic exposure and also many drug-drug interactions may only be detected after the drug is released (5, 6).

It is known that serious health problems and hospitalization rates are increasing due to ADRs and therefore the ADRs are considered as an important public health issue. It is reported that ADRs constitute approximately 6.5% of all hospital admissions and 15% of ADRs develop in patients who are hospitalized and treated. In the United States in 0.32% of all hospitalized patients fatal adverse drug reactions being expected (7, 8).

According to Turkey Pharmacovigilance Center (TPC), the rate of ADR per year was 1.5 for one million people in 2005, while it increased to 32.1 in 2013 (9). The percentage of patients reported an ADR during hospitalization has been ranged between 1.5- 35 % in recent studies (10).

Against the chance of side effects due to drug use, TPC is developing protective measures in Turkey. By this way mortality and morbidity rates due to preventable events can be reduced. ADR reporting is one of the main data sources of TPC (11).

Reporting of ADRs can be done by spontaneously and accumulated. Spontaneous reporting is used in many countries to improve pharmacovigilance. Spontaneous ADR reporting aims to improve the system of recognition of early signals for drug toxicity not previously recognized (12, 13).

It is known that the responsibility to reporting ADRs belong to medical care providers such as medical doctors, nurses, pharmacists and databases can be developed worldwide, especially with the leadership of doctors for self-reporting (2, 11, 14).

As far as we know, there is only a few number of studies on the knowledge and attitudes of physicians about adverse event reporting and pharmacovigilance in Turkey (14-16).

However, there is no study for physicians working in our university hospital. In this study, we aimed to evaluate the knowledge levels and attitudes of the resident physicians about ADRs and pharmacovigilance in our university.

MATERIAL AND METHODS

A prospective study was designed and performed by using a questionnaire form consisting of 14 questions to evaluate the knowledge and attitudes of the physicians about the reporting of ADRs. The study was started after the approval of Harran University of Faculty of Medicine Ethics Committee was taken at the meeting dated 27.06.2014 numbered 07-12. Among the 131 resident physicians working at Harran University Hospital, 88 people who agreed to participate in the study were included in the study. The questionnaire, which was prepared by the researchers by scanning the literature, was validated on 15 resident physicians. The results of the questionnaires were evaluated by using SPSS 18.0 package program by frequency and percentage tests. The resident physicians, who agreed to participate in the research, filled the questionnaire and collected the data. The data were evaluated with frequency and percentage tests using SPSS 18.0 package program.

RESULTS

Numbers of male physicians were 59 (67.05%) and female were 29 (33.95%). The mean age was 29.1 ± 3.1 years. The responses of physicians to the knowledge and attitude related questions such what ADR is, whether they have made ADR notification and how much reports are presented in Table 1. When participants were asked to give an example to ADRs, 63.6% replied as "diarrhea after antibiotic use", 23.9% of the responses were "drowsiness after using cough syrup" and 8.0% of were "accidents after drinking cough syrup". The rate of the participants reported that they had no idea was 4.5%. The ratio of the answers given to the question "to whom the ADR reaction should be reported"; 65.9% were to pharmacovigilance officers, 26.1% were to the doctors, 6% were to the pharmacists and 1.1% were to the nurses. When the physicians were asked the question "Who do you think is more susceptible to the adverse drug reaction?", 38.6% stated elderly people, 22.7% children, while 38.6% stated there would be no difference between individuals. Only 6.8% of the physicians stated that they received a

professional information or training about the ADRs notification.

When the participants were asked "how the ADR reporting method should be", 69.3% of the answers were "by computer filling forms", 12.5% " by filling out the forms manually", 8.0% "by phone reports". The rate of those who did not comment on this question was 10.2%. About the necessity of informing patients about ADRs, 93.2% of doctors thought that it was necessary to inform patients. When resident physicians were asked how the method of informing patients about ADRs should be, 62.5% of the answers were "by doctors", 20.5% were "by the information leaflet during hospitalization" and 15.9% were "by nurse".

Table 1. Responses of the physicians to the knowledge and attitude related questions.

ADR	N	%
What is an adverse drug reaction?		
The appearance of the harmful effects of drugs after taking at normal dose	45	51.1
The occurrence of side effects after taking drug	39	44.3
The occurrence of any of the undesired effects after taking the drug	3	3.4
No idea	1	1.1
As a healthcare professional, do you report any unexpected adverse effects that may be caused by the use of the medicinal product for human use and which may be thought to be related to the product?		
No	61	69.3
Yes	15	17.1
Reporting number		
1-2	11	12.5
3-5	2	2.3
6-10	1	1.1
More than 10	1	1.1
I never matched	12	13.6
***What is the reason for not reporting adverse drug reactions that you have identified?**		
Being not sure, uncertainty	13	14.7
Insufficient time	18	20.3
Do not know where to report	41	46.5
Think that it is not the responsibility	8	9.1
Every time I did report	4	4.5
Others	15	17.0
What do you think is the purpose of reporting adverse drug reactions?		
To strengthen drug safety	45	51.1
To prevent the repetition of adverse drug reactions among other people	38	43.2
To help the doctor to determine ADRs	5	5.7
Are adverse drug reactions a serious problem in Turkey in your opinion?		
Yes	64	72.7
No	24	27.3

DISCUSSION

Although the reporting rate of ADRs has increased worldwide in the last decade, Güner et al. reported that this rate is relatively lower in Turkey compared to developed countries and health care providers are unaware of their responsibility for ADR reporting (9, 16). The reasons for underreporting may be the intensive working conditions, not knowing how and where the notification will be made and fear of misrepresentation (5). In the present study, it is seen that the ADR reporting rate is low, ADRs reporting system is not well known and not used adequately by physicians in our hospital.

The rate of the physicians who had no idea about ADR reporting is 1.1% in this study. Paveliu at al. reported this rate as 4.7% (17). The definition of ADRs was correctly known by 51.1% of the physicians in our study. Similarly, Şencan et al. reported this rate as 53.3% in their study (14).

The researchers reported that the proportion of participants who had never reported ADRs from both India (83.6%) and Romania (72.93%) were high. In our study, 69.3% of the physicians reported that they had never do ADR reporting. However, in a study performed in Bulgaria, this rate was lower (37.4%). Ergün et al. reported that only 8% of the physicians did ADR reporting and Altıntaş Aykan et al. showed that none of the physicians found to make any ADR reporting (15, 17-20).

Palaian et al. noted that the rate of not reporting ADRs due to not knowing where to be reported was as low as 3.6%. Although it was reported as 27.2% in another study from Turkey, our result was very high (46.5%) compared to other results (16, 21).

The rate of not doing ADR reporting is 20% due to not knowing where to report in the study by performed by Paveliu et al. in Romania. They reported that the most common cause of not reporting ADRs was uncertainty of the relationship between the drugs and ADRs (37.4%). Güner et al. found the result of uncertainty rate as 29.6%. This rate is twice of that of in our study (14.7 %). Khan et al. reported this rate as 30.9% in their study (16, 17, 22).

In this study the rate of the participants who think that it is not the responsibility of the healthcare professionals to make ADR reporting is 9.1%. Güner et al. found this rate to be 9.1% in the same way as in our study (16). This rate is reported as 2% by Ergün et al. and 19.1% by Palain et al. (15, 21).

Şencan et al. report that most (20%) of the physicians do ADR reporting to drug company while most of our participants (65.9%) were seen to report ADRs to pharmacovigilance officers (14).

Time deficiency as another reason for not reporting ADRs was reported as the second cause both in the present study (20.3%) and in Bulgaria (12.2%) whereas it was reported as 28.76% in Romania and 33.3% in Nigeria (17, 19, 23). Ergün et al. reported this rate higher (%55) than all of them (15).

Most common answer (51.1%) as a purpose for reporting ADRs is "drug safety" in the present study. Ergün et al. reported the most common answer (86%) given for the same question as "to define and determine new ADRs". In both studies, the second most common answer given as the reason for reporting ADRs was "safety and to prevent the repetition of adverse drug reactions among other people" (15).

The studies showed that training has a positive effect over gaining ADR reporting attitude (24-26). The participant doctors of the study of Khan et al. offer some methods as refresher courses and continuous medical education to improve ADR reporting status (22). In the present study only 6.8% of the physicians stated that they received a professional information or training on the ADR notification. Only %2 of the participants think that they are sufficiently trained about spontan ADR reporting in the study performed by Ergün et al. Stoynova et al. found the training rate as 47.2% in the entry research of their survey. The rate of the health professionals having sufficient knowledge about ADR reporting was found 34.2% in another study (15, 19, 27).

Özcan et al. reported that ADR reporting rate is observed to be high on elderly and females in Turkey. In this study most common answer as 38.6% of the physicians stated that elderly people is more susceptible to the ADRs (9).

In this study, the most common method of reporting an ADR (69.3%) is found to be done by computer filling forms. In another study that questioned the best method for obtaining a spontaneous reporting form, with the rate 59%, the e-mail method was found to be the most common way (15).

In the present study, 72.7% of the physicians consider an ADR as a serious problem in Turkey. Özcan et al. reported that many ADRs developed due to self-medication in Turkey (9). It is known that self-medication related ADRs cause widely public health problem not only in Turkey but also all over the world (28, 29).

CONCLUSION

In today's world unwanted drug reactions become a medically major problem as a result of increased drug use. Sharing global knowledge about adverse effects strengthens drug safety in countries and is important to ensure patient safety. ADRs can occur in all areas where health care services are provided, including the primary care department and hospitals. Not only for the hospital doctors but also for family physicians who meet patients at the first admission, it is vital to be aware of the adverse drug effects they face. As a result of the present study we have seen that despite their important role in ADR reporting system, knowledge and the attitude level of doctors about ADR reporting is not sufficient. In our estimation this has a negative effect on the ADR underreporting and may be clarified by further studies. We believe that it is important to raise awareness among the healthcare professionals about the ADR reporting system and the status can be improved by effective and periodical training methods.

Limitations: This study is a survey-based study; the results are only due to the answers of the participant.

Conflict of interest: The authors declare no conflicts of interest.

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RESEARCH ARTICLE

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Understanding the Psycho-Social Differences Between Mothers of Infants Who Do and Do Not Have Dyschezia

ABSTRACT

Objective: Infant dyschezia is one of the as yet little known infant functional gastrointestinal disorders and data on dyschezia is extremely limited. In this study, thus, we aimed to investigate the relationship between the psychological and psycho-social states of mothers of 1-6 month-old infants with dyschezia, and the dyschezia of their infants.

Methods: The sample consisted of 127 mothers of 1-6 months old infants with dyschezia and 127 mothers of 1-6 months old infants without dyschezia. The psychological symptoms of mothers were evaluated using the Brief Symptom Inventory (BSI). The data within the specially prepared personal information sheet were obtained by face-to-face interviews.

Results: We found that the mothers of infants with dyschezia had more social and economic difficulties such as lower education and income levels, lower employment rate, having more children, and less support from their partners in infant care. Compared to the mothers in the control group, the scores of the mothers, whose infants had dyschezia, were significantly higher in both the total, and all of 9 subscales in the BSI.

Conclusions: In conclusion, the mothers of infants with dyschezia have more psychological problems and socioeconomic difficulties. It is possible to say that there may be a relationship between the mother's psychological symptoms and her infant's dyschezia problem. We believe that this report would be beneficial to pediatricians, child psychiatrists, pediatric surgeons, and physicians and nurses working in this field.

Keywords: Maternal Mental Health, Dyschezia, Infants, Defecation, Mother-Baby Interaction

Diskezisi Olan ve Olmayan Bebeklerin Anneleri Arasındaki Psiko-Sosyal Farklılıkları Anlamak

ÖZET

Amaç: İnfant diskezisi henüz az bilinen bebeklik fonksiyonel gastrointestinal bozukluklarından biridir ve diskezi hakkındaki veriler son derece sınırlıdır. Bu nedenle, bu çalışmada, 1-6 aylık diskezisi olan bebeklerin annelerinin psikolojik ve psiko-sosyal durumları ile bebeklerinin diskezisi arasındaki ilişkiyi araştırmayı amaçladık.

Gereç ve Yöntem: Örneklemi 1-6 aylık diskezisi olan bebeklerin 127 annesi ile 1-6 aylık diskezisi olmayan bebeklerin 127 annesi oluşturdu. Annelerin psikiyatrik belirtileri Kısa Semptom Envanteri (KSE) kullanılarak değerlendirildi. Özel olarak hazırlanmış kişisel bilgi formundaki veriler yüz yüze görüşülerek elde edildi.

Bulgular: Bebeklerinde diskezi sorunu olan annelerin daha düşük eğitim ve gelir düzeyi, daha düşük istihdam oranı, daha fazla çocuk sahibi olma ve bebek bakımında eşlerinden daha az destek gibi daha fazla sosyal ve ekonomik güçlükler yaşadıklarını bulduk. Kontrol grubundaki annelerle karşılaştırıldığında, bebeğinde diskezi olan annelerin KSE'de hem toplam hem de 9 alt ölçeğin tümündeki puanları anlamlı olarak daha yüksekti.

Sonuç: Sonuç olarak, diskezisi olan bebeklerin annelerinin daha fazla psikiyatrik sorunları ve sosyoekonomik zorlukları bulunmaktadır. Annenin psikiyatrik belirtileri ile bebeğinin diskezi sorunu arasında bir ilişki olabileceğini söylemek mümkündür. Bu yazının çocuk doktorları, çocuk psikiyatristleri ve cerrahları, bu alanda çalışan doktorlar ve hemşireler için faydalı olacağına inanıyoruz.

Anahtar Kelimeler: Anne Ruh Sağlığı, Diskezi, Bebek, Dışkılama, Anne-Bebek Etkileşimi

INTRODUCTION

Infant dyschezia which just means uncoordinated defecation is one of the childhood functional gastrointestinal disorders. According to the most recently revised Rome IV criteria, infant dyschezia is defined as at least 10 minutes of straining and crying before the successful or unsuccessful passage of soft stools in an otherwise healthy infant younger than 9 months of age (1). These episodes, which are exhausting for the infant and induce anxiety in the parents, happen several times daily, but, usually, they then pass normal and soft stools several times daily in contrast to constipation. Parents frequently report that their healthy infant cries for 20 to 30 minutes, appears to strain and grunt, turns red or purple in the face and grunts or screams while making an effort to defecate (2-4). The prevalence of infant dyschezia is reported as 3.9%, 0.9%, and 0.9% in 1, 3, and 9 months-old infants, respectively (5). However, it is emphasized that infant dyschezia is easily mistaken for constipation and both parents and physicians commonly misinterpret dyschezia as constipation, and it is important to distinguish between these two disorders. As cues for eliminating this misconception, it is suggested that infant dyschezia is more likely if the infant is younger age and the stool has a soft consistency (2, 3, 6). The symptoms of dyschezia usually begin in the first months of life and resolve spontaneously as the child develops and no tests or treatments are necessary (7-9). In the developmental process, to be able to have a bowel movement, an infant needs to coordinate the increase in intra-abdominal pressure with pelvic floor relaxation. An infant with dyschezia has not yet developed this coordination (2, 3, 7). On the other hand, the etiology of functional constipation has not been clarified yet and it is considered to be a phenomenon affected by numerous factors. Psychosocial factors have an important role in functional constipation (10, 11). However, data regarding the natural history of infant dyschezia are scarce. Previous studies have shown that psychosocial factors, the mental state of mothers (primary caregiver), and the mother-infant relationship are implicated in the defecation problems during infancy (12, 13), but the evidence is limited to a few studies and to generally functional constipation. For this reason, the aim of this study is to obtain information about the relationship between the psychological and psycho-social states of mothers of 1-6 month-old infants, and the dyschezia of their infants and to compare these relationships with a cohort of mother-infant dyads where infant dyschezia is not present. Our study has the potential to fill the information gap in this field.

MATERIAL AND METHODS

The mothers of the 1- 6 month-old infants who were enrolled to in the Family Health Centers (FHCs) (22 centers) located in the city center of Sivas were included in the study. Dyschezia group consisted of 127 mothers who had the infants that were exclusively breastfed, had dyschezia according to the Rome IV criteria but no additional disorders including other infant functional gastrointestinal disorders such as functional constipation. We excluded mothers with severe psychiatric disorders (schizophrenia, mental retardation etc.) and who used medication that may cause constipation other than an antibiotic, vitamin D, and iron preparation for both herself and her infant. Control group was composed of 127 mothers who were also followed up by the same FHCs, had 1-6 month-old infants, exclusively breastfed their infants but did not have dyschezia and other functional gastrointestinal disorders in their infants. In order to keep the effect of the confounding factors at a minimum level, the groups were matched in terms of the usage of the iron and vitamin preparations, which may be associated with constipation.

This study received the approval of the local Ethics Committee of the Sivas Cumhuriyet University and Sivas Provincial Directorate of Health. All participants provided written informed consent. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice procedures.

Data Collection Tools:

Personal Information Form: This form was prepared specifically by the researchers based on the relevant literature. The form includes questions about sociodemographic information, the health status of mothers, and infant care. In addition, the form includes questions about the birth and health information of infants, the time of their first bowel movement and their defecation habits, the presence of gas pain and regular sleep pattern. The researchers filled out this form by conducting a face-to-face interview with the mothers.

Brief Symptom Inventory-BSI: BSI is a 53-item self-report inventory developed by Derogatis (1992) to scan various psychological symptoms and complaints (14) It is composed of 9 subscales, additional items, and 3 global indices. These subscales are "depression", "somatization", "interpersonal sensitivity", "obsessive-compulsive disorder", "anxiety", "paranoid ideation", "hostility", "phobic anxiety" and "psychoticism". This Likert type scale is scored as Not at all (0), A little bit (1), Moderately (2) Quite a bit (3), and Extremely (4). The total score ranges from 0–212. High scores signify high levels of psychological symptoms. General Severity Index (GSI), Positive Symptom Total (PST), and the Positive Symptom Distress Index (PSDI) constitute 3 global indices. GSI is calculated by dividing the total scale score into 53. If GSI values are between 0 and 1, the psychological symptom levels are considered as low and if it is higher than 1, the psychological

symptom levels are considered as high. Şahin and Durak (1994) adapted the scale into Turkish (15).

Statistical Method: Statistical data were analyzed using SPSS 22.0 (IBM SPSS, Version 22.0, IBM Corporation, Armonk, NY, USA). Kolmogorov-Smirnov Test was used to test the compatibility of the data to normal distribution. The numerical and categorical data were expressed as mean±standard deviation (SD), median (min-max), number (n) and percentage (%). The groups were compared by chi-square test for the categorical variables and by Mann-Whitney U test for continuous variables. The value of $p<0.05$ was considered as statistically significant.

RESULTS

Demographic and Clinical Characteristics of the Infants: Table 1 shows the sociodemographic data of the infants. The two groups were similar in gender, but the infants in the dyschezia group were significantly younger (in month) than the control infants (p<0.001). The two groups were similar in terms of some natal characteristics (type and weight of birth) and the time of first bowel movement (all p-values >0.05). However, the prematurity rate was significantly higher (18.1% vs. 6.3%) and the first breastfeeding time of the infants in the dyschezia group was significantly late than those of controls. The rate of breastfeeding within the first half hour-first hour was significantly lower in the dyschezia group (10.2% vs. 38.6%, p<0.001). There were differences in terms of the development and daily routines of the infants. Accordingly, the infants in the dyschezia group had more problems in regular weight gain (74% vs. 39.4%, p<0.001), sleep pattern (84.3% vs. 66.1%, p=0.001) and, gas pain (50.4% vs. 17.3%, p<0.001) compared to the infants in the control group. But, the bowel habits of the infants did not differ (p=0.250).

No statistical difference was found between the groups in terms of functional gastrointestinal disorders history in the family and the mothers' amount of daily consumption of caffeine-free beverage consumed in a day (both p-values >0.05) (Table 1).

Table 1. Demographic, developmental and clinical features of infants

	Dyschezia Group (n=127)	Control Group (n=127)	P-value[a]
Gender (n,%)			0.602
Male	48 (37.8)	44 (34.6)	
Female	79 (62.2)	83 (65.4)	
Age (months)			**<0.001**
1st and 2nd months	96 (75.6)	57 (44.9)	
3rd and 4th months	22 (17.3)	34 (26.8)	
5th and 6th months	9 (7.1)	36 (28.3)	
Birth Type (n, %)			1
Vaginal Delivery	109 (85.8)	110 (86.6)	
Cesarean Section	18 (14.2)	17 (13.4)	
Gestational age at birth (n,%)			
Premature (<36 weeks)	23 (18.1)	8 (6.3)	**0.004**
Miad (37-42 weeks)	104 (81.9)	119 (93.7)	
Birth weight (n,%)			0.090
Under 2500 gr	24 (18.9)	12 (9.4)	
Between 2500-4000 gr	98 (77.2)	108 (85)	
Over 4000 gr	5 (3.9)	7 (5.5)	
First defecation time (n,%)			
1-4 hours	54 (42.5)	48 (37.8)	0.888
5-8 hours	50 (39.4)	53 (41.7)	
9-12 hours	11 (8.7)	12 (9.4)	
12 hours or more	12 (9.4)	14 (11)	
First breastfeeding time (n,%)			
First half hour	13 (10.2)	49 (38.6)	**<0.001**
First hour	20 (15.7)	33 (26)	
The first 2-4 hours	47 (37)	20 (15.7)	
5 hours or more	47 (37)	25 (19.7)	
Regular weight gain (n,%)*			**<0.001**
Yes	33 (26)	77 (60.6)	
No	94 (74)	50 (39.4)	
Number of daily defecation (mean±SD)	2.82±1.03	2.97±0.890	0.250
Gas pain (n,%)**			**<0.001**
No-Mild	63 (49.6)	105 (82.7)	
Moderate-Severe	64 (50.4)	22 (17.3)	
Sleep pattern (n,%)**			**0.001**
Regular	20 (15.7)	43 (33.9)	
Irregular	107 (84.3)	84 (66.1)	
Family history of functional gastrointestinal disorders (n,%)			0.071
Yes	56 (44.1)	42 (33.1)	
No	71 (55.9)	85 (66.9)	
Mothers' daily consumption of caffeine-free beverage (n,%)			0.716
At least four cups	16 (12.6)	19 (15)	
5 and above cups	111 (87.4)	108 (85)	

[a]The chi-square test for categorical variables and the Mann-Whitney U Test for continuous variables were used to test group differences. Data were given as mean±standard deviation or number (%). Bold font indicates statistical significance: P < 0.05

*Regular weight gain was determined using records of Family Health Centers (FHCs).

**A standard psychometric test was not used in the measurement of sleep patterns and gas pain, it was based on the mother's reports.

Sociodemographic Characteristics of the Mothers: Table 2 shows the sociodemographic characteristics of mothers. The mothers differed significantly in terms of education level, family structure, family income level, place of residence, employment status, and the number of living children. The mothers of the infants with dyschezia had a lower education level compared to the mothers of the non-dyschezia infants (p<0.001). There was no participant with a single-parent family (divorced, separated, or death) in the study population. However, the mothers of the infants with dyschezia had an extended family at higher rates compared to the control group (41.7% vs. 26%, p=0.012). The mothers of the infants in the dyschezia group had an "income less than expenses" at a higher rate (33.9% vs. 20.5%, p=0.024) and a regular job at a lower rate (10.2% vs. 26.8%, p=0.001), and resided in the rural areas at a higher rate compared to the mothers in the control group (45.7% vs. 26%, p=0.002). No difference was found between the two groups in terms of the gender of the children they have, however, the mothers in the dyschezia group had more children compared to the mothers in the control group (3 or more alive children). The rate of having one child was higher in the mothers in the control group (p<0.001) (Table 2).

Table 2. Sociodemographic characteristics of mothers of infants with and without infant dyschezia

	Dyschezia Group (n=127)	Control Group (n=127)	P-value[a]
Age group (n,%)			0.702
19-34 years	50 (39.4)	54 (42.5)	
35 and over	77 (60.6)	73 (57.5)	
Education Level (n,%)			**<0.001**
Primary education	59 (46.5)	25 (19.7)	
High school	40 (31.5)	48 (37.8)	
University and above	28 (22)	54 (42.5)	
Family type (n,%)			**0.012**
Nuclear	74 (58.3)	94 (74)	
Extended	53 (41.7)	33 (26)	
Family Income Level (n, %)			**0.024**
Income is equal to or more than expenses	84 (66.1)	101 (79.5)	
Income is less than expenses	43 (33.9)	26 (20.5)	
Place of residence (n,%)			**0.002**
Rural	58 (45.7)	33 (26)	
Urban	69 (54.3)	94 (74)	
Regular job (n,%)			**0.001**
Yes	13 (10.2)	34 (26.8)	
No	114 (89.8)	93 (73.2)	
Number of living children (n,%)			**<0.001**
None	21 (16.5)	49 (38.6)	
1	46 (36.2)	41 (32.3)	
2	22 (17.3)	28 (22)	
3^{+}	38 (29.9)	9 (7.1)	
Gender of the living children (n,%)			0.250
Female only	39 (30.7)	43 (33.9)	
Male only	18 (14.2)	26 (20.5)	
Both genders	70 (55.1)	58 (45.7)	

[a]Chi-square test. Data were given as number (percent%). Bold font indicates statistical significance: P < 0.05

With respect to the health status of the mothers and their drug use, none of the mothers in sample of the present study had a chronic physical disease requiring regular drug use.

Characteristics Related to Infant Care: Table 3 shows the data regarding the qualities of infant care. No difference was observed between the groups in terms of the attitude of the mothers toward their infants (relaxed vs. anxious/doting). However, mothers of infants with dyschezia reported that they were more anxious about failing to provide adequate care to their babies compared to mothers in the control group (78.7%vs. 63.8%, p=0.012). Regarding the support of the fathers in infant care, more than half of the mothers of the infants with dyschezia stated that they had no or

inadequate support from their partners and this was significantly lower in the mothers in the control group (54.3% vs. 15.7%, p<0.001). The mothers also differed significantly about the traumatic events (death, accident etc.) they experienced during pregnancy and in the postpartum period and the presence of any temporary separation from their infants and, accordingly, the mothers in the dyschezia group experienced more traumatic events and they separated temporarily from their infants at a higher rate (22.8% vs. 9.4%, p=0.006) (Table 3).

Table 3. Variables related to infant care

	Dyschezia Group (n=127)	Control Group (n=127)	P-value[a]
Mother's attitude towards her infant (n,%)*			1
Relaxed	65 (51.2)	64 (50.4)	
Anxious/doting	62 (48.8)	63 (49.6)	
Anxiety about the adequacy of infant care (n,%)*			**0.012**
None-Mild	27 (21.3)	46 (36.2)	
Moderate-severe	100 (78.7)	81 (63.8)	
Father's support in infant care (n,%)*			**<0.001**
None or inadequate	69 (54.3)	20 (15.7)	
Adequate	58 (45.7)	107 (84.3)	
Traumatic life events after pregnancy and delivery and temporary separation from the infant (n,%)	29 (22.8)	12 (9.4)	**0.006**
Yes	98 (77.2)	115 (90.6)	
No			

[a]Chi-square test. Data were given as number (percent%). Bold font indicates statistical significance: P < 0.05
*Mother's perceived support and anxiety were asked and a standard psychometric test was not used.

Psychological Assessment of the Mothers: Table 4 shows the scores of the Brief Symptom Inventory used to obtain information about the mental health of the mothers. The mothers of the infants with dyschezia had significantly higher scores in overall BSI and in all the 9 subscales of the inventory (somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, additional items), compared to the mothers in the control group. Also, the global severity index scores of these mothers were statistically significantly higher (all p-values <0.001) (Table 4).

Table 4. Comparison of the mothers' Brief Symptom Inventory scores

	Dyschezia Group (n=127)	Control Group (n=127)	P-value[a]
Somatization (mean±SD)	2.98±2.47	0.64±0.97	**<0.001**
Obsessive-compulsive disorder (mean±SD)	5.59±2.96	1.47±2.16	**<0.001**
Interpersonal sensitivity (mean±SD)	2.45±2.04	0.70±0.82	**<0.001**
Depression (mean±SD)	5.07±2.59	1.10±1.44	**<0.001**
Anxiety (mean±SD)	4.13±2.55	1.02±1.32	**<0.001**
Hostility (mean±SD)	2.57±1.94	1.06±1.10	**<0.001**
Phobic anxiety (mean±SD)	3.29±2.11	0.65±1.30	**<0.001**
Paranoid ideation (mean±SD)	2.12±1.55	0.25±0.79	**<0.001**
Psychoticism (mean±SD)	2.20±1.98	0.34±0.87	**<0.001**
Additional items (mean±SD)	2.87±1.80	0.81±1.02	**<0.001**
Total score (mean±SD)	33.29±13.70	8.02±8.04	**<0.001**
General Severity Index (mean±SD)	0.62±0.26	0.15±0.15	**<0.001**

*The Mann–Whitney U test was used to test group differences. Data were given as mean±standard deviation (SD). Bold font indicates statistical significance: P < 0.05.

DISCUSSION

In the study, mainly, the psychological and psycho-social states of mothers of 1-6 month-old infants with dyschezia and their infant care-related properties were investigated and compared to a cohort of mother-infant dyads where infant dyschezia is not present. The results of this study indicated that the mothers of the infants who are exclusively breastfed but have functional dyschezia exhibit more psychological disturbances and more disadvantageous sociodemographically. It has been highlighted that psychogenic factors may affect or contribute to functional gastrointestinal disorders in

infancy. However, existing data is limited to very few studies investigating that the importance of the psychological characteristics of the mothers in order to understand the relationship between psychic aspects and constipation in this early period (12, 13, 16-18). Moreover, in the literature, the published results regarding the data of functional dyschezia are extremely scarce. In fact, the etiological reason for dyschezia is the failure to coordinate increased intra-abdominal pressure preceding defecation with pelvic floor relaxation. Therefore, it is defined as a problem in learning to defecate and uncoordinated pooping, but it is often incorrectly labeled "constipation" by parents and physicians.

Although dyschezia is a very common problem of infants, there is currently no available evidence on whether psychosocial factors and psychological profiles of the mothers are effective and/or contributory in infant dyschezia, just as with functional constipation. Our outcome showing the mothers of the infants with dyschezia have more and severe psychological symptoms suggests that infant dyschezia can be affected by the mother's mental health, and attention should be paid on the psychological state of the mothers. Until now, these outcomes offer a unique result to the literature, however, we cannot make adequately a comparison of our results. Nevertheless, we can make some speculations. For example, the association between the psychological state of mothers and infant defecation problems may be bidirectional. First, as the most likely direction, mothers who are mostly contacted by infants in the early period may be more distressed as a consequence of their child's dyschezia or the child's dyschezia is able to provoke the mother's pre-existing psychological problems. Because in this situation, which is an exhausting process for the infant, parents try many methods such as bicycling the child's legs, use of medication (homeopathic or otherwise, e.g., glycerin suppositories, sorbitol or sorbitol-containing juices, barley malt extract, or corn syrup), rectal thermometer stimulation, enemas, changing formula and mom's diet, even sticking something in their child's bottom with no relief, and unfortunately, they cannot experience the effectiveness of any of these techniques. This can lead to increased anxiety and other negative emotions of the mother, who already experiences stressful fussy days, long exhausting nights and too much physical or mental stress due to the child's symptoms, or can exacerbate these undesirable emotions if they exist Also, our result indicating infants with dyschezia have more disturbances in the development and daily routines (e.g., regular weight gain, sleep patterns, and gas pain) may be a possible explanation for more psychological problems of their mothers who worried about her infant. In conclusion, it can impair the parents' quality of life and well-being in the mother-infant relationship context for both infants and mothers. Second, in the reverse direction, mothers with psychological symptoms can react to or portray the child's temporary, common and very normal this problem in an excessively dramatic manner, which in turn, can cause the problem to be an overrepresentation in such mothers' children. In this context, it can be extremely valuable to inform parents that their infants are normal and no tests or treatments are necessary and the distressing situation/condition will be resolved spontaneously as the infant soon learns to the bowel movements.

More importantly, in both possible situations, this negative psychological profile or psychological problems of the mothers can result in the mothers to enjoy her role of motherhood less and a dysfunctional motherhood style, and indirectly, pathological attachment. Previous studies have suggested that the mothers with psychological symptoms have more difficulties or fall behind in recognizing and meeting the needs of their infants, they can't understand the distress messages of infants adequately and their emotional interaction with their infants is unsatisfactory. There are reports in the literature showing that the psychiatric symptoms and disorders and/or temperament of mothers may be a factor for various emotional and behavioral problems or even psychosomatic symptoms for their infants/children (12, 19-21). Because the mother's psychiatric symptoms or psychological problems not only adversely affect her own quality of life but can also cause the mother-baby relationship which negatively influences the emotional and mental-motor development of their infants. The studies conducted about the mental health of mothers in the postpartum period have focused mainly on depression, anxiety, bipolar disorder, and psychosis. However, it has also been reported that several psychological problems are less recognized since some complaints that may be psychiatric disorder symptoms, especially anxiety and sadness, are considered to be normal for new mothers (21).

Examining sociodemographic characteristics, the results of our study revealed that the mothers of infants with dyschezia have more familial and socioeconomic difficulties and high levels of anxiety about giving adequate care for their infants. It is possible that these unfavorable conditions create a disadvantageous status on the mothers and hence their mental health is negatively affected. Therefore, our finding demonstrating that the mothers of infants with dyschezia have more mental problems is not surprising. Our findings are consistent with the results of the studies investigating the negative risk factors on the mental health of mothers in the postpartum period and sociodemographic variables (22-24).

The present study is one of the few studies on "infant dyschezia" which has little data and is often overlooked, or misdiagnosed as constipation.

Other strengths of this study are that it is conducted with a large sample and population-based and the data were collected with the face-to-face interview method. However, this study has some limitations. First, the data collection tools including subjective evaluation criteria that we used as the screening method might have caused response bias and they are not diagnostic as the symptoms are screened only. Second, the results of the present study cannot be generalized as the study was conducted only in one province. Finally, no diagnostic interview was applied to these mothers. For this reason, the results of this study should be reproduced and deepened with future studies.

CONCLUSION

The present study indicated that the mothers of infants with dyschezia have more psychological symptoms, and it can be asserted that there is a relationship between the dyschezia symptoms of infants and the psychological symptoms of the mother based on our results. The most plausible explanation seems to be that infant dyschezia symptoms can be distressing to parents, in particular mothers, hence, they can produce the psychological problems of the mothers. Primary care physicians and general practitioners, pediatricians, child surgeons, and other healthcare professionals should be aware that the relationship between infant dyschezia and the psychological state of mothers. From this point of view, it would be advisable to screen the mothers of infants with dyschezia in terms of the risk of developing psychological problems.

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RESEARCH ARTICLE

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The Effect of Ozone Treatment on Thermal Burn Wound Healing; an Experimental Study

ABSTRACT

Objective: Ozone has been advised as a metabolic excitative in cell, immuno-modulatory agent and antioxidant enzyme actuator. The present study was performed to designate the profit of ozone therapy on the burn wound healing in the rats.

Methods: 40 adult Wistar type rats divided into 4 groups: a control group (burn not created and topical and systemic agents not used), a burn group (burn created but only saline given), a burn+silver sulfadiazine group (silver sulfadiazine was applied for 21 days), a burn+ozone/oxygen mixture group (ozone/oxygen mixture was applied for 21 days).After anesthetizing, second-degree burn (2 cm^2 areas) was done on the dorsal of the animals byaluminum plate in boiling hot water (100 ˚C for 15 seconds) and other groups except control group were treated topically, based on the time scheduled. Tissue samples were harvested on day 7st and 21st after burn injury. Biochemical and histological analyzes were performed in tissue and blood samples. The results were assessed with appropriate statistical tests and given as Means±SD.

Results: The histopathologic damage level was significantly different in all groups. Fibrosis and inflamation levels decreased in ozone treatment and silver sulphadiazine groups compared to burn+normal saline group on the 21 days according to 7 days. In the ozone treatment group, Glucose 6-phosphate dehydrogenase activities were significantly higher than the silver sulfadiazine treated group. But glutathione reductase enzyme activities were lover in the ozone treated group and hydroxyproline concentration decreased in ozone group compared to burn+normal saline group on 7 and 21 days.

Conclusions: Ozone has a detractive effect in the development of inflamation, fibrosis, and granulation via decreasing tissue damage and increasing the antioxidant enzyme activity on burn wound healing.

Keywords: Wound Healing, Hydroxproline, Burn

Ozon Tedavisinin Termal Yanık Yara İyileşmesine Etkisi; Deneysel Bir Çalışma

ÖZET

Amaç: Ozon, hücre içinde, immüno-modülatör unsur ve antioksidan enzim işleticisinde metabolik bir uyarıcı olarak önerilmiştir. Bu çalışma, sıçanlarda yanık yarası iyileşmesinde ozon tedavisinin yararını belirlemek için yapılmıştır.

Gereç ve Yöntem: Bu çalışma için 40 adet Wistar tipi sıçan 4 gruba ayrıldı: Bir kontrol grubu (yanık oluşturulmadı, bölgesel ve sistemik unsurlar kullanılmadı), bir yanık grubu (yanık oluşturuldu, ancak sadece salin verildi), bir yanık + gümüş sülfadiazin grubu (21 gün boyunca gümüş sülfadiazin uygulandı), bir yanık + ozon / oksijen karışımı grubu (21 gün boyunca ozon / oksijen karışımı uygulandı) oluşturuldu. Anestezi uygulandıktan sonra, kaynar sıcak suda (15 saniye boyunca 100 ˚C) alüminyum plaka ile hayvanların sırtında ikinci derece yanık (2 cm^2 alan) oluşturuldu ve kontrol grubu dışındaki diğer gruplar planlanan sürede bölgesel olarak tedavi edildi. Doku örnekleri yanık hasarından sonraki 7. ve 21. günlerde elde edildi. Doku ve kan örneklerinde biyokimyasal ve histolojik analizler yapıldı. Sonuçlar uygun istatistiksel testlerle değerlendirildi ve ± SD ortalamalar olarak verildi.

Bulgular: Histopatolojik hasar düzeyi tüm gruplarda anlamlı olarak farklıydı. Ozon tedavisi ve gümüş sülfadiazin gruplarında fibroz ve inflamasyon seviyeleri, 7 güne göre 21 günde yanık + normal tuzlu su grubuna kıyasla azaldı. Ozon tedavi grubunda, Glikoz 6-fosfat dehidrogenaz aktiviteleri gümüş sülfadiazin ile tedavi edilen gruptan önemli ölçüde yüksekti. Ancak glutatyon redüktaz enzim aktiviteleri, ozon ile tedavi edilen grupta daha düşüktü ve hidroksiprolin konsantrasyonu, 7 ve 21 günde yanık + normal tuzlu su grubuna kıyasla ozon grubunda azaldı.

Sonuç: Ozonun, doku hasarını azaltarak ve yanık yara iyileşmesinde antioksidan enzim aktivitesini artırarak iltihaplanma, fibrozis ve granülasyon gelişiminde bozucu bir etkisi bulunmaktadır.

Anahtar Kelimeler: Yara İyileşmesi, Hidroksiprolin, Yanık

INTRODUCTION

Burns are widely conceived as the most disruptive kind of traumatic injuries. Tissue damage starts as a consequence of interrelate of the skin with high heat (40°C) and this damage is intensified as parallel with increase of heat. Burn is very frequently encountered in the society, especially epileptic patients, drug addicts, children, alcoholics and the elderly are at risk (1). In fact, the unsuitable healing of the burn is evinced via high amount of free radical intervened damage, decreasing angiogenesis, collagen regeneration, and delayed granulation tissue evolvement. For this reason, the quiddity of the wound re-modelling depends essentially on the proficiency of wound care (2).Therefore, the quality of the wound regeneration depends mainly on the efficiency of wound care (2). Nevertheless, biomaterials of tissue engineering are extremely expensive and burn charge entails heavy expenses outside the reach of most of the patients in developing countries (3). Burn injuries lead to tissue damage, edema and crusting. Inflammation, granulation tissue formation, contraction and epithelialization play a role in normal wound healing (4).

Ozone is a unstable, sharp fragrant and colorless natural gas that is consisted of three oxygen atoms. Also, it is very powerful oxidizing and talented disinfect. Ozone not only kill viruse and bacteria but also oxidize all microorganisms and its toxins (5). Even though, initial years after its exploration, it was used as disinfection, today investigations have focused on dubitante for medical usage of ozone. Ozone should never be pure and require to mix a particular amount of oxygen (5). Ozone treatment may be explained as "a significant quantity of ozone/oxygen mixture is administered into circulation or body cavities". Ozone/oxygen gas mixture can be used by intramuscular, intravenous, intrapleural, intraarticular, intradiscal and intrarectal as well as topically (6). It is reported that ozone has the various biological mechanisms. Some of those mechanisms are related with activity of some enzymes as catalase, glutathione, and superoxide dismutase which are influential in the scavenging of free radicals and stimulates the immune system in small dosages. Ozone as other gases (O_2, CO_2) is water soluble. Ozonated water that used in wound care is one of strong germicides. Ozone applications have shown favourable influences in several cases as wound healing, hepatitis, ischemic, age-related macular degeneration and oral infections (5).

As a result, when we search in various databases as PUBMED, SCIENCE DIRECT, MEDLINE and GOOGLE SCHOLAR, we have not found any study on comparing the effects of topically of silver sulfadiazine and ozone/oxygen mixture in burn wounds. Therefore, the present study was designed to compare the effects of local aplications silver sulfadiazine and Ozone on second degree thermal burns in rats.

MATERIAL AND METHODS

Ethical Approval and Animals: The experimental procedures with the animals which used in this study were assented by the Ethics Committee of the Atatürk University, Faculty of Veterinary, Erzurum, Turkey (the reference code:2015/67). The present study was planned under the criteria of the Health Guide for the Care and Use of Laboratory Animals by the National Institutes of Health (NIH Publication No: 86-23, Revised 1985 Bethesda).

In the present study, fourty Wistar male rats weighing 380±20 g were obtained from research center the experiment animals of Atatürk University. The animals that used in the experiment were maintained in plastic cages (360 mmx200 mmx190 mm) under the appropriate conditions in laboratory (12-hour light/dark cycle, a temperature 25±1 ^{o}C, humidity 55±5 %) and expensed a standard pellet and water ad libidum. The rats used in the experiment were starved for 12 hours before experiment, but we were allowed to drink just water.

Groups and Induction of Burn in Rats: After 24 hours' acclimatization, second-degree burns were formed in 40 adult Wistar rats. Rats were randomly divided into four group. Each group involved of ten rats: Group 1 was the control group and burn was not created (no topical agent was applied) and tissue biopsy samples were taken on 7 and 21 days. After the rats were sacrificed at the end of 21 days, tissue and blood samples were obtained. Group 2 was the burn group (other topical agent wasn't applied except normal saline). After, burn wound was closed with sterile gauze and the rats were sacrificed at the end of 21 days. For Group 3, wound dressing was done with 1% silver sulfadiazine once on a day. Group 4 was treated with ozone/oxygen mixture once on a day and topically administrated on burns and the rats were sacrificed. Later, tissue samples were taken as the Group I. Also, ozone/oxygen mixture were dissolved in physiological saline. All the treatments were administrated topically and binded by using sterile gauze until the first group completely healed. The healing period was followed up clinically. Four parameters were histopatologically assessed in the determination of wound healing: inflammation, fibrosis, granulation, and macroscopic healing. In all groups, wound dressings were done under anesthesia at the same time in the morning and once on a day.

Drugs and the Experimental Procedure: Group 3 was treated with 1% silver sulfadiazine. It was commercially found as 1% Silvadiazin cream (Toprak Drug Co.). Group 4 was treated with ozone/oxygen mixture. Ozone/oxygen mixture was prepared by dissolving in normal saline. Pursuant to

our treatment protocol, the drugs were performed as a thin layer on the wounds. Also, all wounds were conserved with sterile gauze with adhesive elastic bandage (Setanet® No: 3) and changed on a daily. Anesthesia was reachedvia a single dose of intraperitoneal60 mg/kg of ketamine hydrochloride (Ketalar® Eczacıbaşı Warner-Lambert Drug Industry, Levent, İstanbul) and 10 mg/kg of xylazine hydrochloride (Rompon® Bayer, Şişli, İstanbul) mixture. The dorsal region of the rats was shaved and cleaned with 10% of povidone-iodine solution (Kim-Pa, Poviiodeks, 10% povidone-iodine). Especially, contemplated aluminum plate with 10 cm² of surface area (2.5x4 cm diameter) was used for the generation of burns. The aluminum plate has been sterilized in boiling water (100 ^{o}C) for 5 minutes, after then, it was applied on the skin of anesthetized rats for 30 seconds with pressure (Figure 1). Using this procedure, second-degree burn were formed (Figure 2). After the formation of burns, all the rats were placed and kept in individual cages. After operation, analgesia for rats was provided subcutaneously of fentanyl citrate at the dose 0.02 micg/kg of 2x1 (Fentanyl Citrate ampul Abbott, Beykoz, İstanbul).

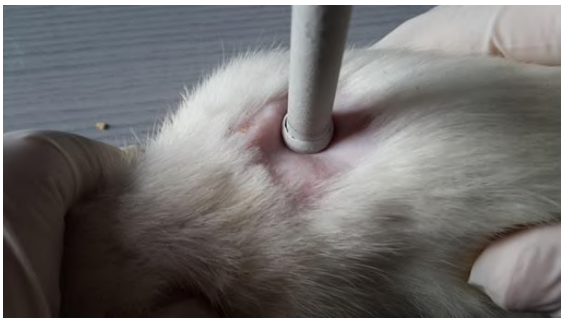

Figure 1. Induction of burn in rats

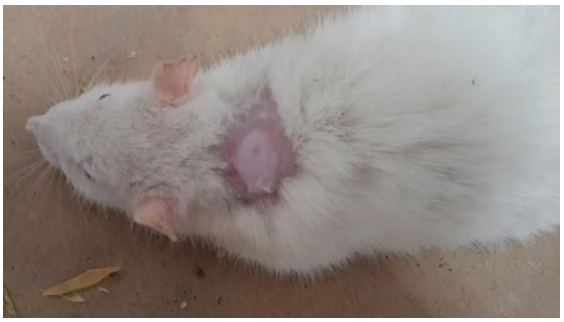

Figure 2. Formation of bull in rats.

Ringer's lactate for 2 mL according to the Parkland formula was given intraperitoneally for resuscitation post burn. All the rats under anesthesia was sacrificed by cervical dislocation. The blood and tissue samples were evaluated in pathology laboratories, additionally level of recovery in burn wounds was assessed, macroscopically (Figure 3).

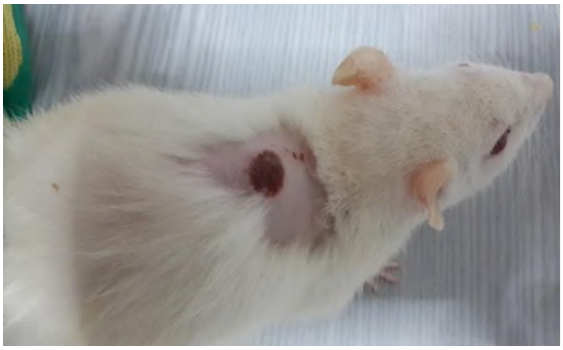

Figure 3. Macroscopic view of the burn wound one week late

Also, the effects of ozone was examined on the oxidative system, biochemically. The concentration of hydroxyproline was assessed in the blood samples and given as nmol/ml. Glucose 6-phosphate dehydrogenase, Glutathione reductase, and 6-phosphogluconate dehydrogenase were measured in tissue. The results were presented as nmol/gr.

Biochemical Analysis

Measurement of G6PD Enzyme Activity: Glucose 6-phosphate dehydrogenase (G6PD) activity was defined by monitoring Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) production at 340 nm and 25 ^{o}C. The assay mixture contains 10 mM magnesium chloride, 0.2 mM $NADP^{+}$, and 0.6 mM G6PD in 100 mM Tris-hydrochlorid buffer solution at pH 8.0. Analyses were performed in triplicate and the activities were followed up for 60 s. One unit of activity (U) is defined as the amount of enzyme required to reduce 1 µmol/min of $NADP^{+}$ under the assay conditions (7).

G6PD

Glukoz 6-fosfat + $NADP^{+}$ ⟶ 6-Fosfoglukono -lakton + NADPH + H^{+}

Measurement of 6PGD Enzyme Activity: 6-phosphogluconate dehydrogenase (6PGD) activity was measured by monitoring NADPH production at 340 nm and 25 ^{o}C. The assay mixture contained 10 mM magnesium chloride, 0.2 mM $NADP^{+}$, and 0.6 mM 6PGD in 100 mM Tris-hydrochlorid buffer solution at pH 8.0.

Assays were carried out in triplicate and the activities were followed up for 60 s. One unit of activity (U) is defined as the amount of enzyme required to reduce 1 µmol/min of $NADP^{+}$ under the assay conditions (7).

6PGD

6-fosfoglukonat + $NADP^{+}$ ⟶ Riboluz-5-fosfat + NADPH

Measurement of Glutathione Reductase Enzyme Activity: Glutathione reductase enzyme activity was measured by Beutler's method. One enzyme unit is defined as the oxidation of 1 mmol NADPH per min under the assay condition (25 ^{o}C, pH 8.0) (8).

Measurement of Hydroxyproline: Hydroxyproline concentration was determined by the procedure of Reddy and Enwemeka[2] with a slight modification. Hydroxyproline concentration is determined by the reaction of oxidized hydroxyproline with 4-Dimethylaminobenzaldehyde. It can be measured at 560 nm (8).

Histopathological Examination: For histological analysis, the formalin-fixed skin samples were prepared for paraffin sections. Then, 4-µm sections were made and placed on slides. These slides were stained with hematoxylin and eosin (H&E). Histopathological examination of the rat tissue damage was done for each parameter: dermal inflammation, granulation tissue and fibrosis based on a scoring system where none=0, mild=1 +, moderate=2 +, and severe=3 +. Histopathological evaluations were done using a light microscope (Olympus BX53, Tokyo, Japan).

Statistical Analysis: Our results were denoted as Mean±Standard Deviation (Mean±SD). In case of multiple comparisons, repeated measurements of analysis of variance were performed to compare the mean differences between and within groups followed by Tukey tests. The Student's test was used to compare the average weight of rats before and after the experiment. The level of statistical significance was received as $p<0.05$.

RESULTS

In beginning of the study, all the burn wounds were similar. At the end of three weeks, no unhealed wounds were present. These results are suggested that ozone is influential in healing experimentally formed second-degree burns in rats. Prospectived, randomized, controlled clinical studies are exigenced to estimate the safety, profit, and effectualness of this treatment procedure for patients with second-degree burn wounds.

Table 1 shows tissue G6PD, 6PGD, and Glutathione Reductase (GR) activities of burn and experimental groups. In ozone treated group, a significant increase were observed in G6PD and 6PGD, whereas the GR level decreased significantly in the ozone group compared to treated with silver sulfadiazine group.

Table1. Effect of burn+normal saline, 1% silver sulphadiazine, and ozone on G6PD, 6PGD, and GR activities in the samples taken at the end of 3rd week(21st days) on burn wound healing model in rats. Values are presented as the Mean±SD (n=10).

	Control^{a,b,c} (n=10)	**Burn+Normal Saline^{b,c} (n=10)**	**1% silver sulphadiazine^{c} (n=10)**	**Ozone/Oxygen mixture dissolved in saline (n=10)**	
G6PD (nmol/gr)	14.01±1.57	13.37±1.47	13.47±1.41	23.43±2.28	**
6PGD (nmol/gr)	2.29±1.13	3.67±0.65	3.90±1.83	3.94±0.58	*
GR (nmol/gr)	13.77±1.74	16.24±2.59	14.09±2.26	12.70±1.28	*

Note: Each value represents mean +S.D. a: different from the burn+normal saline group b: different from the 1% silver sulphadiazine group c: different from the ozone group. *p<0.05, **p<0.01levels of significance.

The hydroxyproline levels are presented in Table 2. Hydroxyproline levels were significantly increased in the burn group ($p<0.01$). We have observed that a reduction on concentration of hydroxyprolinehas been seen in treated with ozone and silver sulfadiazine ratson 21st day.

Table 2. The concentration of hydroxyproline in the samples taken at the end of 1st and 3rd weeks is presented on burn wound healing model in rats for all groups**.** Values of are presented as the Mean±SD. (n=10).

	Control^{a,b,c} (n=10)	**Burn+Normal Saline^{b,c} (n=10)**	**1% silver sulphadiazine^{c} (n=10)**	**Ozone/Oxygen mixture dissolved in saline(n=10)**	
The concentration of hydroxyproline (nmol/ml) (1st Week)	0.04±0.00	0.27±0.05	0.23±0.05	0.24±0.02	**
The concentration of hydroxyproline (nmol/ml) (3rd Week)	0.04±0.00	0.02±0.03	0.01±0.02	0.01±0.02	

a: Different from the normal saline group b: Different from the 1% silver sulphadiazine group c: Different from the ozone group. **p<0.01. Hydroxyproline concentration was varied depending on the week in all groups except the control ($p<0.01$).

Histopathological assessments have been shown greater healing in both ozone and silver sulfadiazine groups compared to the control group on 7 and 21 days. Haematoxylin and eosin stained sections of granulation tissue collected were examined on 7th and 21st days. The level of the inflammation was decreased and fibrosis area was abated as a result of treatment with ozone (Table 3, 4, and 5).

Table 3. Score of the inflamation in the samples taken at the end of 1st and 3rd weeks (7th and 21st days) is presented on burn wound healing model in rats for all groups**.** Values are presented as the Mean±SD. (n=10).

	Control[a,b,c] (n=10)	**Burn+Normal Saline[b,c] (n=10)**	**1% silver sulphadiazine[c] (n=10)**	**Ozone/Oxygen mixture dissolved in saline(n=10)**	
Inflamation (1st Week)	0.00±.0.00	2.00±0.82	1.20±0.42	1.20±0.42	**
Inflamation (3rd Week)	0.00±.0.00	1.20±0.42	1.10±0.74	0.90±0.74	

a:Different from the normal saline group b: Different from the 1% silver sulphadiazine group c: Different from the Ozone group. **p<0.01 Inflamation was varied depending on the week in all groups except the control (p<0.01).

Table 4. Score of the granulation in the samples taken at the end of 1st and 3rd weeks is presented on burn wound healing model in rats for all groups**.** Values are presented as the Mean±SD (n=10).

	Control[a,b,c] (n=10)	**Burn+Normal Saline[b,c] (n=10)**	**1% silver sulphadiazine[c] (n=10)**	**Ozone/Oxygen mixture dissolved in saline(n=10)**	
Granulation (1st Week)	0.00±.0.00	2.80±0.42	2.10±0.57	1.60±0.52	**
Granulation (3rd Week)	0.00±.0.00	1.50±0.53	1.20±0.63	1.10±0.57	

a: Different from the normal saline group b: Different from the 1% silver sulphadiazine group c: Different from the ozone group. **p<0.01; Granulation was varied depending on the week in all groups except the control (p<0.01).

Table 5. Score of the fibrosis the samples taken at the end of 1st and 3rd weeks is presented on burn wound healing model in rats for all groups**.** Values are presented as the Mean±SD (n=10).

	Control[a,b,c] (n=10)	**Burn+Normal Saline[b,c] (n=10)**	**1% silver sulphadiazine[c] (n=10)**	**Ozone/Oxygen mixture dissolved in saline(n=10)**	
Fibrosis (1st Week)	0.00±.0.00	2.20±0.63	1.90±0.32	1.60±0.52	**
Fibrosis (3rd Week)	0.00±.0.00	2.00±0.00	1.40±0.52	1.40±0.52	

a: Different from the normal saline group b: Different from the 1% silver sulphadiazine group c: Different from the ozone group. **p<0.01. Fibrosis was varied depending on the week in all groups except the control (p<0.01).

Granulation tissue whichwell-organizated was observed in rats that treated with ozone compared to control group on 21st day. A greater reduction on level of granulation was observed in treated with ozone rats on 7thdayaccording to 21stday, whereas organization of granulation tissue was escalated in the group of burn+normal saline. Macroscobic healing have showed differences in all groups except control group. A better macroscobic healing was observed in ozone treated according to silver sulfadiazine on 21st day (Table 6).

Table 6. Score of the macroscobic healing are presented for all groups.

	Control[a,b,c] (n=10)	**Burn+Normal Saline[b,c] (n=10)**	**1% silver sulphadiazine[c] (n=10)**	**Ozone/Oxygen mixture dissolved in saline(n=10)**	
Macroscobic Healing Scor (1st Week)	0.00±0.00	6.80±1.32	5.70±1.25	6.10±0.57	
Macroscobic Healing Scor (2nd Week)	0.00±0.00	2.30±1.06	1.90±1.29	1.10±0.57	*
Macroscobic Healing Scor (3rd Week)	0.00±0.00	0.60±0.69	0.20±0.42	0.20±0.42	

a:Different from the normal saline group b: Different from the 1% silver sulphadiazine group c: Different from the ozone group. *p<0.05. Macroscobic healing was varied depending on the week in all groups except the control (p<0.05).

DISCUSSION

Deterioration of the skin usually leads to infection, scarring, increased fluid loss, hypothermia, compromised immunity and altered in body image (9, 10). All these factors are very important; besides, enlarged skin damage can end up with mortality. The mortality rate from burns has rejected in the past decade; however, it is still high if more than 70% of the body surface is burned (11). Burns are classified according to the depth of the injury. In superficial second-degree burns, the epidermis and the superficial dermis are mainly affected. These kinds of burns are very painful. The main reasons of a superficial second-degree burn are hot liquids (12). Healing of skin wounds is a quite complicated process containing many mechanisms, such as inflammation, epidermal regeneration, fibroblast proliferation, neovascularization and synthesis, coagulation, matrix synthesis and deposition, angiogenesis, and epithelization (13-15). Although there have been some developments, the best treatment is still unclear. Ozone is a potent oxidizing agent and an important disinfectant. The bactericidal effect of ozone is based on a direct attack on microorganisms by oxidation of biological materials (16, 17). Datas have been shown that bacteria, spores, and viruses are inactivated by ozone after only few minutes (18, 19). Ozone may act through mechanisms other than oxidation, including the activation of erythrocyte metabolism and immune cells (20, 21). Besides, the explanation of the disinfectant activity and the activation of immune system of ozone has been reported (18). Either ozonated bidistilled water or oil have been used in treatment of war wounds, anaerobic infection, trophic ulcers and burns (22). Enhancement of circulation with ozone therapy may provide normal healing with removal of the breakdown products, unclogging the blood vessels, resulting in increased oxygenation of the tissues (6, 23-25). It seems likely that ozone therapy prevents smooth muscle death, by supporting increased O_2 and Adenosine Triphosphate (ATP) to injured cells, which decrease the fibroplasia during healing of corrosive esophageal burns. However, our findings provide a novel therapeutic agent for skin injuries in humans have shown the beneficial action of ozone. Several experimental studies have been shown that ozone therapy ameliorates the tissue injury depends on free radicals in various forms of shock, stroke, inflammation, and reperfusion injury (6, 23, 24, 26, 27). In addition, it is reported that ozone enhances the glycolysis enzymatic pathway in ATP production. This is significant in the management of stroke and burns (23). From these studies, it can be concluded that ozone therapy has beneficial effects on healing and preventive effects on the generation of fibrosis in skin burn in rats. Also, in the study of caustic esophageal burn is demonstrated that collagen deposition in the submucosa and damage to the muscular is mucosa and tunica muscular is in the ozone treatment group was found less than in the un-treatment group and these histopathologic findings showed correlation with hydroxproline levels (28). A significant difference was determined between the topically applied ozone compared to the control group in the acute cutaneous wound healing created in pigs (28). Martinez-Sanchez et al. have evaluated the efficacy of ozone therapy in the patients with diabetic foot and remarked to be expedited wound healing and increased antioxidant enzyme activities in patients used ozone therapy compared to used antibiotic therapy (29).

Different experiment animals such as Guinea pig (30) and rat (31, 32) were used in various studies. We have used rat model in the present study similar to some investigators (31, 32). The model used in the experiment is simple and repeatable. The burned wound healing model provides *in-vivo* approach on the healing of burned wounds in domestic animals.

The pentose phosphate pathway is a key section of metabolism and composed of the oxidative portio and the non-oxidative portio. The NADPH is important co-factor for many enzymatic reactions enable cells to counterbalance the oxidative stress via the generation of glutathione (GSH) by GR. The pentose phosphate pathway is one of the major sources of reduction equivalents for the glutathione peroxidase/glutathione reductase (GPx)/GR antioxidant system. The oxidative pentose phosphate pathway is known as one of the basic regions of NADPH production in cell and catalyzed by some enzymes as G6PD, G6PD. G6PDis the first enzyme in the pentose phosphate pathway (33). It catalyses the oxidation of glucose-6-phosphate using $NADP^+$, yielding pentose phosphates for nucleotides synthesis, as well as NADPH/NADH for reductive biosynthesis and protection from oxidative stress (34). G6PD is the main intracellular source of NADPH generation, involved in diverse physiological processes. Moreover, increasing evidences have pointed that NADPH play a fundamental role as a common mediator of numerous biological processes such as carbohydrate metabolism, mitochondrial functions, calcium homeostasis, oxidative stress generation, immunological functions, aging and cell death (35). The redox status of the cell is the key regulator of energy production and intermediary metabolism which play a crucial role in the repair process. As a consequence, this enzyme finds numerous applications in medical and biochemical studies (36). Recently, we discovered that 6PGD also plays a role in human cancer (37). Antioxidant effect may also help to control wound oxidative stress and thereby accelerate wound healing (38).

We have found that bioenergetic pathways including tissue 6PGD, GR and G6PD enzyme activities were decreased in burn+normal saline

group, whereas they were increased treatment of ozone in rats. Several studies have been revealed that reactive oxygen species are generated at the burn site immediately after injury and these radicals causes tissue injury (39-43). On the other hand, it is well documented that ozone stimulates the production of interferon and interleukins in the body. Therefore, ozone may have a possible beneficial effect to reduce tissue damage by enhanced antioxidant enzyme activity (6, 26). Also, ozone is known as an activator of the immune system, namely, based on reports related to diseases characterized by immuno-depression such as chronic viral diseases, cancer and AIDS (6, 23, 25). This study demonstrated that ozone treatment lead to a significantly increase of G6PD activity which might collectively maintain the redox environment of the cell. This indicates that ozone causes the cellular machinery to resort to those biochemical and molecular responses which fasten the healing mechanism post-burn injury.

CONCLUSION

The purpose of this study is to determine the role of topical treatment with ozone on burn wound healing in rats. The present study shows that in burn wound healing has a significant improvement by ozone. Also, our findings demonstrates that ozone are safe for topical use. There was no withdrawal or serious adverse reaction reported. However, these events were common signs and symptoms in burns, and they were present in both the ozone, silver sulfadiazine and the burn groups. Further studies is necessary to understand the molecular mechanism of action of ozone on burn wound healing.

Conflict of interest statement: All the authors indicate that they have no financial and/or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

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RESEARCH ARTICLE

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Investigation of Serum Seladin-1/DHCR24 Levels in Breast Cancer Patients

ABSTRACT

Objective: Seladin-1, an enzyme that catalyzes the cholesterol formation reaction from desmosterol, has been shown to be expressed at different levels in various types of tumor. The purpose of this study was to investigate the relationship between serum seladin-1 levels and clinical characteristics of patients with non-metastatic breast cancer, and to examine the prognostic value of seladin-1 in breast cancer.

Methods: Patients aged 18 and over diagnosed with breast cancer using histopathological methods at our medical oncology clinic, whose tumor tissue had been surgically removed and who had not yet received any oncological treatment, and with no distant organ metastasis or additional malignancy, and healthy women volunteers as a control group were included in the study. Demographic and laboratory data were recorded. Serum seladin-1 levels were compared between the patient and control groups.

Results: Seventy-three women, 46 patients and 27 controls, were enrolled. Mean ages were 56±12 years in the patient group and 62±12 in the control group (p=0.055) Seladin-1 levels were lower in the patient group than in the control group (p=0.038). No statistically significant relationship was observed between tumor size and seladin-1 levels (p=0.138). No relationship was also determined between patient grades and stages and seladin-1 (p=0.720; p=0.092, respectively).

Conclusions: Seladin-1 levels were lower in the serum of breast cancer patients than in the control group. However, no statistically significant relationship was found between breast cancer prognostic factors and seladin-1 levels. Further research is needed to clarify the mechanisms underlying the low seladin-1 levels in breast cancer patients.

Keywords: Breast Cancer, Seladin-1, DHCR24, Prognostic Value

Meme Kanserli Hastalarda Serum Seladin-1/DHCR24 Düzeyinin Araştırılması

ÖZET

Amaç: Meme kanseri kadınlarda önemli bir morbidite ve mortalite nedenidir. Desmosterolden kolesterol oluşum reaksiyonunu katalizleyen enzim olan Seladin-1 daha önce çeşitli tümör türlerinde farklı düzeylerde exprese edildiği gözlenmiştir. Çalışmamızda; serum seladin-1 düzeyleri ile metastatik olmayan meme kanseri hastalarının klinik özellikleri arasındaki ilişkiyi ve seladin-1'in meme kanserinde prognostik değerini araştırmayı amaçladık.

Gereç ve Yöntem: Tıbbi onkoloji kliniğimizde, 18 yaş üstü, histopatolojik olarak meme kanseri tanısı almış, cerrahi olarak tümör dokusu çıkarılmış, herhangi bir onkolojik tedavi henüz almamış, uzak organ metastazı ve ek malignitesi olmayan hastalar ile kontrol grubu olarak sağlıklı kadın gönüller çalışmaya dahil edildi. Demografik veriler ve laboratuvar verileri kaydedildi. Serum seladin-1 düzeyleri hasta ve kontrol grupları arasında karşılaştırıldı.

Bulgular: 46 hasta ve 27 kontrol grubu olmak üzere toplam 73 kadın hasta çalışmaya dahil edildi. Hasta grubunun yaş ortalaması 56±12 yıl, kontrol grubunun 62±12 yıldı (p=0.055) Seladin-1 düzeyleri gruplar arasında karşılaştırıldığında; hasta grubunda kontrol grubuna göre daha düşük seviyede saptandı (p=0.038). Tümör boyutları ile Seladin-1 düzeyi arasında istatistiksel bir ilişki yoktu. (p=0.138). Bunun yanında, hastaların stage ve gradelerine göre seladin-1 düzeyi karşılaştırıldığında istatistiksel fark olmadığı görüldü (p=0,720; p=0,092, sırasıyla).

Sonuç: Çalışmamızda meme kanseri hastalarının serumlarında seladin-1 düzeyi kontrol grubuna göre daha düşük saptandı. Ne var ki, meme kanserinin prognostik faktörleri ile seladin-1 düzeylerinin ilişkili olmadığı görülmüştür. Seladin-1'in meme kanserli hastalarında düşük olmasının altında yatan mekanizmaların aydınlatılabilmesi için daha ileri araştırmalar gerekmektedir.

Anahtar Kelimeler: Meme Kanseri, Seladin-1, DHCR24, Prognostic Değer

INTRODUCTION

Breast cancer is the most frequent cancer and the second major cause of cancer-related deaths in women (1, 2). The global prevalence of breast cancer is also increasing. However, despite this increase, survival rates have improved continually in recent years thanks to intensive research and new therapeutic modalities (3, 4). However, survival rates and quality of life can also decrease significantly once failure in treatment occurs. Finding a reliable prognostic factor capable of improving survival is therefore of great importance.

Selective Alzheimer Disease Indicator-1 (Seladin-1), also known as DHCR24 for 24-dehydrocholesterol reductase, is an enzyme that catalyzes cholesterol formation from desmosterol (5), The name derives from its being less expressed in brain specimens from Alzheimer's patients compared to healthy individuals (6). It has also been found to prevent neuron degeneration in the brain with its anti-apoptotic functions (7). Seladin-1 is a multifunctional protein expressed by the DHCR24 gene. It is associated with oxidative stress, cell proliferation, anti-apoptotic, and anti-inflammatory effects (8). Seladin-1 acts by inhibiting activation of caspase 3, an important apoptosis modulator (9). DHCR24 was determined to be associated with cell differentiation and senescence in a study of DHCR24 gene knockout mice (10) However, the cytoprotective mechanisms of seladin-1 have not been fully explained. For example, the response to acute and chronic oxidative stress differs. In acute oxidative stress seladin-1 expression is up-regulated by increasing intracellular cholesterol synthesis, while in chronic oxidative stress it is down-regulated (11). Due to the cytoprotective effect of seladin-1, its role in various cancers has also been investigated, including melanoma, adrenal cancer, bladder cancer, pituitary tumors, prostate cancer, and endometrium cancer (12-17). However, seladin-1 has been observed to be expressed at different levels in these cancer types compared to normal tissues.

The aim of this study was to investigate the prognostic value of serum seladin-1 by analyzing its levels and the clinical features of patients with non-metastatic breast cancer.

MATERIAL AND METHODS

Participants: Forty-six patients aged 18 and over diagnosed with breast cancer using histopathological methods at the Duzce University Medical Faculty Medical Oncology Clinic, whose tumor tissue had been surgically removed and who had not yet received any oncological treatment, and with no distant organ metastasis or additional malignancy, and 27 healthy women were included in the study.

Individuals aged under 18, pregnant women, and individuals with additional malignancy, distant organ metastasis, and acute or chronic infection were excluded. Informed consent forms were obtained from all participants. Demographic data and laboratory parameters of both groups were analyzed.

Sample Collection and Biochemical Analysis: Blood samples were collected following 12-14 h fasting. Serum was separated by centrifugation for 10 min at 4000 rpm. Routine parameters were investigated using photometric methods at the Biochemistry Laboratory Research Hospital with the help of an IDS B0728 auto Seladin-1 levels were determined using a commercially available ELISA kit (ABIN1129410, Biocompare, Georgia) with spectrophotometric methods. Concentrations of seladin-1 in samples were determined by comparison of ODs against a standard curve at 250 nm**.**

Statistical Analysis: Statistical analyses were performed on SPSS (Statistical Package for Social Sciences) for Windows 22 software. The Kolmogorov–Smirnov test was employed to assess the distribution of variables. Results were expressed as mean ± standard deviation and median (min-max). P data were compared using the independent-samples t-test in case of parametric parameters, or using the Mann-Whitney U test for non-parametric parameters. The chi-square or Fisher exact tests were applied for the comparison of qualitative data. $p<0.05$ was regarded as statistically significant.

Ethics: This study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrolment. The study protocols and consent forms were approved by the ethics committee of the Duzce University Medical Faculty (approval number: 2019/136).

RESULTS

Seventy-three women, 46 patients and 27 controls were included in this study. The mean ages were 56±12 years in the patient group and 62±12 in the control group (p=0.055). Body mass index values were 30.60±5.49 kg/m^2 in the patient group and 29.43±4.23 kg/m^2 in the control group (p=0.374). No statistically significant difference was determined in lipid parameters between the groups (p>0.05). Seladin-1 levels were lower in the patient group than in the control group (0.28461±0.10181 ng/ml vs 0.40530±0.15130 ng/ml respectively, p=0.038). Basic characteristics and laboratory parameters of the patient and control groups are summarized in Table 1.

Table 1. A comparıson of patıent and control group parameters

Parameters	Patients n=46	Controls n=27	*P*
Age (year), mean±SD	56±12	62±12	.055
Comorbids (n)			
Diabetes Mellitus	12	3	.353
Hypertension	18	12	.299
Hyperlipidemia	4	1	.323
Weight (kg)	75.98±12.92	72.43±14.23	.423
BMI kg/m^2	30.60±5.49	29.43±4.23	.374
Waist circumference (cm)	98.07±14.64	95±12.3	.612
Glucose (mg/dl)	112.97±42.01	120.80±59.98	.563
HOMA-IR (mg/kg^2)	4.6±2.1	4.1±1.5	.683
Total cholesterol (mg/dl)	212.06±38.54	214.40±31.31	.907
LDL (mg/dl)	132.83±34.18	118.31±14.27	.355
Trygliseride (mg/dl)	163.70±96.44	162.14±80.61	.973
ALT (U/L) Median (min-max)	15.82(5.40-79.10)	16.77(7.45-38.51)	.494
Urea (mg/dl)	29.78±9.07	33.82±9.42	.119
Creatinin (mg/dl)	0.68±0.15	0.67±0.13	.812
WBC (mm^3x10^3)	6.09±1.92	7.33±2.98	.051
ESR (mm)	30.20±17.92	24.61±16.49	.415
Seladin-1 (ng/ml)	0.28461±0.10181	0.40530±0.15130	.038*

*p<0,05; BMI: Body Mass Index, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, LDL: Low-density lipoprotein, ALT: Alanine transaminase WBC:White Blood Cell ESR: erythrocyte sedimentation rate

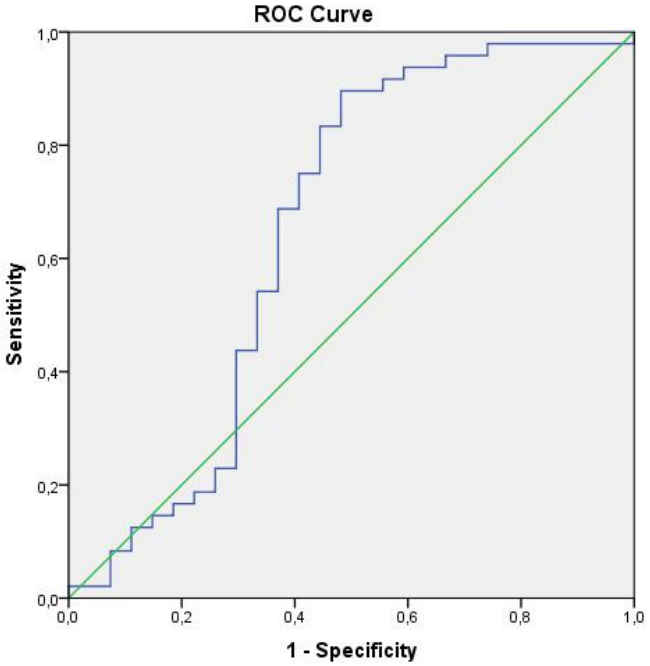
A family history of breast cancer was present in 20 patients (43.5%), but not in 26 (54.3%) (p=0.698). There was no statistically significant association between tumor size and seladin-1 levels (p=0.138). In addition, no statistically significant difference was observed when seladin-1 levels were compared in terms of patients' grades and stages (p=0.720 and p=0.092, respectively). A comparison of patients' seladin-1 levels and clinicopathological characteristics is summarized in Table 2.

Table 2. Relations between patients' clinicopathological factors and seladin-1

Charecteristic	n (%)	Serum Seladin-1 level. median (min-max)	*P*
Age			
≤45 y	10 (21.7)	0.2507 (0.1164-0.3309)	.456
>45 y	36 (78.3)	0.2430 (0.1977-1.6006)	
Family History			
Positive	20 (43.5)	0.2451 (0.1977-1.6006)	.698
Negative	26 (54.3)	0.2437 (0.1164-0.4961)	
Tumor size			
T1	21 (45.7)	0.2373 (0.1977-0.2978)	
T2	22 (47.8)	0.2455 (0.1164-1.6006)	.138
T3	3 (6.5)	0.3046 (0.2391-0.3654)	
Metastatic LAP			
Positive	12 (26)	0.2438 (0.2217-0.3654)	1.000
Negative	34 (74)	0.2472 (0.1977-1.6006)	
Stage			
I	15 (32.6)	0.2381 (0.1977-0.2978)	
II	15 (32.6)	0.2437 (0.1986-1.6006)	.720
III	16 (34.8)	0.2455 (0.1164-0.3654)	
Grade			
I	3 (7.7)	0.2250 (0.2225-0.2824)	.092
II	27(69.2)	0.2431 (0.1977-0.3309)	
III	9 (23.1)	0.2629 (0.1986-0.4961)	
ER			
Positive	39 (84.8)	0.2439 (0.1164-1.6006)	.771
Negative	7 (15.2)	0.2431 (0.1986-0.4961)	
PR			
Positive	38 (82.6)	0.2443 (0.1160-1.6006)	.908
Negative	8 (17.4)	0.2357 (0.1986-0.4961)	
CERBB2			
Positive	18 (39.1)	0.2434 (0.1164-0.4961)	.770
Negative	28 (60.9)	0.2443 (0.2102-1.6006)	
Ki-67			
<14%	14 (32.6)	0.2438 (0.2102-0.3135)	.876
≥14%	29 (67.4)	0.2431 (0.1164-0.4961)	
LVI			
Positive	24 53.3	0.2443 (0.1977-0.3654)	.802
Negative	21 46.7	0.2431 (0.1164-1.6006)	
PNI			
Positive	12 (26.1)	0.2530 (0.1164-0.3654)	.230
Negative	34 (73.9)	0.2430 (0.2211-1.6006)	

ER=estrogen receptor . PR=progesterone receptor

The area under the curve (AUC: 0.651) for seladin-1 was analyzed in all groups to confirm whether seladin-1 serum level may be a reliable predictor of breast cancer. The cut-off point identified for seladin-1 was 0.2735 ng/mL, and this exhibited 75% sensitivity, 59.2% specificity, a 76.5% positive predictive value (PPV), and a 57.1% negative predictive value (NPV) at receiver operator characteristic (ROC) analyses (p=0.031). The results are shown in Figure 1.



AUC	Cut-off	Sensitivity	Spesivity	PPV	NPV	*P*
0.651	0.2735	75%	59.2%	76.5%	57.1%	.031*

*p<0.05 **p<0.001

Figure 1. ROC analysis of seladin-1 levels between the patient and control groups

DISCUSSION

Our findings revealed lower serum seladin-1 in breast cancer patients than in the control group. Nonetheless, prognosis did not vary in line with serum seladin-1 levels. The present research is the first study to investigate seladin-1 in patient serum.

DHCR24, an enzyme that catalyzes cholesterol formation from desmosterol, was given the name seladin-1 due to its being downregulated from the brains of Alzheimer's patients and to its neuroprotective characteristics (18). Seladin-1 expressed at high levels from brain cells has also been shown to exhibit a protective role against oxidative stress-related neuron apoptosis (9, 14, 19). Seladin-1 is expressed at varying levels from different tissues and tumors (20, 21). It also contributes significantly to cell survival and death regulation (22).

The role of seladin-1 in various types of cancer has also previously been investigated. In one such study, Wu et al. determined a high level of upregulation of endogenous seladin-1 levels in oxidative stress (23). One noteworthy finding in that study was that seladin-1 is also associated with the tumor suppressor gene p53. Seladin-1 binds to the p53 amino terminal following exposure to oncogenic and oxidative stress, and displaces E3 ubiquitin ligase Mdm2 from p53, thus leading to p53 accumulation. Additionally, in the light of these data, seladin-1 was shown to prevent senescence Ras/p53-mediated oncogenic signaling supporting the tumor suppression role of p53 (23).

A defect in seladin-1 converted into cholesterol from desmosterol can result in impairment of the lipid cell membrane, free radical activation, and thus cell death (24, 25). One striking piece of evidence for this is 'desmosterolosis syndrome,' a rare autosomal recessive entity characterized by desmosterol accumulation in the body and progressing with severe multiple congenital anomalies developing due to seladin-1 gene mutation. Lipid profiles in this study were similar between the patient and control groups since we anticipated that these might affect seladin-1 levels.

Serum seladin-1 levels were lower in the patient group in the present study. Luciani et al. compared seladin-1 levels in adrenal carcinoma, adrenal adenoma, and normal adrenal gland groups and observed lower seladin-1 levels in the adrenal carcinoma group than in the other groups (26). In another study involving adrenal carcinoma, Simi et al. also reported significantly lower seladin-1 mRNA expression in adrenal carcinomas compared to normal adrenal glands (27). Battista et al.

investigated the relationship between prostate cancer and seladin-1 and reported that seladin-1 expression increased in low-risk prostate cancer while decreasing in advanced prostate cancer (28). They attributed this to seladin-1 expression increasing in order to inhibit cell proliferation as the first stages of cancer develop (low-grade, Gleason grade 3), with this increase probably being in order to slow the progression of the cancer. However, seladin-1 is no able to longer interfere with the progression of high grade (Gleason grade 4 and 5) cancer, with seladin-1 expression being though to decrease as other factors leading to progression of the cancer assume control. This is also supported by Kuehnle et al.'s study of the response of seladin-1 to acute and chronic oxidative stress. Those authors determined that seladin-1 is up-regulated in acute stress, but gives a downregulated response in long-term oxidative stress (10). In that context, the cytoprotective effect of seladin-1 was explained in terms of intracellular cholesterol concentrations increasing by raising seladin-1 levels in exposure to acute oxidative stress (11). In agreement with the previous literature, seladin-1 levels were significantly lower in the patients with breast cancer than in the control group in the present study. However, in contrast to Battista et al.(28) we observed no statistically significant relation between disease prognosis parameters (tumor size, grade, stage, lymph node metastasis, etc.) and seladin-1 levels.

There are several limitations to the present study. Our patient number was low. It would also have been useful to have examined response seladin-1 levels following administration of oncological therapy. In addition, had long-term follow-up been performed an association might have been shown between prognosis and seladin levels depending on whether patients were metastatic or not. However, our patients consisted of newly diagnosed and not yet treated non-metastatic individuals. In addition, seladin levels being lower in the patient group compared to the control group despite the surgical removal of the tumor burden, may also be important in terms of monitoring the benefit of adjuvant oncological therapies.

CONCLUSION

To the best of our knowledge, this is the first study to investigate seladin-1 levels in human serum using ELISA. Selain-1 levels were lower in serum from breast cancer patients compared to the control group, but no association was observed between seladin-1 levels and cancer progression. There is a strong link between seladin-1 and cancer, but this association depends on the type and course of the cancer. Further research is therefore needed to clarify the underlying mechanism involved in the lower serum seladin-1 levels observed in breast cancer patients.

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RESEARCH ARTICLE

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Relationship between Trigeminocardiac Reflex, QT, QTc and Anesthesia in Septorhinoplasty Surgeries

ABSTRACT

Objective: Trigeminocardiac reflex is a reflex characterized by hypotension, bradycardia, gastric hypermotility or asystole that develops as a result of stimulation of the trigeminal nerve. In our retrospective study, in septorhinoplasty operations performed under general anesthesia, trigeminocardiac reflex development was investigated primarily during the periods where the reflex was surgically stimulated. Secondly, the effect of different inhalation anesthetic agents on the emergence of this reflex was investigated.

Methods: Anesthesia notes and Datex Ohmeda icentral central monitor records of septorhinoplasty cases operated between 01 / January / 2016 - 30 / November / 2016 were retrospectively examined and detected through the Hospital Information Management System software. Induction, application of local anesthesia, surgical incision, initiation of incision suturing and 5 minutes after extubation were recorded from the records. It was determined that two different inhalation anesthetics were administered in 60 patients who met the criteria, and analyzes were performed in 2 separate groups as group sevoflurane and group desflurane, and the development of QT, QTc and Trigeminocardiac reflex was investigated.

Results: Although there was no difference between the groups, when the basal values were compared with the other periods, it was found that the development of TKR and QT and QTc experts were mostly observed in the periods of local anesthesia, surgical incision and incision suturing. ($p < 0.001$).

Conclusions: We think that the inhalation anesthetic agents used mostly in the sevoflurane group play a facilitating role in the development of TKR, especially by creating a cumulative effect during periods when the trigeminal nerve is maximally stimulated.

Keywords: Trigeminocardiac Reflex, QT Intervale, QTc, Electrocardiogram, Anesthesia, Septorhinoplasty

Septorinoplasti Ameliyatlarında Trigeminokardiyak Refleks, QT, QTc ve Anestezi İlişkisi

ÖZET

Amaç: Trigeminokardiak refleks trigeminal sinirin uyarılması sonucu gelişen hipotansiyon, bradikardi, gastrik hipermotilite veya asistoli ile karakterize bir refleksdir. Genel ve lokal anestezi altında yapılan septorinoplasti operasyonları sırasında trigeminokardiyak refleks gelişebildiği gözlenmiştir. Retrospektif çalışmamızda genel anestezi altında yapılan septorinoplasti operasyonlarında birincil olarak cerrahi olarak refleksin uyarıldığı düşünülen periyodlarda trigeminokardiyak refleks gelişimi araştırılmıştır. İkincil olarak da farklı inhalasyon anestezik ajanların bu refleksin ortaya çıkışında etkisi araştırılmıştır.

Gereç ve Yöntem: 01/ Ocak/2016- 30/Kasım/2016 tarihleri arasında opere edilmiş septorinoplasti vakalarının anestezi notları ve Datex Ohmeda icentral merkezi monitör kayıtları ve MİA-MED Hastane Bilgi Yönetim Sistemi yazılımı üzerinden retrospektif olarak incelenerek saptandı. İndüksiyon, sınırlı uyuşturma uygulaması, cerrahi insizyon, insizyon sütürasyonu başlangıcı ve ekstübasyondan 5 dakika sonra değerleri kayıtlardan saptandı. Kriterlere uyan 60 hastada 2 farklı inhalasyon anestezik madde uygulandığı tespit edilerek grup sevofluran ve grup desfluran olarak 2 ayrı grupta analizler yapıldı ve QT, QTc ve Trigeminokardiyak refleks gelişimi araştırıldı.

Bulgular: Gruplar arasında fark olmamasına rağmen bazal değerler ile diğer periyodlar karşılaştırıldığında TKR gelişiminin ve QT, QTc uzmanlarının en fazla lokal anestezi uygulaması, cerrahi insizyon, insizyon sütürasyonu periyotlarında izlendiği saptandı. ($p<0,001$).

Sonuç: En fazla sevofluran grubunda olmak üzere kullanılan inhalasyon anestezik ajanların özellikle trigeminal sinirin maksimal uyarıldığı periyodlarda kümülatif etki yaratarak TKR gelişiminde kolaylaştırıcı bir rol oynadığını düşünmekteyiz.

Anahtar Kelimeler: Trigeminokardiyak refleks, QT intervali, QTc, elektrokardiyogram, anestezi, septorinoplasti.

INTRODUCTION

Trigeminocardiac reflex (TCR) is a type of reflex that is encountered in the practice of anesthesia, and which could even develop to a cardiac arrest and asystole. Controlled, randomized, or retrospective trials are very few in the literature regarding this reflex, which is induced by the stimulation of the trigeminal nerve and its sensory branches in some procedures that involve facial regions, though there are abundant case reports in the literature. Our study aimed to make a contribution to the literature in this regard. Our primary objective is to examine the development of the Trigeminocardiac reflex (TCR) in patients who underwent septorhinoplasty, and our seconder objective is to investigate the contribution of the anesthetic medications to the occurrence of this reflex through the QT and QTc intervals.

MATERIAL AND METHODS

Our study was established through examining retrospectively the anesthesia records of the patients who underwent septorhinoplasty between January 01, 2016, and November 30, 2016, as well as the central monitor records of Datex Ohmeda Icentral, and the software of Hospital Information Management System. Ethical approval of the Local University Clinical Research Ethics Committee was obtained with the decision number 2016/10, and dated January 2nd, 2017.

Patients who have ASA 1-2 physical status concerning the anesthetic risk classification, aged between 18 and 65 years, who were planned to undergo an elective septorhinoplasty surgery and the patients who were induced by propofol, rocuronium, remifentanil and inhaled anesthetic agents as anesthetic agents were included in the reviewing.

Patients; who have cardiac pathology, congenital, and acquired long QT syndrome, who receive medications that lead to prolongation of the QT-interval, who receive antiarrhythmic drugs, who have electrolyte disorders, renal failure, thyroid hormone disorders, liver failure, and pregnant women were excluded from the study.

Given the fact that the challenges that might be experienced throughout the intubation and the number of multiple intubation attempts might impact the heart rate adversely, patients who were recorded to had been intubated in more than 2 attempts were excluded from the research.

Data acquisition: The values of all patients who underwent septorhinoplasty between January 1st, 2016, and November 30th, 2016 that includes the data related to induction, local anesthesia, surgical incision, the initiation of incision suturing and 5 minutes after extubation were filled in the anesthetic follow-up forms routinely. Concurrently, the vital parameter and electrocardiogram records of the patients were retrospectively obtained from the patient registry, which is recorded incessantly on to the external memory device from the Datex-Ohmeda Icentral L-NET (C) 05, software system, version 5.1 of the main computer that is located at in the operating room. The values of QT and QTc were evaluated and calculated based on these records. Bazett's formula was used manually for the calculation of QTc. The amount of administered medication, durations of anesthesia and surgery were determined through anesthesia follow-up forms, and the software of the MIA-MED Hospital Information Management System.

Heart rates and non-invasive blood pressure values, as well as peripheral oxygen saturation, and end-tidal carbon dioxide (EtCO2) values of the patients throughout the related durations were obtained from the anesthetic records. Upon examining the data retrospectively, it was determined that 2 different inhaled agents were administered in all patients who underwent septorhinoplasty. The patients were divided into 2 groups regarding these inhaled anesthetic agents, and these groups were also compared statistically among themselves in addition to the general assessment. Patients were subdivided as Desflurane Group (The group administered with Desflurane) and Sevoflurane Group (the group administered with sevoflurane) based on the administration of the inhaled anesthetic agents. It was determined from the surgical records and through the software of the Hospital Information Management System that the solution of adrenaline at a concentration of 1: 80000 with prilocaine 2% was administered to all groups as a local anesthetic solution during the mucosal injection.

Identification of TCR: Having a decrease in heart rate below 60 beats/min or 20% or more of baseline measurement values, namely bradycardia, and/or development of asystole was considered as TCR. Meanwhile, a decrease of 20% or more in the mean values of arterial blood pressure from the baseline measurement values were considered to be hypotension (1).

Statistical Analysis: Descriptive statistics (values of mean, standard deviation, median, minimum, maximum, percentage) of all variables, which were involved in the study, were computed. The normality assumption of quantitative variables was analyzed through the Shapiro-Wilk test. Independent samples t-test and Mann-Whitney U-test were conducted for group comparisons. In order to compare the time-dependent variables, Repeated Measures ANOVA (either post hoc Tukey' HSD test or Dunn's test) was used. Relationships between qualitative variables were analyzed through the Pearson's Chi-Square test. The software of SPSS 22 was used for statistical analyses, and results were considered statistically significant at $p < 0.05$.

RESULTS

It was found that a total of 60 patients had undergone a septorhinoplasty procedure. There is no statistically significant difference between the groups regarding gender (p=0.562) (Table 1).

In addition to that, there was no significant difference between the groups in terms of age, weight, duration of anesthesia and surgery. The median value of the anesthesia score in the sevoflurane group was significantly higher compared to the value measured in the desflurane group (p=0.010) (Table 1).

Table 1. Demographic data. Anesthesia risc score was found to be higher in the desflurane group. All other features are homogeneously distributed between the 2 groups.

		Desflurane (n.30)	Sevoflurane (n:30)	p
Age	Mean± Std. Deviation	35.00±11.75	37.97±12,69	0.351
	Median	35.00	36.50	
Weight (kg)	Mean± Std. Deviation	74.13±12.85	75.07±10.75	0.761
	Median	75.00	75.00	
Anesthesia Risc Score	Median	1.00	2.00	0.010*
Duration of anesthesia (minute)	Mean± Std. Deviation	93.23±44.64	89.23±35.85	0.900
	Median	83.50	85.00	
Duration of operation (minute)	Mean± Std. Deviation	83.77±42.63	79.00±35.22	0.796
	Median	75.00	72.50	
Gender	Female (number)	12 (54%)	10 (45.5%)	0.592
	Male (number)	18(47.4%)	20 (52.6%)	0.592

There was no significant difference between the groups regarding total propofol dose, total rocuronium dose (mg), and total remifentanil dose (mcg) (p> 0.05) (Table 2).

There was no significant difference between the groups in terms of systolic blood pressure (SBP) values that were measured at different periods (p=0.311). However, it was determined that SBP values in both groups significantly changed depending on time (p <0.001).

Table 2. Except for sevoflurane and desflurane drug amounts, there is no difference between drug doses used. (Mean± Std. Deviation)

	Desflurane (n:30)	Sevoflurane (n:30)	p
Total propofol dose (mg)	186.33±.12	184.50±22.45	0.516
Total rocuronium dose (mg)	54.67±10.90	57.17±9.26	0.536
Total remifentanyl dose (μg g)	350.30±178.44	332.43±116.64	0.935
Total inhalated Anesthetic agent dose (mL)	93.34±71.78	50.35±30.42	0.396

In the desflurane group, the basal SBP value was significantly higher compared to the values, which were measured following the mucosal injection and mucosal incision, as well as the values during the incision suturing (p <0.001). The measurement value 5 minutes after intubation is significantly higher than the measurement values after mucosal incision, during the incision suturing (p=0.049), and 5 minutes after extubation (p <0.001). Whereas, SBP measurement value following the mucosal injection is significantly lower than the value that was measured 5 minutes after extubation (p <0.001). Furthermore, the SBP value, which was measured following the mucosal incision, is significantly lower than the value that was measured 5 minutes after extubation (p <0.001). Yet, the SBP value that was measured 5 minutes after extubation is significantly higher than the value measured during the incision suturing (p <0.001).

Meanwhile, it was detected that the basal SBP value in the sevoflurane group was significantly lower compared to the values that were measured after mucosal injection and mucosal incision, as well as the value, measured during incision suturing (p <0.001). The SBP value of 5 minutes after intubation was determined to be significantly higher than the values that were measured during the incision suturing and after the mucosal incision (p<0.001). Moreover, It was determined in the sevoflurane group that value of SBP following the mucosal injection was significantly higher compared to the values measured after mucosal incision and after incision suturing (p <0.001), whereas it was significantly lower than the value, which was measured 5 min after extubation (p=0.002). Besides, it was found that SBP value among the sevoflurane group, which was measured 5 minutes after extubation, was significantly higher compared to the values of SBP that were measured following the mucosal incision and during incision suturing (p <0.001).

There was no significant difference between the groups regarding diastolic blood pressure (DBP) values that were measured in different periods (p=0.312). However, it was determined that DBP values in both groups changed significantly over

time (p<0.001). Basal DBP value in the desflurane group was significantly higher compared to the values, which were measured after the mucosal injection and mucosal incision, as well as the values during the incision suturing (p <0.001). The value, which was measured 5 min. after intubation, was significantly higher than the value measured during incision suturing as well as the values that were measured after mucosal injection, and mucosal incision (p <0.001); however, it was significantly lower than the value, which was measured 5 min. after extubation (p=0.021). Meanwhile, DBP value, which was measured after mucosal injection, was significantly lower than the value measured 5 minutes after extubation (p<0.001). Furthermore, DBP value, which was measured after mucosal incision, was significantly lower compared to the value that was measured 5 minutes after extubation (p<0.001). The DBP value, which was measured 5 minutes after extubation, was significantly higher than the value that was measured during the incision suturing (p<0.001). Moreover, it was determined that the basal value of DBP in the sevoflurane group was significantly higher than the values that were measured following the mucosal injection and after the mucosal incision, as well as the value, measured during the incision suturing (p <0.001). It was detected that the DBP value of the sevoflurane group, which was measured 5 minutes after intubation, was significantly higher than the values measured following the mucosal injection and after mucosal incision, as well as during incision suturing (p <0.001). In the sevoflurane group, DBP value that was measured after mucosal injection was significantly higher than the value, which was measured after mucosal incision (p <0.001), whereas it was significantly lower than the value, which was measured 5 minutes after extubation (p<0.001). Besides, the DBP value in the sevoflurane group, which was measured 5 min. after extubation was significantly higher compared to the DBP values that were measured after the mucosal incision and during incision suturing (p<0.001).

There was no significant difference between the groups in terms of CO2 measurement values that were measured at different durations (p=0.595). However, it was determined that CO2 values in both groups changed significantly over time (p<0.001).

Basal CO2 value in the desflurane group was significantly higher compared to the values that were measured after the mucosal injection and during the incision suturing (p<0.001). Moreover, the value, which was measured 5 minutes after intubation, was significantly higher than the value that was measured during the incision suturing (p<0.001) (Table 3).

Table 3. Mean blood pressure, heart rate, oxygen saturation QT and QTc values in the desflurane group.(Mean± Std. Deviation)

Desflurane (n=30)	Basal	After 5 minutes of intubation	After mucosal injection	After mucosal incision	After incision suturation	5minutes After extubation
Mean arterial pressure (mmHg)	95.17±10.04	89.03±15.09	80.27±11.74 p<0.001 $^{\alpha}$	72.30±9.84 p<0.001$^{\alpha}$	77.40±14.97 p<0.001$^{\alpha}$	100.3±9.48
Heart rate (beat per minute)	72.93±6.63	87.13±12.23 p<0.001	80,03±15,77 p<0.001	75.43±12.74	65,03±10,76 p<0.001 Σ	81.07±11.97 p<0.001
QT (msn)	374.43±27.48	364.97±47.67	381.97±41.25 p<0.001$^{\&}$	386.30±32.33 p<0.001$^{\&}$	390.00±38.90 p<0.001$^{\&}$	365.43±26.81
QTc	383.70±23.63	388.57±38.38	401.20±21.16	405.87±31.97	402.97±41.08	388.23±18.91
End-tidal carbondioxide (mmHg)	39.47±2.67	38.60±11.65	36.63±3.48	35.57±3.46 p<0.001	34.03±3.52 p<0.001	37.13±2.99
Oxygen saturation (%)	97.73±1.31	98,50±0.94	98.40±0.72	98.07±0.78	98.37±1.00	97.87±1.20

& According to the baseline values, there are statistically significant QT prolongations at a statistically high level of values after mucosal injection, mucosal incision, and incision suturing.

α According to the baseline values, there is a statistically significant mean blood pressure in the values after mucosal injection, mucosal incision, and incision suturing.

Σ It is statistically significantly lower than basal values.

Meanwhile, it was detected that the basal CO2 value in the sevoflurane group was significantly higher than the values that were measured after mucosal injection and during the incision suturing (p<0.001). The value of CO2 in the sevoflurane group, which was measured during the incision suturing, was significantly lower compared to the values that were measured 5 minutes after intubation, and mucosal injection, as well as the values measured after mucosal incision, and 5 minutes after extubation (p<0.001) (Table 4).

There was no significant difference between the groups regarding the values of heart rate (HR) that were measured in different periods (p=0.467). It was found out that HR values in both groups varied significantly throughout the period (p<0.001) (Table 4).

Table 4. Mean blood pressure, heart rate, oxygen saturation QT and QTc values in sevoflurane group. (Mean± Std. Deviation)

Sevoflurane (n=30)	Basal	After minutes	After mucosal injection	After mucosal incision	After incision suturation	5minutes after extubation	p Ω
Mean arterial pressure (mmHg)	97.47±13.03	95.23±17.22	86.47±16.72 p=0.014	72.80±12.37 p<0.001	77.37±10.48 p<0.001	100.87±12.52	0.561
Heart rate (beat per minute)	74.07±11.33	85.47±9.58 p<0.001	76.50±14.41	71.93±11.11	65.50±8.63 p<0.001 Σ	75.27±11.87	0.467
QT (msec)	371.43±23.55	372.17±27,00	385.53±22.23 & p<0.001	392.57±32.08 & p<0.001	400.07±32.61 & p<0.001	383.60±24.37	0.203
QTc	387.17±21.54	396.17±22.81	401.30±22.70 & p<0.001	403.50±19.70 & p<0.001	406.83±20.31 & p<0.001	394.10±18.25	0.565
End-tidal carbondioxide (mmHg)	39.47±2.67	38.60±11.65	36.63±3.48	35.57±3.46	34.03±3.52	37.13±2.99	0.595
Oxygen saturation (%)	97.73±1.31	98.50±0.94	98.40±0.72	98.07±0.78	98.37±1.00	97.87±1.20	0.388

& According to the baseline values, there are statistically significant QT prolongations at a statistically high level of values after mucosal injection, mucosal incision, and incision suturing.
Ω These are the p values for the comparison of the values in the sevoflurane and desflurane groups according to the recording periods. Accordingly, there is no significant difference between the groups in all recording periods.
Σ Statistically significantly lower than basal values.

Basal HR value in the desflurane group was significantly lower than the values that were measured 5 minutes after intubation, after mucosal injection and 5 minutes after extubation; whereas, it was significantly higher than the value that was measured during the incision suturing (p<0.001 for each). The value, which was measured 5 min after intubation, was significantly higher than the value that was measured throughout the other periods (for each of them, p<0.001). Besides, the value, which was measured after mucosal injection, was significantly higher compared to the value of incision suturing. The post-mucosal incision value was significantly higher compared to the value that was measured during the incision suturing, whereas it was lower than the value which was measured 5 min after extubation (for each of them, p<0.001). The HR value that was measured 5 minutes after extubation is significantly higher compared to the value measured during the incision suturing (p<0.001) (Table 3).

The basal HR value in the sevoflurane group was significantly lower than the value that was measured 5 minutes after intubation, whereas it was significantly higher compared to the value which was measured during the incision suturing (for each of them, p<0.001). The HR value of the sevoflurane group, which was measured 5 minutes after the intubation, was significantly higher compared to the values that were measured after mucosal injection, after mucosal incision, 5 minutes after incision suturing, and extubation (p<0.001 for each of them) (Table 4).

It was determined that the HR value after mucosal injection was significantly higher than the value that was measured during the incision suturing (p<0.001). In this group, the HR value, which was after mucosal incision, was found to be significantly higher than the value that was measured during the incision suturing (p=0.010). The HR value of the sevoflurane group, which was measured during the incision suturing, was significantly lower compared to the value that was measured 5 minutes after extubation (p=0.010).

There was no significant difference between the groups regarding the QT values that were measured at different periods (p=0,203). However, it was found out that the QT values of both groups varied significantly in the course of time (p<0.001).

The basal QT value of the desflurane group was significantly lower compared to the values that were measured following the mucosal incision and during the incision suturing (For each of them, it was detected to be significantly higher than the value of post-mucosal injection) (p=0.010) (Table 3).

The basal QTc value of the desflurane group was significantly higher compared to the values that were measured after the mucosal injection, and mucosal incision, as well as the value during the incision suturing (p<0.001). Whereas, the value of post-mucosal injection was significantly lower than the post-mucosal incision value and the value that was measured during the incision suturing (for each of them, p<0.001). The QTc value, which was measured 5 min after intubation, was significantly lower compared to the values that were measured after mucosal injection, following the mucosal incision, and during the incision suturing (for each of them, p<0.001). Furthermore, the QTc value, which was measured following the mucosal incision, was significantly higher than the value that was measured 5 minutes after extubation (p<0.001). Besides, the value, which was measured after mucosal injection, was significantly higher compared to the value of incision suturing. The post-mucosal incision value was significantly higher than the value that was measured during the incision suturing, whereas it was lower than the value which was measured 5 min after extubation (for each of them, p<0.001). The QTc value, which was measured 5 minutes after extubation, was significantly lower than the value that was measured during the incision suturing (p<0.001).

The basal QTc value of the sevoflurane group was significantly lower than the values that were measured after mucosal injection and during the incision suturing, whereas it was found to be significantly higher than the value which was after mucosal incision (for each of them, $p<0.001$). The QTc value of the sevoflurane group, which was measured 5 min after intubation, was determined to be significantly higher compared to the values that were measured following the mucosal injection, after mucosal incision, 5 min after incision suturing and extubation (for each of them, $p<0.001$). The QTc value of this group, which was measured after mucosal injection, was found to be significantly higher than the value that was measured after mucosal incision ($p<0.001$), whereas it was significantly lower than the value that was measured during the incision suturing ($p=0.022$). QTc value that was measured after mucosal incision was found to be significantly lower compared to the value, which was measured during the incision suturing and 5 minutes after the extubation ($p=0.010$). The QTc value of the sevoflurane group, which was measured during the incision suturing, was detected to be significantly higher than the value that was measured 5 minutes after extubation ($p=0.010$).

DISCUSSION

The trigeminocardiac reflex is a type of brainstem reflex. Trigeminocardiac reflex (TCR) is the sudden onset of parasympathetic dysrhythmia, sympathetic hypotension, apnea, or gastric hypermobility during the stimulation of the trigeminal nerve itself or its sensory branches by a mechanical or thermal stimuli (2).

As defined by Schaller et al.; TCR is the sudden decrease in heart rate and mean arterial blood pressure by more than 20% compared to basal values, which occurs due to the physical (mechanical, electrical) or chemical stimulation of the trigeminal nerve and its branches. (3- 5).

Whereas, other sudden autonomic responses that come into existence without any hemodynamic fluctuation were considered as trigeminovagal reflex (TVR), which occurs in response to stimulation of the trigeminal nerve at any point (6-7).

The stimuli that increase the trigeminocardiac reflex most substantially are the stimuli in the form of distension (8). Chowdhury et al. revealed that a moderate stimulus such as suturing the skin could induce a temporary asystole (9). Moreover, it has also been put forward that the bradycardia that is induced by vagal stimulation, which occurs due to the stimulation of nasopharyngeal receptors, is associated with the shortening of the QT interval, which is a measure of simultaneous and ventricular repolarization. It has been disclosed in the literature that simultaneous sympathetic activation, which is combined with parasympathetic, is more effective on cardiac functions (10). Thus, in order to examine the trigeminocardiac reflex that was caused by the stimulation of the trigeminal nerve and its sensory branches, patients who had a single type of surgical intervention, namely septorhinoplasty, were included in this study. Through this methodology, it was intended to prevent the potentially misleading and possible deviations that might occur during diagnosis due to the different types and duration of the stimulus as well as because of the different medications. Hence, it was attempted to uniform any result that might arise in various formations and to clarify the results. It was investigated through reviewing the records of routine anesthetic follow-up registry retrospectively, designing the inclusion criteria limited and exclusion criteria comprehensive that whether the incidence of TCR in these procedures and the inhaled anesthetic agents, which had been administered, would increase the incidence rate of this reflex. The reason behind the exclusion of fluctuations in specific episodes when performing the reviewing is to try to focus on the incidence of the examined reflex through considering the maximal stimulation points generated by this surgical procedure.

The periods, which are our review based on, are baseline, 5 minutes after intubation, post-mucosal injection, post-mucosal incision, after incision suturing, and 5 minutes after extubation. TCR was detected in 17 of 60 patients through our review. TCR was determined in 6 of 17 patients who developed TCR in 2 separate periods and for 1 of the TCR was detected in 3 separate periods. Of these 17 patients, 8 were from the sevoflurane group, while 9 were from the desflurane group. Of the patients in the sevoflurane group, TCR was determined in one of them in 3 separate periods and 5 of them in 2 periods; while of the 9 patients in the desflurane group, TCR was determined in 1 patient in 2 separate periods (Table 5,6,7).

Table 5. The distribution of those whose mean blood pressure is 20% below the baseline value and whose heart rate is 20% below the baseline value are monitored according to the groups and periods.

Mean blood Pressure 20% Below baseline and Heart rate 20% below baseline value (TCR)	After 5 minutes of intubation	After mucosal injection	After mucosa L incision	After incision suturation	5 minutes After extubation	Total (number)
Group Desflurane (n=30)	0 patient (0%)	2 patient (6.6%)	2 patient (6.6%)	7 patient (26.6%)	0 patient (% 0)	11
Group Sevoflurane (n=30)	0 patient (0%)	1 patient (3.3%)	6 patient (20.0%	6 patient (20.0%)	1 patient (3.3%)	14

Table 6. The distribution of values with heart rate below 20% of the baseline value according to groups and periods is monitored.

Heart Rate 20% below baseline	After 5 minutes of intubation	After mucosal injection	After mucosal incision	After incision suturation	5 minutes after extubation
Group Desflurane (n=30)	0 patient (0%)	3 patient (10.0%)	2 patient (6.6%)	10 patient (33.3%)	1 patient (3.3%)
Group Sevoflurane (n=30)	0 patient (0%)	5 patient (16.6%)	5 patient (16.6%)	8 patient (26.6%)	3 patient (10.0%)

Table 7. Only cases with mean blood pressure below 20% of the baseline value are monitored according to groups and periods.

Mean arterial pressure 20% below baseline	After 5 minutes (	After mucosal injection	After mucosal incision	After incision suturation	5 minutes after extubation
Grup Desflurane (n=30)	9 patient (% 30.0)	11 patient (% 36.6)	18 patient (60.0%)	15 patient (50%)	1 patient (% 3.3)
Grup Sevoflurane (n=30)	7 patient (23.3%)	10 patient (33.3%)	18 patient (60.0%)	13 patient (43.3%)	1 patient (3.3%)

In a prospective study conducted in rhinoplasty procedures in our clinic in 2013, it was revealed that stimulation of the columellar region gave rise to the development of TCR under general anesthesia. In this study, unlike our scan, the periods were recorded based on the milestones including; just before (basal) mucosal injection, during mucosal injection into the columella and nasal dorsum, and at the 1st, 5th, 10th, 30th, and 60th seconds after the mucosal injection. In this study, local anesthetic was injected into the columella area in one group, while local anesthetic was injected into the nasal dorsum in the second group. Meanwhile, for the third group, 2 ml of local anesthetic solution was injected into the mid-columella and anterior maxillary cleft 10 minutes after the injection into the nasal dorsum, and the related data were recorded. TCR was detected in 8 patients in group 1 and 1 patient in group 2. TCR did not occur in group 3. And consequently, it was revealed that an increased incidence of TCR was determined due to the stimulation of the columellar region. It was determined from the surgical records that the same local anesthetic injection protocol was performed routinely in our health care center, similar to the previous study, and it was injected into the columellar region and nasal mucosa (11).

One of our drawbacks for these retrospective reviewing records is that there are no records regarding the depth of anesthesia; and the other one is that the volume of the gas, which was used in the procedures, is not contained in the records.

In a systematic review of the trigeminocardiac reflex, it was reported that the incidence of asystole increased by 1.2 times in surface analgesia; however, when the surface analgesia was compared with deep anesthesia, the risk of asystole increased by 4.5 times (12). It has been revealed in the literature that some medications, which are administered in the practice of anesthesia, might lead to the shifts in the QT interval. It has given rise to the question that whether life-threatening arrhythmias and death cases could occur in the perioperative period due to the prolonged QT interval (13). These drugs include inhaled anesthetic agents, opioids, and dexmedetomidine (14-15). Previous studies have put forward that the administration of sevoflurane could also prolong the QT. Hence, the impacts of 2 anesthetic agents, which had been administered in the procedures, on QT and the occurrence of TCR was also intended to be investigated in the research. Fluctuations might occur in the QT interval due to sympathetic activation. The duration of induction, laryngoscopy, tracheal intubation, and inadequate anesthesia during the practice of anesthesia, might give rise to increase in the sympathoadrenal activity, hence, the prolongation of the QT interval even in healthy adults (16).

Nathanson et al. revealed that the mean arterial pressure values after induction of anesthesia dwindled during the period, which lasted until the incision of the skin, in the both group who had been administered with sevoflurane and desflurane, and the values of heart rate reduced; however, these reductions were greater in the sevoflurane group. Mean arterial pressure and heart rate values did not surpass the 20% of baseline values throughout the maintenance of anesthesia. It has been underscored

that both inhaled anesthetic agents manifest similar characteristics regarding hemodynamics (17).

Even though both groups exhibited analogous characteristics regarding hemodynamics in our study, reductions in the values of blood pressure values were observed, notably in sevoflurane, during the periods when the trigeminal nerve was stimulated intensely. Viskin et al. revealed in their research about the assessment of QT prolongation that automatic measurements could be used in selected patients, but manual measurements were safer in normal patients (18). Luo et al. concluded that there is a significant correlation between the interval of QTc and R-R values, which were calculated through the formula, and so the manual measurement is reliable (19). In order to find the related values of QTc, we used Bazzet's formula and calculated QT manually in our study. Whyte et al. determined a dose- dependent prolongation of QTc between 28 and 55 milliseconds among children whose induction and maintenance of anesthesia had been performed with the administration of sevoflurane (20). In our study, it was detected to be a prolongation of 29 ± 9 milliseconds compared to baseline in the sevoflurane group, while a prolongation of 16 ± 12 milliseconds was detected in the desflurane group. Since it has been revealed that it does not impact the RTD (transmural dispersion of repolarization), sevoflurane is considered as safe in torsadogenic terms; though it is well-known in the literature that sevoflurane might lead to prolongation in QTc through causing prolongation in the duration of action potential and repolarization (21). Furthermore, there is information on that it generates a downward trend in QTd and QTc. QTd was not studied in our research. Considering all this information, it is noteworthy that prolongations in QT and QTc can facilitate the development of TCR. From this point of view, it is evident that prospective studies are needed.

Kuenzberg et al. have revealed in their study, which is based on the administration of sevoflurane that the QTc interval was prolonged progressively compared to the duration of sevoflurane administration. Even though there was no significant difference between the two groups in our reviewing, compared to basal values, the intervals of QT and QTc were significantly prolonged in both groups, particularly in the sevoflurane group, after mucosal injection, after mucosal incision and after incision suturing; and it was observed that it reached its longest interval during the incision suturing (Table 3,4). These periods were also found to be periods when the trigeminal nerve was stimulated maximally and the most frequent development of TCR occurred. It was determined that a mean volume of 50.35 ±30.42 mL sevoflurane was administered in the sevoflurane group, and a mean volume of 93.34 ± 72.78 mL desflurane was administered in the desflurane group (Table 2). No statistically significant difference was found between the groups regarding the duration of procedures (Table 1). Given that all these findings, we consider that the inhaled agents, which were administered predominantly in the sevoflurane group, particularly sevoflurane play a facilitating role in the development of the TCR, through generating a cumulative impact during the maximal stimulation of the trigeminal nerve (22).

Leung et al. revealed that narcotics, which are used during induction, could suppress sympathetic stimulus effects of desflurane (23).

It was determined in our reviewing that remifentanil had been administered as a narcotic in the procedures. There is no significant difference between the two groups regarding the administration of remifentanil (Table 2).

Since they could affect the subsequent measurement values, the patients who had been administered with atropine for bradycardia in the reviewing were excluded from the study. It was detected that there were merely 2 patients whose characteristics conformed to the above-mentioned criteria. One of them occurred at the end of extubation and the other one after the induction, which was due to bronchospasm.

CONCLUSION

It was found that there was no difference between the two groups regarding the development of TCR; however, there were longer prolongation values in QT and QTc during the periods with maximal trigeminal nerve stimulation in sevoflurane, compared to basal values. This finding is also in line with the literature. We are of the opinion that the choice of anesthetic agent is a facilitating factor regarding the development of trigeminocardiac reflex. We also consider that more elaborate studies, which are randomized, controlled, prospective, and examine the depth of anesthesia as well, should be performed related to the development of TCR and the impact of anesthetic agents.

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RESEARCH ARTICLE

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Examination of Systemic Inflammation Related Hemogram Biomarkers in Children and Adolescents with Generalized Anxiety Disorder

ABSTRACT

Objective: In this study, we aimed to examine the complete blood count parameters and blood-based systemic inflammatory markers in children with generalized anxiety disorder (GAD).

Methods: Retrospectively, complete blood count of 48 GAD diagnosed children and adolescents and age-gender matched 46 healthy controls were compared in terms of hemoglobin (Hb), erythrocyte distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), white blood cell count (WBC), neutrophil, lymphocyte and monocyte counts and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet to lymphocyte ratios (PLR). Chi-square test, independent samples t-test and Mann-Whitney U test were used for statistical evaluation.

Results: MPV levels were found to be significantly higher (p=0.020), while PLT and PDW levels were found to be significantly lower (p=0.018 and p=0.011, respectively) in children and adolescents with GAD. There was no statistically significant difference in terms of Hb, RDW, PCT, WBC neutrophil, lymphocyte and monocyte counts and NLR, MLR, PLR between case and control groups.

Conclusions: Platelet parameters that have been postulated to be associated with inflammation, such as MPV and PDW may be related to possible inflammatory back ground of GAD in children and adolescents and comprehensive prospective studies are required on this subject.

Keywords: Anxiety Disorder, Inflammation, Hemogram, Complete Blood Count, Children and Adolescents

Yaygın Anksiyete Bozukluğu Olan Çocuk Ve Ergenlerde Sistemik İnflamasyon İlişkili Hemogram Biyobelirteçlerinin İncelenmesi

ÖZET

Amaç: Bu çalışmada yaygın anksiyete bozukluğu olan (YAB) çocuk ve ergenlerde tam kan sayımından bakılan sistemik inflamasyon biyo-belirteçlerinin düzeylerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Retrospektif olarak 48 YAB tanılı çocuk ergen ile yaş-cinsiyet açısından eşleştirilmiş 46 sağlıklı kontrol çocuk ve ergenin tam kan sayımı sonuçları; hemoglobin (Hb), eritrosit dağılım genişliği (RDW), trombosit sayısı (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), plateletkrit (PCT), beyaz kan hücre sayımı (WBC), nötrofil, lenfosit ve monosit sayıları ve nötrofil / lenfosit oranı (NLR), monosit / lenfosit oranı (MLR), trombosit / lenfosit oranları (PLR) açısından karşılaştırıldı. İstatistiksel değerlendirmede ki-kare testi, bağımsız örneklemler t-testi ve Mann-Whitney U testi kullanıldı.

Bulgular: YAB olan çocuk ve ergenlerde, MPV düzeyleri anlamlı olarak yüksek (p = 0,020) ve PLT ve PDW düzeyleri anlamlı olarak düşük (sırasıyla p = 0,018 ve p = 0,011) bulundu. Hb, RDW, PCT, WBC, nötrofil, lenfosit ve monosit sayıları, NLR, MLR, PLR açısından olgu ve kontrol grupları arasında istatistiksel olarak anlamlı bir farklılık saptanmadı.

Sonuç: MPV ve PDW gibi inflamasyonla ilişkili olduğu öne sürülen trombosit parametreleri, çocuk ve ergenlerde YAB'nin olası inflamatuar arka planıyla ilişkili olabilir ve bu konuda kapsamlı ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Anksiyete Bozukluğu, İnflamasyon, Hemogram, Tam Kan Sayımı, Çocuk ve Ergenler

INTRODUCTION

Anxiety Disorders are considered among the most common psychiatric conditions in children and adolescents with a prevelance of 18 % worldwide (1) and a prevelance of 16.7% in Turkey (2). Anxiety disorders are related to significant impairments in emotional, social, and academic functioning (3) and predispose to other types of psychopathology, in particular depression (4).

Increasing evidence support that immunological and inflammatory processes play an important role on major psychiatric disorders (5,6,7). Inflammatory processes in anxiety disorder has not been examined widely (5). However, there is evidence of increased inflammatory activity in anxiety related disorders (6) and in particular generalized anxiety disorder (8).

When compared to other biomarkers of inflammation, systemic inflammation biomarkers obtained from hemogram are known to be superior for low price, routine use and high reproducibility across laboratories. Furthermore, inflammatory rates are supposed to combine information on both innate and adaptive parts of immunity and to represent a reliable and practical measure of inflammation (9).

We encountered no study evaluating systemic inflammation biomarkers in children and adolescents with anxiety disorder. We encountered only one study investigating the effect of comorbid anxiety disorder on systemic inflammation biomarkers in adolescents with obsessive compulsive disorder (OCD) (10).

In this study, we aimed to evaluate systemic inflammation biomarkers in children and adolescents with generalized anxiety disorder (GAD).

MATERIAL AND METHODS

Children and adolescents aged between 7–18 years who referred to child and adolescent psychiatry clinic of Düzce University Medical Faculty between July 2017 and February 2019, diagnosed generalized anxiety disorder and whose hemogram results were available, were included in the study. In this retrospective study, we compared blood count of 48 GAD diagnosed children and adolescents with age and gender matched 46 healthy controls. The diagnosis was made according to DSM-5 by an experienced child and adolescent psychiatrist at Düzce University Child and Adolescent Psychiatry Department. Children and adolescents with other psychiatric comorbidities, taking medication, having an infectious or inflammatory disease, chronic medical disease were not included. Patients and controls whose data were missing or incomplete were also not included in the study.

Hemogram parameters, measured from peripheral blood obtained at the initial presentation, were evaluated. Hemoglobin (Hb), erythrocyte distribution width (RDW), platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), white blood cell count (WBC), neutrophil, lymphocyte and monocyte counts and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), and platelet to lymphocyte ratios (PLR) were recorded. NLR was calculated by dividing the neutrophil count by the lymphocyte count, MLR was calculated by dividing the monocyte count by the and lymphocyte count, PLR was calculated by dividing PLT by lymphocyte count.

Ethics committee approval was obtained from Düzce University Medical Faculty Research Ethics Committee, with approval date 04.03.2019 and protocol number 2019/47.

Statistical Analyses: SPSS version 21 (SPSS™, IBM Inc., Armonk, NY) was used for the statistical analyses. Relationships between dichotomous variables were assessed with pearson chi-square test. Shapiro-Wilk test was used to determine the conformity of the data to normal distribution. Values conforming to normal distribution were presented as mean ± standard deviation (SD), values not conforming to normal distribution were presented as median and interquartil range. Variables normally distributed were compared using Student's t-test, and Mann-Whitney U test was used when normal distribution was not established. A p value of 0.05 (two-tailed) was considered significant.

RESULTS

The mean age of child and adolescents was (151,00 ± 37,93 month) in the case group and (155,74 ± 22,41 month) in the control group. There were 19 (%39,6) male, 29 (%60,4) female children and adolescents in the case and 17 (%36,96) male, 29 (%63,04) female children and adolescents in the control group. The mean age and gender distribution were not significantly different between two groups (z= -0.434, p=0.664 and x2= 0.069, p=0.793 respectively).

There was no statistically significant difference in terms of Hemoglobin (Hb), erythrocyte distribution width (RDW), plateletcrit (PCT), white blood cell count (WBC), neutrophil, lymphocyte and monocyte counts and neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR) platelet to lymphocyte ratio (PLR) between case and control groups (Table 1).

MPV levels were found to be significantly higher (z=-2.320, p=0.020), while PLT and PDW levels were found to be significantly lower (t=2.405, p=0.018 and z= -2.531, p=0.011, respectively) in the patient group (Table 2).

Table1. Comparison of hemogram parameters of patient and control groups except platelet parameters

	ANX (n=48)	Control (n=46)	P	z/t
Hb	12.94 ± 1.18	13.31 ± 1.53	0.182	-1.346[a]
RDW	13.70 (13.20-14.98)	13.90 (13.35- 15.13)	0.859	-0.178
WBC	7.64 ± 1.62	7.39 ± 1.46	0.431	0.790[a]
Lymphocyte	2.44 (2.06-2.80)	2.37 (2.08-3.04)	0.961	-0.049
Neutrophil	1.60 (1.17-2.29)	1.50 (1.20-2.38)	0.414	-0.817
Monocyte	0.55 (0.46-0.64)	0.51 (0.44-0.60)	0.552	-0.594
NLR	1.60 (1.17-2.29)	1.50 (1.20-2.38)	0.540	-0.613
PLR	120.13 (96.34-145.79)	117.41 (87.81-140.54)	0.356	-0.923
MLR	0.22 (0.18-0.29)	0.21 (0.17-0.25)	0.452	-0.753

Mann Whitney U test, [a] student t test

Hb: Hemoglobin, **RDW:** Erythrocyte distribution width, **WBC:** White blood cell count, **NLR:** Neutrophil lymphocyte ratio, **PLR:** Platelet lymphocyte ratio

Table 2. Comparison of platelet parameters of patient and control groups

	ANX (n=48)	Control (n= 46)	P	z/t
PLT	315.58 ± 67.34	283.37 ± 62.31	0.018*	2.405[a]
MPV	8.50 (7.90-9.20)	8.00 (7.40-8.95)	0.020*	-2.320
PDW	16.20 (15.93-16.58)	16.50 (16.20-16.80)	0.011*	-2.531
PCT	0.24 (0.21-0.27)	0.22 (0.20-0.25)	0.085	-1.721

Mann Whitney U test, [a] student t test, *p <0.05

PLT: Platelet count, **MPV:** Mean platelet volume, **PDW:** Platelet distribution width, **PCT:** Plateletcrit

DISCUSSION

In this study, we examined systemic inflammation biomarkers obtained from hemogram in children and adolescents with GAD and found increased MPV and decreased PLT and PDW levels in children and adolescents with GAD compared to healthy controls. Furthermore, we found no significant alterations in the other hemogram parameters related to systemic inflammation.

There are limited number of studies indicating alterations of inflammatory biomarkers in children and adolescents with anxiety (10,11). We encountered only one study investigating systemic inflammation biomarkers obtained from hemogram in OCD and anxiety comorbidity in children and adolescents. In that study conducted in adolescents, it was reported that a comorbid anxiety disorder in addition to OCD increased the inflammatory response and that adolescents with comorbid anxiety and OCD had significantly higher WBC, neutrophil counts and log neutrophil-lypmhocyte ratio than adolescents with pure OCD (10). However, we found no significant difference in terms of white blood cell count (WBC), neutrophil, lymphocyte, monocyte counts or neutrophil to lymphocyte ratio (NLR), monocyte to lymphocyte ratio (MLR), platelet to lymphocyte ratios (PLR) between case and control groups.

We encountered studies investigating only platelet parameters as systemic inflammation biomarkers obtained from hemogram in adult panic disorder (PD) (12-18). The results of those studies are conflicting. Consistent with our result, majority of these studies found increased MPV in the PD group (12-15). In one of those studies anxiety symptoms was found to be positively correlated with MPV (15). The other studies found decreased MPV in the PD group (16-18). MPV values were also evaluated in schizophrenia, bipolar disorder and depression in adults (19-24). In adolescents, Ozyurt et al studied MPV, PLT and PLR as platelet indices in depression and found no alterations compared to healthy controls (25).

MPV is known as a marker and determinant of platelet action (16). In addition, PDW is considered among the indicators of platelet activity (26). Platelet parameters are considered to reflect the central serotonergic functions and to present windows of brain serotonergic functions (27). On the other hand, sympathetic system activation and serotonergic system dysfunction are considered to play a crucial role in the neurobiology of GAD (28,29).

Stressful life events and anxiety have been indicated to elevate blood catecholamines. Sympatho-adrenal activation is considered to activate platelets through α-2 receptors, resulting in an increase in platelet volume and activity, and by causing an increase in platelet activity, increased catecholamine levels are considered to activate thrombotic process (12, 30, 31). Increased stress and anxiety have been indicated to cause serotonin to bind 5-HT-2 receptors on platelets and to mediate the release of factors promoting platelet aggregation (32). Supporting this serotonergic hypothesis, treatment with selective serotonin reuptake inhibitors was also shown to cause a decrease in platelet activity (23,33).

The result of increased MPV levels in our study is consistent with the hypothesis of increased platelet activation due to sympathetic system activation and serotonergic imbalance. Also PLT levels were found to be significantly lower in GAD

patients in our study. This finding is consistent with the known inverse relation between MPV and PLT (34). In general, MPV and PDW are also known to be inversely related to each other (35,36). In line with this, decreased PDW levels were found in our study.

Ataoğlu at el (23) and Canan et al. (24) showed that MPV values increased in adult major depression. Ataoğlu et al additionally showed that MPV values decreased after 8 weeks of escitalopram treatment (23). On the other hand, increased MPV levels are indicated to be related to cardiovascular disorders in adults (37). Among multiple mechanisms, changes in platelet reactivity are considered to be one of the major mechanisms linking depression and cardiovascular disease (38). Interestingly, anxiety symptoms in patients with coronary artery disease have been found to be more effective in increased platelet activity than depression (39). This result may point out the inflammatory common aspect of depression, anxiety and cardiovascular disease given that increased platelet activity is known to be related to inflammation (40).

This study has some limitations, including relatively small sample size and retrospective design. However, evaluating almost all of the possible systemic inflammation biomarkers obtained from hemogram is the strength of our study.

In conclusion, we suggest that platelet parameters that have been indicated to be associated with inflammation, such as MPV and PDW, may be related to possible inflammatory background of GAD in children and adolescents and comprehensive prospective studies are required on this subject.

Disclosure

The authors have no conflict of interest.

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RESEARCH ARTICLE

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Should Children With Sub-Threshold ADHD Predominantly Inattentive Subtype (ADHD-I) Symptoms Be Treated With Sensory Integration Therapy? A Case-Control Study

ABSTRACT

Objective: Sensory integration therapy is one of the promising preventive therapy options for behavioral and developmental disorders. Hypothesizing a degree of parallelism, this study provides an insight into the effectiveness of the sensory integration therapy potencies for school-aged children with subthreshold ADHD predominantly inattentive subtype.

Methods: The study was a single-arm clinical trial and 20 patients aged 7–10 years with subthreshold ADHD predominantly inattentive subtype, were included. The sensory integration intervention was prepared in accordance with sensory modulation principles and intervention strategies and lasted 12 weeks with two sessions per week. The effectiveness was assessed using the Conner's teacher/parent scales, the Clinical Global Impression scale, the Canadian Sensory integration Performance Measure and the Sensory Profile.

Results: The rate of patients with typical or better performance in auditory processing domain of the Sensory Profile were found significantly increased after sensory integration therapy; 9 patients (45%) before and 15 patients after (75%) (p=0.031). The rates of participants with typical or better performance in inattention–distractibility factor score of the Sensory Profile were found significantly increased after sensory integration therapy; 6 before (30%) and 16 after (80%) (p=0.006).

Conclusions: Sensory integration therapy focuses on supporting persons with varied disability terms to engage in daily life activities that they find significant and purposeful. Difficulties experienced by individuals with subthreshold attention-deficit hyperactivity disorder are addressed in this study and aspects of daily life are explored while swiping through different sensory modalities. Impaired auditory processing improvable through sensory integration therapy was observed in these children.

Keywords: Attention Deficit Hyperactivity Disorder, Sensory Profile, Sensory Integration Therapy

Eşik Altı Dikkat Eksikliği Hiperaktivite Bozukluğunun Dikkatsizlik Baskın Görünümünde (DEHB-I) Olan Çocuklar Duyu Bütünleme Terapisi İle Tedavi Edilmeli Mi? Bir Vaka Kontrol Çalışması

ÖZET

Amaç: Duyu bütünleme terapisi, davranışsal ve gelişimsel bozukluklar için umut verici olan önleyici terapi seçeneklerinden biridir. Bu çalışma, Dikkat eksikliği hiperaktivite bozukluğunun dikkatsizlik baskın görünümünde (DEHB-D) olan okul çağındaki çocuklar için duyu bütünleme terapisinin etkinliğine dair bir fikir vermektedir.

Gereç ve Yöntem: Tek kollu bir klinik çalışma olan bu çalışmaya, ağırlıklı olarak dikkatsizlik baskın görünümde olan 7-10 yaş arası 20 eşik altı DEHB-D tanısı olan çocuk dahil edildi. Duyu bütünleme terapisi, duyusal modülasyon ilkeleri ve müdahale stratejilerine uygun olarak hazırlanmış ve haftada iki seans olacak şekilde 12 hafta devam etmiştir. Etkinlik, Conners Öğretmen / Ebeveyn ölçekleri, Klinik Global İzlenim ölçeği, Kanada Duyusal Bütünleştirme Performans Ölçümü ve Duyusal Profil kullanılarak değerlendirildi.

Bulgular: Duyu bütünleme terapisi sonrasında, duyusal profilin işitsel işlemleme alanında "tipik" veya "daha iyi" performansa sahip hastaların oranı, önemli ölçüde artmıştır; terapi öncesinde 9 hasta (% 45); terapi sonrasında 15 hasta (% 75) (p = 0,031). Duyusal Profilin dikkatsizlik-dikkat dağınıklığı faktör puanında "tipik" veya "daha iyi" performans gösteren katılımcıların oranları, duyu bütünleme terapisinden sonra anlamlı olarak artmıştır; öncesi 6 (% 30) ve sonrası 16 (% 80) (p = 0,006).

Sonuç: Duyu bütünleme terapisi, özel gereksinime sahip olan kişilerin önemli ve amaçlı buldukları günlük yaşam aktivitelerine katılmalarını desteklemeye odaklanır. Bu çalışmada eşik altı dikkat eksikliği hiperaktivite bozukluğu olan bireylerin yaşadıkları zorluklar ele alınmış ve farklı duyusal modaliteler ile ilişkili olabilecek günlük yaşamın yönleri araştırılmıştır. Bu çocuklarda özellikle Duyu bütünleme terapisi yoluyla iyileştirilebilen bozulmuş işitsel işlemleme süreçleri gözlenmiştir.

Anahtar Kelimeler: Dikkat Eksikliği Hiperaktivite Bozukluğu, Duyu Bütünleme Terapisi, Duyusal Profil

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by hyperactivity, impulsivity, and inattention, which are judged excessive for the child's age or level of the overall development (1). A study of ADHD prevalence using a population-based sample, multiple informants, and DSM-IV criteria reported that the overall prevalence of ADHD was 15.5% (2).

The symptoms are multifaceted and affect cognitive, academic, behavioural, emotional, and social functioning (3). Thus, children with ADHD may experience a number of difficulties such as academic failure, substance misuse, behaviour problems, poor peer relationships and impaired psychosocial functioning when they become adolescents or adults (4-6). ADHD can accompany difficulties in activities of daily living (ADLs), instrumental activities of daily living (IADLs), education, rest and sleep, leisure, play, and social participation (4). Similarly, children with sub-threshold ADHD symptoms may have negative experimentations in daily life which are poorer academic, achievements, lower self-esteem, and poorer relationships with family members and peers (7). It is known that there is an interaction between the child (psychological, neurological and behavioural functions) and child's environment in the occurrence of these complaints (2). Previous studies indicated that sub-threshold ADHD symptoms may be formed in a part of children who are possibly more reactive to environmental risk factors (7).

Researches showed that the prevalence of sub-threshold ADHD reached to 11.7 % in the 6-12 age group children (9,11). These studies showed that sub-threshold cases were found to be more prevalent than full syndrome cases. Also, Kim et al. (9) reported that the comorbidity rate, except for anxiety disorders, was similar between full-disorder and sub-threshold ADHD and they found higher rates of internalizing problems in children with sub-threshold ADHD. It was furthermore shown that in a follow-up study, the sub-threshold cases in young adulthood have a predictive importance for full syndrome disorders in later adult years (8). And this study reported that the prevalence of sub-threshold ADHD was estimated to 5.9% (8). Therefore, addressing the sub-threshold cases and applying appropriate aimed inhibition strategies are of great importance to prevent full-syndrome disorders (12).

With its focus on enabling occupation, sensory integration therapy, a nonpharmacological approach addressing activity disruptions is an important component of psychiatric treatment (13). Sensory integration therapy focuses on case-centered approaches to facilitate daily life with meaningful works (14). Sensory integration therapists are able to fulfill some needs in daily routine activities about social and motor skills, cognition, impulsivity, inattention, and hyperactivity (5). Especially family and child focused intervention programs have an improving effect on cognitive, sensorial, locomotor and play related fields (5). The antecedence of sensory integration therapy interventions is conformation to the environmental conditions, resolution of sensory integrative dysfunction, satisfaction appropriate solutions to developmental and functional problems, training of families and administration of education for ADHD (15).

There have been a few studies about the role of sensory integration therapy in ADHD (16,17). Yet, there is no study in the literature specifically investigating the effect of sensory integration therapy for sub-threshold ADHD, to the best of our knowledge. Since, sensory integration therapy is one of the promising preventive therapy options for ADHD it may have a role in the management of sub-threshold ADHD as well. The aim of this study is to provide a deeper perspective on the impact of the sensory integration therapy interventions for school-aged children with sub-threshold ADHD symptoms and to increase the awareness of the parents about their child's problem.

MATERIAL AND METHODS

The study was a single-arm clinical trial (ClinicalTrials.gov Identifier: NCT03976570) conducted at the child and adolescent psychiatry outpatient clinic of a tertiary referral hospital and involved 20 children with sub-threshold ADHD predominantly inattentive subtype (ADHD-I). Patients aged 7–10 who applied to the outpatient clinic between January 2018 and July 2018 were included in the study. The reason for selecting this age range was in terms of remaining within the same developmental period. Middle childhood is a stage when children are increasingly developing their own social, emotional and physical skills that will be needed in adolescence. Patients not adhering to regularly scheduled follow-ups were excluded from the study. Other reasons for exclusion were a personal history of any comorbid psychiatric disorder, mental retardation, learning disability, audio/visual impairment and psychiatric medicationuse. The study was approved by the Erzurum regional education and research hospital ethics committee.

Structured psychiatric meetings were conducted with the children whose parents complained of inattentive symptoms but a diagnosis of ADHD could not be confirmed with the Conner's Teacher and Parent Rating Scales (CTRS-R:S and CPRS-R:S, respectively) and the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria(American Psychiatric Association, 2013). The proposed DSM-V criteria for sub-threshold ADHD were used to identify patients. All of the children were evaluated with the schedule for

affective disorders and Schizophrenia for school-age children-present and lifetime version (KSADS-PL), and ADHD Rating Scale was given to teachers and parents in order to determine eligibility.The same child and adolescent psychiatrist, the lead author, administered the interviews and rated the severity of the child's illness on the Clinical Global Impression (CGI) scale at the time of assessment. Then the child and parents were referred to the sensory integration therapist for the implementation of Sensory Profile and the designation of a client-centred therapy program for each child and parent.

The sensory integration intervention was prepared in accordance with sensory modulation principles and intervention strategies and lasted 12 weeks with two sessions per week. Every session was set to approximately 1 hour. The therapy included the interpretation of assessment results, treatment planning with parents, behavioural management of the child, environmental adaptation, classroom management, feedback session and goal-setting treatment regulating with families and children. Tactile (Brush, containers filled with beans, tactile discs, different types of fabric, ball pool, river road balance stones, shaving foam, climbing wall, ramp cushions, balls of different sizes and shapes, stones), proprioceptive (heavy suit, exercise ball, vests with pockets, ball pool, tunnel, climbing wall, cloth ball, double coordination bicycle with handle) and vestibular (trampoline, ramp cushions, balance board, swing, river road balance stones, bowl, ball pool, climbing wall, hammock) senses were studied in these children.

The effectiveness of the sensory integration therapy in the management of sub-threshold ADHD was assessed using the Conner's teacher and parent scales, the CGI form and the Canadian Sensory integration Performance Measure (COPM) before and after the intervention. Tests measuring sensory skills were administered by the same sensory integration therapist.

Instruments used:

1. The K-SADS-PL: This test is a semi-structured interview form used to detect psychopathologies in children and adolescents (18). İnterviews with children were conducted by a child and adolescent psychiatrist. The diagnoses were revised according to the DSM-V criteria.

2. The Sensory Profile: The Sensory Profile is a questionnaire that definesanswers to sensory events in daily life, is filled out by the parents. It is a likert scale showing how frequently the child uses that reply to certain sensory incidents (higher scores reflect higher performance). This tool scores the effects of sensory processing on a child's performance with a total of 125 items (19). The assessed sensory sections included: (1) Sensory processing, (2) Modulation, (3) Behavioral and emotional responses.

3. CPRS-R:S: This standard measure is used as a diagnostic tool of ADHD. Ithas 27 items, each item rated on a Likert scale (0=not true at all to 3=very much true). The subscales are divided into 4 groups which are oppositional, hyperactivity, cognitive problems and ADHD group (20).

4. CTRS-R:S: This scale is mostly used to measure behavioral problems related to ADHD. There are 28 items in this scale. The subscales are divided into three groups which are Oppositional, Cognitive Problems/Inattention, and Hyperactivity (20).

5. COPM: This measure is a semi-structured interview to assign targets in the fields where the child has difficulty with self-care, creativity or play. In our study, three or four targets are chosen for each child, and after then families and children scored their performance and satisfaction scales (with a 10-point scale). Baseline and post-therapy scores were scored separately. Two or more points constitute significance (21).

6. CGI Scale: This scale is a short observation that the clinician evaluates the functioning of the patient. There are two subdivisions in which the disease assesses severity and improvement (22).

Statistical Analysis: The sample selection consisted of children with sub-threshold ADHD predominantly inattentive subtype (ADHD-I). For sample size selection, a study comparing the COPM scores to measure sensory integration performance outcomes before and after sensory integration therapy for children with ADHD was analysed (23). Median performance scores of COPM before and after intervention were 3.55 (min-max: 2.00–5.25) and 7.43 (min-max: 5.20–8.25) respectively. Treatment effect was so obvious that a minimum sample size of 2 was calculated on the basis of a hypothesis that would yield results sensitive enough to reveal a similar difference while the alpha level for rejecting the null hypothesis was set to 0.05. However, in this calculation the data was assumed to be parametric. Besides, such a treatment effect might be less evident in sub-threshold ADHD. Thus, it is decided that ensuring at least ten-fold oversampling is necessary (i.e. 20 patients). Statistical Package for the Social Sciences (IBM Corporation, Armonk, NY, USA) version 20.0 was used for the analyses. Normality was determined by Shapiro Wilk test. Descriptive statistics were expressed as follows; mean, standard deviation, and percentage. Continuous variables with normal distribution were indicated with the mean and standard deviation, and those without normal distribution with the median and interquartile range. For non-parametric conditions, Wilcoxon signed-rank test was used. Pearson correlation analysis for parametric data and Spearman correlation analysis for nonparametric data were used. For paired 2x2 table comparisons McNemar Test was used. Statistical significance limit was accepted as $p < 0.05$.

RESULTS

There were 20 participants who were generally low-middle-income, school-aged children. The ethnicity of all children was Caucasian. The median age of the patients was 8 (IQR: 7-10). The median age of the patients was 8 (IQR: 7-10). There were 11 male (55%) and 9 females (45%). Sociodemographic characteristics of the childrenare givenin Table 1.

Table 1. Demographic characteristics

Gender, n (%)	
Male	11 (55)
Female	9 (45)
Academic performance, n (%)	
Poor	8 (40)
Moderate	8 (40)
High	4 (20)
Education of father, n (%)	
High school or lower	19 (95)
University or higher	1 (5)
Education of mother, n (%)	
High school or lower	18 (90)
University or higher	2 (10)
Intelligence score, mean ± SD	99.8 ± 5.6
School year, n (%)	
1	6 (30)
2	6 (30)
3	2 (10)
4	2 (10)
5	4 (20)

The Sensory Profile, CTRS, CPSQ and COPM Scores of the participants were compared before and after the sensory integration therapy. Median performance scores of COPM before and after intervention were 3.55 (min-max: 2.00–5.25) and 7.43 (min-max: 5.20–8.25) respectively. The mean behaviour emotional response category score of the Sensory Profile was significantly higher after the therapy; 96 (±13) before and 100 (±12) after (p= 0.036). Median inattention-passivity domain score of CTS was significantly lower after the therapy; 11 (IQR: 8-13) before and 8 (IQR: 6-10) after (p=<0.01). Median inattention-passivity domain score of CPSQ was significantly lower after the therapy; 6 (IQR: 3-8) before and 5 (IQR: 3-7) after (p=0.002). Comparison of categorical domains of the Sensory Profile, CTRS, CPSQ and COPM Scores of the participants with respect to the time is displayed in Table 2.

Table 2. The Sensory Profile, CTRS, CPSQ and COPM Scores

	Week 0	Week 12	Pvalue
The Sensory Profile			
Sensory processing, median (IQR)	273 (252-292)	277 (260-285)	0.064
Modulation, mean (±SD)	126 ±34	128 ±17	0.293
Behavior emotional response, mean (±SD)	96 ±13	100 ±12	0.036*
Dunn total score, median (IQR)	496 (449-530)	506 (470-528)	0.062
CTRS, median (IQR)			
Inattention-passivity	11 (8-13)	8 (6-10)	0.000*
Hyperactivity index	4 (2-9)	4 (2-9)	0.603
CPSQ, median (IQR)			
Conduct problem	2 (1-5)	2 (1-5)	0.023*
Inattention-passivity	6 (3-8)	5 (3-7)	0.002*
Hyperactivity index	4 (2-9)	4 (2-7)	0.153
Oppositional index	2 (2-4)	2 (1-4)	0.161
COPM			
Performance, mean (±SD)	3 ±1.37	5.5±1.96	0.00*
Satisfaction, median (IQR)	3 (2-4)	6 (4-8)	0.00*

CTRS: Conner's Teachers Rating Scale, CPSQ: Conner's Parents' Symptom Questionnaire, COPM: Canadian Sensory Integration Performance Measure, * stands for p <0.05.

Individual scores of specific domains in the Sensory Profile were analysed after categorization with respect to the normative data, and only the rate of patients with typical or better performance in auditory processing domain were found significantly increased after sensory integration therapy; 9 patients (45%) before and 15 patients after (75%) (p=0.031). The rates of participants withtypical or better performance in all domains before and after the sensory integration therapy were displayed in Table 3. The rates of participants with typical or better performance in inattention–distractibility factor score of the Sensory Profile were found significantly increased after sensory integration therapy; 6 before (30%) and 16 after (80%) (p=0.006).

The psychiatrist's ratings on the CGI scale indicated that symptoms of sub-threshold ADHD dramatically improved in 20% of the patients, minimally improved in 70% and there was no change from baseline after therapy in 10%. None of the participants showed any deterioration during the course of the program.

Table 3. Typical or better performance rate in the section summary outcome of the Sensory Profile, n (%)

Item Categories	Before therapy	After therapy	p value
Sensory processing			
A. Auditory processing	9 (45)	15 (75)	0.031*
B. Visual Processing	15 (75)	17 (85)	0.500
C. Vestibular Processing	8 (40)	12 (60)	0.219
D. Touch Processing	15 (75)	15 (75)	1.000
E. Multi-sensory Processing	13 (65)	17 (85)	0.125
F. Oral sensory processing	15 (75)	16 (80)	1.000
Modulation			
G. Sensory processing related to Endurance/Tone	5 (25)	7 (35)	0.500
H. Modulation Related to Body Position & Movement	5 (25)	4 (20)	1.000
I. Modulation of Movement affecting activity Level	15 (75)	16 (80)	1.000
J. Modulation of Sensory Input affecting Emotional Responses	12 (60)	13 (65)	1.000
K. Modulation of Visual Input Affecting Emotional Responses and Activity Level	15 (75)	17 (85)	0.500
Behavioral and emotional responses			
L. Emotional/Social Responses	13 (65)	14 (70)	1.000
M. Behavioral outcomes of Sensory Processing	6 (30)	11 (55)	0.063
N. Items indicating Thresholds for Response	17 (85)	17 (85)	1.000

DISCUSSION

As seen in previous studies, it was found that children with ADHD diagnosis had lower sensory profile scores than the control groups (15,24,25). However, no study has been found on children diagnosed with sub-threshold ADHD-I. In our study, a significant improvement was observed especially in the auditory area in patients with sub-threshold ADHD-I symptoms. This condition may suggest that the first degraded area was the auditory area. Perhaps when this problem in the auditory areas is detected early, precautions that can be effective in treatment can be taken and full syndromes can be prevented with the necessary sensory integration treatment. This remark served as an effective idea to identify difficulties of children with sub-threshold ADHD and it was certainly a useful starting point for formulating potential improvement plans thereto. The probable difficulties experienced by children with sub-threshold ADHD-I are addressed and aspects of daily life are explored while swiping through different sensory modalities. As a result, an intriguing observation was made. That is the importance of auditory processing in this population.

The study brought new insights into the plasticity phenomenon of the human brain.Plasticity is described as the capability to modify the structure and/or function of the nervous system. It is related to the sensory experience in the auditory cortex (26). Although, sub-threshold ADHD-I is not a complete sensory deprivation due to hearing loss this disability might share some common pathophysiological mechanisms.

Previous studies have generally shown that sensory integration therapy increased improvements in both goals and motor performance in ADHD patients (27). And this study shows it works for sub-threshold ADHD-I children as well. According to CPRS-R:S ratings on conduct problem subscales, problematic behaviours may also be ameliorated. This situation can be explained by the fact that the child is more likely to cooperate as a result of the skills gained after this therapy. So, the stress experienced by the families may also decrease.Inattention problems such as, having a short attention span and being easily distracted, making careless mistakes, appearing forgetful or losing things; all might be ameliorated with a simple sensory integration intervention. Being unable to stick to tasks which are tedious, appearing to be unable to carry out instructions, constantly changing activity, having difficulty organising tasks and following with parental directions may all be improved with sensory integration therapy. During the first interview, the child's psychological and

sensory tests were performed. Descriptive tests were conducted on the child's performance. Information about the child's performance was transferred to the family. The family was asked to transfer the information to the teacher. This is especially important in determining the common goals with families and teachers. The necessity of this situation for a better treatment is emphasized in some studies (28,29).

A target treatment program was set for each child according to COPM scores and there was a significant improvement in both of the performance and the satisfaction scores. After the therapy sessions, only about 10% of the children were rated by psychiatrist as "no change from baseline" compared with their status at baseline and there was no worsening child. Parents and teachers reported an improvement after the sensory integration therapy sessions on Conner's inattention-passivity subscales. Likewise, parent's ratings reflected significant changes on Conner's conduct problem subscale. However, both of CPRS-R:S and CTRS-R:S ratings on hyperactivity index scales reflected no significant changes after the therapy. The inattention-passivity subscales arevery important not only for children with sub-threshold ADHD children but also for their parents.

Yet, this study has several limitations. First the sample size was small. Second, investigators and participants were not blinded to the therapy conditions. Thus, the ratings were subject to observer bias. Despite these limitations, the results of this study suggested that the sensory integration therapy on sub-threshold ADHD could be successfully applicable especially inattention-passivity symptoms.

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RESEARCH ARTICLE

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Incidental Gallbladder Cancer Diagnosed During Or After Laparoscopic Cholecystectomy, What Did We Do ?

ABSTRACT

Objective: Gallbladder cancer is a rare neoplasm. We report our experience with gallbladder cancer that was incidentally diagnosed during or after laparoscopic cholecystectomy performed for gallstone disease.

Methods: This study included all laparoscopic cholecystectomies due to gallstone disease undertaken from January 2010 to April 2015. Exclusion criteria were suspicion of malignancy and/or existence of gallbladder polyps detected with ultrasonography preoperatively. Patients with incidentally diagnosed gallbladder cancer were recorded, and the clinical and demographic characteristics of these patients were reviewed.

Results: Of 6,114 patients in whom laparoscopic cholecystectomy was attempted, 5.948 were included in this study. Incidental gallbladder cancer was found in thirty-six patients, with a mean age of 64.08 years. The histological tumor stages were adenocarcinoma in situ in seven patient, pT1b in nine patient, pT2 in eleven patient, and pT3 in nine patients. Sixteen patients who underwent laparoscopic cholecystectomy alone underwent no additional surgery because of the low stage of the tumors. The twenty remaining patients, whose laparoscopic cholecystectomies were converted to open surgeries, underwent cholecystectomy, excision of the liver bed and lymph node dissection. The overall median survival time was 28 months.

Conclusions: The incidence of incidental gallbladder cancer has been reported to vary, up to 2.85%. In this single-center study, the rate of incidental gallbladder cancer was found to be 0.60%. Female gender and advanced age are demographic risk factors for gallbladder carcinoma. Although gallbladder cancer is well known for its poor prognosis, tumors that are incidentally diagnosed are often found at an early stage and have a better prognosis.

Keywords: Cholecystectomy, Gallbladder Carcinoma, Incidence, Laparoscopy, Prognosis

Laparoskopik Kolesistektomi Sırasında veya Sonrasında Teşhis Edilen İncidental Safra Kesesi Kanseri. Biz Ne Yaptık?

ÖZET

Amaç: Safra kesesi kanseri nadir görülen bir neoplazmdır. Kolelitiazis nedeni ile yapılan laparoskopik kolesistektomi sırasında veya sonrasında tesadüfen teşhis edilen safra kesesi kanseri ile ilgili deneyimlerimizi sunuyoruz.

Gereç ve Yöntem: Bu çalışma, Ocak 2010'dan Nisan 2015'e kadar yapılan kolelitiazis e bağlı tüm laparoskopik kolesistektomileri içermiştir. Çalışmada dışlama kriterleri; ameliyat öncesi ultrasonografi ile tespit edilen malignite şüphesi ve / veya safra kesesi poliplerinin varlığıydı. Safra kesesi kanseri tanısı konan hastalar incelendi ve bu hastaların klinik ve demografik özellikleri gözden geçirildi.

Bulgular: Laparoskopik kolesistektomi yapılan 6,114 hastadan 5,948'i çalışmaya dahil edildi. Yaş ortalaması 64,08 olan otuzaltı hastada rastlantısal safra kesesi kanseri saptandı. Histolojik tümör evreleri yedi hastada in situ adenokarsinom, dokuz hastada pT1b, onbir hastada pT2 ve dokuz hastada pT3 idi. Sadece laparoskopik kolesistektomi yapılan 16 hastaya tümörlerin düşük evresi nedeniyle ek cerrahi uygulanmadı. Laparoskopik kolesistektomileri açık ameliyatlara dönüştürülen kalan 20 hastaya kolesistektomi, karaciğer yatağı eksizyonu ve lenf nodu diseksiyonu uygulandı. Genel ortalama sağkalım süresi 28 aydı.

Sonuç: İnsidental safra kesesi kanseri insidansının % 2,85'e kadar olabildiği bildirilmiştir. Bu tek merkezli çalışmada, rastlantısal safra kesesi kanseri oranı % 0,60 olarak bulunmuştur. Kadın cinsiyet ve ileri yaş safra kesesi karsinomu için demografik risk faktörleridir. Safra kesesi kanseri kötü prognozu ile iyi bilinmesine rağmen, tesadüfen teşhis edilen tümörler sıklıkla erken bir aşamada bulunur ve daha iyi bir prognoza sahiptir.

Anahtar Kelimeler: Kolesistektomi, Safra Kesesi Karsinomu, İnsidans, Laparoskopi, Prognoz

INTRODUCTION

Gallbladder cancer is the fifth most common gastrointestinal cancer (1). It is well known for its poor prognosis, and 15–30% of patients show no preoperative or intraoperative evidence of gallbladder cancer (2). Gallstone disease, porcelain gallbladder, sclerosing cholangitis, and advanced age are the best known risk factors for gallbladder cancer. Laparoscopic cholecystectomy (LC) has been the gold standard treatment for gallstone disease for over two decades. LC performed for gallstone disease rarely results in a diagnosis of unexpected gallbladder cancer. In the English-language research literature, the incidence of gallbladder cancer diagnosed during or after LC is 0.2%-2.85% (3-11). In this single-center study, we report our experience with gallbladder cancer incidentally diagnosed during or after LC performed for gallstone disease.

MATERIAL AND METHODS

We evaluated the medical records of patients with gallstone disease who underwent LC in the Surgery Department of Ankara Numune Research and Education Hospital over the past 5 years. Routine preoperative assessment was performed in all patients, including liver biochemical assessment and abdominal ultrasonography of the hepatobiliary system. Exclusion criteria were suspicion of malignancy and/or existence of gallbladder polyps detected during preoperative ultrasonography. All operations were carried out by senior surgeons or trainees under supervision using the standard four-port, two-hand technique. Following direct 10 mm trocar insertion, a 15 mmHg CO2 pneumoperitoneum was created. Intraoperative cholangiograms and drains were used when necessary. The presence of a nodular pattern and/or irregularity in the gallbladder wall during or after dissection was evaluated as a cause for suspicion of cancer. Tumor staging was based on the 7th edition of the American Joint Committee on Cancer (AJCC) manual (12). Recorded data included patient demographics, operative procedures, perioperative outcomes, tumor histopathology, follow-up, and long-term survival. Postoperative follow-up was done with clinical examination and determination of CA19-9 and carcinoembryonic antigen (CEA) levels, and ultrasound and computed tomography (CT) scans were performed regularly. Follow-up data were obtained for all patients by establishing contact with them and their treating physicians. Approval was obtained from the ethics committee of Lokman Hekim University on 30/06/2020 with the decision number 2020/056.

RESULTS

Of 6.114 patients in whom LC was attempted, 5.948 were included in this study. Patients with pathologically proven gallbladder polyps (n=149) and suspicion of malignancy before surgery (n=17) were excluded. The mean age of patients was 49.3±11.1 years (range: 18-83 years); 4.234 of them (71.2%) were female. An abnormal gallbladder wall was found intraoperatively in 124 patients (2.1%), while in the remaining 5.824 patients (97.9%), the morphologic appearance of the gallbladder was normal. Adenocarcinoma was diagnosed histopathologically in 36 cases (25 females, 11 male) out of 5.948 attempted LCs (0.60%). The mean age in this group was 64.08 ±18.2 years (range: 36- 83 years) and was significantly higher than the mean age in the group of remaining patients ($p<0.05$). Demographic features and pathological results are shown in Table 1. All patients with adenocarcinoma presented with symptoms of acute cholecystitis but no jaundice on admission. Conversion to open surgery was required due to a diagnosis of malignancy on frozen section analysis in sixteen of thirty-six patients. They underwent cholecystectomy, excision of the liver bed and lymph node dissection. In the remaining twenty patients, there was no suspicion of malignancy intraoperatively and routine histopathological studies revealed the diagnosis of gallbladder carcinoma. Only LC was performed and no additional surgery was necessitated because of the low stage of the tumors (adenocarcinoma in situ [pTis] and pT1b) in these patients. No retrieval bag was used to extract the gallbladder and there was no port site metastasis in these twenty patients. The histological tumor stages were pTis in seven patient, pT1b in nine patient (Table 1), pT2 in eleven patient and pT3 in nine patients. None of the patients had pT4 disease or evidence of metastasis. The overall survival time ranged from 7 to 42 months (median: 28 months).

DISCUSSION

Gallbladder cancer is known for its poor prognosis. The highest gallbladder cancer incidence rates have been reported in women from India, Chile and Pakistan (13). The incidence of incidentally diagnosed gallbladder cancer has been reported to vary, up to 2.85% (11). In recent years, the incidence of incidental diagnosis has increased, probably because of an increase in the number of elective cholecystectomies (14). In the present study, the rate of incidental gallbladder cancer diagnosis was found to be 0.60%. To the best of our knowledge, this is the lowest rate in the published English language literature. The possible cause of this low incidence rate may be diagnoses at advanced stages caused by the avoidance of elective cholecystectomies in our population. Thus, all patients with adenocarcinoma presented with symptoms of acute cholecystitis. Sixteen patients in our series had been diagnosed with gallstone disease before but had rejected elective cholecystectomies. If these patients had not had complaints caused by cholecystitis, they probably would have been diagnosed at an advanced stage. Female gender and advanced age are demographic risk factors for gallbladder carcinoma (15).

Table 1. Patient characteristics and follow-up

Patient No.	Age (years)	Sex	Diagnosis	Stage	Operation	Outcome
1	72	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease,6m
2	70	F	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease, 18 m
3	65	M	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease,9 m
4	57	M	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease, 17 m
5	50	M	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease,8m
6	70	F	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease, 11 m
7	57	M	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease,7 m
8	66	F	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease, 16 m
9	52	M	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease,8 m
10	50	M	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease, 14 m
11	61	M	Postoperatively	pTis	LC (no additional surgery)	No evidence of disease,6 m
12	76	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease, 18 m
13	66	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease,9 m
14	75	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease, 18 m
15	75	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease, 17 m
16	63	F	Postoperatively	pT1b	LC (no additional surgery)	No evidence of disease, 15 m
17	66	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 54 m
18	54	M	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 28 m
19	72	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 32 m
20	73	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 52 m
21	68	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 25 m
22	49	M	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 34 m
23	72	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 54 m
24	61	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 22 m
25	58	M	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 42 m
26	53	M	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 52 m
27	69	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 32 m
28	66	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 44 m
29	36	F	Intraoperatively	pT3	Converted from LC to OC + LBx + LND	No evidence of disease, 52 m
30	76	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 32 m
31	78	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 57 m
32	80	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 52 m
33	81	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 33 m
34	85	F	Intraoperatively	PT2	Converted from LC to OC + LBx + LND	No evidence of disease, 26 m
35	85	F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 22 m
36		F	Intraoperatively	pT2	Converted from LC to OC + LBx + LND	No evidence of disease, 18 m

F: Female. M: Male. LC: Laparoscopic cholecystectomy. OC: Open cholecystectomy. LBx: Excision of the liver bed. LND: Lymph node dissection. M: Months. MI: Myocardial infarction.

In the present study, the male to female ratio was found to be 1:2 in patients with incidentally diagnosed gallbladder cancer, and the mean age of this group was significantly higher than the mean age of the remaining patients. The median survival for the incidentally-found group has been reported to range from 8.1 to 68 months (Table 2) (3-10).

Table 2. Patient and pathological characteristics of incidental gallbladder cancer series

Author	Year	N	Cancer (%)	Female /Male ratio	Mean age	pTis, pT1 pT2,	pT3, pT4	Median survival (months)
Sarli et al. (3)	2000	2300	9 (0.39)	6/3	62.3	4	5	**12**
Antonakis et al. (4)	2003	5539	11 (0.2)	8/3	57	0	11	8.1
Yamamoto et al. (5)	2005	1663	9 (0.54)	4/5	73	4	5	19
Shimizu et al. (6)	2006	1195	10 (0.84)	7/3	61.4	4	6	62.5
Kwon et al. (7)	2008	1793	38 (2.12)	21/17	66	20	18	68
Tantia et al. (8)	2009	3205	19 (0.59)	14/5	56	16	3	18.4
Choi et al. (9)	2009	3145	33 (1.05)	24/9	63	12	21	46.3
Zhang et al. (10)	2009	10466	20 (0.19)	16/4	65.7	8	12	43

In the present study, the median survival time was 28 months, which compares favorably with previously reported survival times in the literature. The therapeutic approach for gallbladder cancer was applied according to the stage of the tumors. In the present study, five patient with a pTis and six patient with a pT1b underwent simple cholecystectomies without any additional surgery. There was no suspicion of malignancy intraoperatively, and routine histopathological studies revealed the diagnosis of gallbladder carcinoma in these patients. When we examined the treatment of early stage tumors in the literature, cholecystectomy alone was a sufficient therapy for T1a tumors (7,16,17), but the possible necessity of further surgery for T1b tumors is under debate (7,16,18-23). Some authors have recommended simple cholecystectomy for T1b tumors (7,16,19,21), while others have recommended additional surgery including liver bed resection and lymph node dissection (20,22,23). Liver resection and regional lymphatic dissection should be performed for T2 tumors because nodal metastasis has been reported in up to 50% of cases (16). Furthermore, T3 tumors have also been treated in the same way as T2 tumors, but the long-term survival rate for patients with T3 tumors has been approximately 5% (22). We performed excision of the liver bed and lymph node dissection in addition to a cholecystectomy in five patient with T2 tumors and eleven patients with T3 tumors.

CONCLUSION

The incidence of incidental gallbladder cancer has been reported to vary, up to 2.85%. In this single-center study, the rate of incidental gallbladder cancer was found to be 0.60%. Female gender and advanced age are demographic risk factors for gallbladder carcinoma. Although gallbladder cancer runs a short course with a poor prognosis, incidentally diagnosed tumors are often found in early stages and have a better prognosis.

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RESEARCH ARTICLE

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Approaches of Dealing with Primary Dysmenorrhea and Relationship between Kinesiophobia and Pain Severity

ABSTRACT

Objective: In this study, the most preferred methods of Primary Dysmenorrhea (PD) individuals to cope with menstrual pain and the relationship between kinesiophobia and pain severity were investigated.

Methods: This prospective study was conducted at Yozgat Bozok University Obstetrics and Gynecology Clinic. Sociodemographic information and complementary and alternative tecniques which used to reduce pain with PD diagnosis were recorded. Pain severity with visual analog scale and motion fear levels of PD patients were evaluated with Tampa Kinesiophobia questionnaire.

Results: The study included 100 PD individuals with an average age of 20.05 ± 2.6 years and Body Mass Index (BMI): 22.17 ± 3.35 kg / m2. As a result of the study; it was stated that in order to overcome the pain related to PD, 72% of individuals lay down and rest, 63% cotton dressing, 56% rub the abdomen, 54% listen to music, 52% apply hot on feet, 50% take analgesics, 49% apply hot to the lower abdomen, 47% take hot shower, 36% pray, 34% classic massage, 31% distraction, 31% keep the waist area warm, 26% lie facedown, 26% drink chamomile tea, 25% drink green tea, 25% daydreaming, 22% do diaphragmatic breathing exercises, 23% do aerobic exercises. In addition, a positive correlation was found between kinesiophobia and pain severity. ($p<0,05$).

Conclusions: This study showed that traditional methods were more preferable than exercise in PD and individuals with high pain severity had more fear of movement. The fear of movement of women with PD, doing or not doing exercise should be investigated.

Keywords: Pain, Exercise, Movement, Fear, Primary Dysmenorrhea, Complementary Treatments

Primer Dismenore ile Baş Etmek için Kullanılan Yöntemler ve Kinezyofobinin Ağrı Şiddeti ile İlişkisi

ÖZET

Amaç: Bu çalışmada Primer Dismenoreli (PD) bireylerin menstrüel ağrı ile baş etme konusunda en çok tercih ettiği yöntemler ve kinezyofobinin ağrı şiddeti ile ilişkisi araştırıldı.

Gereç ve Yöntem: Bu prospektif çalışma Bozok Üniversitesi Kadın Hastalıkları ve Doğum Polikliniğinde gerçekleşti. PD tanısı alan bireylerin sosyodemografik bilgileri ve ağrıyı azaltmak için kullandığı tamamlayıcı ve alternatif yöntemler kaydedildi. PD'li bireylerin ağrı şiddeti vizüel analog skalası ile hareket korku düzeyleri ise Tampa Kinezyofobi anketi ile değerlendirildi.

Bulgular: Çalışmaya yaş ortalaması 20,05± 2,6 yıl, ortalama Vücut Kütle İndeksi (VKİ): 22,17 ± 3,35 kg/m2 olan 100 PD'li birey dahil edildi. Çalışmanın sonucunda bireylerin %72'si yatıp dinlenme, %63'ü pamuklu giyinme, %56'sı karnı ovalama, %54'ü müzik dinleme, %52'si ayaklara sıcak uygulama, %50'si ağrı kesici, %49'u alt karına sıcak uygulama, %47'si sıcak duş, %36'sı dua etme, %34'ü klasik masaj, %31'i dikkati dağıtma, %31'i bel kısmını bağlama, %26'sı yüzüstü yatma, %26'sı papatya çayı, %25'i yeşil çay, %25'i hayal kurma, %22'si diyaframatik nefes egzersizleri, %23'ü aerobik egzersiz yaptığını belirtti. Ayrıca kinezyofobi ile ağrı şiddeti arasında pozitif yönde bir korelasyon bulundu ($p<0,05$).

Sonuç: Bu çalışma PD'de geleneksel yöntemlerin egzersizden çok daha fazla tercih edildiğini ve ağrı şiddeti yüksek olan bireylerde hareket korkusunun daha fazla olduğunu göstermektedir. Egzersiz yapan ve yapmayan PD'li kadınların hareket korkusu araştırılmalıdır.

Anahtar Kelimeler: Ağrı, Egzersiz, Hareket, Korku, Primer Dismenore, Tamamlayıcı Tedaviler

INTRODUCTION

Primary Dysmenorrhea (PD) is described pain during menstruation without any organic pathology (1). The incidence is greatest in young women and decreases with age (2). Pain is the most common symptom that is localized in the lower abdomen, resembling birth pain and can spread to the suprapubic region, thighs, lumbar region and lower back. Also headache, nausea, constipation, diarrhea, incontinence and vomiting can be seen. It usually starts on the 1st day of menstruation and ends on the 3th day (3). Women with PD participate in less social activities, are less able to take responsibility, need more time to rest, have higher rates of absenteeism at work or school (4). Although PD does not threaten life, it negatively effects the quality of life and has become a public health problem in the world (5). Many women with PD have used complementary and alternative medicine, for examples reducing physical activity, change their diet, apply hot application, reducing sleep duration, walking, using ginger, vitamin and mineral supplements (eg. magnesium and vitamin B1), omega 3 and 6, wearing cotton clothes, taking hot showers, taking hot liquids, and taking analgesics (6-8). These methods inhibit prostaglandin production, which causes pain with their physiological or psychological aspects, and some of them have been traditionally practiced for years.

In studies, vitamin B and E and omega-3 inhibit protein kinase C, inhibiting the conversion of arachidonic acid and phospholipids into prostaglandins in the cell membrane. The anti-inflammatory feature of ginger is that fennel tea inhibits the production of prostaglandins by secreting mefenamic acid, and rose tea contains abundant amounts of vitamin A, B, C, E, K; local temperature application reduces pain as it causes vasodilation, listening to music provides cognitive pain management and methods such as lying down can reduce uterine contraction (9-12). It is also stated in the literature that regular exercises can decrease the menstrual pain and symptoms by increasing the blood flow to the uterus. In this way, inflammatory cytokines are removed faster (13-16).

Kinesiophobia means fear of movement, and as a result of increased pain perception, the person is afraid of move and shows the avoidance response to coping with pain. It shows that kinesiophobia usually occurs between low back and neck region, and as a result, individuals avoid to act (17). Our aim in this study, which we came up with the hypothesis that symptoms such as thigh, abdomen, and lower back pain, which are frequently encountered during menstrual pain, can also cause movement avoidance, and that immobility may increase pain, is to determine the alternative and complementary treatment methods preferred by women with PD in the treatment and to evaluate the relationship of dysmenorrhea with kinesiophobia.

MATERIAL AND METHODS

This prospective study consisted of 18-35 ages nulliparous women who applied to the Obstetrics and Gynecology outpatient clinic of Yozgat Bozok University and diagnosed with PD. According to the Primary Dysmenorrhea Consensus Guide, our study was performed on 100 individuals having a regular menstrual cycle (28 ± 7 days) and menstrual pain higher than 4 mm according to Visual Analogue Scale (VAS) for the last 6 months. "Informed consent form" was taken from the cases and the cases were informed about the study in accordance with the Helsinki Declaration. This study was approved by the clinical ethics committee (Decision No: 2017-KAEK-189_2020.02.12_02).

Gastrointestinal, urogynecological, autoimmune, psychiatric diseases, other chronic pain syndromes, childbirth, positive pregnancy test, those who use intrauterine devices, those who have had pelvic surgery, those with irregular menstrual cycles (those who have a cycle period shorter than 21 days or longer than 35 days) and those who have a pathological history of secondary dysmenorrhea and ultrasonographic imaging were not included in the study.

Physical (age, height, body weight, body mass index) and demographic (age of menarche, mean cycle time, duration of menstruation, painful menstrual condition, duration of pain due to dysmenorrhea) informations were recorded for all participants.

VAS (ranging from 0 to 10 cm) was used to determine the severity of menstrual pain of each individual. VAS has also been shown to be a sensitive, valid and reliable tool for minor changes in pain intensity as a result of clinical pain and treatment (18). The point marked on the line was measured with a ruler, and the pain intensity that people felt during menstruation was recorded in cm. The most severe pain severity level experienced by the individuals in the first 3 days of menstruation was evaluated.

The questionnaire form included the most used methods in the literature used to reduce menstrual pain, such as green tea, rose tea, chamomile tea, black tea, fennel tea, ginger, linden, salt-free diet, Omega-3, vitamin E and B capsules, massage, praying, yoga, acupuncture, acupressure, reflexology, hypnosis , listening to music, breathing exercises, imagination, applying warm to the abdomen, applying warm to the feet, taking a hot shower, keeping the waist area warm, lying on her stomach, rubbing the abdomen, cotton dressing, lying down and resting, distraction, regular exercises were asked to mark which method the participants preferred.

The fear of movement that individuals experienced due to pain during menstruation was evaluated using the Tampa Kinesiophobia Scale (TKS). Vlaeyen et al. revised this scale in 1995. TKS

is a 17-question scale developed to measure the fear of injury again during the movement. TKS includes pain, injury/re-injury and fear-avoidance parameters in work related activities. The person gets a total score between 17-68. The high score on the scale shows that kinesiophobia is also high. It is recommended to use the total score in the studies. Tunca Yılmaz et al. validated the Turkish version of TKS (17).

Statistical Analysis: Statistical package program SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data. Data was expressed as mean±SD and in percentages. Continuous variables were investigated using analytical methods (Kolmogrov-Simirnov) to determine whether or not they are normally distributed. Bivariate correlations were investigated by Spearman's correlation analysis. $p < 0.05$ were accepted as statistically significant.

RESULTS

A total of 105 cases with PD diagnosis were evaluated for this study. 3 people who were not willing to participate in the study and 2 people who had undergone surgery were excluded from the study.

The study was carried out with 100 PD individuals with an average age of 20.05 ± 2.6 years, average BMI: 22.17 ± 3.35 kg / m2. The physical and demographic characteristics of the individuals in the study were shown in Table 1 and the features associated with menstruation were shown in Table 2.

Table 1. Age and BMI information of cases with Primary Dysmenorrhea

	n	Min ± Max	X±S.D.
Age (years)	100	17 ± 35	20.05 ± 2.60
BMI(kg/ m^2)	100	17 ± 32	22.17 ± 3.35

Min ± Max: Minimum ± maksimum, X±S.D: Aritmetik ortalama ± Standart Sapma, BMI: Vücut kütle indeksi

Table 2. Menstrual information of women with Primary Dysmenorrhea

		n	%
Time since menarche (y)	10-12	32	%32
	13	52	%52
	14-18	16	%16
Discontinuity to school	No	37	%37
	Yes	63	%63
Pain duration (hours)	<48	78	%78
	48-72	20	%20
	>72	2	%2
Medication use (number)	Yes	50	%50
	No	50	%50

Percentage expression of the complementary and alternative methods used by individuals to reduce menstrual pain were presented in Table 3. As a result of the study it was stated that, 72% of individuals lie down, 63% preferre cotton dressing, 56% rub the abdomen, 54% listen to music, 52% apply hot on feet, 50% take analgesics, 49% apply hot to the lower abdomen, 47% take hot shower, 36% pray, 34% had classical massage, 31% distraction, 31% keep the waist area warm, 26% lie facedown, 26% drink chamomile tea, 25% drink green tea, 25% daydream, 22% do diaphragmatic breathing exercises, 23% do aerobic exercise (which consists of 25% walking, 1% swimming, 7% plates, 3% cycling activity), 15% drink black tea, 15% drink fennel, 12% had unsalted diet, 10% drink ginger, 7% take vitamins E and B, 5% take omega 3 and 6, 3% take vitamin D and 2% do yoga.

Regarding the effect of these methods on their pain, 57% of these participants of reduced their pain with the method they used, 14% claimed to be psychological, 13% stated their complaints passed, 8% of them said that they were useless and 8% of them stated that they affected their health negatively (Table 4). There was a strong positive correlation between the pain severity levels experienced by the individuals during the menstrual period and the average fear of movement score obtained from the Tampa kinesiophobia questionnaire (Table 5) ($p < 0.05$, $r = 0.667$).

Table 3. Distribution of CAM used by women with PD to deal with dysmenorrhea

CAM	n	%
Nutritional methods		
Green tea	25	%25
Rose tea	1	%1
Chamomile tea	26	%26
Black tea	25	%25
Fennel	15	%15
Ginger	10	%10
Salt-free diet	12	%12
Vitamins E and B	7	%7
Omega	5	%5
Vitamin D	3	%3
Other methods		
Massage	34	%34
Praying	36	%36
Listening to music	54	% 54
Yoga	2	%2
Breathing exercises	22	%22
Imagination	25	%25
Applying hot to the lower abdomen	49	%49
Applying hot on feet	52	%52
Hot shower	47	%47
Keeping the waist area warm	31	%31
Lying down	26	%26
Rubbing the abdomen	56	%56
Cotton dressing	63	%63
Lay and rest	72	%72
Drawing attention to another direction	31	%31
Exercises	23	%23
Walking	25	%25
Swimming	1	%1
Plates	7	%7
Cycling activity	3	%3

CAM: Complementary and Alternative Methods

Table 4. Effect of CAM used by Primary Dysmenorrhea individuals

	n	%
Complaints passed	13	%13
Reduce pain	57	%57
No benefit	8	%8
Negative impact on health	8	%8
Psychological effects	14	%14

Table 5. The relationship between pain severity and Tampa kinesiophobia score

		Tampa kinesiophobia score
Pain severity	Correlation coefficient (r)	0.679
	p	**0.001***

DISCUSSION

PD is one of the most common non-pathological gynecological problems in young women. Individuals want to use fast and non-pharmacological methods without side effects in order to cope with this pain for many years. It is also stated that exercise and physical activity reduce pain, but there are still not enough studies whether individuals restrict their physical activities due to pain. In our study, we investigated the most commonly used methods of coping with PD. We determined that 72% of individuals with PD lie and rest, 54% listen to music, 49% prefer warm application to lower abdomen, 52% prefered warm applications to feet, 47% prefered traditional practices such as hot showers but exercise rates (23%) were quite low. In addition, we concluded that individuals with higher fear of movement had higher pain severity.

In his study on dysmenorrhea, Demirci found that 78.8% of women preferred more complementary and alternative methods (CAT) to cope with pain and that CAT was more common in women who did not use drugs to deal with dysmenorrhea (19). Kahyaoğlu et al. (20) found that 35.2% of individuals with PD had linden tea, 31% of whom preferred green tea, 30% chamomile tea, 27.3% hot milk, 22.4% black tea, 18.2% cinnamon, 14% fennel tea and 13.5% cherry stalk tea. Gün et al. (21) were determined that women with dysmenorrhea prefered more herbal methods (28.4%)such as 15.1% chamomile tea, 11.8% black tea, 11.8% sage, 7.9% linden, 6.6% parsley tea, 6.0% rose tea, 5.3% yarrow tea, 5.3% thyme tea, 5.3% balm tea, 2.6% green tea and 5.7% drink warm milk. Graz et al. (22) found that 23% of individuals with dysmenorrhea problems prefered nutritional supplements and herbal drinks. Houston et al. (23) concluded that 20% of individuals with dysmenorrhea used black tea. In our study, the rate of using herbal beverages in dealing with PD was similar to the literature. This might be due to the fact that the beliefs and traditional structure of the different society continues and they did not know much about different herbal products. Eryılmaz et al. (24) investigated the drug use rate of adolescents in dealing with dysmenorrhea and found the amount 46.1%. Gün et al. (21) found that 51.7% of individuals with dysmenorrhea used analgesics in their studies. In our study, we found that the rate of analgesia use in women with PD 50%. These results showed that women used medication to deal with menstrual pain without consulting a Physician. So their health might be effected negatively.

Chen et al. (25) talked about reducing physical activity, using herbal or pain medication, paying attention to nutritional changes and emotional support in terms of personal care strategies of women with PD. Şentürk Erenel et al. (26) in his studies, resting (65.4%) took the first place to deal with the complaints of dysmenorrhea. Yılmaz et al. (27) stated that the most preferred methods of dysmenorrhea students in dealing with pain were sleep (64.2%), massaging the painful area (53.4%) and hot showers (51.6%). In our study, we found that their methods were more traditional and did not require sufficient physical activity. We found that exercise was very low (23%) and these exercises were mostly walking. The high rate of pain intensity of these individuals and the low rate of relieving their pain suggested that sedentary life might contribute to their pain.

In studies related to kinesiophobia, it was mostly investigated in problems such as chronic low back pain and knee pain, and it was mentioned that it made individuals' daily activities difficult, and that immobility could cause chronic diseases and this may effect the rehabilitation process negatively (28). Güçlü et al. (29) stated in his study on 105 people with low back pain that as the severity of pain increased, the level of kinesiophobia increased. Many symptoms such as lumbal, sacral, abdominal, general body ache and headache, limb cramps, difficulty in normal activities, tenderness and edema in breasts can cause movement limitation (30). In the literature, studies showing whether the level of physical activity for individuals with PD will increase or decrease pain severity (31). William et al. (32) stated that exercise will decrease the sense of pain and symptoms by increasing beta endorphin levels. Motesharee et al. (33) found that PD symptoms decreased with 8-week stretching exercises in women with PD. Abbaspour et al. (34) stated that physical exercise had positive affects in students with dysmenorrhea and decreased their situations such as discontinuity to school. There was no complete clarity about the relationship between exercise and dysmenorrhea. In our study, individuals with high kinesiophobia levels had higher severity of pain and a relatively low rate of exercising might show that individuals had avoided exercise due to pain.

Lack of a healthy control group was among the limitations of the study. The strength of the study was that it addressed both alternative and

complementary methods used in PD and raised awareness that individuals with PD might have exercise avoidance behaviours for fear of pain. In the future, studies involving individuals who control and do not exercise that should be planned.

As a result, individuals with PD used various complementary and alternative methods and prefered methods that did not require high physical activity. Kinesiophobia could be seen in individuals with PD due to pain. This situation created a tendency for negative behaviours such as beeing sedentary and discontinuity to school in individuals with PD. Therefore, it may be more effective in order to manage pain by prefering methods such as exercise in order to ensure the combination of daily work life in women with PD.

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CASE REPORT

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Family Therapy in Cigarette Addiction: Case Report

ABSTRACT

Tobacco use, which causes the deaths of more than 8 million people every year, is an important health problem all over the world, especially in low and middle-income countries. Behavioral education-motivational support treatment can be used alone or in combination with pharmacological treatment in tobacco addiction. In this case series, we wanted to emphasize the importance of the social support in the family with the medical and motivational support provided by 7 members of the same family at the same time by applying to our outpatient clinic. In addition to medical treatment, motivational support and family support are important in smoking cessation treatment.

Keywords: Smoking, Family Treatment, Motivational Interview

Sigara Bağımlılığında Aile Terapisi: Olgu Sunumu

ÖZET

Her yıl 8 milyondan fazla insanın ölümüne yol açan tütün kullanımı, düşük ve orta gelirli ülkeler başta olmak üzere tüm dünyada önemli bir sağlık sorunudur. Tütün bağımlılığı ile mücadelede bağımlılığın derecesi, aile, sosyal çevre, hastanın sahip olduğu ek hastalıklar da dahil olmak üzere çok yönlü bir şekilde değerlendirilerek kişiye özel tedavi yöntemi belirlenmelidir. Tütün bağımlılığında davranış eğitimi-motivasyonel destek (DE) tedavisi tek başına ya da farmakolojik tedavi ile birlikte kullanılabilir. Bu olgu serimiz aynı ailenin 7 üyesinin aynı anda sigara bırakma kararı vererek polikliniğimize müracaat etmesiyle verilen medikal ve motivasyonel destekle, aile içindeki sosyal desteğin önemini vurgulamak istedik.

Anahtar Kelimeler: Sigara Kullanımı, Aile Terapisi, Motivasyonel Görüşme

INTRODUCTION

Tobacco use, which causes more than 8 million deaths every year, is an important health problem all over the world, especially in low and middle income countries. Passive exposure to cigarette smoke contributes to the development of cardiac diseases, cancer and other diseases, causing about 1.2 million additional deaths per year (1). In the literature, it is thought that there will be 8 million deaths worldwide due to smoking in 2030 (2). Tobacco causes addiction with nicotine and may cause cardiovascular diseases, stroke, chronic lung disease, lung cancer and other types of cancer (3, 4). It is thought that smoking during pregnancy may cause complications such as placenta previa, abruptio placenta, stillbirth, low birth weight, preterm birth, spontan abortus, newborn short stature and congenital anomalies (5-9). In addition to its effects on health, tobacco use causes a financial burden of 1.4 trillion dollars a year and 40% of this occurs in developing countries (10). Considering all this, the fight against tobacco addiction becomes more and more important day by day. In the fight against tobacco addiction, the degree of addiction, family, social environment, and the additional diseases that the patient has, should be evaluated in a multifaceted way and a personalized treatment method should be determined. Fagerström Nicotine Dependency Scoring (FNDS) is the most widely used assessment for measuring nicotine addiction level (11). Carbon monoxide measurement in respiratory air and the number of cigarettes smoked per 24 hours are among the other methods used (12, 13). Behavioral education-motivational support therapy can be used alone or in combination with pharmacological treatment in tobacco addiction (14). As pharmacological treatment methods, nicotine replacement therapy, bupropion and varenicline treatments are used in our country. Nicotine replacement treatments are classified as nicotine gum, transdermal tape, intranasal spray and inhaler.

In this case series, we wanted to emphasize the importance of the social support in the family with the medical and motivational support provided by 7 members of the same family at the same time by applying to our outpatient clinic.

CASE REPORT

In our case series, we examined 7 people from the same family to apply for smoking cessation, and to discuss them individually and collectively, and to quit smoking.

Case 1: A 70 years old male patient. In the anamnesis received; learned to retire, coronary artery disease. The FNDS score was 7 in the evaluation of the patient who smoked 28 packs / year and had 4 quits before. When asked why he wanted to quit smoking, he reported that he had difficulty breathing and had financial difficulties. Motivational support and nicotine replacement therapy were initiated due to age and coronary artery disease. A control appointment was made by informing about how to use and side effects.

Case 2: Case was 60 years old male patient. He stated that he retired and had no additional disease in the anamnesis. FNDS score was determined as 8 in the evaluation of the patient who had 42 packs / year of smoking and had multiple quitting experiences before. When asked why he wanted to quit smoking, he stated that he had shortness of breath. Motivational support and varenicline treatment were started, since the patient had no additional diseases. A control appointment was made by informing about how to use and side effects.

Case 3: Fifty five years old female patient. It was learned that the patient was a housewife in her anamnesis and that she was treated for depression. The FNDS score was found to be 8 in the evaluation of the patient who smoked 30 packs / year and had previous quitting experience. The patient stated that he wanted to quit smoking due to financial difficulties. In addition to motivational support therapy, nicotine replacement therapy was started. A control appointment was made by informing about how to use and side effects.

Case 4: Thirty two years old female patient. It was learned that she had a wife in her anamnesis and she did not have any concomitant disease. FNDS score was determined as 9 in the evaluation of the patient who had 22 packs / year of smoking and had previous quitting experience. When asked why he wanted to quit smoking, he stated that he had financial concerns. Since the patient did not have any additional diseases, motivational support therapy and varenicline treatment were started. A control appointment was made by informing about how to use and side effects.

Case 5: Case was 25 years old male patient. It was learned that he had a student in the anamnesis and had no concomitant disease. The FNDS score was found to be 7 in the evaluation of the patient who used 3 packs / year of smoking and had no previous quitting experience. When asked why he wanted to quit smoking, he stated that he wanted to quit because of the smell of his friends. Since the patient had no additional disease, varenicline therapy was started in addition to motivational support therapy. A control appointment was made by informing about how to use and side effects.

Case 6: Twenty two years old male patient. It was learned in the anamnesis that he was engaged in self-employment and did not have additional diseases. FNDS score was found to be 9 in the evaluation of the patient who used 3 packs / year cigarette and had no previous cessation experience. When the patient was asked why he wanted to quit smoking, he stated that the desire of the family

members to quit had also created a desire to quit. Since the patient had no additional disease, varenicline therapy was started in addition to motivational support therapy. A control appointment was made by informing about how to use and side effects.

Case 7: Twenty years old female patient. It was learned that she was a mother-in-law and breastfeeding her baby. The FNDS score was found to be 8 in the evaluation of the patient who used 4 packs / year of cigarettes and had previous quitting experience. When asked why the patient wanted to quit smoking, she stated that she did not want to expose her baby to the smell of cigarettes. Pharmacological treatment was not given to the patient because she was breastfeeding her baby, and motivational support treatment was given. A control appointment was made by informing.

The 12th day of the patients was planned as a common smoking cessation day. A control appointment was made 1 week after the day of quitting. Contact information was shared to reach patients in case of additional complaints or emergency situations. Patients were interviewed at the control appointment. There were no side effects or additional complaints in the patients. It was observed that all of the patients had quit smoking. It was learned that some of them had difficulties in this period, but they had a more comfortable time with family support. One month later, a check-up appointment was made. At the control appointment, the patients stated that they still did not smoke and talked about finding new hobbies. After 3 months, a control appointment was made and the contact information was shared again in order to reach additional complaints.

DISCUSSION

It is known that individuals who feel suggestions and suggestions to quit smoking even once from physicians are more motivated and quit smoking (15). It is thought that environmental and genetic factors play a role in cigarette addiction besides nicotine (16). The investigations show that the smoking between the family members increase if there is already already a smoking person within the family (17). The main challenge in cigarette addiction should be to prevent smoking (16). As there are many methods used in smoking cessation, the important thing is to choose the method that is suitable for the patient. Because smoking cessation treatment is actually creating a behavior change. In order to do this, it is very important to choose an individual-specific method in which the individual will be included and internalized. Although we are from the same family, different cigarettes addiction treatments have been started for 7 patients who have been examined and it has been seen that individuals benefit. Since the patients are from the same family, the social support they provide to each other is thought to be effective in the success rate. At the same time, it is thought that the patients are away from smoking in the home environment because the patients live in the same house and the planned smoking cessation date is the same day. In addition, behavioral training provided to patients - motivational support treatment may have increased the effectiveness of the treatment, both individually and collectively, for each examination. The FNDS score in the study ranged from 7 to 9 with a high and very high level of nicotine dependence. it was stated that the desire to quit smoking was also high in those with a high score (18).

It is known by physicians that psychosocial support is important in addition to smoking cessation treatments, especially in individuals over 65 years of age (19). In this respect, despite the 4 times of unsuccessful experience of our 70-year-old patient, it was ensured that both the healthcare professionals and the family members quit smoking thanks to the strong motivational support. The literatures often mention that the success of medical treatment increases in line with the GP s active involvement within the treatment together with them investing the required time for the treatment (20). We have created interactive communication environments with our patients to answer any questions they have in mind by taking 20 minutes each and 45 minutes collectively.

Smoking during breastfeeding causes hyperactivity syndrome, sudden infant death, and middle ear infection and lung infection in the baby (21). Our case, who was in breastfeeding period and continued to smoke while breastfeeding her baby and had previous experience of quitting, also quit smoking. In the control, especially when the changes in her baby were questioned, she said that the baby slept more comfortably and her milk was enough for her baby. It has been reported in the literature that smoking in the breastfeeding mother reduces the mother's milk. In our case, we reached a conclusion similar to the literature.

CONCLUSION

Cigarette addiction level is a very high substance. It is obvious that medical treatment is not only beneficial for smoking cessation treatment, but motivational support must be applied. Besides health professionals, regulation of social environment, family support and individualized approach are important factors affecting the success of treatment. We think that the support of the family to each other and the necessary time for each of the patients, finding the answers to every question they have in mind, and the individuality of their treatments are of great importance in the success of the treatment in our patients.

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IGT and SS examined and wrote manuscript, BKT wrote manuscript and checked the examination.

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