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EDITORIAL/ *EDİTÖRYAL*

RESEARCH ARTICLE/ *ARAŞTIRMA MAKALESİ*

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EDITORIAL

EDİTÖRYAL

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Hip Fracture in The Elderly: An Overview

Yaşlılarda Kalça Kırığı: Genel Bir Bakış

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ABSTRACT

In this paper, the available information about hıp fracture ın the elderly is briefly reviewed. Intracapsular and extracapsular hip fractures, which usually occur due to low energy trauma in elderly patients, are one of the most important causes of functional disability, morbidity and mortality. Treatment of hip fractures; it requires the management of a broad spectrum from prevention to surgery and post-operative care. It is important to mobilize elderly patients with hip fractures as soon as possible by treating them with the appropriate method and to avoid systemic complications that may occur due to immobility.

Key words: Hip Fracture, Elderly, Treatment, Surgery, Morbidity, Mortality

ÖZ

Bu yazıda, yaşlılarda kalça kırığıyla ilgili mevcut bilgiler kısaca gözden geçirilmiştir. Genellikle yaşlı hastalarda düşük enerjili travmaya bağlı olarak ortaya çıkan intrakapsüler ve ekstrakapsüler kalça kırıkları, fonksiyonel yetersizlik, morbidite ve mortalitenin en önemli nedenlerinden biridir. Kalça kırıklarının tedavisi; önlemeden ameliyata ve ameliyat sonrası bakıma kadar geniş bir yelpazenin yönetimini gerektirir. Kalça kırığı olan yaşlı hastaların uygun yöntemle tedavi edilerek en kısa sürede mobilize edilmesi ve hareketsizliğe bağlı oluşabilecek sistemik komplikasyonların önlenmesi önemlidir.

Anahtar Sözcükler: Kalça Kırığı, Yaşlı, Tedavi, Ameliyat, Morbidite, Mortalite

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Intracapsular and extracapsular hip fractures, which usually occur due to low energy trauma in elderly patients, are one of the most important causes of functional disability, morbidity and mortality [1]. It has been reported that only about one-third of elderly patients with hip fractures will survive for more than 5 years, and only 25% of these patients can return to their previous functional status [2]. In a study conducted in our country; it was found that the risk of death in patients with hip fractures is 11.7 times higher than in the general population of similar age [2]. Treatment of hip fractures; it requires the management of a broad spectrum from prevention to surgery and post-operative care. Timely surgery for hip fracture is an important support of treatment. Although there is a consensus on the surgical treatment of these fractures today, the issue of which method should be used is controversial. Osteosynthesis methods are generally recommended for extracapsular intertrochanteric fractures with high union potential. On the other hand, arthroplasty is recommended for displaced intracapsular fractures [1,3]. It is important to mobilize elderly patients with hip fractures as soon as possible by treating them with the appropriate method and to avoid systemic complications that may occur due to immobility. When deciding on the method to be

chosen in the treatment of these patients; factors such as age, general condition and accompanying systemic diseases, bone quality and fracture type should be taken into consideration [3].

Elderly patients with hip fractures are often osteoporotic and this causes difficulties in treatment. Bisphosphonate therapy has been proven to be beneficial in prevention and may reduce the risk of osteoporotic hip fractures [4]. On the other hand, most of the elderly patients treated for hip fractures have systemic pathologies, some risk factors and malnutrition. Numerous risk factors for geriatric hip fractures can affect morbidity and mortality, such as age, gender, American Society of Anesthesiologist (ASA) score, degree of dementia, walking ability, fracture type, timing of surgery, type of surgery, length of hospital stay, and albumin level [2]. At the same time, long preoperative time, low blood albumin levels, and urine culture growth indicate that these are important risk factors for postoperative surgical site infection [5]. Although much emphasis is placed on the risk factors related to the physical comorbidities accompanying the majority of hip fractures, such as diabetes, hypertension, and chronic obstructive pulmonary diseases; mental and cognitive factors are as important as providing physical integrity during the treatment process [6,7]. Although overlooked in most elderly patients, depression is the most common psychological disorder and can negatively affect the daily life of patients with hip fractures [6]. On the other hand, the development of delirium after surgery in elderly hip fracture patients is an important cognitive problem. It should be kept in mind that metabolic disorders and general anesthesia are important risk factors in the development of delirium [7].

Hip fractures in the elderly still remain an important physical and social problem. Even during the Covid-19 pandemic, the number of hip fractures has not decreased. Moreover, hip fracture mortality rates in the elderly population have been reported to increase during the Covid-19 pandemic [8].

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RESEARCH ARTICLE

ARAŞTIRMA

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The effect of regularly performed moderate-intensity exercise program on thiol/disulfide homeostasis, and ischemia-modified albumin

Düzenli olarak uygulanan orta şiddetteki egzersiz programının tiyol/disülfid homeostazı ve iskemi modifiye albümin üzerine etkisi

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ABSTRACT

Aim: Thiol/disulfide homeostasis is an indicator of oxidative stress and antioxidant capacity. Ischemia-modified albumin (IMA) is an important marker for both oxidative stress and ischemia. We aimed to evaluate the possible effects of regularly performed moderate-intensity exercise on thiol/disulfide homeostasis, and IMA levels.
Methods: Sprague Dawley rats were used. The study was composed of an Exercise group (EG, n=9) and Control group (CG, n=6). A 10-weeks swimming exercise was performed. Thiol/disulfide homeostasis measurement method was used in this study. IMA levels were measured by a cobalt-albumin binding method.
Results: In the EG, total thiol levels were significantly higher compared to the CG ($p<0.01$). The disulfide/total thiol ratio was lower in the EG compared to the CG ($p<0.01$). We observed that there was a slight increase in IMA levels in EG ($p=0.18$). This increase was not statistically significant.
Conclusion: Regularly performed moderate-intensity exercise has increased native and total thiol levels. Increase of thiol levels can prevent oxidative stress. Regularly performed moderate-intensity exercise programs appear to provide favourable effects on oxidative stress.

Key words: Swimming, oxidative stress, thiol/disulfide homeostasis, ischemia-modified albumin

ÖZ

Amaç: Tiyol/disülfid homeostazı, oksidatif stresin ve antioksidan kapasitenin bir göstergesidir. İskemi-modifiye albümin (İMA), hem oksidatif stres hem de iskemi için önemli bir belirteçtir. Düzenli olarak uygulanan orta şiddetteki egzersizin tiyol/disülfid homeostazı ve IMA seviyeleri üzerine olası etkilerini değerlendirmeyi amaçladık.
Yöntemler: Sprague-Dawley sıçanlar kullanıldı. Çalışma, Egzersiz grubu (EG, n=9) ve Kontrol grubundan (KG, n=6) oluşturuldu. 10 haftalık bir yüzme egzersizi yaptırıldı. Bu çalışmada tiyol/disülfid homeostazı ölçüm yöntemi kullanıldı. İMA seviyeleri, bir kobalt-albümin bağlama yöntemiyle ölçüldü.
Bulgular: EG'da, total tiyol seviyeleri KG ile karşılaştırıldığında anlamlı derecede daha yüksekti ($p<0.01$). Disülfid/total tiyol oranı EG'da KG ile karşılaştırıldığında daha düşüktü ($p<0.01$). EG'da IMA seviyelerinde hafif bir artış olduğunu gözlemledik ($p=0,18$). Bu artış istatistiksel olarak anlamlı değildi.
Sonuç: Düzenli olarak uygulanan orta şiddetteki egzersiz, nativ ve total tiyol seviyelerini artırdı. Tiyol seviyelerinin artması oksidatif stresi önleyebilir. Düzenli olarak uygulanan orta şiddetteki egzersiz programlarının oksidatif stres üzerinde olumlu etkiler sağladığı görülmektedir.

Anahtar Kelimeler: Yüzme, oksidatif stres, tiyol-disülfit homeostazı, iskemi-modifiye albumin

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Introduction

Exercise plays an important role in maintaining physical fitness and health [1]. Swimming exercises are generally of an aerobic nature and involve large muscle groups of the body. In physical exercises, as the energy demand of the body increases, oxygen consumption levels increase as well, compared to resting consumption [2]. Regularly performed swimming exercise is considered to be a good model of endurance exercise training [3]. Skeletal muscle metabolism changes in adaptation to endurance exercise [4]. Specifically, endurance exercises increase the oxidative capacity of skeletal muscles and this increase in metabolic rate can lead to a 100-fold increase in oxygen consumption in these muscles [5].

Oxidative stress (OS) causes the production of reactive oxygen species (ROS) and ROS induces the oxidation of disulfide groups to sulfhydryl containing amino acids [6]. In case of tissue damage, thiol groups can take part in the defence mechanism by reacting with free radicals. Thiol groups may be involved in the antioxidant defence system of the body by reacting with free radicals, having the potential to prevent tissue damage [7]. Under oxidative stress conditions, thiol groups are reversibly oxidized and converted into disulfide bonds and these can turn into thiol groups. Disruption of this homeostasis may lead to different diseases such as diabetes mellitus, cancer and cardiovascular diseases [7]. The intensity and duration of the exercise affects redox balance; regularly performed moderate-intensity exercise programs appear to provide favourable effects on oxidative stress [8].

Ischemia modified albumin (IMA) results from the damage caused by ROS at the N-terminus of albumin, and this conversion in albumin leads to a decrease in its metal binding capacity. IMA has been evaluated in various states of ischemia, such as exercise-induced myocardial ischemia, acute coronary syndromes, after a percutaneous coronary intervention [9,10]. Previous studies have shown that IMA is an ideal biomarker for ischemia and increased OS. Our study aimed to examine the effects of regularly performed moderate-intensity exercise on thiol/disulfide homeostasis and IMA levels.

Material and method

Experimental design

Male Sprague Dawley rats (300 to 350g, n=15) were housed 3 to 5 individuals per cage under controlled conditions (12-12 h light-dark cycle, room temperature 20±22°C, humidity 55 to 60%) with chow and tap water available ad libitum. All experimental procedures were approved by the Bezmialem Foundation University Ethics Committee (2021/127). Rats were randomly divided into two groups: Exercise Group (EG, n=9) and Control group (CG, n=6). The control group subjects remained in their cages throughout the study.

Exercise training program

The pre-training period in the swimming exercise group lasted for seven days. The first day lasted only 20 minutes, in the following days, duration of the exercise was increased 10 min per day until the duration of 60 minutes a day was achieved. Swimming sessions were applied as 60 min/day, 5 days/week, for 8 weeks. On the 9th week, rats swam twice a day, and on the 10th-week rats swam three times a day with sessions of 60 min duration [11]. A cylindrical beaker filled with water (35 cm deep and 50 cm wide) was used for swimming exercises. The temperature of the water was kept between 30°C and 32°C. The body weights were measured before and after exercise program.

Anaesthesia of the rats was ensured by intraperitoneally administered ketamine (45 mg/kg) and xylazine (5 mg/kg) and rats were sacrificed at the end of the tenth week of the swimming exercise protocol. Blood samples were collected by the intracardiac puncture and centrifuged at 3.000 rpm for 10 minutes at room temperature, just after the collection. After centrifugation, serum samples were separated to be frozen and stored at -80°C.

Biochemical analysis

Until now, thiol and disulfide groups were measured in one direction. Erel and Neselioglu have developed a new method that measures the levels of both variables, either separately and

together. In our study, disulfide concentrations were calculated using half the difference between total thiol and natural thiol levels. The percentage of disulfide/total thiol, the percentage of disulfide/native thiol and the percentage of native thiol/total thiol, were then calculated [12]. Albumin levels were measured using the bromocresol green method. Cobalt-albumin binding assay, which is a colorimetric method, was used to measure IMA levels [13].

Statistical analysis

Statistical analyses were performed using the SPSS 13.0 (SPSS Inc. Chicago, IL, USA). Quantitative data was given as mean±SD or medians (interquartile ranges, IQR). Normal distribution and differences between variances were determined using Kolmogorov-Smirnov and Levene tests, respectively. Student's t-test and Mann Whitney U tests were used to comparing the groups. A p-value of <0.05 was considered statistically significant.

Results

Effect of exercise on body weight

After the exercise program, bodyweight of the EG decreased significantly compared to CG (352.38±20.74g vs 411.67±30.02g, p<0.05).

Biochemical analysis

Disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol and IMA/albumin ratios of CG and EG, are presented in Table 1. Native thiol, total thiol, native thiol/total thiol ratio and albumin levels, were significantly higher in the EG compared to the CG (p values <0.01, <0.01, <0.01, and p value=0.04, respectively). Total and native thiol levels in the groups are shown as whiskers graphs in Figure 1. In comparison to the CG, the EG had significantly higher native thiol levels (243.4±28.69 vs 179.6±20 µmol/L, p<0.01) and higher total thiol levels (298.6± 30.50 vs 240.2±24.53 µmol/L, p<0.01). Albumin levels were significantly higher in the EG (2.95±0.56 vs 2.37±0.52 g/dL, p<0.04). IMA/albumin ratio decreased in the EG compared to the CG, although this decrease was not statistically significant (p=0.17). Although not statistically significant, there was a slight increase in IMA levels in the EG (p=0.18). Disulfide/total thiol and disulfide/native thiol ratios were significantly lower in the EG compared to the CG (p values <0.01, both). Native thiol/total thiol ratio increased significantly in the EG compared to the CG (p<0.01). The disulfide level was lower in the EG compared to the CG, however this decrease was not statistically significant (p=0.19). No other significant difference in the measured parameters was found between the groups.

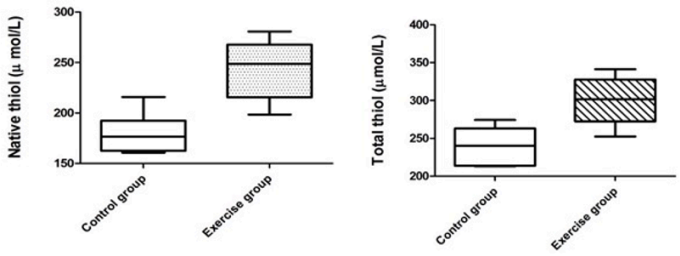

Figure 1. Box-and-whisker plot of native thiol and total thiol levels in the exercise and control groups (Whiskers: 10 and 90 percentile). The middle lines, upper and lower margin of boxes represent medians.

Discussion

The relationship between exercise and oxidative stress is complex. The occurrence of different responses to exercise varies depending on the duration and intensity of the exercise. One study examined the effect of a high-intensity exercise program on oxidative stress in post pubertal boys and girls. High-intensity exercise has been shown to cause oxidative stress and increase skeletal muscle damage in these cases [14].

Physical exercises cause an increase in metabolic demands of the body and to meet this demand, the body increases its oxygen consumption. As a result of this process, exercise causes an increase in the formation of free radicals, the amount of which depends on the duration and intensity of the exercise. As the intensity of the exercise increases, oxidant levels in the body increase in line with the intensity [15]. Munoz et al. performed cycling exercises with two different intensities in male cyclers, showing that short-term cycling exercises cause an increase in oxidative stress parameters [16]. In another study, Goto et al. applied training with different intensities (25%, 50%, 75%VO2Max) [17]. They showed that a 75% intensity exercise significantly increased oxidative stress parameters. In addition, they stated that

mild intensity exercise caused a decrease in oxidative stress parameters.

Regularly performed moderate-intensity exercise programs are beneficial in reducing oxidative stress and protecting health. Acute and exhausting exercise programs can cause excessive ROS production, an increase in oxidative stress and an upregulation of antioxidant defence systems. Therefore, regular moderate exercise programs cause a decrease in oxidative stress, provides protection against diseases and improve quality of life [8].

In addition, regular exercise programs cause a decrease in body weight [18]. Oscai et al. showed that rats subjected to a regular endurance exercise program had lower body weight than controls [19]. In our study, we showed that regularly performed moderate-intensity swimming exercises caused a significant decrease in body weight ($p < 0.05$). The other response was observed in the antioxidant defence system: regular exercise provides more resistance to oxidative stress damage. Generally, antioxidant capacity increases in athletes and rats who exercise regularly [18].

Different results were obtained in studies evaluating the relationship between exercise and antioxidant parameters. This difference appears to occur depending on the model, duration, intensity and type of exercise and the methods used to measure antioxidant parameters. Therefore, it is crucial to use simple, dependable and sensitive methods [20]. Inayama et al. have shown that after a marathon race, plasma protein thiol concentrations were decreased and they suggested protein sulfhydryls were oxidized during the competition [21]. Oxidative stress causes thiol groups are reversibly oxidized and converted to disulfide bonds, which can convert to thiol groups [7]. Thiol groups can react with free radicals to create an antioxidant defence system. This antioxidant defence mechanism is maintained by thiol/disulfide homeostasis and disruption of this homeostasis can lead to various disorders such as diabetes, cancer and cardiovascular diseases [20].

Kayacan et al. applied treadmill exercise training to rats (5 min/week for 10 weeks) and measured thiol and disulfide levels. It was seen that the disulfide levels were significantly lower in the EG. This study demonstrated that moderate exercise reduced oxidative stress [20].

We investigated the effects of regularly performed moderate-intensity swimming exercise on thiol/disulfide homeostasis and to the best of our knowledge, this is the first study of its kind. We have shown that in the exercise group, thiol levels increased and disulfide levels decreased. Disulfide/thiol ratios were significantly lower in the EG compared to the CG (Table 1). These results show that a regularly performed moderate-intensity exercise program is effective in reducing oxidative stress, by reducing disulfide levels and increasing thiol levels.

Table 1. Thiol, disulfide levels, and IMA levels in the exercise and control groups.

	Control Group (n=6)	Exercise Group (n=9)	p value
Albumin (g/dl)	2.37± 0.52	2.95 ± 0.56	0.04
IMA (IU/mL)	0.51 ± 0.02	0.55 ± 0.05	0.18
IMA/Albumin Ratio	0.23 ± 0.06	0.19 ± 0.04	0.17
Native thiol (µmol/L)	179.6 ± 20	243.4 ± 28.69	< 0.01
Total thiol (µmol/L)	240.2 ± 24.53	298.6 ± 30.50	< 0.01
Disulfide (µmol/L)	30.33 ± 4.46	27.64 ± 2.96	0.19
Disulfide/Native thiol (%)	16.94 ± 2.34	11.47 ± 1.68	< 0.01
Disulfide/Total thiol (%)	12.62 ± 1.31	9.3 ± 1.11	< 0.01
Native Thiol/Total thiol (%)	74.77 ± 2.63	81.40 ± 2.23	< 0.01

IMA: Ischemia modified albumin, $p<0.05$ was considered significant for statistical analyses and only significant statistics were shown bold in the table.

The mechanisms that cause changes in IMA levels during exercise are not yet clear. IMA levels change depending on the type of exercise applied [21]. After a marathon run, Apple et al. showed that the level of IMA had not changed immediately [22]. Other researchers have reported a mild decrease in mean IMA concentration after a marathon run [23]. In a study on plasma, IMA levels of patients with coronary artery disease were measured after a treadmill exercise. Decreased IMA levels were observed, and levels returned to initial concentrations 60 min after the exercise [9]. IMA levels were measured in healthy individuals after the hand-grip test. IMA levels were found to decrease at 1, 3 and 5 min after the forearm ischemia, whereas afterwards, IMA levels returned to baseline. The same changes have been seen in the IMA/albumin ratio [24].

Bhagwan et al. showed that IMA levels increase in patients with coronary ischemia [25]. Bar-Or et al. showed that after ischemia, IMA levels returned to baseline level within 6 hours [13]. In the present study, as we investigated albumin and IMA levels, we observed that in the EG, albumin levels were significantly higher compared to the CG (Table 1) and that there was a slight increase in IMA levels in the EG. Additionally, we showed that IMA/albumin ratios in both groups were similar (Table 1). Finally, we found that the exercise program applied can cause a slight increase in the IMA plasma level.

This study showed that a swimming exercise program applied as 60 min/day for 10 weeks can prevent oxidative stress. In this context, we can say that the regularly performed moderate exercise will result in an increase in the antioxidant capacity thiol/disulfide ratio.

Limitations

Our study had some limitations. Studies that have evaluated exercise and antioxidant parameters together, showed that a range of variables affected the findings. These variables depend on variations in experimental design (exercise intensities, duration, type, etc.) and methods used to assess oxidative stress.

Conclusion

In our study, we demonstrated that regularly performed moderate-intensity exercise decreases oxidative stress and increases antioxidant capacity with increasing thiol groups, without creating an ischemic load. In addition, in this study, a new method of thiol/disulfide measurement was used to evaluate oxidative stress. This measurement method is proposed as a useful and practical method.

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RESEARCH ARTICLE

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Does adipose tissue thickness affect the duration of rotator cuff operations?

Omuz bölgesi yağ kalınlığının rotator manşet operasyonlarının süresine etkisi var mıdır?

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ABSTRACT

Objective: Accurate estimation of operation time will reduce operating room costs and increase patient satisfaction. In recent studies, authors have found that thicker adipose tissue at the operation site is associated with a higher rate of complications. However, there is no study in the literature investigating the effect on operation time of an increase in adipose tissue thickness. This present study hypothesized that thicker adipose tissue in shoulder surgeries would prolong the operation time, therefore the study was planned accordingly.
Material and Methods: Preoperative magnetic resonance images of patients applied with rotator cuff repair between 2015 and 2020 were independently evaluated by two observers. The acromial fat thickness was measured as the fat thickness of the operation area, and the scapular fat tissue thickness as the fat thickness of the region relatively far from the operation area. The data obtained were evaluated using multivariate analysis and a binary logistic regression model.
Results: Evaluation was made of a total of 106 patients. The mean total operation time was 89±33 mins. The mean acromial fat thickness was 12.2±4.89 mm and the mean scapular fat thickness was 27.9±12.5mm. The increase in acromial fat thickness was determined to have extended the operation time (OR=5.75, 29.21, p<0.05).
Conclusion: The thickness of fat tissue in the surgical area is one of the factors affecting operating time. Patients can be informed about the risk of prolonged surgery time and associated complications before surgery and costs can be reduced by optimizing operating room planning. In addition, it should be considered that tendinous pathologies may be more common in individuals with increased adipose tissue thickness and thus contribute to prolonging the operation time.

Keywords: adipose tissue thickness, rotator cuff repair, surgery time

ÖZ

Amaç: Ameliyat süresinin doğru tahmin edilmesi ameliyathane maliyetlerini azaltacak ve hasta memnuniyetini artıracaktır. Son çalışmalarda yazarlar, operasyon bölgesinde artan yağ dokusunun komplikasyonları arttırdığını bulmuşlardır. Ancak literatürde yağ dokusu kalınlığındaki artışın operasyon süresine etkisini araştıran bir çalışma bulunmamaktadır. Bu çalışmanın hipotezi, omuz bölgesinde artan yağ dokusu kalınlığının ameliyat süresini uzatacağıydı ve çalışma buna göre planlandı.
Yöntemler: 2015-2020 yılları arasında rotator manşet tamiri uygulanan hastaların ameliyat öncesi manyetik rezonans görüntüleri iki gözlemci tarafından bağımsız olarak değerlendirildi. Akromiyal yağ kalınlığı operasyon bölgesinin yağ kalınlığı olarak, skapular yağ dokusu kalınlığı ise operasyon bölgesine görece uzak bölgenin yağ kalınlığı olarak ölçüldü. Elde edilen veriler çok değişkenli analiz ve ikili lojistik regresyon modeli kullanılarak değerlendirildi.
Bulgular: Toplam 106 hasta değerlendirildi. Ortalama toplam operasyon süresi 89±33 dakika idi. Ortalama akromiyal yağ kalınlığı 12.2±4.89 mm ve ortalama skapular yağ kalınlığı 27.9±12.5 mm idi. Akromiyal yağ kalınlığındaki artışın operasyon süresini uzattığı belirlendi (OR=5.75, 29.21, p<0.05).
Sonuç: Ameliyat bölgesindeki yağ dokusunun kalınlığı ameliyat süresini etkileyen faktörlerden biridir. Ameliyathane planlaması optimize edilerek hastalar ameliyat öncesi uzamış ameliyat süresinin ve buna bağlı komplikasyonların riskleri hakkında bilgilendirilebilir ve maliyetler düşürülebilir. Ayrıca yağ dokusu kalınlığı artan bireylerde tendinöz patolojilerin daha fazla olabileceği ve bu yollada ameliyatı süresini uzamasına katıkıda bulunabileceği göz önünde bulundurulmalıdır.

Anahtar kelimeler: yağ dokusu kalınlığı, rotator manşet tamiri, ameliyat süresi

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Introduction

With the developments in imaging methods such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT) and X-rays, orthopedic surgeons can better evaluate muscle, bone, tendons, ligaments and similar structures and make a more accurate preoperative plan. Adipose tissue however, which shows a good deal of interpersonal variations, is often not taken into account, although it can provide some information for preoperative planning. Previous studies have stated that the thickness of fatty tissue around the surgical area increases complications, such as postoperative surgical site infections [1, 2]. It has been suggested that the increase in complications may be a result of prolongation of the operation time [3-5]. However, no study in the literature has yet investigated the effect of increased adipose tissue thickness on operation time and this information may be useful in distinguishing whether these complications are due to immunological and metabolic causes of obesity, or to prolongation of the actual operation time, as some have suggested.

When all elective surgical procedures are taken into account, rotator cuff operations present much more variability in terms of surgical time. Based on this observation, we determined that examining the operation time of these types of surgeries would provide the greatest clinical benefits. By determining the possible complications, an accurate estimation of operating time will help to reduce the operation costs by providing more effective operating room usage [6, 7]. Furthermore, with a more efficient operating room schedule, patient satisfaction rates can be improved by providing shorter waiting times [8]. Estimation of the operation time, patient age, body mass index (BMI), primary surgery, anesthesia type, secondary procedures and surgeon type data have been taken into consideration in the published literature [9,10]. In addition to these defined factors, the operation area adipose tissue thickness and non-operation area adipose tissue thickness were added to the multivariate logistic model in the current study.

This study hypothesized that an increase in the thickness of the adipose tissue in the surgical area would prolong the operation time. No study on this subject could be found in the literature, therefore this study aimed to investigate the relationship between increased thickness of fat tissue and operating time, in patients applied with rotator cuff repair.

Materials and methods

Approval for this study was granted by the Local Ethics Committee. The data used was obtained from the hospital electronic records system and the electronic Picture Archiving Communication Systems (PACS). The patients included in the study were those who underwent shoulder rotator cuff operation between January 2015 and March 2020 and had shoulder MRI taken less than 6 months pre-operatively. All the operations were performed by two surgeons, each with twelve and six years of experience, respectively.

Patients were excluded from the study if the MR images had not been captured with the appropriate technique or if the data regarding the operating time or the procedures applied during the operation was not available. A record of demographic data, including age and gender, was made for each patient. Surgeon type (surgeon 1, surgeon 2) and operating time were recorded and the preoperative MRIs were evaluated according to the DeOrio and Cofield classification [11]. The BMI values of the patients, American Society of Anesthesiologist (ASA) scores and the anesthesia method used, were also examined. The thickness of fat tissue was measured on the preoperative MR images. The acromial fat thickness was recorded as the fat thickness of the operation area, whereas the scapular fat tissue thickness was recorded as the fat thickness of the region relatively far from the operation area.

Images were obtained using a 1.5 Tesla MRI device. The acromial fat distance was measured in series obtained with coronal oblique fat suppressed PD (proton density) sequences, and scapular fat distance was measured in series created with axial fat-suppressed PD sequences. For standardization of the measurement of fat tissue thickness in each patient, the spina scapula axis was first determined on the transverse section that showed the longest view of the spina scapula, and from the midpoint of the spina scapula on this

image, fat tissue thickness was determined over the vertical line drawn from the determined axis (Figure 1). Then, the thickness of the adipose tissue on the line joining the superior and inferior corners of the glenoid was measured in the section where the glenoid was seen to be largest in coronal sections (Figure 2).

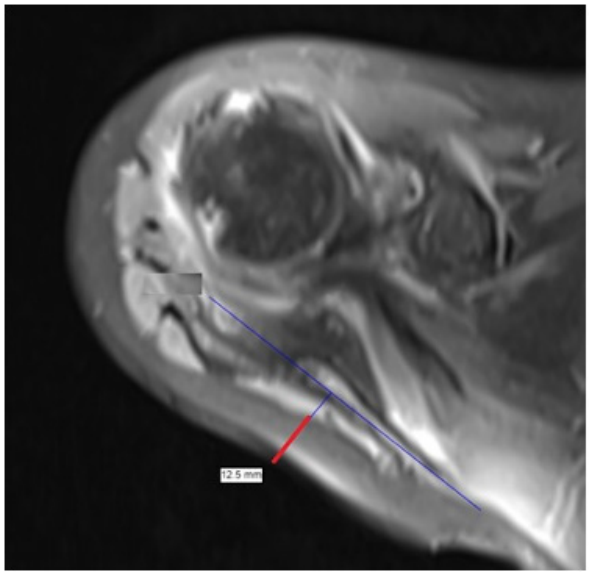


Figure 1. Measurement of the scapular fat thickness.

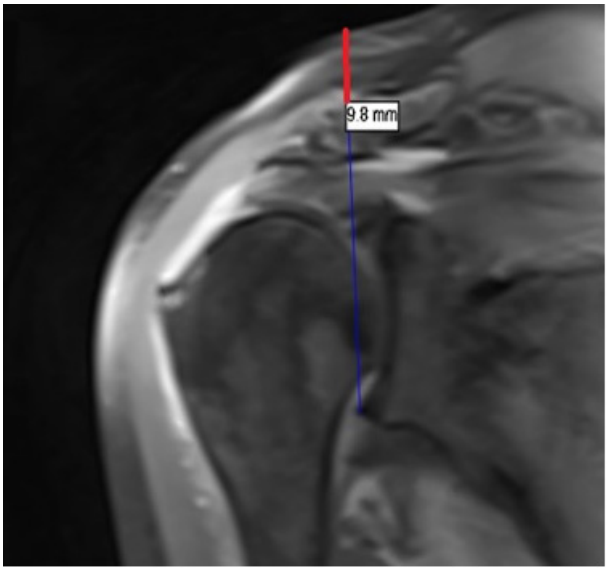


Figure 2. Measurement of the acromial fat thickness.

An orthopedic surgeon and a radiology specialist took the measurements, both with over 10 years of experience. The measurements were taken twice at an interval of 4 weeks between the two measurements of the orthopedic surgeon and the radiology specialist. The interclass and intraclass coefficient (ICC) values were calculated for the results obtained. In addition to the cuff repair, additional procedures such as biceps tenotomy, tenodesis, acromioplasty, superior labrum anterior and posterior (SLAP) repair and Bankart repair, were all recorded.

Data obtained in the study was analyzed statistically using the SPSS vn. 23.0 software (IBM, Armonk, NY, USA). Continuous variables were compared between the groups using the Mann Whitney U-test or the Kruskal Wallis test and categorical variables were analyzed using the Chi-square test. Multivariate analysis and a binary logistic regression model were applied in the evaluation of the data. A value of $p<0.05$ was accepted as statistically significant.

Results

Initially, 113 patients were included in the study and seven were then excluded from the analysis: four patients with preoperative MRIs not available and three with unavailable operation information. Thus, the evaluation of 106 patients was performed, with a mean age of 57±10.6 years and a mean operating time of 89±33 min. The demographic characteristics of the patients are shown in Table 1. The sex and age of the patients had no significant effect on operation time ($p>0.05$) (Table 1). The mean acromial fat thickness was determined to be 12.2±4.89 mm and the mean scapular fat thickness was 27.9±12.5 mm.

Table 1. Operation Time according to Demographic Characteristics.

	n (%)	Operation Time	P value	Operation Time Class		P value
Overall	106	89.00 ± 33.52		<90	90>	
Sex			0.603[a]			0.378[c]
Male	40 (37.7)	93.68 ± 41.23		22 (55.0)	18 (45.0)	
Female	66 (63.3)	86.69 ± 28.45		42 (63.6)	24 (36.4)	
Age (years)			0.251[b]			0.427[c]
<50	28 (26.4)	99.29 ± 39.90		14 (50.0)	14 (50.0)	
51- 60	34 (32.1)	82.66 ± 33.62		24 (70.6)	10 (29.4)	
61- 70	34 (32.1)	88.64 ± 29.93		20 (58.8)	14 (41.2)	
71>	10 (9.4)	84.50 ± 22.91		6 (60.0)	4 (40.0)	

a Mann Whitney U-test, b Kruskall Wallis test, c Chi-Square test

In this study, the operation time was categorized as a binary variable (>90/<90 minutes). To investigate the risk factors affecting the operation time, the binary logistic regression analysis was first performed, which included independent risk factors that could affect the operation time. Using this model, surgeon type, acromial fat thickness, SLAP repair and Bankart repair, were all determined to be significant risk factors affecting the operation time. It was an expected result that SLAP and Bankart repairs would increase the operation time; we included these in the study to demonstrate that the binary logistic regression model works properly (p<0.05, p:0.001) (Table 2). The increase in the acromial fat thickness of the patients was determined to have extended the operation time (OR= 5.75, 29.21, p<0.05). The BMI value, scapular fat thickness and ASA class were not determined to have any significant effect on operation time (p> 0.05) (Table 3). When the predictive value of the results of the regression model was evaluated, operation time longer or shorter than 90 mins was determined to be predictive at 87.4%.

Table 2. Surgical procedures.

Description	Cases (n) (% of total)	Operation Time (Mean±SD)	Operation Time Class n (%)		P value
Procedures			<90	90>	
Biceps tenotomy	76 (71.7)	86.91 ± 30.93	48 (63.2)	28 (36.8)	0.352
Tenodesis	28 (26.4)	96. 61 ± 38.39	15 (53.6)	13 (46.4)	0.391
Acromioplasty	69 (65.1)	84.71 ± 31.07	48 (69.6)	21 (30.4)	0.008
SLAP Repair	19 (17.9)	117.63 ± 35.29	5 (26.3)	14 (73.7)	0.001
Bankart Repair	14 (13.2)	120.71 ± 27.59	2 (14.3)	12 (85.7)	0.001
Surgeon Type					0.001
Surgeon 1	65 (61.3)	74.69 ± 20.29	53 (81.5)	12 (18.5)	
Surgeon 2	41 (38.7)	111.71 ± 37.81	11 (26.8)	30 (73.2)	

Considering the reliability of the measurements taken on the preoperative MRIs, the interclass coefficient and intraclass coefficient values were found to have excellent reliability (ICC>90) in the scapular and acromial fat thickness values, as well as in the DeOrio and Cofield classification.

Table 3. Binary Logistic Regression Analysis of Factors Affecting Operation Time.

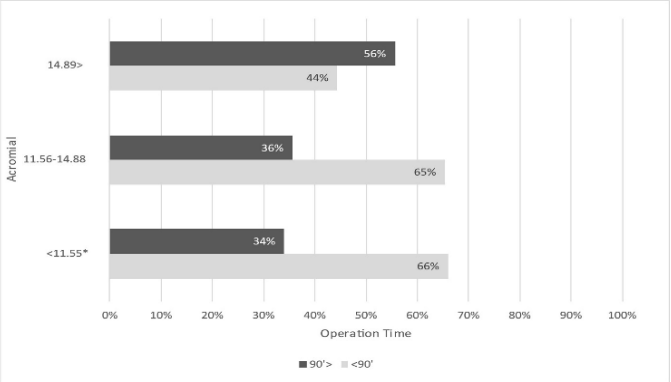
	Operation Time		P value	OR
	<90 min	90> min		
Acromial fat thickness			**0.022**	
<11.55	35 (66.0)	18 (34.0)		**5.75**
11.56-14.88	17 (65.4)	9 (35.6)		**29.21**
14.89>	12 (44.4)	15 (55.6)		
Scapular fat thickness			0.482	
<24.58	36 (67.9)	17 (32.1)		
24.59-32.83	11 (42.3)	15 (52.7)		
32.84>	17 (63.0)	10 (37.0)		
BMI Index			0.127	
<25	15 (71.4)	6 (28.6)		
26-30	30 (53.6)	26 (46.4)		5.51
31>	17 (65.4)	9 (34.6)		1.51
ASA Class			0.581	
1	13 (48.1)	14 (51.9)		
2	50 (64.1)	28 (35.9)		0.42
3	1 (100.0)	0 (0.0)		0.00

Reference class in Binary Logistic Regression. Bold values are statistically significant (p <0.05).

Discussion

The most important finding of this study was that an increase in acromial fat thickness significantly prolonged the operating time (OR=5.7, p<0.05) (Figure 3). Several studies have reported that increased fat thickness in the surgical area increased infection locally [1,4,5]. It has been reported that for every 1 mm increase in lumbar region adipose tissue thickness, the risk of infection in the operated area increases by 6% [5]. In similar studies, an increase in fat tissue thickness in the operation region has also been reported to increase the rate of postoperative infection [2]. Another significant factor increasing postoperative infection in the operation region is the operation time [12]. There are other studies in the literature which have also shown that an increase in fat tissue thickness leads to more infection and the reason for this could be prolonged operating time [3-5]. However, no study could be found that aimed to research the effect of fat tissue thickness on operating time in rotator cuff surgery.

Figure 3. As the acromial fat thickness increases, so the rate of operations lasting longer than 90 minutes increases.



In addition to infection, an increase in operating time in shoulder operations may also cause other complications. Rotator cuff operations lasting longer than 90 mins have been shown to prolong the postoperative length of stay in the hospital [13]. In the current study, it was found that the operation time exceeded 90 minutes in more than half of the patients with an acromial fat thickness greater than 14.89 mm (Figure 3). Agarwalla A. et al. reported that every increase of 15 mins in operating time led to postoperative transfusion, pulmonary embolism, surgical site infection and prolonged postoperative stay in hospital [14]. As in the current study, it was reported that each of the concomitant procedures (biceps tenotomy, tenodesis, acromioplasty, SLAP repair and Bankart repair) increased operating time, however it was concluded that none of these concomitant procedures increased complications in the short term [14]. When publications related to the duration of shoulder operations were examined, the mean operating time in the current study of 89±33 mins was found to be consistent with the findings of those studies [13,14].

Another important finding of the current study was that while an increase in the acromial fat thickness in the operation area was observed to increase operating time, scapular fat thickness and BMI had no significant effect. Similarly, Wagner R.A. et al. found that prepatellar fat thickness had a greater effect than BMI in the determination of the risk of postoperative infection [2]. In several studies that have examined the relationship between fat tissue thickness and complications, fat tissue thickness has been reported to be a better predictor of complications than BMI [1,3]. The reason for the lower predictive power of BMI than fat tissue thickness is that BMI is not always related to body fat mass and the distribution of body fat varies according to age, gender, race and genetic factors [15]. Therefore, the surgical area fat tissue thickness may not be the same in different individuals with the same height, weight and body fat ratio.

It can be estimated that the increase in the thickness of the adipose tissue prolongs the operation time, such as difficulty in orientation to the surgical field, difficulty in exposure, difficulty in using the cannula and difficulty in applying anchors, however the increase in the severity of existing tendon pathologies due to metabolic and genetic reasons in individuals with increased fat tissue thickness, is one of the factors affecting the operation time. Whole body MRI studies have shown that the thickness of the fat tissue in the shoulder and neck region of individuals with insulin-resistant diabetes is increased compared to individuals without insulin resistance [16]. A systematic review on this subject concluded that an increase in adiposity increased the frequency of tendon injuries, and further studies were recommended [17]. However, in the current study, when the acromial and scapular fat thickness values of the patients were compared with the DeOrio and Cofield classification of rotator cuff tears, no significant correlation was determined ($p>0.05$). In another study of 298 cases, the relationship between asymptomatic Achilles tendon pathologies and fat tissue distribution was investigated. Achilles tendon pathology was seen more frequently in males of advanced age with central fat tissue distribution, and in postmenopausal females with peripheral fat distribution. The condition seen in males was explained with mechanical reasons, but in the paradoxical condition formed in females, it was stated that the hormonal infrastructure and the change in postmenopausal estrogen level could both account for changes in fat tissue distribution and lead to tendon pathologies [18]. The results obtained in the current study are consistent with these findings. The acromial and scapular fat thickness values of the females with rotator cuff tear were found to be statistically significantly higher than those of the male patients ($p<0.05$) and this finding is consistent with the study

investigating the fat signal distribution in the muscle. In that study, the fat fraction within the muscles in some muscles around the shoulder was found to be higher in women than in men [19].

In addition to increased postoperative complications, another disadvantage of prolonged operating time is the longer use of the operating theater and personnel, which both increase the costs of the operation [7]. According to the Healthcare Cost and Utilization Project (HCUP), operating rooms are the costliest units in a hospital [6]. The knowledge that the adipose tissue thickness affects the operation time, provides a better estimation of the operative time, thus a more accurate schedule can be prepared and the operating rooms can be used more efficiently. In addition, the appropriate operating room program will shorten patient waiting times. A study published in 2010 showed that 15% of the reasons for patient dissatisfaction were due to prolonged wait times [8]. In the literature related to the estimation of the operation time, patient age, BMI, primary surgery, secondary procedures and surgeon type data were taken into consideration [9,10,20]. In a comprehensive study in which these factors were used in a multi-regression model in different types of surgery, it was stated that 80% of the surgical time was correctly estimated in the applied model [21]. In the multivariate regression model of the current study, in which fat tissue thickness was added to these factors, the results were able to predict the probability of the operation being over or under 90 minutes at 87.4%.

The main limitation of this study was the retrospective design. The relatively small size of the sample and the fact that it was not a multicenter study were also limiting factors. In addition, operation time in the literature has been separated into operation room duration and surgery time. However, in our hospital records, surgical time was not recorded separately, so the operating room time was used as the operation time in this study.

Conclusion

In conclusion, adipose tissue thickness in the surgical area is one of the factors affecting operation time. For shoulder surgery patients, these values can be easily measured on preoperative MRIs. Thus, the risk of a prolonged operation and associated complications can be predicted, and a more accurate schedule can be prepared with more efficient use of the operating rooms. In addition, it should be considered that tendinous pathologies may be more common in individuals with increased adipose tissue thickness, and thus contribute to prolonging the operation time.

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RESEARCH ARTICLE

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The Relationship Between Serum 25-hydroxyvitamin D and Calcium Levels and Idiopathic Benign Paroxysmal Positional Vertigo

Serum 25-hidroksivitamin D ve Kalsiyum Düzeyleri ile İdiyopatik Benign Paroksismal Pozisyonel Vertigo Arasındaki İlişki

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ABSTRACT

Aim: We aimed to compare 25-hydroxy vitamin D (25-OH vitamin D) and Ca2+ levels of patients admitted to our clinic with the complaint of dizziness and diagnosed with idiopathic benign paroxysmal positional vertigo (BPPV) with those of healthy control group without dizziness and investigate the role of Ca2+ and 25-OH vitamin D in the development of BPPV.

Material and methods: This study is a retrospective case-control study. The study sample consisted of 409 patients admitted to Alanya Training and Research Hospital Neurology outpatient clinic and diagnosed with idiopathic BPPV between 01.01.2018 and 01.08.2021, and of 338 control patients without any physician consultation due to vertigo, dizziness or imbalance in the last 1 year before admission to our clinic and whose serum vitamin D levels were measured, the Chi-square and T-test were utilized for statistical analysis.

Results: Mean blood 25-OH vitamin D levels were 15.74 ng/mL and 17.91 ng/mL in BPPV and control groups, respectively. Serum 25-OH vitamin D levels were significantly lower in BPPV group than control group (p=0.01, p<0.05). Mean serum Ca2+ levels did not exhibit any difference in BPPV and control groups.

Conclusion: Decreased serum levels of 25-OH vitamin D have been associated with the occurrence of BPPV independently of other key markers.

Key Words: Benign paroxysmal positional vertigo, 25-OH vitamin D, Ca2+

ÖZ

Amaç: Kliniğimize baş dönmesi şikâyeti ile başvurup idiopathic benign paroksismal pozisyonel vertigo (BPPV) tanısı alan hastalar ile baş dönmesi olmayan sağlıklı kontrol grubunun 25-hidroksi vitamin D (25-OH vitamin D) ve Ca2+ düzeylerinin karşılaştırılması Ca2+ ve 25-OH vitamin D'nin BPPV gelişimindeki rolünün araştırılmasıdır.

Gereç ve Yöntem: Çalışmamız geriye dönük vaka kontrol çalışması olup, 01.01.2018-01.08.2021 arası Alanya Egitim ve Araştırma Hastanesi Nöroloji polikliniğine başvuran İdiopatik BPPV tanısı alan 409 hasta ile kontrol grubu olarak kliniğimize başvuru öncesi son 1 yıl içerisinde vertigo, dizziness ya da dengesizlik nedeniyle hekim başvurusu olmayan serum D vitamini düzeyi ölçümü yapılmış 338 hasta seçilerek oluşturuldu. İstatiksel değerlendirmeler için ki-kare ve T testi testi kullanıldı.

Bulgular: Ortalama serum 25-OH vitamin D düzeyleri BPPV ve kontrol grubunda sırasıyla 15,74 ng/mL ve 17,91 ng/mL idi. Serum 25-OH vitamin D düzeyleri BPPV grubunda kontrol grubuna göre anlamlı derecede düşük bulundu (p=0,01, p<0,05). Ortalama serum Ca2+ düzeyleri BPPV ve kontrol grubunda anlamlı farklılık göstermedi.

Sonuç: Düşük 25-OH vitamin D serum seviyeleri BPPV gelişimi ile diğer anahtar belirteçlerden bağımsız olarak ilişkilidir.

Anahtar kelimeler: Benign paroksismal pozisyonel vertigo, 25-OH vitamin D, Ca2+

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INTRODUCTION

Vertigo is derived from the Latin verb “vertere” meaning to turn. Vertigo may occur both secondary to visual pathologies, proprioceptive system disorders, metabolic disturbances and cardiological abnormalities and to peripheral and central vestibular disorders, as well as side effects of drugs [1]. Among the peripheral vestibular disorder [2] Benign paroxysmal positional vertigo (BPPV) is a reported very common [2]. The prevalence of BPPV is reported to be around 2%, its annual prevalence 1.6%, and 1-year incidence 0.6% [3]. Schuknecht asserted that BPPV is mechanistically linked with attachment of basophilic staining deposits to the cupula within the posterior semicircular canal and called this pathological finding cupulolithiasis [4]. According to the widely accepted cupulolithiasis theory, vertigo and nystagmus occur when the rotation of the canal changes the direction of the cupula, associated with the adherence of the otoconia to the cupula rendering it sensitive to gravity. Furthermore, the canalolithiasis theory has been defined as the formation of stimulation in the hairy cells and the development of vertigo and nystagmus, as a result of stimulating the canal cupula by the endolymph, that they move along due to gravitational displacement of otoconia or canaliths separated from utricle macula into the semicircular canal [1,5,6]

Otoconia are calcite-based nanocomponents containing calcite crystals (>90%) and organic materials (<10%). The average size of otoconia is about 10 μm (within the range of 2 to 25 μm) [7,8]. Otoconia could be damaged by drugs. Also age-related decalcification and trauma, are commonly reported. Herein, an accelerated demineralization process associated with advancing age might lead to dissolution and disintegration of the otoconia, ultimately resulting in balance disorder [9].

Vitamin D, is a fat-soluble vitamin, produced in the skin related to UVB radiation exposure . Around 90-95% of the vitamin D present in the body is produced upon skin’s exposure to sunlight. Most of the circulating vitamin D is 25-OH vitamin D, of which half-life is 20 days. Therefore, 25-OH vitamin D is the first value to measure when determining vitamin D levels in the body. There is a significant balance between vitamin D and its metabolites and calcium and phosphorus in the body. Vitamin D helps regulate hormonally the serum calcium levels by acting on intestinal absorption of calcium taken up from outside, into the body [10].

Vitamin D plays maintains normal otolith function by stabilizing the calcium level in the vestibular endolymph, which ensures proper mineralization of the otoconia [11]. In this respect, many studies evaluated the role of vitamin D deficiency in BPPV development. Therefore, there are limited studies investigating the association between deficient vitamin D levels and vertigo, and their interrelationship has not been fully explored [12].

Here, we assessed blood 25-OH vitamin D and Ca2+ levels in patients with BPPV. In this respect, we investigated the relationship between the occurrence of BPPV and low 25-OH vitamin D and Ca2+ levels.

PATIENTS AND METHOD

In this retrospective case-control study the patients’ general characteristics were expressed as, mean, SD (standard deviation), percentage and frequency. Chi-square analysis was adopted for proportional variables to examine the general characteristics, disease states, Ca 2+ and Vit D OH groups of the patients. Probability values based on Fisher’s correction were given if the number of groups was insufficient. In addition, the independent-samples t-test and ANOVA test were performed to examine patient measurements according to groups. The study sample consisted of 409 patients admitted to Alanya Training and Research Hospital Neurology outpatient clinic and diagnosed with idiopathic BPPV between 01.01.2018 and 01.08.2021, and of 338 control patients without any physician consultation due to vertigo, dizziness or imbalance in the last 1 year before admission to our clinic, and whose serum vitamin D levels were measured. The BPPV diagnosis was based on observation of typical nystagmus during the characteristic tests (Dix-Hallpike, hyperextension tests and supine roll). Non- cooperation, presence of secondary factors for BPPV, and chronic disease conditions were defined as exclusion criteria. Patients who took vitamin and/or calcium supplements during the study and had systemic disease affecting vitamin

D levels were omitted from the study. Local ethics committee approval was obtained for this study (with the decision no: 14-04 of September 22, 2021) and accordance with the Declaration of Helsinki Ethical Principles.

Statistical analysis

The data was analyzed through the statistical program (SPSS, IBM Corp., Armonk, NY, USA) 18.0 package program for Windows. Intergroup comparisons were made through independent 2-sample T- test and chi-square test, p value < 0.05 was deemed statistical significance.

RESULTS

Age, calcium and vitamin D levels were evaluated in the control and vertigo groups. Of the patients, 35.6% were male, 64.4% were female, and 45.2% were in the control group and 54.8% in the vertigo group. Of the patients, 48.5% were aged 50 and under, 51.5% were aged 50 and over. Calcium values were below 8.5 ng/mL in 3.7% of the patients, 8.6-10 ng/mL in 84.7% and 10 ng/mL and over in 11.5%. 25-OH vitamin D values were below 20 ng/mL in 68,9% of the patients, 20-29 ng/mL in 20.2%, and 30 ng/mL and over in 10.8%. The calcium and 25-OH vitamin D levels (ng/mL) in the control and vertigo groups were different. The vertigo group had greater calcium levels compared to the control group (p = 0,03, p<0,05), but showed lower levels of 25-OH vitamin D (p = 0,01, p<0,05)(Table 1).

Table 1: Assessment of Age, Calcium and Vitamin D Levels by Groups

Measurement	Category	Group				p
		Control		Vertigo		
		n	%	n	%	
Age group	50 and below	207	61,2%	155	37,9%	0,01*
	50 and over	131	38,8%	254	62,1%	
Calcium levels (ng/mL)	below 8,5	18	5,3%	10	2,4%	0,02*
	8,6-10	309	91,4%	324	79,2%	
	over 10	11	3,3%	75	18,3%	
25-OH vit D levels (ng/mL)	below 20	205	60,7%	310	75,8%	0,02*
	20-29	101	29,9%	50	12,2%	
		32	9,5%	49	12,0%	

* Indicates a significance level of 0.05

There were differences in 25-OH vitamin D levels (ng/mL), but not calcium levels (ng/mL) (p = 0.83, p>0.05), according to age groups in the control group. Patients aged 50 and under had greater 25-OH vitamin D levels (ng/mL) than patients aged 50 and over, which explained the control group difference (p = 0.03, p<0.05). However, calcium levels (ng/mL), but not the levels of 25-OH vitamin D (ng/mL) (p = 0,06, p>0,05), changed among age groups in the vertigo group. This difference explains why patients under 50 showed greater 25-OH vitamin D levels (ng/mL) than those over 50 (p = 0.03, p<0.05)(Table 1).

The age range of the patients was different between the control and vertigo groups. Most patients in the vertigo group were over 50, and most of those in the control group were under 50 (p = 0,01, p < 0,05). The calcium levels (ng/mL) were different in the control and vertigo groups. Calcium levels in the vertigo group were largely 10 ng/mL and higher, whereas calcium levels in the control group varied from 8.6 to 10 ng/mL (p = 0.02, p<0.05). In terms of 25-OH vitamin D levels (ng/mL), we found no difference between the control and vertigo groups. The vertigo group's 25-OH vitamin D levels were predominantly below 20 ng/mL , while the control group's levels were between 20 and 29 ng/mL (p = 0.02, p<0.05) (Table2).

Table 2: Assessment of Age, Calcium and Vitamin D Levels in Groups by Gender

Measurement	Control		p	Vertigo		p
	Male	Female		Male	Female	
	X±s.s.	X±s.s.		X±s.s.	X±s.s.	
Age	43,07± 14,75	43,64± 13,78	0,23	56,96± 17,86	52,22± 17,05	0,09
Calcium levels (ng/mL)	9,36± 1,29	9,21± 0,54	0,04*	10,2± 7,03	9,54± 0,69	0,01*
25-OH vit D levels (ng/mL)	18,87± 7,94	17,45± 9,39	0,03*	16,91± 13,9	15,02± 12,73	0,02*

* Indicates a significance level of 0.05

Patient ages were no different in the control and vertigo groups according to gender (p>0.05). Gender differences in calcium and 25-OH vitamin D levels (ng/mL) were seen in the control group. The gender difference was attributable to the fact that male patients had greater calcium and 25-OH vitamin D levels (ng/mL) than female patients (p=0.04, p<0.05 for Ca2+; p=0,03, p<0,05 for 25-OH vitamin D). In the vertigo group, there were gender-specific variations in calcium and 25-OH vitamin D levels (ng/mL). Male patients had

greater calcium and 25-OH vitamin D levels (ng/mL) than female patients (p = 0,01, p<0,05 for Ca2+; p = 0,02, p<0,05 for 25-OH vitamin D), resulting in gender-specific differences (Table2).

D level measurements were found to be 17.91 ng/mL in the control group and 15.74 ng/mL in the vertigo group. The calcium level of the patients was found to be 9.26 ng/mL in the control group and 9.79 ng/mL in the vertigo group (Table 3).

Table 3: Assessment of Calcium and Vitamin D Levels in Groups by Age

Measurement			p			p
	50 and below	50 and over		50 and below	50 and over	
	X±s.s	X±s.s		X±s.s	X±s.s	
Calcium levels (ng/mL)	9,26± 1	9,26± 0,58	0,83	9,58± 0,9	9,92± 5,51	0,03*
25-OH vit D levels (ng/mL)	18,33± 9	17,26± 8,88	0,03*	15,99± 13,94	15,59± 12,77	0,06

* Indicates a significance level of 0.05

DISCUSSION

This study compared patients with idiopathic BPPV to those without vestibular complaints, regarding serum 25-OH vitamin D and calcium levels. When compared to control patients, serum 25-OH vitamin D levels were found to be decreased in BPPV patients, although total blood Ca2+ levels were not different. Furthermore, we found that lower blood 25-OH vitamin D levels may be an independent factor associated with BPPV development.

It has been considered that the presence of cupulolithiasis or canalithiasis lead to BPPV. Its exact etiology is uncertain, however calcium metabolism is important for the production and absorption of calcium carbonate-based otoconia, being a possible etiological factor for BPPV [4].

Vitamin D regulates the production of several Ca2+ binding proteins through specific vitamin D receptors (VDR) localized in the inner ear and epithelial cells. The epithelial Ca2+ channel system along with Na+/Ca2+ exchangers, and membrane-located Ca2+ pumps help balance the calcium levels through Ca2+ absorption from the endolymph [13]. A study of VDR-deficient mice showed that mice with mutant VDR have poor balance function, indicating that vitamin D deficiency may lead to vestibular dysfunction [14].

Vitamin D levels of BPPV patients were assessed only at the time of diagnosis in our study, but their post-treatment status was not examined. Further studies are required to obtain robust evidence as to whether vitamin supplementation may help cure BPPV patients, particularly those with vitamin D deficiency. Sheikhzadeh et al. showed that returning serum vitamin D levels to normal significantly reduced the recurrences of BPPV [15]. Buki et al. obtained similar results, showing that BPPV did not recur after supplementation with vitamin D was corrected the deficiency [16]. Gu et al. showed that treatment with 1α-hydroxy vitamin D3 could decrease the symptoms of BPPV, and that amin D3 levels and disease conditions such as osteopenia / osteoporosis are clinical indications of whether treatment regimen would be successful in preventing BPPV [17]. Talaat et al. revealed that vitamin D supplementation therapy improved the recurrence of BPPV [12].

Vivert et al. found that the rate of osteoporosis was higher in female patients with BPPV than the control group, and that impaired calcium metabolism was related to the BPPV development [18]. Another study reported that the recurrence of BPPV in female patients aged 50 years and over with osteoporosis was approximately 3.5-fold higher than same age group patients with normal bone mineral density. In their investigation on the link between osteoporosis and BPPV, Jeong et al. found that the T scores of both male and female patients with BPPV were lower than the control group, whereas the osteoporosis and osteopenia incidence in these patients was greater than the control group [11]. Buki et al. discovered that patients with BPPV had lower blood 25-OH vitamin D levels, and that vitamin D deficiency and osteoporosis were risk factors that could considerably affect BPPV recurrence in these patients [16]. These findings fit well with our findings, which showed that total Ca2+ levels and 25-OH vitamin D levels were decreased in female patients over 50 than in male patients (Table 2-3).

Results fromboth Rhim et al. and Güler et al.'s studies have reported that vitamin D insufficiency play an important role in BPPV development,

regardless of age, gender or type of BPPV [19]. However, Karataş et al. and Parham et al. suggested that BPPV and 25-OH vitamin D deficiency were not significantly associated and such a finding may be a mere coincidence [20,22]. In the present study, 25- OH vitamin D levels were decreased in 68.9% of all patients, with BPPV patients having significantly lower levels than the control group (Table 1). Furthermore, we found lower blood 25-OH vitamin D levels play a critical role in the development of BPPV, independently of age or gender.

Some studies have asserted that vitamin D deficiency causes aberrant otoconia production leading to otolith malfunction, and is linked to the development and recurrence of BPPV [3,8,9,12,21]. Other studies have reported, however, that low vitamin D levels are not linked to the development and/or recurrence of BPPV [20, 22]. Therefore the association of BPPV with vitamin D deficiency is still debated because of these discrepancies.

Limitations

Our study has some limitations since patients with idiopathic BPPV are only assessed at the diagnostic stage and it is unknown how much symptoms and attack frequency are relievedin BPPV patients, who have 25-OH vitamin D deficiency and receive replacement therapy.

CONCLUSION

Our findings suggest that 25-OH vitamin D deficiency is a potential causal factor in the development of BPPV, independent of age or gender. Further research could better delineate the strong link between BPPV and 25-OH vitamin D deficiency.

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Our experiences of laparoscopy in the non-palpable testes

Ele gelmeyen testiste laparoskopi deneyimimiz

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ABSTRACT

Aim: To demonstrate the superiority of laparoscopic undescended testicular surgery for non-palpable testicles in children in diagnosis and treatment.
Methods: The files of patients between the age of 6 months and 18 years who underwent laparoscopic undescended testis investigation due to non-palpable testis in our clinic, between January 2010 and September 2021, were reviewed retrospectively. Patients with palpable testicles and patients with disorders of sex development in the examination performed under general anaesthesia were excluded from the study.
Results: Fifty-three patients were included in the study. The mean age of the patients is 3.2 years (min: 8 months-max 17 years). Laparoscopic intervention was performed for a total of 59 non-palpable testicles which were left-sided in 54.7% (n=29) of the patients, right-sided in 34% (n=18), and bilateral in 11.3% (n=6). Throughout these 59 testicles, cords and vessels of 31 testicles were visualized entering the inguinal canal, atrophic testes in the abdomen were detected in 7 patients, the cord and vessels had an intraabdominal blind ending (vanishing testis) in 7 patients, and 14 testicles were in the abdomen with normal aspect.
Conclusion: Simultaneous laparoscopic orchiectomy is performed in case of atrophic testis in laparoscopic exploration for non-palpable testicles. It allows the ligation of vessels of testes farther than 2 cm away from the inguinal canal, and for testes that are closer than 2 cm it grants the vessels to be released under a more precise vision thereby protecting from the complications of conventional surgery.

Keywords: Laparoscopic orchiopexy, non-palpable testis, children

ÖZ

Amaç: Çocuklarda ele gelmeyen testisler için yaptığımız laparokopik inmemiş testis amaliyatlarının tanı ve tedavide üstünlüğünü ortaya koymak.
Yöntemler: Kliniğimizde Ocak 2010 ile Eylül 2021 tarihleri arasında ele gelmeyen testis nedeniyle laparoskopik inmemiş testis araştırması yapılan 6 ay-18 yaş altı hastaların dosyaları retrospektif olarak incelendi. Genel anestezi altında yapılan muayenede palpe edilen testisler ve cinsiyet gelişim bozukluğu bulunan hastalar çalışma dışında tutuldu.
Bulgular: Çalışmaya 53 hasta dahil edildi. Hastaların ortalama yaşı 3,2 yaştır (min:8 ay-max 17 yaş). Hastaların %54,7'sinde (n=29) sol, %34'ünde (n=18) sağ ve %11,3'ünde (n=6) bilateral olmak üzere toplam 59 ele gelmeyen testis için tanı ve tedavi amacıyla laparoskopik girişim yapılmıştır. 59 testis için yapılan laparoskopide 31 tane testisin kord ve damarlarının inguinal kanala girdiği, 7 hastada karın içindeki testisin atrofik olduğu, 7 hastada kord ve damarların intraabdominal olarak kör sonlandığı (vanishing testis), 14 adet testisin karın içinde normal boyutta olduğu saptandı.
Sonuç: Ele gelmeyen testisler için yapılan laparoskopik eksplorasyonda atrofik testis bulunması durumunda eş zamanlı laparoskopik orşiektomi yapılmakta, özellikle inguinal kanala 2 cm'den uzak testisler için damarların bağlanmasına olanak vermekte, 2 cm'den yakın olan testisler için ise daha iyi bir görüş altında damarlarının serbestlenmesine izin vererek açık cerrahi komplikasyonlarından korumaktadır.

Anahtar Kelimeler: Laparoskopik orşiopeksi, ele gelmeyen testis, çocuk

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INTRODUCTION

Undescended testis is the most common congenital malformation of the genital tract in boys. The testicles follow a path descending from the abdomen to the scrotum during the intrauterine period. It is seen in 3 to 5% of term newborn boys, while the incidence decreases to 1.5 to 3% at 6 months of age due to postnatal migration [1,2]. Undescended testicles can be classified according to their position as peeping (glides in and out of the inner inguinal ring), canalicular, extra canalicular (superficial inguinal pouch), suprapubic (high scrotal) or intraabdominal [3]. Some 20 to 25% of non-palpable testicles are in the intra-abdominal space and 65% are in the inguinal canal. A number of testicles TABend up in atrophy in the intrauterine period [4]. Undescended testes are recommended to be operated between 6 months and 1.5 years due to the potential for future infertility and malignancy.

Eighteen percent of non-palpable testicles become palpable under general anaesthesia [5]. In such a case, the standard inguinal approach is preferred. Imaging methods such as ultrasonography (USG), magnetic resonance imaging (MRI), computed tomography (CT), venography and angiography have been used to determine the localization and size of previous non-palpable testicles, but none of them have a specificity and sensitivity over 90%. Routine use of imaging methods is not recommended in the European Urology Guidelines, except in specific cases such as suspicious genitalia [6].

In this study, we aimed to present our laparoscopic exploration experiences for non-palpable testicles in our clinic.

MATERIAL AND METHOD

After the approval from the clinical research ethics committee of our university, the files of patients between the age of 6 months and 18 years who underwent laparoscopic ectopic testicular investigation due to non-palpable testis in our clinic, between January 2010 and September 2021, were retrospectively analyzed according to preoperative imaging findings, testicular dimensions, findings during surgery, type of surgery performed and the outcome of the testis after surgery. Patients with palpable testicles and disorders of sex development in the examination performed under general anaesthesia were excluded from the study.

After inserting a nasogastric and urinary catheter in all patients under general anaesthesia, a Veress needle was inserted from the umbilicus to create a pneumoperitoneum with CO2 at a rate of 8-12 mmHg at 2-3 lit/min, depending on the age of the child, and a 5 mm trocar was advanced into the abdominal cavity. Abdominal exploration was performed with a 5 mm optic (Karl-Storz®, Germany) and it was checked whether the testis was in the abdomen. In the case of blind-ended spermatic cord and vein in the laparoscopic exploration, after the testicular descent path was explored and no other structures belonging to the testis were observed, the diagnosis of vanishing testis was established and the exploration was terminated. In the presence of testis in the abdomen, two more 5 mm trocars were inserted in the right and left lower quadrants. In patients with testis closer than 2 cm to the inguinal canal and in cases with peeping testis, the vessels of the testis and the spermatic cord were released laparoscopically, and the testis was advanced from the inguinal canal to the scrotum with a grasper. The two-stage Fowler-Stephens surgery was performed on testicles that were more than 2 cm away from the inguinal canal. In the first operation, testicular vessels were ligated with endoclips away from the testis and the testis was left over intraabdominal cavity. In the laparoscopy performed 6 months later, if the testicular dimensions were deemed as good, laparoscopy-assisted orchiopexy was performed. A new path was created aside medially from the inguinal canal in patients when the inguinal canal was closed. If the testis was atrophied, laparoscopic orchiectomy was performed. If the testis could not be brought up to the scrotum in patients who underwent laparoscopic orchiopexy, we fixed it in the superficial inguinal pouch or scrotum and brought it down to the scrotal position after 6 months of the previous operation. Laparoscopic orchiectomy was performed in the presence of intraabdominal hypoplastic or atrophic testis. Laparoscopy was terminated and inguinal exploration was performed in the same session in cases where the spermatic cord and vessels were observed to enter through

the inguinal canal. Postoperatively, the patients were discharged after being followed up in the hospital for 24 hours.

RESULTS

The mean age of fifty-three patients included in the study was 3.2 years (min: 8 months-max 17 years). Laparoscopic intervention was performed for a total of 59 non-palpable testicles which were left-sided in 54.7% (n=29) of the patients, right-sided in 34% (n=18), and bilateral in 11.3% (n=6). A total of 62.3% (n=33) of the patients were younger than 2 years old. The mean operative time was calculated as 26 min (15 min to 55 min). The mean post-operative hospital stay was 20.6 hours.

Routine abdominal USG was requested in all our patients, but testis could be detected in only 9 (15.2%) patients. In three of these nine patients, the testis was detected in the upper inguinal canal. MRI was requested priorly from twelve patients before the admission to our hospital by pediatricians and testis could only be detected in three patients (25%).

In the laparoscopy performed for fifty-nine testicles, cords and vessels of 31 testicles were visualized entering the inguinal canal (Figure 1), the testis was atrophic in 7 patients, the cords and vessels were intraabdominally blind-ended (vanishing testis) in 7 patients (Figure 2), and 14 testicles with no other obvious pathology were seen in the abdominal space. Gender development disorder was detected in one patient, and thus the procedure was terminated, and the patient was referred to pediatric endocrinology.

Seven atrophic testicular tissues in the abdomen were removed by laparoscopic orchiectomy. In cases with vanishing testis, both the spermatic cord and the spermatic vessels were found to end blindly close to the inguinal canal, and the operation was terminated.

First session Fowler-Stephens surgery was performed by clipping the testicular vessels for eight testicles where the testis in the abdomen was farther than 2 cm away from the inguinal canal. When re-laparoscopy was performed 6 months later, atrophy was observed in two testicles so laparoscopic orchiectomy was performed. Laparoscopy-assisted scrotal orchiopexy was performed for six testicles. Since the inguinal canal was completely closed in two patients, orchiopexy was performed by creating a new medially located tract. Since the spermatic cord of one testis was not long enough to bring down to the normal scrotal position, it was fixed in the scrotal inlet. Since there was no regression in the size of the testis 6 months later, it was placed in its normal location in the scrotum.

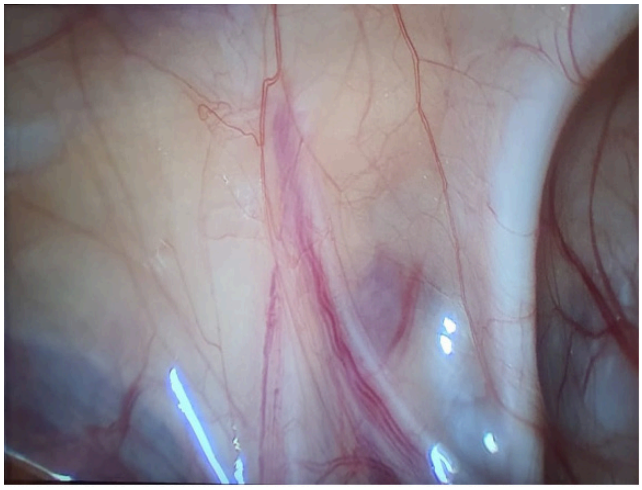

Figure 1: The spermatic cord and vessels entering the inguinal ring

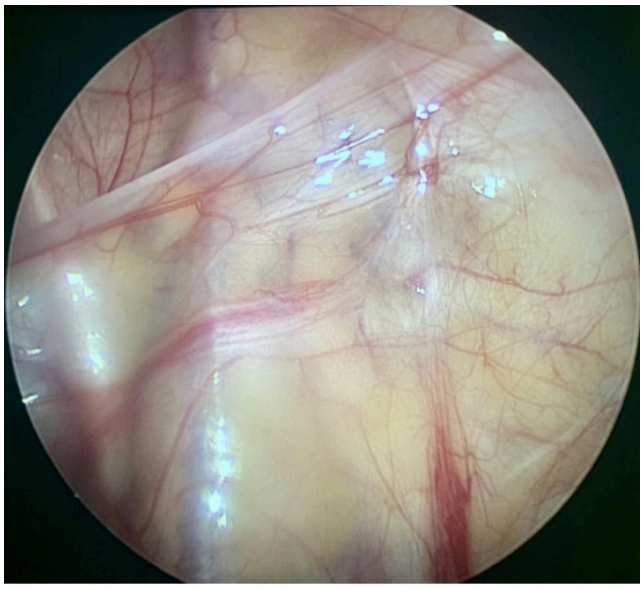

Figure 2: The spermatic cords and vessels were intraabdominally blind-ended (vanishing testis)

Laparoscopy-assisted scrotal orchiopexy was performed in four testicles that were closer than 2 cm to the inguinal canal and in two peeping testicles, after the spermatic cord and vessels

were released. In one patient, it was observed that the inguinal canal was completely closed, and a new canal was created medially and orchiopexy was completed. A superficial inguinal pouch was detected because the veins of one testis and spermatic cord were not long enough to "pex'' them into the scrotum. Inguinal orchiopexy was performed 6 months later.

Inguinal exploration was performed in the presence of thirty-one cords and vessels entering the inguinal canal; Orchiectomy was performed in twenty-six patients with atrophic testis and cord structure, and standard inguinal orchiopexy was performed in five patients with testicular tissue in small sizes compared to the contralateral testis. The surgical algorithm we used for non-palpable testicles in our clinic is shown in Figure 3 and the operations performed are shown in Table 1.

Complications were detected in three patients, including port infection in one patient, scrotal hematoma in one patient, and preperitoneal emphysema in one patient. In the pathological examination of thirty-four testes that underwent orchiectomy, immature tubule structure was detected in seven testes in histology and no malignancy was detected.

All patients were followed up with physical examination and abdominal USG at the end of the 1st month, 6th month, 1st year and 2nd year. Atrophy was detected in two patients who underwent single-session laparoscopy-assisted scrotal orchiopexy, and an orchiectomy was performed. All patients who underwent an orchiectomy and those who were found to have vanishing testicles were informed that testicular prosthesis could be placed in a further session during puberty.

Table 1: Operation type performed and surgical findings

	n (%)	Testis morphology	Operation	Complication
Vanishing testis	7 (%11,9)	Testis not detected	Terminated	1 preperitoneal emphysema
Distance to inguinal canal <2 cm	6 (%10,2)	4 normal	Laparoscopic orchiopexy	1 atrophy
	3 (%5,1)	3 atrophied	Laparoscopic orchiectomy	1 wound site infection
Distance to inguinal canal >2cm	8 (%13,6)	8 normal	Fowlers-Stephens	3 atrophies
	4 (%6,8)	4 atrophied	Laparoscopic orchiectomy	None
Peeping testis	2 (%3,2)	2 normal	Laparoscopic orchiopexy	1 scrotal hematoma
Cord and vessels entering the inguinal canal	4 (%6,8)	5 normal	İnguinal orchiopexy	None
	27 (%45,8)	26 atrophied	İnguinal orchiectomy	None

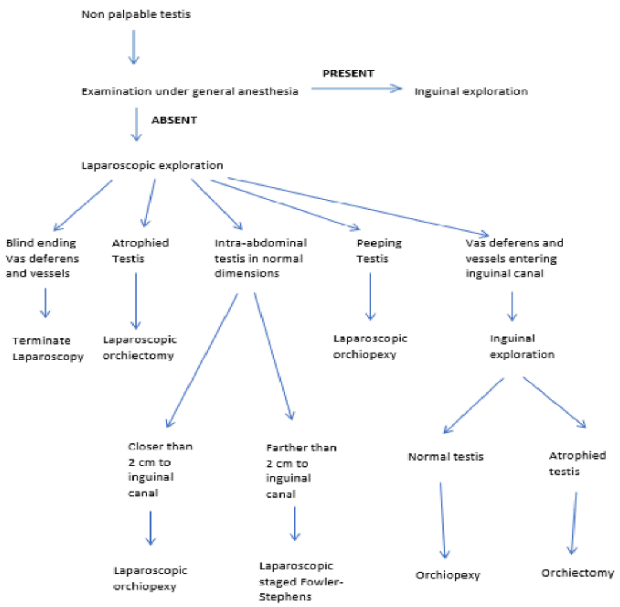

Figure 3: Treatment algorithm in non-palpable testes

DISCUSSION

The testicles normally follow a descending path from the abdomen to the scrotum during the intrauterine period. Sometimes along this path, an arrest during migration occurs in this route and they cannot reach the final position in the scrotum, resulting in an undescended testis. Undescended testis is a complex and not fully elucidated process in which hormonal, genetic, anatomical and environmental factors play a role [7]. Non-palpable testis is the inability of the testes to be identified in the inguinal canal and scrotum on physical examination and constitutes approximately 20 to 25% of all undescended testicles.

None of the current imaging techniques such as USG, CT or MRI performed to detect the presence or absence of non-palpable testicles have shown 100% reliability [8]. In the study of Erdoğan C et al., they were able to detect the location of only three testicles (15.7%) in USG performed for nineteen testicles [9]. For this reason, some authors have recommended the use of laparoscopy, which can provide diagnosis and treatment, when necessary, as the first choice without resorting to another imaging method [10,11]. In our study, we were able to detect the location of non-palpable testes in 15.2% of patients with USG and 25% with MRI. In laparoscopic exploration, however, we were able to detect the location and size of 100% of the non-palpable testicles, and we operated on all these cases with the exception of the vanishing testicles. In some cases, although the blind-ending spermatic cord is seen, the spermatic vascular structures may not be observed. In such cases, the colon should be lifted and laparoscopic exploration should be continued caudally, so that gonads could be observed at the tip of the vessels [12]. In all cases participating in the study, spermatic vessels and spermatic cord were identified separately

In non-palpable testicles during laparoscopy, incidence rate has been reported with spermatic vessels entering the inguinal canal as 40%, those in the abdomen as 40%, peeping testes as 10%, and blind-ended spermatic vessels as 10% [5]. In our series, 52.4% of the testicles were in the inguinal canal, 32.5% were intra-abdominal (15.3% were high intra-abdominal, 17.2% were close to the inguinal canal), 11.9% were vanishing testicles and 1% were in the inguinal canal. It was determined that 3.2% of them had peeping testicles.

Some authors have suggested that testicles that are 2 cm closer to the internal inguinal ring or that can be stretched out to the contralateral inguinal ring may have sufficient vascular length to be fixed into the scrotum [13,14]. We also performed single-session laparoscopic orchiopexy in four patients who were closer than 2 cm to the inguinal canal and in two patients with peeping testicles, and we found our success rate of single-session laparoscopic orchiopexy to be 83.4%. We detected atrophy in only one patient (16.6%).

If the intraabdominal testis was more than 2 cm away from the inguinal canal, we performed a phased Fowlers-Stephens surgery. The basic principle of this surgery is based on the ligation of the main vascular structures of the testis and the survival of the testis by being fed by collaterals, deferential artery of ductus deferens and cremasteric vessels. Orchiopexy can be performed in a two-session Fowlers-Stephens surgery if testicular atrophy has not developed 6 months post operatively after the first operation [15]. An estimated success rate of for single-session Fowlers-Stephens surgery is reported as 80% and 85% for two-session Fowlers-Stephens surgery [16,17]. We detected atrophy in three of eight patients (37.5%) and performed laparoscopic orchiectomy in the second session, we did not detect atrophy in the controls after staged Fowlers-Stephens in the other five patients. We found the success rate of staged Fowlers-Stephens surgery to be 62.5%. We think that the distance of the non-palpable intra-abdominal testicles to the inguinal canal and/or the excision of the vessels to fix them into the scrotum, are effective on the development of atrophy.

Dar SA et al. found that the internal inguinal ring was closed at a rate of 28% during laparoscopic orchiopexy [18]. We found that the internal inguinal canal was completely closed in 3 (25%) of 12 (8 of them >2cm, 4 of them <2cm) intra-abdominal testes cases and we completed the orchiopexy by creating a new canal from the medial of the inguinal canal with a grasper.

In the study conducted by Demir et al., they found that the testicular vessels and spermatic cord entered the inguinal canal in 50% of their patients in the laparoscopy and they found atrophy in 79.1% of the twenty-four testes they explored [19]. In our series where an orchiectomy was performed, the rate of cord and vessels entering the inguinal canal was 52.6% and atrophy was detected in 83.9% of these testes.

Since the histopathological examination of atrophic testes in non-palpable testes shows the presence of seminiferous tubules and viable germ cells in up to 0 to 16%, some authors suggest routine removal of atrophic testicular tissue in order to prevent malignant transformation, on the other hand some authors find orchiectomy unnecessary because no viable testicular tissue is detected so far [16]. In our study, immature tubule structures were found in seven (20.5%) of thirty-four atrophic testis in histopathological examination.

Surgical complications during a diagnostic laparoscopy for nonpalpable testis such as preperitoneal insufflation due to Veress needle insertion, or vascular or intestinal injuries due to trocar insertion, hypercarbia, gas embolism, arrhythmia and cardiac arrest, are rare and seen and at a rate of 5.4% [18]. In our study, our pre- and postoperative complication rate was 5.1%, which is consistent with the literature.

The recommended age for orchiopexy for an undescended testis has declined further over the years. In the 2000s, surgery was recommended between the ages of 1 and 2 years, while today it is currently recommended between 6 and 18 months [3]. In the guideline published by the European Association of Urology in 2019, it is recommended that any treatment for undescended testicles should be completed up to twelve months or by eighteen months at the latest [6]. Although undescended testis surgery is recommended between 6 and 18 months, we had older patients that admitted to us or to a doctor in this area of expertise due to low socio-cultural status and the majority of our patients in this category were living in rural areas.

CONCLUSION

Compared to conventional imaging methods for non-palpable testicles, laparoscopic exploration provides 100% diagnosis and can also be used for treatment. Synchronous laparoscopic orchiectomy is performed in cases of atrophic testes in laparoscopy performed for non-palpable testicles; it allows the vessels to be ligated, especially for testes that lie farther than 2 cm away from the inguinal canal, and for testes that are closer than 2 cm, it allows the vessels to be released under a better vision thereby protecting against surgical complications of conventional orchiopexy.

Limitations

This study was conducted retrospectively and the follow-up period was 2 years. Conducting a prospective study including after puberty may provide more useful information in terms of sperm morphology and fertility.

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RESEARCH ARTICLE

ARAŞTIRMA

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Is there a relationship between NR-2 antibody peptide level and diagnosis, prognosis and coma scores in acute ischemic stroke?

NR-2 antikor peptid düzeyinin akut iskemik inmede tanı, prognoz ve koma skorları ile ilişkisi var mıdır?

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ABSTRACT

Aim: This study aimed to demonstrate the diagnostic and prognostic value of NR-2 peptides as a biomarker in acute ischemic stroke and to evaluate their correlation with the Glasgow Coma Scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS).
Materials and Methods: The importance of NR-2 peptide level in diagnosis and prognosis in acute stroke was investigated cross-sectional and prospectively. The study included 101 patients, who presented to a tertiary healthcare facility and were diagnosed with acute stroke, and 57 healthy controls. In the whole study population, serum NR-2 peptide levels were measured using the ELISA method.
Results: The NR-2 peptide level was 6.32 ± 8.30 in the patient group and 3.91 ± 1.64 in the study group. The NR-2 peptide level was significantly higher in the patient group (p = 0.006). No correlation was detected between NR-2 peptide levels and scores in the GCS or NIHSS. The results indicated that NR-2 was a potential biomarker elevated in the early phase of acute stroke, but had no correlation with the prognosis of acute stroke.
Conclusion: Although our data shed light on the use of the NR-2 peptide level as a biomarker in the acute phase in patients with stroke, data are insufficient to predict prognosis. We think that larger, multicenter studies with longer follow-up periods are needed.

Key words: Stroke, NR-2 peptide, diagnosis, prognosis, biomarker

ÖZ

Amaç: Bu çalışmanın birincil amacı akut iskemik inme'de biyobelirteç olarak NR-2 peptidinin tanısal ve prognostik değerini göstermek, ayrıca Glasgow koma skoru (GKS) ve Ulusal Sağlık Enstitüleri İnme Ölçeği (NIHSS) arasındaki ile ilişkisinin araştırılmasıdır.
Yöntemler: Akut inme de NR-2 peptid düzeyinin tanı ve prognozdaki önemi prospektif kesitsel olarak araştırılmıştır. Çalışmaya üçüncü basamak sağlık kuruluşuna bir yıl içerisinde başvurup akut inme tanısı kesinleşen 101 hasta ve 57 sağlıklı kontrol grubu alınmıştır. Tüm çalışma grubunda serumda NR-2 peptid düzeyi ELISA yöntemi ile ölçülmüştür. Elde olunan sonuçlar hastaların prognoz kriterini öngörebilecek olan koma skorlamaları ile ilişkisine bakılmıştır.
Bulgular: Elisa yöntemi ile ölçülen NR-2 peptid düzeyi hasta grubunda 6,32±8,30, kontrol grubunda 3,91±1,64 saptandı. NR-2 düzeyi hasta grubunda daha yüksek olup istatistiksel olarak anlamlı fark vardır (p:0,006). NR-2 düzeyi ile GKS ve NIHSS arasında ilişki saptanmamıştır. Bu sonuçlar ile NR-2 düzeyi akut inmede erken dönemde yüksek saptanılan potansiyel bir biyobelirteç olmasına karşın bu protein düzeyinin akut inme prognozu ile ilişkisi saptanmadı.
Sonuç: Sonuçlarımız NR-2 düzeyinin inmeli hastalarda biyomarker olarak akut dönemde kullanılabilmesi için ışık tutmakla birlikte, hastalığın prognozunu öngörmede yeterli verilere sahip değildir. Bu konuda daha fazla hasta popülasyonu ile çok merkezli, hastaların daha uzun süre takip prognozlarının izlenildiği çalışmalara ihtiyaç olduğunu düşünmekteyiz.

Anahtar kelimeler: İnme, NR-2 peptidi, tanı, prognoz, biyobelirteç

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INTRODUCTION

Stroke is the second leading cause of disability and death worldwide. Early diagnosis is essential to ensure appropriate and timely management [1]. Although clinical findings diagnose stroke, it is important to define and categorize it [2]. Approximately 80% of strokes are ischemic, while 15 to 20% is hemorrhagic, with different therapeutic and prognostic outcomes. Specific management and treatment protocols recommend thrombolysis in stroke subtypes, including blood pressure control [2]. Although imaging is a mainstay for discriminating ischemic stroke (IS) from intracerebral hemorrhage (ISC), it is not always available. In stroke, biomarker studies rely on pathophysiological aspects of ischemic tissue injury and the likelihood of elevated serum protein levels after tissue injury. There may be some biomarkers secondary to hemostasis, endothelial injury and tissue damage in this process. High-resolution screening of many molecules is another way to identify a biomarker. Other methods include genome and proteomic approaches and RNA expression [3,4]. However, the limitations of biomarkers result from the fact that tissue injury may develop over time, and the blood-brain barrier may hamper the release of these molecules into circulation.

Recently, biomarkers have gained increasing interest, with groups focusing on discovering an optimal biomarker for a certain disease worldwide. Some proteins are promising biomarkers, but there is a deficiency in specificity and sensitivity. In previous studies, several aspects of stroke, including diagnosis, severity, outcome, etiology and correlation, were investigated using biomarkers such as astroglial protein S100B, glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE) and vascular cell adhesion molecule (VCAM)-1. Although results were promising for intercellular adhesion molecule (ICAM)-1, N-methyl-D aspartate (NMDA) receptor antibodies and matrix metalloproteinases (MMPs), as well as acute thrombosis molecules, such as D-dimer and von-Willebrand factor (vWF), none was found to be absolute or specific. However, these biomarkers can reflect the severity of sub-acute or established stroke [5,6]. The lack of a relationship between these biomarkers and stroke may be translated as the blood-brain barrier limiting their release into systemic circulation; thus, they do not correlate with stroke severity [5]. However, clinicians seek a biomarker with predictive value as soon as possible [6]. NMDA receptor peptides and their auto-antibodies (NR-2Ab) have been proposed as biomarkers for neurotoxicity underlying cerebral ischemia and stroke [7]. Anti-NMDA IgG receptor antibodies are formed in response to the release of peptide fragments derived from the NMDA receptor cycle and have long been identified in the sera of stroke patients [7-9]. These antibodies were found in the sera after stroke and remained elevated for months. The preoperative serum concentrations of NR-2Ab may herald severe neurological adverse events. It was found that the likelihood of experiencing postoperative neurological adverse events was 18-fold higher in patients with positive NR-2 antibodies (>2.0 ng/mL) than in those with negative antibodies [10].

This study aimed to demonstrate the diagnostic and prognostic value of NR-2 peptides as a biomarker in acute ischemic stroke and to evaluate their correlation with the Glasgow Coma Scale (GCS) and the National Institutes of Health Stroke Scale (NIHSS).

MATERIALS AND METHODS

Study design

This cohort study measured and compared NR-2 peptide levels in patients with confirmed stroke and controls. The local scientific research projects unit approved it with project number 2014/575/141518022.

Study population

The study included 101 patients (aged >18 years) who presented within 72 hours after onset of acute stroke symptoms and 57 healthy controls without a diagnosis of acute stroke, between February 2014 and February 2015. Patients with hemorrhagic stroke, vascular dementia, hypertensive encephalopathy, pregnancy, were breastfeeding, had chronic renal disease, chronic liver disease, chronic heart failure and an acute transient ischemic attack, were all excluded. In addition, patients with blood sample hemolysis

were also excluded due to the potential for cross-reaction with hemoglobin. Written informed consent was obtained from all subjects (patients and controls) or first-degree relatives.

In patients with a clinical diagnosis of stroke, blood samples (5 ml) were drawn into EDTA vacuum tubes and placed in ice blocks. The samples were centrifuged within 30 minutes to consume the NR-2 peptide by serine proteases. The plasma was obtained by centrifugation at 4000 rpm over 4 minutes, and the samples were transferred to Eppendorf tubes and stored at -80°C until assays. After collecting blood samples from all subjects, NR-2 analysis was performed by a blinded researcher, in accordance with the manufacturer's instructions, at the biochemistry laboratory. In addition, blood samples for routine laboratory evaluations (complete blood count, biochemical assays and coagulation parameters) were obtained from all subjects.

ELISA procedure

Following the manufacturer's instructions, the serum antibody concentrations were measured using the Gold Dot NR-2 Antibody Test (CIS Biotech, Inc., Atlanta, GA). Briefly, 100 µl diluted serum (1:50; 20 µl serum sample +980 µl diluent) and calibration sets were placed into NR-2-coated microtiter plates and incubated in a shaker for 30 minutes at 37°C. The wells were washed using buffer, then 100 µl of protein A-HRP-labelled antibody was added, and the mixture was incubated in a shaker for 30 minutes at 37°C. After 100 µl, a ready-to-use TMB substrate was added. NR-2Ab titter was calculated using standards provided by the Gold Dot NR-2 antibody test in each sample.

Clinical evaluation

Physical examination, neurological examination, history and standard neurological stroke examination were performed on all patients. In all patients diagnosed with a stroke, standard neurological and physical examinations were performed using NIHSS and GCS [11,12]. All stroke patients underwent immediate CT scans, and MR imaging was obtained within 24 hours. An experienced neurologist examined all patients during admission. Clinical definitions were made before the N2Ab measurement. All controls, medical history, risk factors for stroke, medication and previous strokes were recorded using a questionnaire.

Magnetic resonance imaging and analysis

The MR images were captured by a standard MRI device using single-pulse echo-linear gradients. The standard dataset included T1-weighted sagittal sequences, diffusion-weighted sequences, visible diffusion coefficient, FLAIR and T2-weighted images.

Statistical analysis

All statistical analyses were performed using the SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The normal distribution was tested for numerical variables. The Wilcoxon sign test was used in dependent groups. The Kruskal-Wallis test was used in more than two independent groups, while the Mann-Whitney U test was used in more than two independent groups with skewed distribution. Correlation analyses were performed using Pearson's and Spearman's correlation tests for numerical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 presents the demographic characteristics of patients (n = 101) and controls (n = 57). The NR-2 peptide level was 6.32 ± 8.30 in the patient group and 3.91 ± 1.64 in the study group. The NR-2 peptide level was significantly higher in the patient group (p = 0.006). Table 2 compares NR-2 peptide levels and laboratory evaluations between the groups. No correlation was detected between NR-2 peptide levels and GCS or NIHSS scores (r = -0.666, p = 0.001). Table 3 presents the results of the correlation analyses.

DISCUSSION

To the best of our knowledge, this study is the first to compare biomarker levels and neurological coma scales, although there are many biomarker studies on stroke in the literature.

Biomarkers offer the opportunity for both acute stroke detection and prediction of stroke risk. However, no optimal biomarker for ischemia and stroke has been defined. In the case of

Table 1: Demographics and patient characteristics of the patient and control groups, vital signs

Parameters	Patient (n=101)	Control (n=57)	p- value
Age(years)	72.35±13.33	62.95±15.41	0.001
Gender (%male)	42/101(45.5)	32/57(70)	0.133
Body temperature (°C)	36.52±0.33	37.5±15.6	0.219
Pulse (/ minute)	83.28±20.03	90.72±18.19	0.006
Systolic blood pressure (mmHg)	144.7±31.3	137.1±28.9	0.134
Diastolic blood pressure (mmHg)	84.8±17.7	82.4±14.4	0.47

*p < 0.05 is considered as significant

Table 2: Comparison with laboratory values between groups

Parameter	Patient Group	Control Group	p value
NR-2 (ng/dl)	6.32±8.30	3.91±1.64	0.006
Hgb (gr/dl)	13.51±1.88	13.59±2.63	0.832
Hct (%)	40.23±6.38	41.61±7.73	0.228
Rbc (106/uL)	4.66±0.60	4.79±0.85	0.296
Wbc (103/uL)	9.33±3.25	9.41±4.46	0.901
Neutrophil (103/uL)	6.65±3.13	7.01±4.15	0.542
Lymphocyte (103/uL)	1.91±0.85	1.76±1.15	0.358
Plt (103/uL)	251.07±66.84	251.28±93.01	0.988
PT (sec)	14.27±1.84	16.86±4.59	0.016
İNR (iu)	1.11±0.19	1.38±0.50	0.152
PTT (sec)	30.15±6.67	27.05±4.68	0.227
Glucose (mg/dL)	140.37±62.79	151.53±88.35	0.402
Urea (mg/dL)	45.40±21.08	37.61±19.62	0.024
Creatinine (mg/dL)	1.54±6.79	0.87±0.53	0.463
Sodium (mmol/L)	139.14±3.58	137.82±4.18	0.039
Potassium (mmol/L)	4.33±0.63	4.58±0.65	0.019
AST (u/L)	36.53±74.46	26.11±10.67	0.170
ALT (u/L)	27.30±58.83	20.77±18.22	0.416
CKMB (ng/ml)	3.92±7.56	3.69±6.75	0.864
Troponin-I (ng/ml)	0.04±0.09	0.02±0.02	0.077

Table 3: Comparison of GKS, NIHSS and NR-2 peptide value

		GKS	NR-2	Volume	NIHSS
NR-2	r	-0.073	1	-0.070	0.053
	p value	0.470		0.493	0.597
	n	101	101	99	101
GKS	r	1	-0.073	-0.102	-0.666
	p value		0.470	0.315	0.001
	n	101	101	99	101
NIHSS	r	-0.666	0.053	0.290	1
	p value	0.001	0.597	0.004	
	n	101	101	99	101

r: correlation coefficient NR-2: NR-2 peptide (ng/dl), Volume: volumetric measurement values (cm3), NIHSS: National Institutes of Health Stroke Scale, GKS: Glasgow coma scale,

a stroke, available diagnostic tests, including MR imaging with or without diffusion-weighted images, may provide inadequate diagnostic information. In addition, known methods cannot identify the conditions underlying true stroke. A biomarker reflecting neuronal neurotoxicity and the early stage of ischemic dysfunction may provide additional diagnostic data in true stroke. An ideal blood biomarker should be economical, sensitive, specific and reproducible with high

accuracy, has negative and positive predictive value and must be interpreted readily by clinicians [3,13]. In recent years, there has been growing interest in developing biomarkers to determine etiology and stroke type to distinguish conditions mimicking stroke. A panel including NR-2, S100 B, VWF, MMP9, VCAM or S100B or VWF, MMP9, BDNF and MCP-1 can discriminate stroke from controls with high sensitivity and specificity [14]. In a systematic review on blood biomarkers in the diagnosis of ischemic stroke, the authors found important limitations in the design and reporting of all studies despite high sensitivity or specificity [5]. In a recent update, the authors concluded that there is no sufficient evidence that novel biomarkers can distinguish stroke from other causes [15].

In a multicenter study involving 1146 stroke patients, blood samples were analyzed for MMP9, BNP, D-dimer and protein S100. The authors reported that levels of these proteins were the sensitive biomarker for acute stroke [16]. In our study, the NR-2 level was significantly more sensitive for patients with acute stroke when compared to controls, concurring with the above-mentioned study.

Several studies were conducted to distinguish between ischemic stroke and intracerebral hemorrhage. The studies investigated whether several markers have a basal cut-off value for discrimination of these entities, and such a basal cut-off value was defined for some biomarkers such as GFAP [16,17]. In our study, no cut-off value was determined. This finding may be due to differences in genetics, disease severity and blood sampling.

In a recent meta-analysis, activated protein C-protein C inhibitor complex (AOC-PCI), glial fibrillary acidic protein (GFAP), APC-PCI plus GFAP and retinol-binding protein (RBP)-4 levels were evaluated for discrimination of two stroke types. The authors concluded that the results indicate insufficient reliability for routine clinical use [18]. In our study, no meaningful result could be obtained for using the NR-2 peptide level as a prognostic marker despite higher levels of NR-2 peptide in patients with stroke. Another study observed that vascular endothelial growth factor was associated with outcomes on month three and stroke severity [19]. In the early ischemia phase, thrombin-activated serine proteases are activated, and antibody fragments, namely NR-2 peptides, against NMDA are released into the circulation [20]. Antibodies against NMDA receptor peptides (NR-2Abs) develop in response to the release of NR peptide fragments and can be measured in the blood [15]. Studies of NR-2 peptides (degradation products of NMDA NR-2 receptors) have supported NR-2 peptide use as a biomarker in diagnosing stroke. The level of NR-2 peptide is increased following a stroke. IgG antibodies are defined against NMDA receptor fragments, which can be detected in the blood and represent a potential biomarker [8,9]. However, NMDA-R antibodies are also linked to hypertension, atherosclerosis, previous stroke, epilepsy and encephalitis; thus, their specificity is unknown. In our study, the NR-2 level could have been affected by undefined risk factors. However, all known risk factors that may affect NR-2 levels were excluded, resulting in an alteration in the specificity and prognostic value of the antibody.

In a recent study, the authors assessed the value of lipoprotein-associated phospholipase A2 (Lp-PLA2) protein level as a biomarker for diagnosis and prognosis in clinical use; they found a correlation with poor prognoses [21]. Chen et al. [22] evaluated neutrophil, lymphocyte and platelet: lymphocyte ratios in the prognosis of acute stroke. In another study, the authors studied the association between eosinophil: monocyte as biomarker and prognosis in acute ischemic stroke, reporting the ratio as a potential biomarker for prognosis [23]. Yang et al. [24] investigated the relationship between baseline serum complement levels and prognosis, reporting that elevated serum C3 complement levels at diagnosis are associated with poor prognosis. Another study evaluated the relationship of retinoic acid levels with prognosis, reporting that low serum retinoic acid was associated with poor prognosis [25].

Although our study is the first to assess the association between NR-2 levels and prognosis, no such association was found contrary to the relationship between different biomarkers and prognosis. This result may be due to the plasma availability of these two biomarkers studied and

the clinical variation and differences in the cohort.

Although our data shed light on the use of the NR-2 peptide level as a biomarker in the acute phase in patients with stroke, the data is insufficient to predict prognosis. We think that larger, multicenter studies with longer follow-up periods are needed.

CONCLUSION

In conclusion, the NR-2 peptide level is a potential biomarker for further study and validation in patients with acute strokes. However, no correlation was detected with the coma scores. More studies are needed to identify novel biomarkers or biomarker combinations with better discrimination ability for use in diagnosis.

Limitations of study: This study had limitations, including a single-center design, a shorter study period and a smaller sample size. In addition, there may be differences in the time from symptom onset to presentation due to variations in access to emergency medical services, all of which may affect the NR-2 peptide level. The NR-2 peptide is a candidate for use as a biomarker in diagnosing acute stroke in the absence of such limitations.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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Clinical Outcomes of Uniportal Versus Multiportal Endoscopic Thoracic Sympathectomy in Patients With Severe Palmar and Axillary Hyperhidrosis

Şiddetli Palmar ve Aksiller Hiperhidrozu Olan Hastalarda Uniportal ve Multiportal Endoskopik Torasik Sempatektomi'nin Klinik Sonuçları

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ABSTRACT

Aim: Palmar and axillary hyperhidrosis is caused by overstimulation of the sympathetic nervous system that control the sweat glands. This study compares the clinical consequences of uniportal and multiportal thoracic endoscopic thoracic sympathectomy (ETS), in cases of severe palmar and axillary hyperhidrosis.

Methods: In this retrospective study, forty-one patients who were diagnosed as severe palmar and axillary primary hyperhidrosis were analyzed. These underwent multiportal ETS between 2015 and 2020 at our thoracic surgery clinic. They were divided into two groups, 24 as uniportal (58.5%) and 17 as multiportal (41.5%). They were compared in terms of the length of hospital stay, the initial complications and possible recurrences after three months. Descriptive statistics were used to evaluate stratified and continuous variables.

Results: There was no significant difference in moderate pain between the two groups. There was a significant difference between the two groups in terms of 3 days or more hospitalization. There were no significant difference related to the rate of complications such as ptosis, Horner syndrome, increased duration of surgery and recurrence rate of hyperhidrosis 3 months after surgery. Some mild to moderate side effects disappeared spontaneously at 6-month follow-up.

Conclusion: The results showed that uniportal and multiportal endoscopic thoracoscopic sympathectomy (EST) are very effective, safe and minimally invasive methods for the treatment of palmar and axillary hyperhidrosis. Compared to the multiportal approach, uniportal EST causes less postoperative pain and less surgical duration.

Keywords: Uniportal, Multiportal, ETS, Hyperhidrosis.

ÖZ

Amaç: Palmar ve aksiller hiperhidroz, ter bezlerini kontrol eden sempatik sinir sisteminin aşırı uyarılmasından kaynaklanır. Bu çalışma, şiddetli palmar ve aksiller hiperhidroz vakalarında uniportal ve multiportal torasik endoskopik torasik sempatektominin (ETS) klinik sonuçlarını karşılaştırmaktadır.

Yöntemler: Bu retrospektif çalışmada şiddetli palmar ve aksiller primer hiperhidroz tanısı konulan 41 hasta incelendi. 2015-2020 yılları arasında göğüs cerrahisi kliniğimizde tüm vakalarımıza ETS uygulandı. Uniportal 24 (%58,5) ve 17 Multiportal (%41,5) olmak üzere iki gruba ayrıldılar. Hastanede kalış süreleri, ilk komplikasyonlar ve üç ay sonra olası nüksler açısından karşılaştırıldılar. Tabakalı ve sürekli değişkenleri değerlendirmek için tanımlayıcı istatistikler kullanıldı.

Bulgular: İki grup arasında orta derecede ağrı açısından anlamlı bir fark yoktu. Hastanede 3 gün ve üzeri yatış açısından iki grup arasında anlamlı fark vardı. Ameliyattan 3 ay sonra pitozis, Horner sendromu, ameliyat süresinin uzaması ve hiperhidrozun tekrarlama oranı gibi komplikasyon oranları arasında anlamlı fark yoktu. Bazı hafif ila orta dereceli yan etkiler 6 aylık takipte kendiliğinden kayboldu.

Sonuç: Sonuçlar, palmar ve aksiller hiperhidroz tedavisinde uniportal ve multiportal endoskopik torakoskopik sempatektominin (EST) çok etkili, güvenli ve minimal invaziv yöntemler olduğunu göstermiştir. Multiportal yaklaşımla karşılaştırıldığında, uniportal ETS daha az postoperatif ağrıya ve daha az cerrahi süreye neden olur.

Anahtar Kelimeler: Uniportal, Multiportal, ETS, Hiperhidrosis

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INTRODUCTION

Sweating is a vital defense mechanism that ensures the thermoregulation of our body and it is controlled by the hypothalamus, cerebral cortex and sympathetic autonomic nervous system [1]. In some people, as a result of sympathetic overactivity, hyperhidrosis occurs specifically in some areas, especially the hands, axillary groin, foot soles, back and abdomen [2].

Secondary hyperhidrosis is the result of other causes such as malignancy, endocrine disorders or the side effects of some drugs or medications, whereas in primary hyperhidrosis, the nerves responsible for signaling the sweat glands become overactive [1,3]. Common treatments include the use of skin creams, systemic anticholinergic drugs, topical injection of botulinum toxin A, and even surgical procedures [1, 3, 4]. Surgical procedures include local removal of axillary sweat glands as well as thoracoscopic blocking of certain branches of the thoracic sympathetic chain [5]. The surgical approaches may be performed by open or endoscopic techniques [6].

Endoscopic Thoracic Sympathectomy (ETS) is a closed surgical procedure in which specific branches of the thoracic sympathetic chain is blocked [7]. It is an alternative, safe and durable treatment procedure performed by excision, electrocoagulation or application of surgical clips on the thoracic sympathetic ganglia, between T2 and T4 or T5 (8). It is also an effective and aesthetically remarkable procedure to treat primary hyperhidrosis [9].

As a result of its minimally invasive character, it has become the preferred surgical procedure in the recent years. In such cases, due to the satisfactory early outcomes, namely short hospital stays and low complications, the procedure is highly tolerable[3].

In this study, we aimed to clinically compare the outcomes of uniportal and multiportal endoscopic thoracic sympathectomy (ETS) in cases with severe palmar and axillary hyperhidrosis, in patients who did not respond to the conservative therapeutics.

PATIENTS AND METHODS

In this retrospective study, forty-one patients who were diagnosed as severe palmar and axillary primary hyperhidrosis were studied. They did not respond to conservative therapies and underwent thoracoscopic sympathectomy between 2015 and 2020 in our thoracic surgery clinic.

We excluded the patients who had to undergo thoracotomy due to pleural adhesions and the patients who couldn’t be followed up after 1 and 3 months later. We included all patients who could be operated endoscopically and bilaterally becaue of they didn’t respond to conservative treatment.

For each patient, a questionnaire containing demographic information, underlying diseases, skin perspiration (Hyperhidrosis) and consent was recorded before surgery. Chest X-rays were also performed to ensure the absence of potential pleural symphysis. All this information was obtained once more, one and three months after surgery and their symptoms (in particular skin moisture) were compared with pre-surgery. Similarly, possible complications such as hemothorax, pneumothorax, Horner's syndrome, etc. were followed up. Through the final follow-up, we assessed patients' pain using the Visual Analogue Scale (VAS).

The surgical procedure consisted of the following steps:

Subsequent to a double-lumen endotracheal tube intubation, general anesthesia was induced. The patient was placed on a dorsal decubitus, semi-sitting (trunk with 45° flexion) position. Two small (roll-like) pads were placed under the patient's shoulder. These arrangements created enough space between the axilla and the ports. Another pad was also placed below the knees. To ensure the patient's position when rotating left and right, the hip area was fixed to the bed.

In both uniportal and multiportal modes, the mediastinum pleura was removed and cauterized at the top of the thoracic sympathetic chain using a monopolar endo-hook. Then the thoracic sympathetic chain also appeared and turned.

In the uniportal procedure, a 2 cm incision was required between the middle and anterior axillary lines in the fifth intercostal space. After the

lung was deflated (collapsed), clips was placed between the T2-T4 sympathetic chains by entering through portal. The sympathetic chain along with the Kuntz nerve around the sympathetic ganglia was identified and a clip was placed between T2-T4 of the sympathetic chain.

In the multiportal procedure, the camera was inserted into the chest with a 1 cm incision and the dissector was inserted into the chest using a 5 mm incision. The first incision was made around the anterior axillary line and on the fifth anterior intercostal space, through which the camera entered the thoracic cavity. To reduce possible side effects, the second port entered the thorax under direct vision after the camera was inserted into the thoracic cavity. The patient's pleura in the sympathetic chain pathway was opened from T2 to T4 and a clip was placed between communication branches.

In no case did we cauterize or cut the sympathetic branches. In many of them, the Kuntz branch was cauterized and in no case was the chest tube inserted postoperatively.

In both procedures, after complete homeostasis, the lung was reinflated to fully open the collapsed lung. The direct view of the camera ensured that the lungs opened. The camera was then removed and the incision was sutured.

Based on the objectives of the study, we compared the length of hospital stay, the initial complications and possible recurrence of palmar and axillary hyperhidrosis in both uniportal and multiportal cases, after 3 months.

In this study, descriptive statistics for stratified and continuous variables were used. Homogeneity of variance was assessed by the Levene test and the Shapiro-Wilk test was conducted for normality. Student's t-distribution, one-way variance, Kruskal-Wallis and Bonferroni tests were run. Relationships between class variables were analyzed by the Fisher test and the Chi-square test. In cases which the expected frequencies were less than 20, the Monte Carlo simulation was included. The p values were considered statistically significant less than 0.05 and 0.01. The SPPS 25 software was used to perform the quantitative analysis.

RESULTS

Twenty-three cases (56.1%) were male and eighteen cases were female (43.9%). Descriptive statistics including age, gender, postoperative complications, hospital stay, and recurrence rate of hyperhidrosis after 3 months are summarized in Table 1.

Table 1. Descriptive statistics related to class variables

Variables	Category	N	%
Sex	male	23	56.1
	female	18	43.9
Surgery time	30 minutes or less	11	26.8
	Between 30-60 minutes	23	56.1
	More than 1 hour	7	17.1
Portal	Uniportal	24	58.5
	Multiportal	17	41.5
Ptosis	Occurred	3	7.3
	Did not occur	38	92.7
Horner syndrome	Occurred	2	4.9
	Did not occur	37	95.1
Hospitalization	1 day	24	58.5
	2 days	11	26.8
	3 day and more	6	14.6
Recurrence after 3 months	Occurred	2	4.9
	Did not occur	39	95.1
	Total	41	100.0

The age of the patients varied between 15 and 50 years, with an average of 27 and an average of 25 (most cases between 20 and 30 years of age) (Table 2).

Table 2. Descriptive statistics related to the continuous variable of age

	N	Minimum	Maximum	Average	Standard deviation
Age	41	15.00	50.00	27.6829	8.92591

All of them tried at least one conservative treatment before accepting the surgical approach and failed to get the desired results. Uniportal procedures included twenty-four cases and multiportal seventeen cases, respectively.

Postoperative pain in uniportal cases was significantly lower than in multiportal group (P<0.001(. Complaints of severe pain were seen in 18.2% of cases in the uniportal group and in

81.8% of the multiportal group. Mild to severe pain was also significantly different between the two groups (90.0% in the uniportal group vs. 10.0% in the multiportal group). There was no significant difference in moderate pain between the two groups.

Due to the lower pain severity, the length of hospital stay after ETS was also significantly lower in the uniportal group ($p<0.001$). The difference in the length of one-day hospital stay was also significantly different between the two groups (83.3% in the uniportal group vs. 16.7% in the multiportal group).

Similarly, a significant difference in the length of two-day hospitalization was also seen between the two groups (27.3% in the uniportal group vs. 72.7% in the multiportal group). There was also a significant difference between the two groups in terms of 3 days or more hospitalization (16.7% of the uniportal group vs. 83.3% of the multiportal group).

There were no statistically significant differences between the two groups in terms of side effects such as ptosis ($p<0.767$), Horner syndrome ($p<0.802$), duration of surgery ($P<0.169$) and recurrence rate 3 months after surgery ($p<0.802$) (Table 3).

There were also no deaths in any of the cases. Intraoperative vascular injury, thoracic duct injury, postoperative hemothorax and pneumothorax did not develop in any of cases.

Despite the fact that in no case was the chest tube inserted, we did not encounter hemothorax or pneumothorax after the operation and at the one-week follow-up. Horner's syndrome was observed in only one case in both groups. Ptosis occurred in two cases of uniportal group and in one case of multiportal group. However, in all cases it disappeared spontaneously at the 6-month follow-up. Blepharoplasty was not required and the clinical manifestations of two cases of Horner's syndrome significantly subsided after 6 months.

DISCUSSION

In this comparative study, we found that our patients complained of less pain in the uniportal ETS group and their length of stay in the hospital was significantly shorter.

Although there are many studies in the literature comparing single-port and multi-port methods in endoscopic spontaneous pneumothorax surgery and endoscopic lung resection surgeries [6], we found few publications comparing single and multi-port methods in ETS surgeries. For this reason, we think the results of our study may be useful.

Hyperhidrosis disrupts the quality of life and results in problems ranging from a reduction in social life to isolation. Although treatments such as locally effective ointments, systemic anticholinergic drugs and local botulinum A are used, the most effective results are obtained with the surgical technique called endoscopic thoracic sympathectomy (ETS) [10,11].

In the last two decades in particular, ETS surgeries have been performed effectively in cases of hyperhidrosis. With ETS, the T2-T4 interval of the thoracic sympathetic chain is blocked by various methods, and thus hand and armpit sweating is interrupted [1, 13]. The most preferred methods in sympathetic chain blockade are cauterization of the relevant part of the sympathetic chain, cutting with scissors and clipping [13, 14]. We preferred the clipping method in our cases where we applied ETS in our clinic as it is possible to encounter unexpected conditions, such as ptosis and Horner's syndrome, as the burn effect continues to the lower and upper parts of the sympathetic chain after cauterization [15].

In some patients, after the surgery, symptoms such as compensatory hyperhidrosis may occur, that may negatively affect patient satisfaction. In other cases, permanent bradycardia may develop following surgery [1, 16]. In such cases, it may be necessary to unblock the sympathetic chain again. This is not possible if the thoracic sympathetic chain is cut with scissors or cauterized. Due to the lower incidence of complications, we chose clipping to block thoracic sympathetic branches. However, because of the familiarity on the part of surgeons, cauterization is probably a more common method.

ETS surgeries can be performed from 2 or 3 ports as well as from a single port, which has been increasingly used in recent years [17]. The biggest

Table 3. Comparison of portal categories with variables of gender, duration of surgery and postoperative complications (*p<0,05)

Variables	Category		Portal		Total	X^2	p
			Uniportal	Multiportal			
Sex	Male	n	14a	9a	23	0.117	0.732
		%	60.9%	39.1%	100.0%		
	Female	n	10a	8a	18		
		%	55.6%	44.4%	100.0%		
Duration of surgery	30 minutes or less	n	8a	3a	11	3.554	0.169
		%	72.7%	27.3%	100.0%		
	Between 30-60 minutes	n	14a	9a	23		
		%	60.9%	39.1%	100.0%		
	More than 1 hour	n	2a	5a	7		
		%	28.6%	71.4%	100.0%		
Pain	Very severe	n	2a	9b	11	16.954	0.001*
		%	18.2%	81.8%	100.0%		
	Moderate severe	n	4a	6a	10		
		%	40.0%	60.0%	100.0%		
	Mild severe	n	18a	2b	20		
		%	90.0%	10.0%	100.0%		
Ptosis	Occurred	n	2a	1a	3	0.088	0.767
		%	66.7%	33.3%	100.0%		
	Did not occur	n	22a	16a	38		
		%	57.9%	42.1%	100.0%		
Horner's syndrome	Occurred	n	1a	1a	2	0.063	0.802
		%	50.0%	50.0%	100.0%		
	Did not occur	n	23a	16a	39		
		%	59.0%	41.0%	100.0%		
Hospitalization	1 day	n	20a	4b	24	14.844	0.001*
		%	83.3%	16.7%	100.0%		
	2 days	n	3a	8b	11		
		%	27.3%	72.7%	100.0%		
	3 day and more	n	1a	5b	6		
		%	16.7%	83.3%	100.0%		
Recurrence after 3 months	Occurred	n	1a	1a	2	0.063	0.802
		%	50.0%	50.0%	100.0%		
	Did not occur	n	23a	16a	39		
		%	59.0%	41.0%	100.0%		
Total		n	24	17	41		
		%	58.5%	41.5%	100.0%		

advantage of using multiple ports is the possibility of inserting the camera, surgical instruments and clips from separate ports, thus obtaining more movement space for the procedure and performing it with more ease. When the surgeon uses multiple ports, a greater field of view and wider intervention area can be obtained when necessary, by inserting the camera and instruments from different ports. In contrast to these advantages, the multi-port system causes much more pain in patients compared to the single-port system [18]. Indeed, more than one intercostal space is operated on and more than one intercostal nerve is contacted, which increases the potential for excessive pain [6]. In addition, ETS surgeries are not for the continuation of vital functions, but for the purpose of increasing the comfort of life. Therefore, aesthetic concerns cannot be ignored for this surgery: the multiple port method, which causes two or three scars, is aesthetically more disadvantageous than the single port method.

In the literature, it has been determined that postoperative pain is lower in cases performed

with the single port method, and accordingly, the duration of hospital stay is shorter [6, 17]. When we compared our ETS surgeries performed with both single port and multiple ports, we also found that our patients felt less pain in cases performed with the single port method. Patients who we operated on with multiple ports remained in the hospital for a few more days due to extreme pain. Duration of hospital stay was reduced due to less pain in the patients we operated with a single port, and this was statistically significant.

Intraoperative complications usually include intercostal vein injuries, thoracic duct injuries, subclavian artery injuries and pulmonary injuries [1]. We have not experienced such side effects in either group. Therefore, it was not possible to determine the superiority of one method over the other in terms of complications during operation.

The most common early complications are ptosis, Horner's syndrome, hemothorax and pneumothorax [19]. We did not put a chest tube after the operation in any of our cases and we did not encounter hemothorax or pneumothorax in any of our cases in the operative period, nor in the follow-ups, one week later. Horner's syndrome developed in one of our patients, both groups considered. While ptosis developed in two of our cases operated on with a single port, ptosis developed in one of our cases operated with multiple ports. In all of our cases that developed ptosis, The ptosis picture disappeared spontaneously at the 6-month follow-up. Blepharoplasty was not required and the two Horner syndromes were significantly reduced after 6 months to levels where patients did not complain. We did not find a statistically significant difference between single and multiple port methods in terms of early postoperative complications and this is compatible with the current literature.

In other studies, a recurrence rate of hyperhidrosis of 1 to 3% has been reported in the literature on ETS [20]. One of the important reasons may be that the thin branches separated from the sympathetic chain regenerate over time and restore the connection at the lower and upper parts of the blocked sympathetic chain. Most relapses usually occur after 3 months [21],

In our 3-month follow up, it was found that in one of the two groups, moistening of the hands occurs. For both patients, this condition was not considered unfavorable. There was no significant difference between the two groups in terms of recurrence of hyperhidrosis after 3 months. This was consistent with other findings.

Chen et al. (2009) studied the results of using uniportal and biportal video-assisted thoracoscopic sympathectomy for palmar hyperhidrosis. They showed that both thoracoscopic sympathectomy procedures are effective, safe, and minimally invasive for palmar hyperhidrosis. However, there was no significant difference between the two groups in terms of mean hospital stay, compensatory sweating and patient satisfaction [22].

Georghiou et al. (2004) evaluated the mid-term outcome and value of transaxillary single-port thoracic sympathectomy, using a thoracoscope with an operating channel for treatment of hyperhidrosis. They found that single-port thoracoscopic sympathectomy resulted in positive clinical and aesthetic results, including reducing hospital stays and the risk of side effects. Patients' satisfaction with this treatment was high, although some may experience compensatory symptoms [23].

Murphy et al. (2006) compared uniportal and biportal ablation techniques. The uniportal group showed better results in terms of hospital stay, postoperative pneumothorax and need for chest tube. However, there was no correlation between the number of ports and patient satisfaction [24].

Drott (2003) studied the results of endoscopic thoracic sympathectomy (ETS) for hyperhidrosis. They have shown that severe palmar hyperhidrosis and facial blushing respond well to ETS with high patient satisfaction. Facial hyperhidrosis is effectively treated with ETS but is associated with a high risk of severe compensatory sweating (CS) [25].

Kazemzadeh et al. (2019) compared the single port thoracoscopic sympathectomy with multiport Thoracoscopy in patients with hyperhidrosis. They revealed that since the clinical outcomes and complications in single port and multi-port modes of thoracic sympathectomy are not different, for better aesthetic results, it would be preferable to

use the single-port method as an alternative to the multi-portal method [17].

All of the above studies are consistent with the results of the present study. They confirm that uniportal, biportal and multiportal endoscopic thoracoscopic sympathectomy (EST) are highly effective, safe and minimally invasive surgical procedures for treatment of palmar and axillary hyperhidrosis. Compared to biportal and multiportal procedures, the uniportal approach causes less postoperative pain and shorter surgery duration and is a more rational method of treating hyperhidrosis in these areas. There was no significant difference between the uniportal and the multiportal groups in terms of early postoperative complications, and this finding is consistent with the other studies.

Limitations

The main limitation of our study was that it was retrospective. Pain is a mental data and may vary from person to person after a trauma. Although we have tried to evaluate pain using the VAS pain scale, it is obvious that complete objectivity cannot be provided. Although we had sufficient cases to obtain statistically significant data, our number of cases was smaller than those of other studies.

CONCLUSION

In the uniportal ETS, the postoperative pain experienced by patients is reduced and accordingly, the length of stay in the hospital is decreased. There was no significant difference between uniportal and multiportal groups, in terms of early postoperative complications and recurrence rates of late sweating. A uniportal ETS is more advantageous in terms of aesthetics, hence it seems that the uniportal ETS should be preferred. We recommend that Thoracic Sympathectomy is best started with uniportal ETS and not switched to multiple ports unless it becomes absolutely necessary.

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RESEARCH ARTICLE

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Identification of the hemodynamic correlates of basic emotional states with a mobile functional near infrared spectroscopy system

Temel Duygusal Durumların Hemodinamik Karşılıklarının Taşınabilir bir İşlevsel Yakın Kızılaltı Spektroskopi Sistemi ile Tanımlanması

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ABSTRACT

Aim: The aim of this study was to evaluate the feasibility of a functional near infrared spectroscopy (fNIRS) system, for quantification of the similarities and differences in the spatial localization of cerebral hemodynamic activation, induced by visual presentation of neutral, negative and positive valence emotional stimuli.
Method: Thirteen healthy subjects viewed neutral, pleasant and unpleasant pictures from the International Affective Picture System (IAPS) database in a block design experiment while the prefrontal cortical hemodynamic changes induced by emotional stimuli were continuously recorded with a 20 channel fNIRS system that covered the forehead region.
Results: Negative valence pictures induced higher hemodynamic activity in right lateralized regions involving dorsolateral and orbitofrontal cortex, when compared to neutral and positive valence stimuli (pFDR<0.05). Each stimulus condition induced a distinct cortical activation pattern that could be identified with fNIRS.
Conclusion: Our findings support the notion that different basic emotions have distinct localization and separable hemodynamic correlates in the prefrontal cortex region, which can be detected with a mobile fNIRS system. The distinct cortical hemodynamic activity patterns associated with each emotional state show the potential of fNIRS technology for decoding and differentiating basic emotions objectively and real time for future clinical and daily life applications.

Keywords: Functional near infrared spectroscopy, brain computer interface, prefrontal cortex, emotional valence

ÖZ

Amaç: Bu çalışmanın amacı, bir işlevsel yakın kızılaltı spektroskopi (İYKAS) sisteminin nötral, olumsuz ve olumlu değerlikli duygusal uyarıların sebep oldukları beyin hemodinamik etkinliklerinin uzamsal yerleşimlerindeki benzerlik ve farklılıkları niceliklendirmedeki uygunluğunu test etmektir.
Yöntemler: 13 sağlıklı denek, Uluslararası Duygusal Resim Sistemi (IAPS) veritabanından alınan nötral, hoşa giden ve hoşa gitmeyen içerikli resimleri blok bir deney tasarımı içerisinde izlerlerken, duygusal uyaranların sebep olduğu prefrontal kortikal hemodinamik değişimler alın bölgesine yerleştirilen 20 kanallı bir İYKAS sistemi ile ölçüldü.
Bulgular: Olumsuz değerlikli resimler dorsolateral ve orbitofrontal korteksi kapsayan sağ lateral bölgelerde olumlu ve nötral değerlikli resimlere göre daha yüksek hemodinamik etkinliğe sebep oldu (pFDR<0.05). Her uyarı durumu, İYKAS ile tanımlanabilen, belirgin ve ayrışabilir bir kortikal hemodinamik etkinlik örüntüsüne sebep oldu.
Sonuç: Bulgularımız, farklı temel duyguların prefrontal korteks bölgesinde taşınabilir bir İYKAS sistemi ile ölçülebilen, ayrışabilir ve farklı yerleşime sahip hemodinamik karşılıkları oldukları görüşünü desteklemektedir. Farklı duygusal durumlar ile ilişkili farklı kortikal hemodinamik etkinlik örüntülerinin bulunması, İYKAS teknolojisinin gelecek sağlık ve gündelik hayat uygulamalarında, duyguları nesnel ve gerçek zamanlı çözümleme potansiyelini göstermektedir.

Anahtar Kelimeler: İşlevsel yakın kızılaltı spektroskopi, beyin bilgisayar arayüzü, prefrontal korteks, duygusal değerlik

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INTRODUCTION

Identification of the neuronal basis of how basic emotions are processed and regulated in healthy adult brain has received considerable attention in recent decades thanks to recent advances in mobile brain imaging technologies [1]. From a clinical perspective, precise quantification of the neural correlates of negative and positive emotions in normal, healthy subjects can enable construction of a baseline neurophysiological model, which in turn, can be used for differential mapping of the neuronal underpinnings of the same emotions in psychiatric conditions [2,3]. Besides the potential for assisting clinical diagnosis and follow-up procedures in clinical psychiatry, unravelling the spatiotemporal patterns of the neuronal circuitries involved in emotion processing and regulation can form a basis for designing affective brain computer interfaces (BCI) which aim at real-time decoding of cognitive and affective neural responses to environmental stimuli in daily settings. Such affective BCI designs can be helpful for objective detection of intent, feelings, preferences and emotional responses of patients who cannot verbally communicate with the external environment (e.g., patients with dementia, minimally conscious state and/or locked-in syndrome) [1-3].

The potential of affective BCIs for the above mentioned applications necessitates accurate detection of neuronal processing of emotional stimuli with wearable, ergonomic and miniaturized sensors which should ideally measure and decode neuronally induced signals in real-time and non-invasively, in naturalistic settings [4,5]. To this end, various functional brain imaging modalities have been utilized for characterizing the neuronal processing of emotional stimuli. These modalities include stationary systems such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI) as well as portable systems such as electroencephalography (EEG) and functional near infrared spectroscopy (fNIRS). Among these modalities, fNIRS systems have been found to be ideal candidates for real-time mapping of the neural substrates of basic emotions, thanks to their robustness to electrogenic or motion artifacts, portability, quick set-up time and calibration, low-cost, ease of use and ability to collect biological information in naturalistic daily settings, at any desired frequency and duration [1-5].

fNIRS is a novel, wearable and non-invasive optical brain imaging technology which can measure localized changes in the concentration of oxygenated (HBO) and deoxygenated hemoglobin (HBR), induced by alterations in the metabolic activity of cortical neurons [6]. The operating principle of these systems rely on transmitting two different wavelengths of near infrared light which correspond to the absorption peaks of HBO and HBR molecules in the near infrared portion of the electromagnetic spectrum [7]. Unlike EEG systems, fNIRS systems are not susceptible to electrogenic or motion artifacts and they have quicker set-up time and calibration while providing higher spatial resolution. Although fNIRS systems provide poorer spatial resolution when compared to PET and fMRI, they have the major advantage of having miniaturized, ergonomic probe designs, field deployability, non-invasiveness, ability to collect data at any desired frequency and duration, as well as low operating costs. Similar to fMRI, fNIRS systems measure localized changes in cerebral hemodynamics, but unlike fMRI, these systems do not have loud operating sounds, while they provide higher temporal resolution for sampling local hemodynamic signals. Another major advantage of fNIRS over EEG, fMRI and PET systems relies on the capability of these systems to collect cerebral hemodynamic data in ecologically valid postures and environments during a variety of tasks that require mobility (e.g., walking, biking, driving). Computational cost of fNIRS signal processing is also less intensive than fMRI and EEG systems [6,7]. Overall, these features make fNIRS an ideal candidate for studying the neural basis of emotions as well as developing affective BCIs which can decode feelings, intents and/or preferences of subjects, from measurements of neuronally induced bio-signals.

Previous functional neuroimaging studies have presented compelling evidence that the human brain encompasses cortical and subcortical neuronal circuitries, that interact with each other for processing emotional stimuli. These studies have demonstrated that subregions of

anterior portion of the prefrontal cortex (PFC) have significant roles in processing, appraisal, integration and regulation of emotion related information [8,9]. The ability of fNIRS technology to easily collect functional information from the PFC region makes it an ideal tool to be integrated into affective BCI systems. However, the first step towards integrating fNIRS technology into an affective BCI system is to identify whether processing of different basic emotions have distinct and separable spatiotemporal patterns in the anterior PFC that is detectable by fNIRS. Previous fNIRS studies reported mixed results on the cortical localization and the extent of hemodynamic activation during processing of negative and positive valence stimuli [10-12]. The discrepancies in the reported spatiotemporal patterns of hemodynamic signals might have stemmed from differences in experimental design, stimuli type, possible interferences from other cognitive tasks performed involuntarily or as part of the experimental protocols. Nonetheless, the temporal and spatial characteristics of the fNIRS signals associated with processing of different emotions still remains uncertain.

The present study aimed to evaluate the feasibility of a mobile and wearable fNIRS system for objective identification of the PFC regions involved in the processing of basic emotions. More specifically, we aimed to compare the spatial localization of cerebral activation during presentation of neutral, negative and positive valence pictures in the absence of any interfering stimuli. Our research question focused on whether different basic emotions had distinct and separable hemodynamic correlates in the PFC region that could be measured and identified with fNIRS. In order to answer this question, an experimental protocol was designed in which healthy subjects passively viewed pictures that were rated as pleasant, neutral and unpleasant in the International Affective Picture System (IAPS) database [13], while interference from any other cognitive and/or physical stimuli was minimized. Pictures were chosen from the IAPS database because it provides standardized, high quality and realistic pictures with predefined valence and arousal scores. Within the context of identifying emotions with behavioral data, dimensional models describe each emotion with a two dimensional space [14], which spans valence (i.e., the extent of negative or positive feeling) and arousal (i.e., intensity of perceived feeling). Pleasant and unpleasant pictures with similar valence and arousal scores were selected in order to i) test whether the hemodynamic activity of the PFC regions during processing of basic emotions could be spatiotemporally mapped with fNIRS methodology, and ii) to obtain similarities and differences of the PFC circuitries which were activated during processing of negative, neutral and positive valence stimuli.

METHODS

Subjects

Thirteen right-handed, healthy subjects, with ages ranging from 18 to 25 years (mean age: 21 ± 2 years, 8 females, 5 males) participated in the study. Subject inclusion criteria required the absence of prior history of neurological or psychiatric disorders and being medication-free. All subjects signed informed consents prior to the experiment. The experimental protocol was conducted in accordance with the latest revision of the Declaration of Helsinki. The study was approved by the local ethics committee of Istanbul Medipol University, Istanbul, Turkey.

Experimental Protocol

During the experiment, subjects were seated on a comfortable chair in front of a computer screen which was placed approximately one meter away from their eyes. The experimental protocol was briefly explained to each subject prior to the onset of each experiment. Subjects were instructed to passively look at the images presented on the computer screen, and they were requested to sit relaxed and avoid any movement. The room was dimly lit and quiet.

The experimental protocol was adopted from a pioneer study conducted by Hermann et al. [10]. Briefly, each experiment began with a sixty second baseline recording which was followed by three stimulus blocks of ninety second duration separated with 120 second interstimulus intervals. Within each stimulus block, fifteen pictures with similar valence and arousal scores were presented consecutively for six seconds. The pictures were selected from the IAPS database

[13] and each stimulus block contained pictures of similar valence and arousal scores. Negative pictures had an average pleasure rating of 2.5 and arousal rating of 5.6. Neutral pictures had an average pleasure rating of 4.9 and arousal rating of 2.6. Positive pictures had an average pleasure rating of 8 and arousal rating of 4.8 according to the IAPS norms. The first stimulus block consisted of negative valence stimuli and the last stimulus block consisted of positive stimuli. Neutral stimuli were always presented as the second block. Subjects were requested to passively look at a white crosshair which appeared at the center of a black screen during the 120 second interstimulus rest intervals. Timing of the experimental stimuli blocks is depicted in Figure 1A.

fNIRS Data Acquisition

Hemodynamic signals were collected from the PFC region with a mobile fNIRS instrument (NIRSport, NIRx Medical Technologies, LLC, Berlin, Germany). Light source-detector pairs with a distance of 3 cm were accepted as channels. A total of twenty channels covered the forehead region (Figure 1B). Each light source emitted near-infrared light at 760 nm and 850 nm in continuous wave mode with a sampling frequency of 7.81 Hz. Light intensity changes detected at each detector were transformed to relative concentration changes of HBO and HBR with respect to a baseline reference measurement by use of the modified Beer–Lambert Law [6,7]. The MNI space coregistration of channel locations was performed with the NIRS_SPM toolbox [15]. fNIRS probe configuration and channel locations are presented in Figure 1B-C.

Pre-processing of fNIRS signals and hemodynamic parameter extraction

fNIRS signal pre-processing was carried out with a combination of scripts written in MATLAB software (Mathworks, Natick, MA, USA) and functions from the Homer2 software [16]. For each channel, raw light intensity signals of each wavelength of light were first checked for signal quality. Light intensity signals of channels with good signal quality were first transformed to optical density (OD) change. Motion artifacts in each channel's raw time series were detected with the hmrMotionArtifact.m function in the MATLAB compatible toolbox of Homer2 software. Time segments with motion artifacts were corrected with a Spline interpolation method. Motion corrected OD signals of each wavelength were then band-pass filtered between 0.005Hz and 0.08Hz with a 4th order Butterworh filter. Filtered OD data were transformed to concentration changes of HBO and HBR via Modified Beer-Lambert Law. Only HBO signals were utilized for further analysis because changes in HBO concentration have been reported to be a better indicator of cortical hemodynamic activation induced by changes in neuronal metabolism when compared to HBR signals while having a higher signal to noise ratio [6,7].

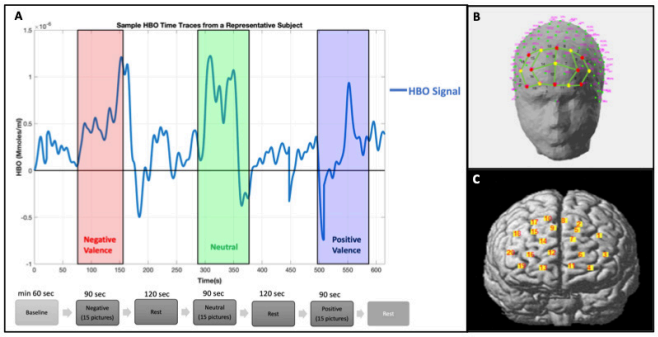

Figure 1. A) Experimental protocol and stimulus timing. A sample time trace of HBO concentration change is plotted on top of stimulus epochs for a representative channel from a representative subject. Stimulus epochs are shaded in red, green and blue for negative, neutral and positive valence stimuli respectively. B) fNIRS forehead probe configuration. Location of light sources and detectors are given according to the international EEG 10-20 system for electrode placement. Red dots represent light sources and yellow dots represent detectors. Source-detector pairs with a distance of 3 cm are accepted as channels which are represented with green lines. C) Location of channels in MNI space.

For each channel HBO time series signal, each stimulus block was truncated with a 10 second prestimulus baseline and a 20 second post-stimulus duration, resulting in 120 second long block segments for negative, neutral and positive valence stimuli periods. Linear trend in each block segment was removed with the 'detrend' function of MATLAB toolbox which performs linear fitting and removal. For each subject data, time points in each block segment were normalized with respect to the extent they deviate from the mean of the signal by a z-score transformation. Area under the curve (AUC) between 20 to 40 seconds after stimulus onset was then computed as the hemodynamic activity parameter for each channel and stimulus block segment.

Statistical Analysis

Localization of significant hemodynamic responses to each stimulus condition was determined by performing one sample student's t-test on the channel-wise AUC parameters of the subject group. For each stimulus condition, channels with t values surpassing the statistical threshold ($p<0.05$) were accepted as significantly activated in response to the presented stimuli. T values of significantly activated channels were coregistered onto a standard brain template which also depicted anatomical locations of the optode positions with respect to the 10-20 EEG system for electrode placement (Figure 2). To evaluate contrasts among different stimulus conditions, one-way repeated measures ANOVA was performed for each channel's group-wise AUC data separately with condition taken as the main effect. For each channel-wise ANOVA test, Greenhouse-Geisser correction was applied to the degrees of freedom when necessary. Post-hoc t-tests were performed with Bonferroni correction for pair-wise comparisons of three contrasts: Negative>Neutral, Negative>Positive and Positive>Neutral. All statistical analyses were conducted with MATLAB software. To localize anatomical regions depicting significant contrasts, t values of channels surpassing the Bonferroni correction were projected onto a standard brain template illustrating the anatomical locations with 10-20 EEG system (Figure 3).

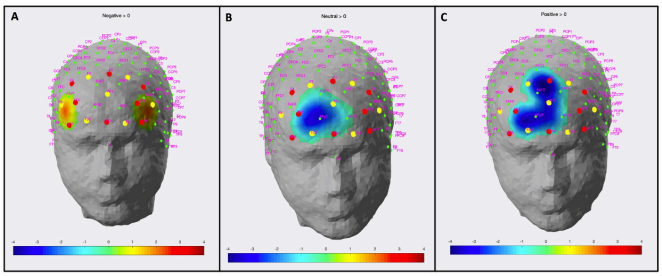

Figure 2. Statistical parameter maps of significant hemodynamic activation during A) negative, B) neutral and c) positive valence stimuli. Thresholded t-statistics of channels with significant activation are projected onto a standard head model for each condition. The color bars represent t values.

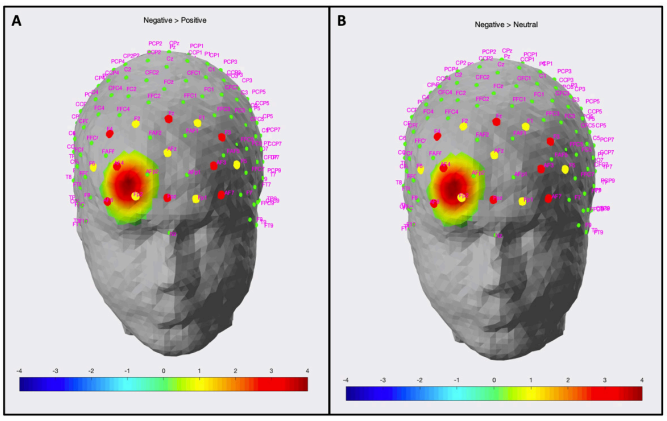

Figure 3. Statistical parameter maps depicting significant hemodynamic activity difference for A) Negative>Neutral, B) Negative>Positive contrasts. Thresholded t-statistics of channels with significant activation are projected onto a standard head model for each condition. The color bars represent t values.

RESULTS

Figure 2 demonstrates localization of statistically significant PFC activation during processing of a) negative, b) neutral and c) positive valence stimuli. Two channels (Channels 3 and 20), located bilaterally at the dorsolateral prefrontal cortex regions (DLPFC), demonstrated significant activation during presentation of negative stimuli ($p<0.05$). Three channels in frontopolar regions (Channels 12,14,16; Brodmann Area 10) demonstrated a significant hemodynamic deactivation with respect to the baseline during presentation of neutral stimuli ($p<0.05$). Four channels located in medial prefrontal cortex (MPFC) and DLPFC regions (Channels 9,10,12,16; Brodmann Area 9 and 10) showed hemodynamic deactivation during presentation of positive stimuli ($p<0.05$).

Results from channel specific one way repeated measures ANOVA analyses demonstrated statistically significant activation differences among the three stimulus conditions in two channels (Channel 16 [$F(2, 36) = 3.36$, $p = 0.046$] and Channel 19 [$F(2, 36) = 5.68$, $p = 0.0072$]). These two channels are located in the right hemispheric portion of Brodmann Area 46 and 10 and they probe right DLPFC and orbitofrontal cortex (OFC) regions. Bonferroni corrected post-hoc t-tests demonstrated that AUC parameters obtained during negative valence stimuli were significantly greater than those of both neutral and positive valence stimuli in these regions. No significant

hemodynamic activity difference was detected between neutral and positive valence stimuli conditions. Activity loci of channels surpassing the Bonferroni corrected t-score threshold are mapped onto standard head models for the following pairwise comparisons: Negative>Neutral and Negative > Positive contrasts in Figure 3. Table 1 demonstrates the extent and localization of significant hemodynamic activation during different conditions and contrasts.

Table 1. Extent and localization of significant hemodynamic activation during different conditions and contrasts

Condition	Number of Active Channels	Activity Localization
Negative Stimuli	2 (Channels 2,3)	Right and Left DLPFC
Neutral Stimuli	3 (Channels 12,14,16)	Frontopolar Area
Positive Stimuli	3 (Channels 9,10,12)	MPFC and Right DLPFC
Negative> Positive	2 (Channels 16,19)	OFC and right DLPFC
Negative>Neutral	2 (Channels 16,19)	OFC and right DLPFC

DISCUSSION

In the present study, we utilized a novel and emerging functional neuroimaging modality named fNIRS to explore the differential cortical hemodynamic activation patterns in the human PFC, during processing of negative, neutral and positive valence emotional stimuli. Our research question focused on whether different basic emotions had distinct hemodynamic correlates in the PFC region that could be identified with fNIRS. We addressed the spatial localization of cortical activation in PFC during presentation of neutral, negative and positive valence pictures which would induce pleasant and unpleasant emotions with a wearable, non-invasive and portable imaging system in a real-world setting. In the subsequent sections, the neuroanatomical and neurophysiological interpretation of the differential activation patterns are discussed in detail.

In our study, negative valence emotional stimuli induced higher hemodynamic activation in the right lateralized regions involving DLPFC and OFC regions, when compared to processing of neutral and positive emotional stimuli (Figure 3). This result is in accordance with the valence hypothesis which is based on the premise that left PFC regions are activated while processing positive valence emotional stimuli, while right PFC regions are activated in response to negative valence emotional stimuli [17,18]. Our study design involved a passive emotion inducing task which did not have any interfering cognitive tasks or self-monitoring requirements. Hence, we propose the resulting activation patterns would be solely induced by the valence of the visual stimuli. DLPFC and OFC have been considered to act as relay centers for integrating emotional, memory-related and sensory information. Such an integration of cognitive and emotional processes has also been stated to have a role in controlling emotional reactions and behavioral responses. Neural activity in OFC has also been related to computation of motivational and emotional value of the presented stimuli [19,20]. Hence, differential activity observed in these regions highlights the fact that our experimental stimuli induced the desired hemodynamic contrast in expected cerebral regions and could be used to test our hypotheses.

Negative valence stimuli induced significant increase in hemodynamic activity in both right and left DLPFC regions. DLPFC has a role in regulating both attention and emotion [20]. Significant activity of DLPFC during processing of negative stimuli might indicate that attention was being reflected towards the presented stimuli. DLPFC regions also regulate emotion through reappraisal of the presented stimuli. Thus, it is possible that the bilateral DLPFC activation occurred due to the cognitive demand for regulating emotion.

MPFC regions are involved in a variety of neural processes involving representation and maintenance of attentional demands during cognitive, motor and/or action monitoring tasks [21], while they also constitute a major hub of the default mode network (DMN). The DMN is a network of brain regions which produce coherent electrical and hemodynamic signals while the individual is at rest and not performing any attention demanding tasks. The hemodynamic activity and coherence of DMN regions are suppressed when the individual is engaged in these types of tasks [22]. The deactivation observed in MPFC regions, which include a major hub region of DMN might be related to suppression of this network due to reappraisal of the presented stimuli as an internal cognitive task. Similar to our study, Hoshi et al.

observed a significant decrease in BA10 during processing of pleasant stimuli [3]. However, we should note that previous studies which aimed at mapping functional anatomy of pleasant emotions with fNIRS, fMRI and PET modalities have revealed mixed results, which may have been due to variations in experimental stimuli and protocol [23,24]. George at al. also observed significant decreases in regional cerebral blood flow in a wide range of cortical regions, including subregions of the right PFC, during processing of transient happiness states [23]. Although the physiological interpretation of decreases in hemodynamic activity was not clearly discussed in the work of George et al., Geday et al. observed a similar decrease in regional cerebral blood flow in response to processing of emotional stimuli, and linked the significant decrease in cerebral blood flow to attenuation of default mode network function [24], which might also be one possible reason for the decrease in hemodynamic activity observed in our study during processing of neutral and negative valence stimuli.

Limitations

Recent studies which focused on gender differences in brain activity during emotional induction tasks, have suggested that women have a tendency to present stronger hemodynamic activity in response to negative valence stimuli, when compared to men [24,25]. However, we were unable to evaluate gender differences due to a limited cohort size. As an extension of this study, future work will involve collecting hemodynamic data with the same experimental protocol from a broader group of subjects, and it will include experimental designs which involve a variety of specific emotion-related tasks that are controlled for valence and arousal scores of each stimuli. To obtain more precise neural activity induced hemodynamic maps of emotional states, the impact of different levels of negative and positive valence emotional stimuli on the resulting spatiotemporal patterns of PFC hemodynamic activations, will also be thoroughly investigated with the presented optical imaging technology in future work. Functional mapping of the same stimuli will be repeated in a larger cohort of subjects, in order to test whether or not the loci of functional activation in response to the three stimulus conditions were biased with any statistical thresholding issues.

CONCLUSION

The presented study aimed to identify the PFC regions involved in the processing of basic emotions through analysis of the spatiotemporal patterns of hemodynamic activity, obtained with a mobile fNIRS system. The distinct cortical hemodynamic activity patterns associated with each emotional state show the promise of fNIRS technology for decoding and differentiating basic emotions objectively and in real time, for future applications.

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ORCID and Author contribution: SBE (0000-0001-6028-3477): Concept and Design, Data collection, Literature search, Analysis and Interpretation, Manuscript Writing, Critical Review.

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Investigation of the Antiepileptics on Levels of Vitamin D and Calcium

Antiepileptiklerin D vitamini ve kalsiyum düzeylerine etkisi

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ABSTRACT

Aim: We investigated the connection between D vitamin and factors such as the type of antiepileptic agent, patient age and gender.
Methods: This retrospective case-control study enrolled a total of 301 participants, including 141 epilepsy patients with (n= 120) without drug (n=21) regimens followed up in Alanya Alaaddin Keykubat University neurology outpatient clinic and 160 healthy individuals who applied to the neurology outpatient clinic for different reasons from January 2018 to January 2021. Demographics, detailed history, use of medications, duration of antiepileptic use, plasma 25-hydroxy Vitamin D and calcium levels were determined.
Results: The mean level of Vitamin D was 15.46 in the epilepsy group and 16.95 in the control group. Level of D Vitamine did not differ significantly by groups (p>0.05). There were no significant relationship regarding age and vitamin D levels in both groups while decreased Vitamin D levels were detected epileptic women. Vitamin D level was below 20 in 69.6% of healthy control group, 78.9% of carbamazepine users, 62.5% of lacosamide users, all lamotrigine users, 66.7% of levatiracetam users, and 72.4% of sodium valproate users. No significant connection were detected between levels of Vitamin D and the drug used (p>0.05) while a significant association was confirmed only between calcium levels and carbamazepine (p<0.05).
Conclusion: Vitamin D and calcium levels can be found to be low in antiepileptic users; however, except for the calcium levels in the carbamazepine group, this decrease does not constitute a significant difference.

Keywords: Epilepsy, antiepileptic, Ca, vitamin D

ÖZ

Amaç: Çalışmamızın amacı, farklı antiepileptik ajan kullanan epilepsi hastalarında D vitamini ve kalsiyum düzeylerini araştırmak ve D vitamini düzeyleri ile antiepileptik ajanın türü, hastanın yaşı ve cinsiyeti gibi çeşitli faktörler arasındaki ilişkiyi araştırmaktır.
Gereç ve Yöntem: Bu geriye dönük vaka-kontrol çalışmasına Alanya Alaaddin Keykubat Üniversitesi nöroloji polikliniğinde takip edilen ve 21 tanesi ilaç kullanmayan (ilaç kontrol) olmak üzere total 141 epilepsi hastası ve Ocak 2018-Ocak 2021 tarihleri arasında nöroloji polikliniğine farklı nedenlerle başvuran 160 sağlıklı birey (sağlıklı kontrol) olmak üzere toplam 301 katılımcı alındı. Demografi, Tüm katılımcıların ayrıntılı öyküsü, ilaç kullanımı, anti-epileptik kullanım süresi, plazma 25-hidroksi D vitamini ve kalsiyum düzeyleri saptandı.
Bulgular: Ortalama D vitamini düzeyi epilepsi grubunda 15.46, kontrol grubunda 16.95 idi. Gruplara arasında D vitamini düzeyi açısından anlamlı farklılık göstermedi (p>0.05). Her iki grupta da yaş ve D vitamini düzeyleri arasında anlamlı bir ilişki bulunmadı ve epilepsi grubundaki kadınlarda D vitamini düzeyleri istatistiksel olarak anlamlı derecede düşüktü. Sağlıklı kontrol grubunun %69,6'sında, karbamazepin kullanıcılarının %78,9'unun, lakozamid kullanıcılarının %62,5'inin, tüm lamotrijin kullanıcılarının %66,7'sinin ve sodyum valproat kullanıcılarının %72,4'ünün D vitamini düzeyi 20'nin altındaydı. D vitamini düzeyi ile kullanılan ilaç arasında belirgin fark yoktu (p>0.05). Sadece kalsiyum düzeyi ile karbamazepin arasında anlamlı bağlantı vardı (p<0.05).
Sonuç: Antiepileptik kullananlarda D vitamini ve kalsiyum düzeyleri düşük bulunabilir; ancak karbamazepin grubundaki kalsiyum düzeyleri dışında bu düşüş anlamlı bir fark oluşturmamaktadır.

Anahtar Kelimeler: Epilepsi, antiepileptik, Ca, D vitamini

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Introduction

Epilepsy is seen in 0.5-0.8% of cases worldwide. Studies have shown that drugs can keep up to 70% of patients seizure-free, even with monotherapy. There are different types of epilepsy as partial, generalized, absence, tonic, clonic, tonic-clonic,atonic and myoclonic. Although each epilepsy category has its own drug choice, phenytoin, phenobarbital, carbamazepine, sodium valproate, levetiracetam and lamotrigine are the mostcommonly used drugs [1]. Antiepileptic drugs (AED) such as carbamazepine and phenytoin stimulate the Vitamin D catabolism by inducing specific liver enzymes leading to hypocalcemia and secondary hyperparathyroidism by decreasing Vitamin D levels [2-4].

Despite no association found between serum Vitamin D and long-term treatment with phenobarbital, carbamazepine, sodium valproate, and levetiracetam [5], a study of 111 patients taking antiepileptics showed that 24 patients (22%) had Vitamin D failure and 45 patients (41%) had Vitamin D deficiency. Vitamin D deficiency [6]. Another study conducted with 198 patients showed that 124 patients had Vitamin D deficiency (62.6%) [7]. Although there are different results about whether antiepileptics cause Vitamin D deficiency, there is no clearity in the literature. Also the effect of the course of epilepsy itself on Vitamin D is still interesting research area.

Our aim was to evaluate Vitamin D and total calcium (Ca) status in epilepsy patients taking antiepileptics while also determining the link between levels of Vitamin D and the type of antiepileptic used, patient age and gender.

Materıal and Methods

This study enrolled a total of 291 participants, including 141 epilepsy patients followed up in AlanyaAlaaddinKeykubat University neurology outpatient clinic and 150 healthy individuals who applied to the neurology outpatient clinic for different reasons from January 2018 to January 2021. This study, designed as a retrospective case-control study (Ethics Committee of AlanyaAlaaddinKeykubat University with the decision no. 14-05 of September 22, 2021). Demographics, detailed history, use of medications, duration of antiepileptic use, plasma 25-hydroxy Vitamin D and calcium levels of all participants were recorded. The differences between the epilepsy group and the control group were compared statistically. Inclusion criteria were as follows: The study group included epilepsy patients aged 18-65 years, who received monotherapy with the same antiepileptic agent for at least 1 year. The healthy group included individuals in the same age group who were not diagnosed with epilepsy and did not receive antiepileptic treatment (n= 150) while the drug control group included epilepsy patients without a current drug regimen (n= 23). Exclusion criteria were as follows: Individuals with a history of severe central nervous system disease, intracranial mass, surgery, trauma, dementia; individuals with chronic liver and kidney disease, alcohol and substance abuse, and malignancy; individuals with endocrinological diseases such as hypothyroidism, hyperthyroidism, hypoparathyroidism; individuals with a history of gout, and individuals who took calcium and/or Vitamin D supplements were excluded from the study.

Statistical Analysis

Our analyzes were performed with the SPSS 21.0 program at a 95% confidence level. The coefficients of kurtosis and skewness from the measurements were between +3 and -3, which was considered sufficient for a normal distribution. Intergroup comparisons were made through independent 2-sample T-test and chi-square test. A p value less than 0.05 was deemed statistical significance.

Results

Demographic features of patients with epilepsy and healthy controls

In our study, the gender distribution was 36.9% men and 63.1% women in the epilepsy group and 27.5% men and 72.5% women in the control group. There was no significant difference in gender distribution between the groups ($p>0.05$). The rate of participants with vitamin D level below 20 was 71.6% in the epilepsy group and 63.8% in the healthy control group. There was no significant relationship between the group and Vitamin D levels ($p>0.05$). The rate of participants

with calcium levels between 8.6-10 was 88.7% in the epilepsy group and 91.3% in the healthy control group. There was a significant relationship between the group and calcium level (p<0.05). The rate of participants with 8.5 and below is higher in the epilepsy group, and the rate of participants between 8.6-10 and over 10 is higher in the healthy control group (Table 1a).

Table 1a: Demographic features of participants

		Groups				Chi-square	p
		Epilepsy		Healthy Control			
		N	%	n	%		
Age	<50 age	111	78,7	96	60,0	12,234	,000*
	>51 age	30	21,3	64	40,0		
Ort±ss		36,29±16,35		44,36±14,10			
Sex	Men	52	36,9	44	27,5	3,036	0,081
	Women	89	63,1	116	72,5		
25_oh_vitd_level	>20	101	71,6	102	63,8	3,319	,190
	20-29	27	19,1	45	28,1		
	>30	13	9,2	13	8,1		
Ca level	<8,5	16	11,3	10	6,3	5,505	,050*
	8,6-10	125	88,7	146	91,3		
		0	0,0	4	2,5		

*p<0.05: Indicates a significance level of 0.05

Relationships Between Vitamin D Levels and Antiepileptics Used Compared With Control Patients Without Drug

Vitamin D level was below 20 in 69.6% of drug control group, 78.9% of carbamazepine users, 62.5% of lacosamide users, all lamotrigine users, 66.7% of levetiracetam users, and 72.4% of sodium valproate users. There was no significant relationship between Vitamin D level and the drug used (p>0.05) (Table 1b).

Relationships Between Calcium Level and the Drug Used Compared With Control Patients Without Drug

Calcium level was between 8.6-10 mg/dl in 95.7% of drug control group, 63.2% of carbamazepine users, 87.5% of lacosamide users, all lamotrigine users, 94.7% of levetiracetam users, and 82.8% of sodium valproate users. There was a significant relationship only between calcium level and carbamazepine (p<0.05). The use of carbamazepine is highest in patients with a calcium level of less than 8.5 mg/dl and the use of levetiracetam is highest in patients with a calcium level of 8.6-10 (Table 2).

Table 1b: Relationship Between Vitamin D Levels and AED Used Compared With Control Patients Without Drug

		25_oh_vitd_level (ng/dl)						Chi-square	P
		below 20		20-29		30 and over			
		n	%	n	%	n	%		
AED	Drug Control group	16	69.6	4	26.1	1	4.3	6.176	.794
	Carbamazepine	15	78.9	2	10.5	2	10.5		
	Lacosamide	5	62.5	2	25.0	1	12.5		
	Lamotrigine	7	100.0	0	0.0	0	0.0		
	Levetiracetam	38	66.7	13	22.8	6	10.5		
	Sodium valproate	21	72.4	4	13.8	4	13.8		

*p<0.05: Indicates a significance level of 0.05

Table 2: Relationship Between Calcium Levels and the AED Used Compared With Control Patients Without Drug

		calcium level				Chi-square	P
		8.5 and below		8.6-10			
		N	%	N	%		
AED	Control group	1	4.3	20	95.2	13.263	.009*
	Carbamazepine	7	36.8	12	63.2		
	Lacosamide	1	12.5	7	87.5		
	Lamotrigine	0	0.0	7	100.0		
	Levetiracetam	3	5.3	54	94.7		
	Sodium valproate	5	17.2	24	82.8		

*p<0.05: Indicates a significance level of 0.05

Intergroup comparison of Vitamin D and calcium levels Compared With Control Patients Without Drug

The average Vitamin D level was 15.46 in the epilepsy group and 16.95 in the drug control group. Vitamin D level did not differ significantly by groups (p>0.05). No significant relationship was found between age and vitamin D levels in both groups, and Vitamin D levels were statistically significantly lower in women in the epilepsy group (p<0.05).

Discussion

Vitamin D has a primary function in calcium and bone metabolism. In addition, recent studies indicated that it plays a critical role in diabetes mellitus, autoimmune diseases, obesity and cardiovascular diseases. Vitamin D2 (ergocalciferol) obtained

only from plant-derived foods by the exogenous route and vitamin D3 (cholecalciferol) synthesized in the skin by the endogenous way, with the help of UV radiation, as well as foods of animal origin. Both forms are converted in the liver to 25-OH cholecalciferol, the main circulating form of vitamin D. 25-OH cholecalciferol is catabolized by enzymes in the cytochrome P450 enzyme system (CYP24, CYP 3A4). It has been shown that antiepileptics may cause Vitamin D deficiency andbone-mineral metabolism such as hypocalcemia, hypophosphatemia, secondary osteoporosis, osteomalacia, and rickets[8,9]. To the best of ourknowledge, there is not enough data in the literature comparing the effects of antiepileptics on Vitamin D and calcium levels in patients receiving monotherapy. In our study, we compared 5 different antiepileptic agents in patients receiving monotherapy with the control group to investigate their effects on levels of Vitamin D and calcium. Antiepileptics - including phenytoin, carbamazepine, phenobarbital - are metabolized in the liver and cause cytochrome P450 enzyme induction, thereby increasing Vitamin D metabolism by upregulating the enzymes that convert Vitamin D to its inactive form. Consequently, the Vitamin D deficiency is thought to indirectly cause secondary hyperparathyroidism, hypocalcemia and, therefore, loss in bone mineral densitometry [10-12]. In a study on 596 epileptic patients, 54% of Vitamin D deficiency was observed in enzyme-inducing antiepileptics [13]. In accord with this, in our study, in patients using carbamazepine, 78.9% had Vitamin D deficiency and 63.2% had hypocalcemia. Also, in a recent on 58 epileptic patients in the young adult age group, Kulak et al. suggested that the loss of bone density resulting from the use of antiepileptics may be due to Vitamin D deficiency indirectly caused by antiepileptics, as well as the direct increase of bone turnover by antiepileptics [14]. The cross-sectional study by Ferhat et al. found low Vitamin D levels in 50% of patients using antiepileptics but did not find any correlation with bone mineral density measurements [15]. Lamotrigine is an antiepileptic that does not alter the cytochrome P450 system [16] and it seems that its relationship with Vitamin D is not due to the liver, but relate to its pharmacological effects. Lamotrigine blocks sodium and calcium channels [17] similar to Vitamin D. Hence, it is reasonable that lamotrigine may potentiate its effect while Vitamin D supplementation may be an effective strategy in controlling seizures in patients using lamotrigine. Several animal studies have revealed that Vitamin D increases the effect of many antiepileptics, in addition to its own anticonvulsant effect. For instance, several studies have shown that Vitamin D potentiates the effects of traditional drugs such as phenytoin, valproate, carbamazepine, as well as second-generation antiepileptics such as lamotrigine and oxcarbazepine. A study using an experimental epilepsy model in rats showed that Vitamin D supplementation increased the effect of lamotrigine on seizure control and cognition [19]. In our study, all patients using lamotrigine had Vitamin D levels below 20 ng/dl, and calcium levels were normal. Valproic acid (sodium valproate) is an antiepileptic frequently preferred in the first-line treatment of both partial and generalized epilepsy, acting by blocking voltage-dependent sodium channels without inducing enzymes in the liver. Long-term use of valproic acid has been shown to result in loss of bone mineral densitometry in both children and adults; however, there are conflicting results in the literature regarding its effect on calcium and Vitamin D metabolism [2,20]. A study suggested that the effect of valproic acid on bone metabolism was due to increased urinary calcium and phosphorus excretion, leading to renal tubular dysfunction [19]. In addition to the use of antiepileptics, there are also other factors that might affect Vitamin D levels, such as geographical features, exposure to sunlight, gender, nutrition in Vitamin D deficiency. Based on this, we created a control group living in the same geographical region, having similar ages and gender ratios in our study. Participants consisted of individuals living in the same geographical region and the same climate. In the literature, it is emphasized that use of multiple antiepileptics and long-term antiepileptic therapy are important risk factors for the development of Vitamin D deficiency. In our study, almost all patients who used the same drug for at least 1 year and received monotherapy. Current literature is scarce of the possible effects of deficient levels of Vitamin D on epilepsy pathogenesis regardless of the use of antiepileptics. Hence it is still unclear whether Vitamin D has a direct epileptogenic effect or

show the reverse pattern. Experimental studies investigating the role of Vitamin D in epilepsy has shown that intrahippocampal and intravenous Vitamin D supplementation increases the seizure threshold especially in mice. In support of this view, another study showed an increased susceptibility to seizures with the elimination of the Vitamin D receptor in transgenic mice [9]. In a pilot study in patients with Vitamin D deficiency and drug-resistant epilepsy, Christian et al. showed that Vitamin D supplementation resulted in significantly reduced number of seizures [20]. Although our current results support the hypothesis that epilepsy itself may cause Vitamin D deficiency rather than antiepileptics, a definitive conclusion can only be made with the data of the epileptic patient population who do not use antiepileptics. However, since this population is difficult to find and its planning will cause ethical problems, it seems difficult to reach a definite conclusion. Considering all of these evidences, our results draw attention to the primary role of epilepsy at the hypothetical level despite our data of low calcium levels in carbamazepine treated groups.

Limitations: The limitation of our study is the low sample size among the drug groups in antiepileptic users. Furthermore, the fact that the participants' exposure to sunlight during the day was not questioned can also be considered as a minor weakness of our studyalthough this effect will be minimal since patients in the same season and in the same geographical region were selected. Additionally, small sample size in evaluating the effect in the population that does not use antiepileptics should be considered as a relative limitation due to ethical concerns. We believe that future longitudinal antiepileptic studies, in which vitamin D levels are measured before and after treatment, will shed some light on this limitation.

Conclusion

Our study shows that decreased levels of Vitamin D and calcium levels can be found in antiepileptic users; however, except for the low calcium in the carbamazepine group, this alterationsdoes not make a significant difference compared to the control group and it is too early to come to a definitive conclusion without replicating the same results in larger treatment cohort.

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Prevalence of perioperative hypothermia and predisposing factors in a children's hospital

Bir Çocuk Hastanesinde Perioperatif Hipotermi Prevalansı ve Predispozan Faktörler

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ABSTRACT

Aim: Perioperative hypothermia is more common in pediatric patients than in adult patients due to increased body surface area/weight ratio and limited subcutaneous fat deposits. Therefore, active and passive warming techniques are used more frequently in the surgeries applied to pediatric patients. This study presents the prevalence of perioperative hypothermia and the predisposing conditions for perioperative hypothermia in pediatric orthopedic surgeries in which active and passive warming techniques are applied.

Methods: This cross-sectional, descriptive, and observational study included 102 children admitted to the pediatric orthopedic clinic of a children's hospital. Temperature measurements were made with a calibrated infrared tympanic thermometer in all cases while they were waiting in the service room, when they entered the operation theater, when they left the operation theater and when they left the postoperative care unit. Their demographic data, hemogram and thyroid hormone parameters, preoperative fasting times related to the procedure and temperature were recorded. Also, the humidity and temperature values of the operating theater, the operation type performed, the duration of the operation, the time spent in the operating theater and the recovery time from anesthesia, were all recorded in their follow-up forms. Data analysis was done using the SPSS V21.0 and was conducted at a 95% confidence interval.

Results: Hypothermia was observed in 20.58% of 102 patients included in the study. Predisposing factors for perioperative hypothermia included the fact that the patient had a diagnosis of concomitant cerebral palsy, the patient's body temperature was low in the service area, low temperature and humidity values in the operating theatre and staying in the operating theatre for a prolonged period of time.

Conclusion: Although active and passive warming techniques are applied during the operation, perioperative hypothermia was observed in 20.58% of pediatric patients who underwent the orthopedic operation. Consideration of predisposing factors together with active and passive warming techniques may reduce the incidence of perioperative hypothermia.

Keywords: Hypothermia, orthopedic surgery, risk factors

ÖZ

Amaç: Perioperatif hipotermi, artmış vücut yüzey alanı/ağırlık oranı ve sınırlı cilt altı yağ depoları nedeniyle pediatrik hastalarda yetişkin hastalara göre daha sık görülür. Bu nedenle pediatrik hastalara uygulanan cerrahilerde aktif ve pasif ısıtma teknikleri daha sık kullanılır. Bu çalışmada aktif ve pasif ısıtma tekniklerinin uygulandığı pediatrik ortopedik cerrahilerde perioperatif hipotermi sıklığının ve perioperatif hipotermi için predispozan durumların belirlenmesi amaçlanmıştır.

Yöntemler: Bu kesitsel, tanımlayıcı ve gözlemsel çalışmaya bir çocuk hastanesinin pediatrik ortopedi kliniğine başvuran 102 çocuk dahil edildi. Tüm olguların servis odasında beklerken, operasyon odasına girerken, operasyon odasından çıkarken, postoperatif bakım ünitesinden ayrılırken kalibrasyonu yapılmış infrared timpanik termometre ile ateş ölçümleri yapıldı. Hastaların demografik verileri, hemogram ve tiroid hormon parametreleri, prosedürle ilgili olarak operasyon öncesi açlık süreleri ve ateşleri kaydedildi. Ayıca operasyon odasının ısı ve nem değerleri, yapılan operasyon, operasyon süresi, operasyon odasında geçirdiği süre, anesteziden derlenme süresi gibi veriler olgu takip formlarına kaydedildi. Verilerin analizi SPSS 21.0 ile yapıldı ve %95 güven aralığında çalışıldı.

Bulgular: Çalışmaya dahil edilen 102 hastanın %20,58'inde hipotermi gözlendi. Perioperatif hipotermi için predispozan faktörler; hastanın eşlik eden serebral palsi tanısının olması, hastanın serviste vücut ısısının düşük olması, operasyon salonunun ısı ve nem değerlerinin düşük olması, operasyon salonunda uzun süre kalınması olarak belirlendi.

Sonuç: Operasyon sırasında aktif ve pasif ısıtma teknikleri uygulanmasına rağmen ortopedik cerrahi uygulanan pediatrik hastaların %20,58'inde perioperatif hipotermi izlendi. Aktif ve pasif ısıtma teknikleri ile birlikte predispozan faktörlerin dikkate alınması perioperatif hipotermi sıklığını azaltabilir.

Anahtar kelimeler: Hipotermi, Ortopedik cerrahi, Risk faktörleri

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Introduction

Since humans are homeothermic creatures, they need to keep their internal body temperatures constant within certain ranges. Keeping the internal body temperature constant within the 0.2°C variation range (threshold range) is achieved by using various positive and negative feedback mechanisms [1]. In addition to the fact that behavioral regulation, which is the first thermoregulatory response, cannot be performed when patients are unconscious and/or paralyzed during general anesthesia applications, body temperature is also lost because of several other factors. These include redistribution of the body's core temperature, decreases in metabolic rates and heat losses from the body surface through radiation, convection, conduction and evaporation [2]. Aside from these, volatile and non-volatile anesthetics, neuraxial anesthesia and analgesia, and opioids also cause deterioration in the response of the hypothalamus that is necessary for thermoregulation and therefore leads to temperature losses below 36°C in anesthetized patients [2].

A decline in body temperature that goes below 36°C under anesthesia and/or during surgery is called perioperative hypothermia [3], which is common namely in pediatric patients [4]. The reported common effects of perioperative hypothermia include postoperative tremor, coagulopathy, bleeding, cardiac dysfunction, delayed anesthesia recovery and wound infection, resulting in a prolonged hospital stays [5]. ERAS (Enhanced Recovery After Surgery) protocols also recommend avoiding hypothermia during the intraoperative period [6]. Therefore, to prevent perioperative hypothermia, active (infrared lamps, electric blankets, warm air blowing systems, heating of intravenous fluids, humidification, and heating of anesthetic gases) and passive (isolation of exposed areas by wrapping cotton, use of closed or semi-closed anesthesia breathing systems), and low flow anesthesia application warming techniques are recommended [7].

This study presents the prevalence of perioperative hypothermia and the predisposing conditions for perioperative hypothermia in pediatric orthopedic surgeries, in which active and passive warming techniques were applied.

Materials and methods

This cross-sectional, descriptive and observational clinical study was evaluated and approved by the clinical research ethics committee (decision number: 2020/16-07; date: 19/11/2020; protocol number:396). All parameters were applied in accordance with the Declaration of Helsinki and EU rules. Our study is a prospective, single-center study designed for cases involving 102 children admitted to the pediatric orthopedic clinic of a children's hospital. Patients and parents were informed of the study and those who gave their consent were included in the study. During the COVID-19 pandemic, all patients hospitalized for orthopedic surgery underwent PCR testing and elective surgery was planned exclusively for patients with negative PCR test results. All necessary precautions were taken to protect the operating theater staff from possible infection of the patients, who were given general anesthesia. The study included patients who were scheduled to have surgeries in the pediatric orthopedic clinic from June 1, 2020 to January 31, 2021, in the operating theater of our hospital. The study evaluated 118 cases in which the patients were admitted between these dates, and 102 cases were ultimately included. These patients met the criteria for inclusion if they did not have any focus of infection, had been scheduled to undergo orthopedic procedures under anesthesia, and had provided their consent to participate in the study.

Inclusion criteria:

a. The patients aged 0 to 18 planned to undergo orthopedic procedures under anesthesia.

b. No symptoms related to COVID-19.

c. No recent family history of COVID-19.

Exclusion or withdrawal criteria:

a. Patients with an abscess-like focus of infection that may cause high fever or disrupt thermoregulation.

b. Cases not willing to have their body temperature measured during the study.

c. Cases whose surgical plan was abandoned for

other reasons.

Temperature measurements of the cases were performed using the calibrated infrared tympanic thermometer. All patients were premedicated with an oral midazolam dose of 0.5 mg/kg (max. 20 mg) 30 minutes before the operation. Such preoperative demographic data as gender, age, body weight, height, Body Mass Index (BMI), any concomitant cerebral palsy, hemogram in addition to thyroid hormone parameters, preoperative fasting times related to the procedure, humidity and temperature values in the operating theater and the operation performed, were all recorded in their follow-up forms. We also added the temperatures taken by a tympanic thermometer in four different periods (in the service room, upon operating theatre entrance, while operating theater exit and upon postoperative care unit exit) to these forms. Standard monitoring was performed in the operating theater. Anesthesia induction was performed on the patients with 8% sevoflurane, 4l/min oxygen/air mixture. Vascular access was established through the peripheral vein. Fentanyl (2 µg/kg), rocuronium (0.6 mg/kg) were administered. The exposed areas were isolated by wrapping them with cotton. The patient was intubated with a suitably sized endotracheal tube. Anesthesia was maintained with remifentanil as 0.2-0.5 µg/kg/min and 2% sevoflurane with a BIS value between 40-60 (Medtronic Covidien 2-Channel Monitor System). Isotonic crystalloid solution warmed to 37 0C (Astoflo Plus; Stihler Electronic, Stuttgart, Germany) and given at 10ml/kg/h. An underbody warming blanket was used actively during the operation. Intravenous paracetamol (10mg/kg) was administered for postoperative analgesia.

Data analysis was done using the SPSS v.21 and was studied at a 95% confidence interval. The kurtosis and skewness coefficients were examined to determine a match between the measurements and the normal distribution. Kurtosis and skewness values were obtained from a scale in the normal distribution range of +3 to -3. When the temperature measurement values were examined, it was seen that the kurtosis and skewness coefficients of each score ranged from -3 to +3, which was analyzed using the repeated ANOVA test. The t-test and ANOVA tests were used to analyze the differences in the measurements according to the categorical variables. While the t-test was used to evaluate demographic variables with two groups, the ANOVA test was used to assess the variables grouped in k (k > 2). While the relationship between quantitative variables with normality was analyzed with the Pearson correlation test, the relationship between those without was analyzed with the Spearman correlation test. The multivariate logistic regression model was used to predict predisposing factors for hypothermia.

Results

Perioperative hypothermia was observed in 21 of 102 patients (20.58% prevalence of hypothermia). The demographic and operative data of patients (female: 39.2%; male: 60.8%) with hypothermia and normothermia are presented in Table 1. Of the 102 patients included in the study, one was a newborn and eight were infants; it was determined that 62 of the patients had cerebral palsy.

Table 1: Demographic data and operational characteristics of the patients

Variables	Hypothermia (n=21)	Normothermia (n=81)	p
Age (month)	71.7±53.4	83.2±56.5	0.400
Gender (n) (Female/Male)	7/14	33/48	0.536
ASA classification (I/II/III)	4/0/17	34/2/45	0.034*
Weight (kg)	18 (4-65)	20 (5-69)	0.167
Height (cm)	106±29.9	116±25	0.154
BMI (kg/m-2)	15.9 (11.9-25.6)	16.4 (12.1-22.5)	0.094
Concomitant cerebral palsy (n)	17 (81%)	45 (55.6%)	0.034*
Body temperature in the orthopedics service room (^{0}C)	36.5±0.33	36.7±0.28	0.010*
Operating theater humidity (%)	34.7±8.4	43.1±9.9	0.001*
Fasting time (hour)	9±1.92	8.1±1.59	0.047*
The duration of the operation (min)	53 (18-198)	33 (17-125)	0.003*
The time spent in the operating theater (min)	62 (26-208)	42 (22-132)	0.003*
Recovery time from anesthesia (min)	4.0±1.34	4.06±1.56	0.869

ASA, American Society of Anesthesiologists; BMI, body mass index. Results were presented as mean ± SD, n, %, median (min-max). * p<0.05

Of the operations performed on the patients under general anesthesia, 62 were release operations

for patients with cerebral palsy, 13 were burned contractures, 10 were incisions operations for polydactyly and syndactyly, six triggered finger release, five were foreign body excision, three were achiloplasty, two were ganglion cyst excision and one was a Baker cyst excision. The operations performed are presented in Table 2.

Table 2. Types of operations performed under general anesthesia

Type of operations, n (%)	
Release operations for patients with cerebral palsy	62 (60.8)
Burned Contracture Opening	13 (12.7)
Incision for Polydactyly and Syndactyly	10 (9.8)
Release for Trigger Finger	6 (5.9)
Foreign Body Excision	5 (4.9)
Achiloplasty	3 (2.9)
Ganglion Cyst Excision	2 (1.9)
Baker's Cyst Excision	1 (1.0)

Temperature data measured from patients in four different periods were examined. The number of patients with hypothermia was observed as i) service room 1 (0.98%), ii) operating theatre entrance 3 (2.94%), iii) operating theatre exit 21 (20.58%) and postoperative care unit exit 6 (5.88%).

While the mean body temperature measurement in the orthopedic service room was the highest (mean: 36.66°C), it significantly decreased as they were taken to the operating theater (mean: 36.55°C), continued to decrease in the operating theater, and their body temperature measurement upon leaving the operating theater was the lowest (mean: 36.22°C). It was observed that there was a significant increase in the measurements of the patients taken to the postoperative care unit after awakening (mean: 36.41°C). The most significant decrease in body temperature occurred in the operating theater. The change in temperature measurements of the patients whose measurements were made at four different times was statistically significant, as shown with the repeated ANOVA test ($p<0.05$). Figure 1 presents the patient's temperature changes at four different times.

Predisposing conditions for hypothermia

When the predisposing conditions related to this decrease in body temperature were examined, we found no statistically significant relationship among variables such as gender, age, body weight, height, BMI, hemogram, thyroid hormone parameters, operating theater temperature and postoperative body temperature.

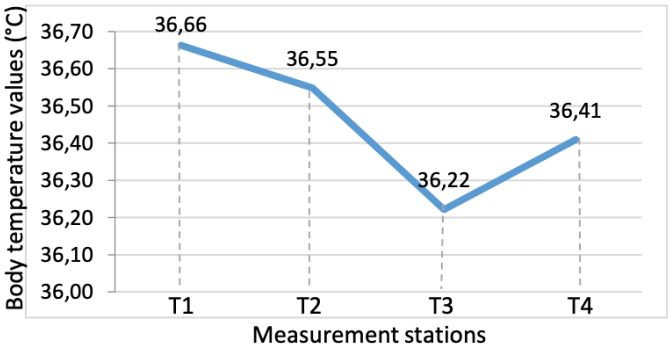

Figure 1: Average body temperature values of measurement stations. Note that; T1, T2, T3, and T4 stand for the service room, operating theatre entrance, operating theatre exit and postoperative care unit exit, respectively.

In the logistic regression analysis, concomitant cerebral palsy, body temperature in the orthopedics service room, operating theater temperature, operating theater humidity and the time spent in the operating theater, were found statistically significant as an independent risk factor for perioperative hypothermia (Table 3).

Table 3. Risk Factors for Perioperative Hypothermia (Binary Logistic Regression Analysis)

	B	SE	Wald	P	OR	95% CI
Concomitant cerebral palsy	2.264	0.872	6.738	0.009*	9.622	1.741-53.178
Operating theater temperature (°C)	-0.691	0.374	3.422	0.064	0.501	0.241-1.042
Operating theater humidity (%)	-0.178	0.051	12.179	0.000*	0.837	0.757-0.925
Body temperature in the orthopedics service room (°C)	-5.651	1.675	11.381	0.001*	0.004	0.000-0.094
The time spent in the operating theater (min)	0.048	0.017	7.948	0.005*	1.049	1.015-1.084
Constant	222.494	63.508	12.274	0.000*		

B, coefficient value; SE, standard error of coefficient; OR, odds ratio. *: $p<0.05$.

Discussion

Perioperative hypothermia is a common and preventable side effect. Therefore, the Surgical Care Improvement Project (SCIP) also recommends active warming, regardless of the patient's body temperature [8]. However, active warming is not widely used in most operating theater and only a small number of patients are actively warmed. As only pediatric patients are operated on in our operating theater, we apply active warming with underbody warming blankets and heating of intravenous fluids, passive warming with wrapping cotton dressing, and low-flow anesthesia applications on all operating tables.

While the incidence of perioperative hypothermia for our patient group was 20.58%, in the study of Yi et al., which is a 28-centered national study, the incidence of hypothermia in patients only 14.2% of whom applied active warming, was 17.8% in the 1 hour following the induction of anesthesia, 36.2% in the 2nd hour, 42.5% in the 3rd hour, and 44.1% in the 4th hour [9]. We think that the ≤90-minute surgical procedure time of our patients helped them maintain their normothermia, thus resulting in a lower incidence of hypothermia.

We measured the body temperature of the patients in the orthopedic service room, operating theater entrance, operating theatre exit and postoperative care unit exit. We found that there were significant changes in these four different periods ($p<0.05$). While the mean temperature of the patients in the service room was the highest (mean: 36.66°C), the postoperative temperature (mean: 36.22°C) was the lowest. There was a significant increase in the body temperature of the patients in the postoperative care unit (mean: 36.41°C). Some factors also add up to the heat loss, such as taking off the patient's clothes for surgery, transferring to the operating theater and waiting in the theater corridors, which cause a significant amount of heat loss. During this period, thermoregulatory vasoconstriction is triggered, peripheral temperature decreases and the temperature gradient increases. When the patient is brought to the operating theater, heat loss continues. There is a linear relationship between operating theater temperature and cutaneous heat loss. Because a temperature increase of approximately 1°C reduces cutaneous heat loss by 10%, the American Society of Perianesthesia Nurses (ASPAN) guidelines recommend that the operating theater temperature should be in the range of 20 to 25°C [10]. However, the recommended operating theater relative humidity values are different. While American Society of Heating and Refrigeration (ASHRAE) standards recommend that the relative humidity be between 20% and 60%, UNE 100713 recommends that the relative humidity should be between 45% and 55% [11]. The fact that the relative humidity values in the operating theater are not at normal values facilitates the proliferation of bacteria [12]. During the study, the temperature values of the operating theater ranged from 19.20°C to 23.80°C, while the relative humidity values of the operating theater ranged between 20.00% and 60.00%.

Skin disinfection solutions used before the patient's surgical incision are also effective in perioperative hypothermia. When a surgical incision is made on the patient, there is heat loss caused by evaporation resulting from the incisions, which is related to factors such as the size of the surgical field, the airflow in the operating theater, the humidity level and the temperature of the operating theater. Cold intravenous and irrigation fluids used for the patient are also among the causes of heat loss, depending on the amount [13]. In our study, to prevent this heat loss, we give all infusions by warming them with a blood-serum warming device.

Kang et al. [14], observed that when active heating and applications to prevent heat loss recommended by ASPAN were applied together in patients undergoing upper extremity surgery, body temperature was maintained, and there was no decrease in body temperature measured in the waiting room before the operation.

While hypothermia was observed in 45 of the cerebral palsy patients (62 patients), hypothermia was not observed in 17 ($p=0.034$). The fact that children with cerebral palsy have less muscle and fat tissue due to malnutrition and dysfunction of the hypothalamus, which provides thermoregulation, makes these children more prone to hypothermia development [15].

There is a negative relationship between

hypothermia and body temperature measurement of the patients in the service room (B=-5.651). The lower the patient's body temperature measurement in the service room, the higher the risk that the body temperature change in the operating theater will be ≥ 0,3°C. Studies have shown that low baseline temperature is a predisposing factor for perioperative hypothermia and that elevated body temperature before anesthesia can prevent intraoperative hypothermia [16,17].

Since the training and research hospital where we conducted the study is located at sea level, it is highly affected by humidity in the external environment. During the study, the humidity values of the operating theater ranged between 20% and 60%. In this study, it was observed that there was a negative relationship between operating theater humidity and perioperative hypothermia. We think that the decrease in heat loss from the patient's skin through evaporation from the operating area with the increase in the humidity level in the operating theater is due to the laws of physics.

We observed that the development of perioperative hypothermia of the patients included in the study increased proportionally with the duration of stay in the operating room. Sahutoglu et al. [4], reported that an increase in the duration of surgery in minor operations, such as circumcision, increases the risk of hypothermia.

Limitations: The limitation of this study is that it included a small patient population and different surgeries were applied to the patients.

Conclusion: The prevalence of perioperative hypothermia is high in pediatric patients undergoing orthopedic surgery. There are some predisposing conditions for perioperative hypothermia, which can be listed as the presence of concomitant cerebral palsy, low operating theater temperature, low operating theater humidity, low body temperature in the service room, as well as prolonged time spent in the operating theater. Paying attention to these predisposing conditions would reduce the incidence of perioperative hypothermia.

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The dose-dependent antiangiogenic potential of apixaban: an experimental outlook

Apıxaban'ın Doza Bağlı Antianjiyojenik Potansiyeli: Deneysel Bir Bakış

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ABSTRACT

Aim: Direct oral anticoagulants (DOACs) are good alternatives to conventional medical regimens for the treatment and prevention of thromboembolism. Apixaban is one of the more popular variations of these newly developed drugs. Aside from its anticoagulant potential, possible cellular effects remain a topic for future studies. The object of this study was to investigate the possible antiangiogenic effects of apixaban in the chorioallantoic membrane (CAM) model.
Method: Drug pellets were prepared at 10-4, 10-5, and 10-6 M concentrations of apixaban and were placed in the chorioallantoic membrane on the fourth day of egg incubation. On the eighth day, all vascular densities of the membranes were compared with a 10-6 M concentration of bevacizumab, which is a known monoclonal, humanized, vascular endothelial growth-factor inhibitor.
Results: We find that a 10-4 M concentration of apixaban has strong antiangiogenic potential similar to that of bevacizumab. However, there was moderate antiangiogenic potential at a lower dose of apixaban (10-5 M, 10-6 M). A comparison of the higher doses of antiangiogenic potential (10-4 M concentration) with lower doses of apixaban (10-5 M, 10-6 M) revealed significant statistical differences ($p < 0.05$).
Conclusion: Our results indicate that a high dose of apixaban has strong antiangiogenic potential. The exact mechanism of this effect remains unknown. These pilot results should be confirmed with further studies to obtain an updated look at DOACs.

Keywords: angiogenesis, anticoagulation, apixaban, DOACs

ÖZ

Amaç: Direkt oral antikoagülanlar (DOAK'lar), tromboembolizmin tedavisi ve önlenmesi için geleneksel tıbbi rejimlere iyi alternatiflerdir. Apixaban, bu yeni geliştirilen ilaçların daha popüler varyasyonlarından biridir. Antikoagülan potansiyelinin yanı sıra, olası hücresel etkiler gelecekteki çalışmaların konusu olmaya devam etmektedir. Bu çalışmanın amacı, korioallantoik membran (CAM) modelinde apiksaban'ın olası **antianjiyogenik etkilerini araştırmaktı.**
Yöntem: Apixaban'ın 10-4, 10-5 ve 10-6 M konsantrasyonlarında ilaç peletleri hazırlandı ve yumurta inkübasyonunun dördüncü gününde korioallantoik membrana yerleştirildi. Sekizinci günde, membranların tüm vasküler yoğunlukları, bilinen bir monoklonal, insanlaştırılmış, vasküler endotelyal büyüme faktörü inhibitörü olan 10-6 M'lik bir bevacizumab konsantrasyonu ile karşılaştırıldı.
Bulgular: 10-4 M apiksaban konsantrasyonunun, bevacizumabınkine benzer güçlü bir antianjiyogenik potansiyele sahip olduğunu bulduk. Bununla birlikte, daha düşük bir apiksaban dozunda (10-5 M, 10-6 M) orta düzeyde antianjiyogenik potansiyel vardı. Daha yüksek antianjiyogenik potansiyel dozlarının (10-4 M konsantrasyon) daha düşük dozlarda apiksaban (10-5 M, 10-6 M) ile karşılaştırılması, önemli istatistiksel farklılıklar ortaya çıkardı ($p <0.05$).
Sonuç: Sonuçlarımız, yüksek doz apiksaban'ın güçlü antianjiyogenik potansiyele sahip olduğunu göstermektedir. Bu etkinin kesin mekanizması bilinmemektedir. Bu pilot sonuçlar, DOAK'lara yeni bir bakış elde etmek için daha ileri çalışmalarla doğrulanmalıdır.

Anahtar Kelimeler: anjiyogenez, antikoagülasyon, apiksaban, DOAK'lar

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INTRODUCTION

Anticoagulation is an important step in the treatment of prothrombotic disorders. Heparin and its derivatives are good solutions that can be administered via an invasive route (e.g., subcutaneous or intravenous) [1,2]. However, oral anticoagulants are better suited for daily use by patients. Warfarin, the most widely used oral anticoagulant in the world [3], requires routine dose management with blood tests to calculate the international normalized ratio (INR); additionally, interactions with various types of drugs and foods limit the use of this oral medication [4,5]. The side effects associated with the use of once-popular anticoagulant drugs have prompted recent investigations, resulting in the development of more safe and effective anticoagulant drugs. Thus, new anticoagulants have been developed that can be administered orally and without the need for routine blood tests to determine a dose range [3,6]. Apixaban, one of the recently developed oral anticoagulants, produces an anticoagulant effect by inhibiting the factor Xa directly, in reversible, competitive, and selective ways. Apixaban is metabolized in the liver and contraindicated for combined used with CYP3A4 inhibitors [7,8].

According to previous reports, the antiangiogenic properties of factor Xa inhibitors depend on the dose administered. Initially, some studies claimed that the prolonged survival of cancer patients who were administered unfractionated heparin could be associated with the stimulation of antiangiogenic mechanisms [9-11]. Also, recent reports have suggested that apixaban is superior to low molecular weight heparin (LMWH) in protecting against cancer-related thrombotic events and other prothrombotic events [12,13]. In the current study, we investigated the antiangiogenic properties of apixaban in the chorioallantoic membrane (CAM) model and completed a review of the relevant literature.

MATERIAL AND METHODS

The model used in this study was designed in accordance with previous studies that have evaluated the antiangiogenic properties of drugs in the CAM model [9-11,14,15]. Ethical approval was not required due to the in-vitro design of study.

Group Creation

In the negative control group (used to evaluate drug-free pellets on chick embryos alone), drug-free pellets were administered to twenty eggs.

In the positive control group (used to determine a standard antiangiogenic base via the use of a well-known antiangiogenic drug), bevacizumab-embedded pellets were administered to twenty eggs.

The study groups (used to compare the antiangiogenic potential of apixaban having different concentrations) consisted of three apixaban-embedded pellet groups having different concentrations (10-4 M, 10-5 M, 10-6 M), and twenty eggs were used to examine the evolution of each concentration (in total, sixty eggs were used in the study groups).

Preparation of Pellets

The preparation of pellets was implemented as described in previous studies [9-11,14,15]. Agarose with a 2.5% weight of total volume was composed by mixing agarose (Merck, Darmstadt, Germany) and distilled water; the solution was then heated in an autoclave for sterilization and placed in sterile containers for cooling, after which the selected drugs were added. A single pellet group embedded with bevacizumab (Avastin™; Roche, Grenzach, Germany), used to create the positive control group, was prepared at a 10-6 M concentration, and three pellet groups embedded with apixaban (Eliquis™; Bristol-Myers Squibb, New York, USA), used to create the study groups, were prepared at concentrations of 10-4 M, 10-5 M, and 10-6 M. Primarily, 10 IU concentrations of drug pellets were prepared with the addition of 1 mL of the selected drug to the cooled agarose, and consecutive serial 1 IU/10 µl dilutions were applied to reach each targeted molar (M) concentration. After reaching the expected concentrations, 10 µl of drops were prepared with micropipettes for application to each egg.

Preparation of the chorioallantoic membrane (CAM) model

The CAM model was designed in accordance with procedures described in the literature [9-11,14,15]. The shells of fertile eggs (Ross 308)

were cleaned with alcohol-soaked gauze and placed inside incubators for embryonic growth at a controlled humidity (~80%) and temperature (~37.5 °C). Up to the fifth day of incubation, eggs were rotated periodically to achieve central placement of the embryos; rotation was stopped before starting the study protocol (Image 1.A, B). The eggs were cleaned with alcohol again, and a syringe was used to draw 5 ml of whole-egg liquid from the oval tip of each egg (Figure 1.C); the hole was created at the sharp tip of each egg with micro forceps (Figure 1.D), and the development of the chick embryos was evaluated via the egg holes (Figure 1.E1, E2). Immature eggs were excluded from the study. Eggs determined as mature were then separated into groups (twenty eggs in each group), and sterile pellets were inserted through the egg holes. The hole of each egg was sealed with a sterile surgical drape and again placed inside the egg incubator. The eggs were controlled on the eighth day of incubation, and angiogenesis was scored (Figure 1.F) as described in previous reports.

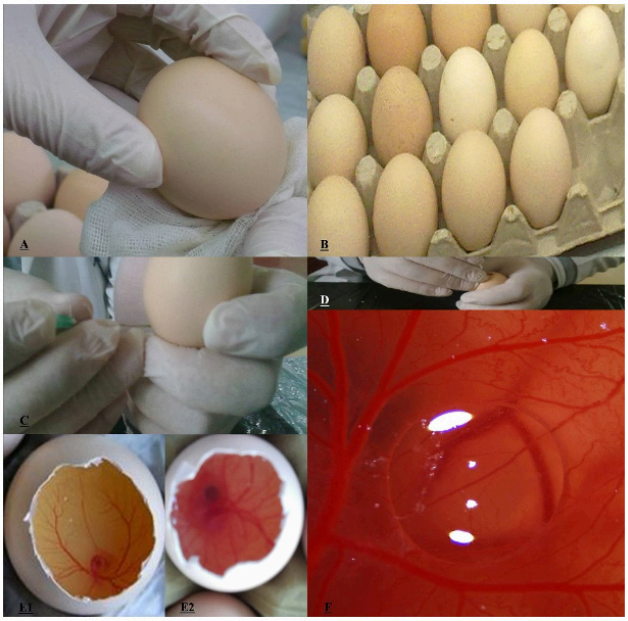

Figure 1. The steps in study protocols: A. Cleaning eggs with alcohol, B. Placement of each egg, C. Withdrawing albumin with syringe, D. Opening a hole with micro forceps, E.1-E.2. Evaluation of maturity in each egg via the egg hole, F. Scoring of anti-angiogenesis (score x2)

The pellets placed in chorioallantoic membranes were scored under light microscopy as described in previous reports on the surrounding capillary density of pellets (Figure 1.F). The degree of inhibition was recorded as follows [16,17]:

A normal surrounding capillary bed indicates a score of 0; slight (indistinct) changes in the capillary bed indicates a score of 0.5; decreased surrounding capillary bed density (less than twice of the pellet diameter) or a small, avascular free zone that surrounds the pellet indicates a score of 1; an extensive avascular free zone around the pellet (greater than twice the pellet diameter) indicates a score of 2.

After recording each score for each egg, an average score was calculated for each group as follows: twice the “score 2” number of eggs was added to the total “score 1” number of eggs egg number and divided into the total number of eggs in each group. An average score of 0.5 or lower indicates no antiangiogenic effect, an average score between 0.5 and 1 indicates a mild antiangiogenic effect, and an average score of >1 indicates a strong antiangiogenic effect [16,17].

Statistical Analysis

The statistical data of the scores were obtained with the Mann-Whitney U test and the Kruskal-Wallis one-way analysis. The antiangiogenic property was considered to be statistically significant for a p-value < 0.05.

RESULTS

The average antiangiogenic scores are summarized in Table 1. A comparison between the study groups and the positive control group (bevacizumab, 10-6 M concentration) revealed similar antiangiogenic effects in the 10-4 M concentration of apixaban (p = 0.367). However, there were statistical differences between the positive control group and the 10-5 M concentration apixaban (p = 0.017) and 10-6 M concentration apixaban (p = 0.001) groups.

The apixaban groups (10-4 M, 10-5 M, and 10-6 M concentrations) were statistically similar when compared each other (p = 0.053). However, there was a significant difference between the 10-4 M concentration apixaban group and the 10-6 M concentration apixaban group (p = 0.019). The distribution of antiangiogenic scores is demonstrated as a scatter graphic which is presented in Figure 2.

Table 1. Average antiangiogenic scores of drug groups

Groups	Number of eggs (with 0, 0.5, 1, and 2 scores)	Average Scores
Bevacizumab 10^{-6} M (n:20)	1 with "0.5" score	1.4 (strong antiangiogenic effect)
	10 with "1" score	
	9 with "2" score	
Apixaban 10^{-4} M (n:20)	3 with "0.5" score	1.2 (strong antiangiogenic effect)
	10 with "1" score	
	7 with "2" score	
Apixaban10^{-5} M (n:20)	5 with "0.5" score	0.9 (mild antiangiogenic effect)
	12 with "1" score	
	3 with "2" score	
Apixaban 10^{-6} M (n:20)	1 with "0" score	0.6 (mild antiangiogenic effect)
	6 with "0.5" score	
	12 with "1" score	
	1 with "2" score	

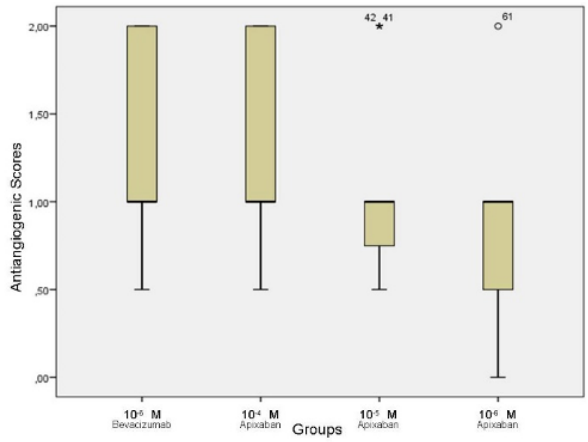

Figure 2. Comparison of antiangiogenic scores in bevacizumab and apixaban groups

DISCUSSION

We found that bevacizumab at a concentration of 10-6 M has similar antiangiogenic effects (strong antiangiogenic effects) to apixaban at a concentration of 10-4 M. On the other hand, apixaban has mild antiangiogenic effects at lower concentrations (10-5 M and 10-6 M). Based on our current knowledge, the present study is unique in that it used an experimental approach to investigate the antiangiogenic effects of different molar (M) concentrations of apixaban.

Anticoagulant drugs are important for the protection and treatment of cardiovascular thrombotic events. Conventional unfractionated heparin, low molecular weight heparin (LMWH) and vitamin K antagonists (e.g., Coumadin), which require blood-clotting test monitoring for determining sufficient or optimal dosages relative to body weight, are used in the management of these kinds of disorders. On the other hand, invasively applied heparin and LMWH (i.e., subcutaneous and intravenous), are negatively affecting patients' compliance and comfort [1-5].

The above-mentioned issues have led to the development of new strategies in the treatment or prophylaxis of thrombotic disorders. Therefore, new anticoagulants have been developed that are administered orally and do not require blood-clot test monitoring [6,7]. Rivaroxaban, dabigatran, apixaban and edoxaban are the most common examples of these types of newly developed drugs. Numerous studies have compared the anticoagulant effects of these drugs with conventional medical therapies, and most have reported favourable results with direct oral anticoagulants (DOACs) [6,7]. However, other systemic effects remain an important topic for future study to gain an understanding of the long-term efficacy and safety of these new drugs [18].

The most recent studies have focused on the angiogenic and vasculogenic effects of anticoagulants. Bevacizumab, which is a type of immune globulin G1 (IgG1), has been recently used to compare the antiangiogenic effects of drugs. It is well-known that Bevacizumab inhibits the activity of the vascular endothelial growth factor-A (VEGF-A) by binds with VEGF-A (forming large molecule) and preventing the binding of their receptors. Thus, bevacizumab shows a marked antiangiogenic effect and is indicated for use as an antitumor agent [19]. Previously published studies have reported that unfractionated heparin and its derivatives exerted significant antiangiogenic effects in the CAM model. These studies have compared the antiangiogenic effects of heparin and LMWH with bevacizumab in the CAM model. For instance, Katrancioglu et al. claimed that heparin showed strong antiangiogenic effects while the antiangiogenic effects of LMWH have been reported as dosage-dependent [10]. In contrast, Rema et al. suggested that heparin has pro-stimulant effects on angiogenesis in the CAM model [20]. In studies investigating the underlying mechanism of the anti-angiogenesis potential of anticoagulants, it was claimed that the possible

antiangiogenic effects of heparin derivatives can be dependent on the inhibition of VEGF expression via the binding of the tissue factor pathway inhibitor, which is a type of factor Xa inhibitor [21]. Rivaroxaban was also investigated in relation to angiogenesis in experimental models. It was claimed that rivaroxaban might promote neovascularization in hyperglycemic conditions in an animal model [22]. In contrast, in another study using the CAM model, it was found that rivaroxaban has dose-dependent antiangiogenic activity [11]. A potential action mechanism for the inhibition of angiogenesis was proposed by Liu et al., who stated that "Rivaroxaban (factor Xa inhibitor) might suppress coagulation-induced angiogenesis, which is related with ischemia during cellular growth in cancer cells or thrombosis [18]. Apixaban, also a type of factor Xa inhibitor, has similar effects to rivaroxaban [23]. In this context, Guasti et al. investigated the in vitro effects of apixaban in cancer cell lines and found that apixaban-treated cancer cells exerted a reduced migration capacity; additionally, it was shown that apixaban had dose-dependent antiproliferative effects [24]. Guasti et al. claimed that their study was the first study on high doses of this direct FXa inhibitor treatment on cancer cell lines. The authors suggested that this potential activity could be related to increased apoptosis in cell lines [25]. Taken together, Guasti et al.'s results could partially explain the results of the present study, and it is reasonable to assume that the antiangiogenic potential of apixaban could be related to dosage-dependent apoptotic and antiproliferative effects. Interestingly, we also have found that apixaban showed great antiangiogenic potential as many VEGF inhibitor agents in high doses. The other possible mechanism for the antiangiogenic potential of apixaban could relate to suppressed coagulation-induced angiogenesis, including the inhibition of factor Xa. From another of point of view, apixaban could also inhibit the VEGF expression via the binding of the tissue factor pathway inhibitor in the growth of embryos which has properties similar to a tumor growth.

Limitations of the study: There are several limitations of the present study. First, the CAM model is used to evaluate the vascular density without explaining cellular mechanism. Second, CAM is accepted as an in vitro model although it is a part of embryogenesis. Relatedly, current results are reflective of rudimentary findings indicating to the weakness of the study model.

CONCLUSION

Our results suggest that apixaban exerts dose-dependent antiangiogenic potential. However, the literature contains conflicting results about other factor Xa inhibitors, including their exact mechanism of action. Therefore, these results should be confirmed via further investigations and the potential mechanism of action needs to be clarified with cell studies.

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RESEARCH ARTICLE

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Pediatric scorpionism in southwest Turkey: the experience of a training and research hospital

Güneybatı Türkiye'de Çocuklarda Akrep Sokması: Bir Eğitim ve Araştırma Hastanesi Deneyimi

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ABSTRACT

Aim: The aim of this study was to evaluate the clinical and laboratory features and prognosis of scorpion stings in children.
Methods: This was a retrospective study of children with scorpion stings, who were admitted to the pediatric emergency department in Alanya Alaaddin Keykubat University (ALKU) Training and Research Hospital between the 1st of January 2019 and the 31st of December 2020. Demographic data, admission date, time periods from sting to admission to hospital and geographical location in which the sting occurred were recorded. Recordings were also made of the affected body sites, local and systemic signs and symptoms of envenomation, results of hematological and biochemical laboratory tests, management, length of hospital stay and outcome.
Results: In total, medical records of 111 children were reviewed. Patients were separated according to the clinical findings into three groups, seventy patients (63.1%) with mild symptoms and thirty-four patients (30.6%) with moderate symptoms, seven patients (6.3%) with severe symptoms. There was one exitus due to scorpion stings in the study period. Forty-one (37%) patients were hospitalised, and seven patients (6.3%) were hospitalised in the pediatric intensive care unit. Five patients (4%) received doxazosin and nineteen (17%) patients had antivenom therapy. Hospitalization in the intensive care unit was necessary for seven cases. No patient exhibited sequelae at the hospital discharge.
Conclusions: Scorpion stings in our region mostly result in mild envenomation. Doxazosin, an analog of prazosin more readily available in our country, can be considered as a treatment option in serious scorpion envenomations with significant sympathetic symptoms.

Key Words: Scorpion, scorpion sting, pediatric emergency, envenomation, antivenom, prazosin

ÖZ

Amaç: Çalışmamızın amacı, akrep sokması nedeni ile başvuran çocukların klinik ve laboratuvar özelliklerini ve prognozunu değerlendirmektir.
Yöntem: Alaaddin Keykubat Üniversitesi (ALKÜ) Eğitim ve Araştırma Hastanesi Acil Servisi'ne 1 Ocak 2019-31 Aralık 2020 tarihlerinde akrep sokması nedeniyle başvuran çocuk hastaların verileri retrospektif olarak incelendi. Vakaların başvuru tarihi, sokulan bölge, hastaneye başvuru saati, olayın saati ve sokulma ile başvuru arasında geçen süre, hastaneye yatış gereksinimi, zehirlenmenin lokal ve sistemik belirti ve semptomları, hematolojik ve biyokimyasal laboratuvar testleri, hastaya verilen medikal tedaviler, hastanede kalış süresi kaydedildi. Bulgular: Toplam 111 hastanın verileri tarandı. Hastalar klinik bulgulara göre üç gruba ayrıldı.Yetmiş hastada (%63.1) hafif, 34 hastada (%30.6) orta, 7 hastada (%6.3) şiddetli semptomlar saptandı. Çalışma döneminde akrep sokması nedeniyle 1 ölüm meydana geldi. Beş (%4) hastaya doksazosin ve 19 (%17) hastaya antivenom verildi. .41 hasta için (%37) hastaneye yatış gerekti. Yedi hastada yoğun bakım ünitesinde yatış gerekti. Hastaneden taburcu olurken hiçbir hastada sekel görülmedi.
Sonuç: Bölgemizde akrep sokmaları çoğunlukla hafif klinik tablo ile sonuçlanmaktadır. Doksazosin ülkemizde daha kolay bulunabilen bir prazosin analoğu olarak sempatik semptomları olan, ciddi akrep zehirlenmelerinde tedavide seçenek olarak düşünülebilir.

Anahtar Kelimeler: Akrep, akrep sokması, çocuk acil, antivenom, prazosin

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Introduction

Scorpion stings are a significant health issue in many parts of the world, particularly in regions with mild and hot climates. The estimated yearly global incidence is 2 600 deaths resulting from 1.5 million scorpion stings based on national health data [1]. Turkey has a high rate of scorpion stings due to its geographic location, where the dangerous species A. crassicauda, L. quinquestriatus, M. gibbosus, and M. eupeus have been observed [2-4]. The Mediterranean Sea region has the second highest rate of sting cases reported in Turkey, and Antalya is the province with the highest rate of scorpion stings in this region [2]. The clinical presentation of scorpion stings may range from mild local symptoms such as paresthesia, pain, erythema and mild edema, to serious autonomic, neurological cardiovascular and gastrointestinal systemic effects. The age and health of patients, the species of the scorpion, the number of stings, depth of the venom injection and location of the stings, determine the severity of the envenomation [4]. The incidence of scorpion stings is greater in adults, but the severity of envenomation is significantly greater in children, in whom the case fatality rate is up to ten times greater than in adults [5-9]. Since studies on scorpion stings in our region are generally carried out in adult patients, there are few studies on this subject in the literature.

The aim of this study was to assess the clinical and laboratory features and prognosis of scorpion stings, in children admitted to the pediatric emergency department of the Alanya Alaaddin Keykubat University (ALKU) Training and Research Hospital.

Methods

The medical records of 111 children admitted to the pediatric emergency department of the ALKU Training and Research Hospital due to scorpion stings, between the 1st of January 2019 and the 31st of December 2020, were retrospectively reviewed. Demographic data, time and date of admission, geographical location in which the sting occurred, affected body sites, colour of the scorpion and time intervals from sting to admission to hospital were recorded.

Also documented were local and systemic signs and symptoms of envenomation, results of hematological and biochemical laboratory tests, management, length of hospital stay, as well as outcome. In terms of geographic location in which the sting occurred, villages were considered rural areas, while towns and city centers were considered to be urban areas.

Patients were separated into three groups based on the severity of clinical findings (mild, moderate and severe). Mild envenomation included patients with local pain, erythema, edema, sweating, tremors and agitation. Moderate envenomation included patients with foreign body sensation in the throat, fever, nausea, vomiting, abdominal pain, joint pain, hyperglycemia, tachycardia, dysphagia, irritability, tachypnea, as well as mild to moderate respiratory distress. Severe envenomation included patients with nystagmus, mental disorientation, severe respiratory distress, heart failure and myocarditis, lethargy, stupor, coma, focal or generalized seizures, increased muscular tone, hypotension, cardiac failure, and/or acute pulmonary edema.

Leukocyte counts above 11 000/mm3 were considered leukocytosis. The glucose cut-off value for hyperglycemia in the literature is >10 mmol/L or 180 mg/dl in critically ill adults and children; we used this cut-off value in accordance with this literature. Values below 135 mEq/L were considered as hyponatremia, values above 145 mEq/L were considered as hypernatremia. Values below 3.5 mEq/L were considered hypokalemia, and values above 5.5 mEq/L were considered hyperkalemia.

Statistical analyses were performed where categorical variables were expressed as number and percentage and numerical variables as mean +/- SD. The t test was used to compare normally distributed data and the Mann Whitney U test was used to compare data with abnormal distribution. The statistical significance was set at 0.05 for all analyses.

This study was conducted with the ethics committee of the ALKU Faculty of Medicine approval, dated 14.04.2021 and numbered 07-04. It was designed as a single center retrospective study.

Results

Between the 1st of January 2019 and the 31st of December 2020, there were 1 188 cases admitted to the ALKU Research and Training Hospital emergency departments with the complaint of scorpion sting and 111 of these were children: namely one child for every ten patients. A total of 111 cases of scorpion cases in Alanya who were admitted to our pediatric emergency department were included in this study. There was one infant who was 9 months old (0.9%), 76 children between 1 and 10 years old (68.5%) and 34 adolescents between 10-18 years old (30.6%). The female to male ratio was similar, 49.5% of the patients were male. Concerning the region of occurrence, 40.9 % were reported from rural areas (Table 1). The age group most affected was between 6 and 10 years old (33%). Medical assistance was received within the first 3 hours after the sting for the majority of the cases (61.6%). There was an escalation in the number of scorpion stings in our region between July and August. In twenty-five cases (22.5%), the colour of the scorpion was known and noted, as follows: fifteen black (60%), eight brown (32%) and two yellow (8%). There was one sting recorded in 97 cases (96.0%), two stings in three cases (2.9%) and numerous stings in one case (1%). Stings occurred mostly in the upper (44.9%) and lower extremities (41.3%), and the sting site was on the neck in one solitary case (1%). The majority of stings occurred during the night (20:00 to 03:00), namely in 57 cases (63%). The highest rates of scorpion stings were seen between 23:00 and 03:00 in 31 cases (27%), 20:00 and 23:00 in 26 cases (23.4%) and between 13:00 and 16:00 in 21 cases (18.9%). Patients were separated according to the clinical findings into three groups, seventy patients (63.1%) with mild symptoms, thirty-four patients (30.6%) with moderate symptoms and seven patients (6.3%) with severe symptoms (Figure1).

Leukocytosis was observed in thirty-two cases (28%). The mean leukocytes count was 9 770± 3 300/mm3. Leukocytosis was significantly associated with moderate and severe clinical findings (p=0.02). Hyperglycemia was observed in two cases (1%). Hyperglycemic patients were all with severe clinical findings. The mean serum potassium level was 4.07 ± 0.50 mmol/L.

Table 1. Baseline characteristics of patients

	N	%
Age		
Infant (0-12 months)	1	0.9
Children (1-10 years)	76	68.5
Adolescents (10-18 years)	34	30.6
Sex		
Male	55	49.5
Female	56	50.5
District		
Urban	66	59.4
Rural	45	40.6
Laboratory findings		
Leukocytosis (>11000/mm3)	32	28
Hypokalemia (<3.5 mEq/L)	7	6
Hyperglycemia (>180 mg/dL)	2	1
Hypernatremia (>145 mEq/L)	1	0,9

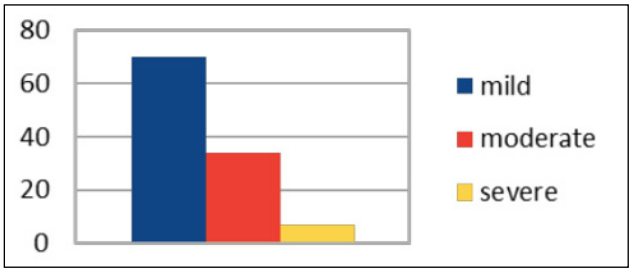

Figure 1. Severity of symptoms: 70 patients (63.1%) with mild symptoms, 34 patients (30.6%) with moderate symptoms, 7 patients (6.3%) with severe symptoms

Hypokalemia was observed in seven patients (6%). All our hypokalemic patients were with moderate to severe clinical findings: one of our patients had hypernatremia, thirty-five patients (31.5%) had no steroid therapy. Sixty patients (54%) received dexamethasone and sixteen patients (14.5%) received methylprednisolone. Four patients (3%) were administered oxygen therapy and only one patient (0.9%) required mechanical ventilation. Analgesics were prescribed to eighty-eight patients (79%). Five (4%) patients received doxazosin and 19 (17%) patients received antivenom. Forty-one patients (37%) were hospitalised; the duration of the hospital length of stay ranged from 1 to 7 days and was below three days in thirty-six patients (87%). Seven cases required hospitalization in the intensive care unit. No patient presented sequelae at the hospital discharge, whereas one exitus was observed during the study period.

Of the nineteen patients who were given antivenom,

seven patients did not require hospitalization and two of them required hospitalization in intensive care; one of these patients died. The deceased patient was a 9-year-old female who was stung on her foot. She came to the hospital with complaints of confusion, vomiting and weakness. She had dilated pupils, difficulty breathing, high blood pressure, and high troponin levels, there was no sign of pulmonary edema in her chest x-ray. Cardiac arrest developed two hours after antivenom administration, after 15 minutes of resuscitation the patient was converted to a sinus rhythm. The patient transferred to a center with a pediatric intensive care unit, but cardiac arrest developed again and the patient did not respond to resuscitation. The second patient in intensive care was a 4-year-old male, who was stung on the hand. He had sweating and priapism, his cardiac marker levels were normal; after antivenom and doxazosin treatment, symptoms regressed.

Four patients who received only doxazosin treatment presented with symptoms such as sweating, tremors, cold extremities and priapism. Vital signs and laboratory findings of all patients were normal, except for one patient whose blood pressure values were above the limits for their age. After the doxazosin treatment, symptoms regressed.

Discussion

Morbidity and mortality due to scorpion stings are a serious health concern in Turkey as well as throughout the world, particularly in tropical areas. Previous reports have revealed that there are fifteen scorpion species that are especially common in the Southeastern region of Turkey and the risky locations for scorpion stings are the south region of Turkey, in particular Antalya. This is the first study that has investigated clinical and laboratory characteristics of children with scorpion stings in Antalya. From Southeastern Turkey some studies that investigated scorpion envenomation were published previously, but for our region which is a highly touristic area, there were no previous publications that investigated scorpion envenomations. In this retrospective study, we reviewed 111 children who were admitted with scorpion stings. The majority of our patients were ranked as Grade I and most of them receiving only symptomatic therapy.

There are few detailed studies analysing the toxicity level of scorpion stings in children. Young, active adolescents and females have been commonly envenomated by scorpions, there was a higher frequency of scorpion stings in the spring and summer months and the majority of the stings occurred in the lower extremities. Most affected cases were from urban areas and the demographic results in this study reflected those reported in previous studies. Stings most commonly occur during the summer season, especially during the months of July and August, mostly at night. Scorpions are active especially at night which explains the increased frequency of envenomation during night hours. Children between the ages of 7 and 10 years old were prone to scorpion stings as well.

The majority of our patients needed only symptomatic treatment, 4% needed doxazosin, 17 % of patients received antivenom. Half of our patients were hospitalized and 15% of all patients needed special treatment such as antivenom and doxazosin. Although scorpion antivenom is the specific therapy for scorpion envenomation, it does not placate most of the sympathetic effects of scorpions stings, such as the cardiovascular effects. The beneficial effects of prazosin, irrespective of different scorpion species with similar cardiovascular manifestations, have been reported in scorpion sting victims, and prazosin seems more effective than scorpion antivenoms [10-15]. Prazosin is often referred to as a “poor man’s” scorpion antivenom and a universal antidote to scorpion venom action, irrespective of different species [10-15]. The World Health Organization is still emphasizing the importance of scorpion antivenom administration in scorpion envenomation, but not prazosin [16].

Doxazosin, a prazosin analog more readily available in our country, and prazosin, might be used safely in cases of scorpion stings with unidentified species. In our case series, the sole case of exitus, a nine-year-old girl, developed systemic collapse and shock on the second day of her hospitalization; her medical records revealed that scorpion antivenom was given to her, however it was not doxazosin. A previous

study from a tertiary pediatric intensive care unit in the Southeast region claimed that neurological manifestations might result in a poor prognosis and that encephalopathy, with or without other complications, may result in higher mortality. One patient in our series also had confusion and dilated pupils [17]. In another study, including 104 patients, in which childhood scorpion stings were investigated in our country, mortality and morbidity rates were found to be higher. This difference may be due to the presence of much more venomous species such as Leiurus Abdullahbayrami and Androctonus crassicauda in the Malatya and Adıyaman regions than the less poisonous and harmless species like Lurus asiaticus and Euscorpius carpathicus, found in the Alanya region [3].

Limitations of the study: We reviewed data for no more than a two-year period and we suspect more extensive investigations of additional cases would reveal additional informative results. Furthermore, had we been able to obtain photographs of the scorpions, their species could have been definitively identified.

Conclusion

Scorpion stings in our region mostly result in mild envenomation. Doxazosin, a prazosin analog which is more easily available in our country, can be considered as a treatment option in serious scorpion envenomations with significant sympathetic symptoms.

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The effect of social network diversity and social support on the thriving of healthcare workers

Sosyal ağ çeşitliliği ve sosyal desteğin sağlık çalışanlarının gelişimine etkisi

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ABSTRACT

Aim: The well-being of healthcare workers is a critical indicator in the provision of high-quality care. Although researchers have stressed the importance of social interactions and social support, scarce data exist about their effects on healthcare workers' well-being. In this study, we aim to advance the research on the relationships between social network diversity (SND), social support, and thriving.

Methods: In a cross-sectional design, an anonymous online link was shared among healthcare workers in a university hospital. The survey included questions on demographics, medical diseases, items from the social network index, the multidimensional perceived social support scale, and the brief and comprehensive inventories of thriving scales.

Results: A total of 103 individuals participated in the study (median age, min-max=33 (18-57); male/female = 33/70). Men and women did not differ in SND, perceived social support, or thriving scores. The brief inventory of thriving demonstrated healthcare workers older than 38 years exhibited higher scores in thriving compared to those younger than 27 years (p=0.001). According to comprehensive inventory of thriving, belonging (p=0.032), skills (p=0.006), self-worth (p=0.048), meaning and purpose (p<0.001), optimism (p=0.009), life-satisfaction (p=0.012), and positive emotions (p=0.042) differed by age groups. SND (r=.56, p<0.001) and perceived social support (r=.53, p<0.001) were positively correlated with thriving. After adjusting for potential confounders, SND, perceived social support, and age accounted for 46% of the total effects on thriving.

Conclusion: This study expands on the literature and provides evidence that by increasing the diversity of social networks and improving the quality and functionality of social support, a significant and positive impact on HCWs' well-being may be achieved.

Keywords: social networks, psychological well-being, healthcare workers, social support, eudaimonism, thriving

ÖZ

Amaç: Sağlık çalışanlarının refahı, verilen sağlık hizmetinin yüksek nitelikli olmasını sağlayan çok önemli bir göstergedir. Araştırmacılar sosyal etkileşimlerin ve sosyal desteğin önemini vurgulamıştır ancak, bu etkenlerin sağlık çalışanlarının refahına etkisini araştıran çalışmalar kısıtlı kalmıştır. Bu çalışmada sosyal ağ çeşitliliği, sosyal destek ve sağlık çalışanlarının gelişimi arasındaki ilişkiyle ilgili araştırmaları bir ileriye taşımayı amaçladık.

Yöntemler: Kesitsel bir tasarımda, bir üniversite hastanesindeki sağlık çalışanları arasında anonim çevrimiçi bir bağlantı paylaşıldı. Anket demografik özellikler ve tıbbi hastalıklarla ilgili sorular ve sosyal ağ göstergesi, çok boyutlu algılanan sosyal destek ölçeği, kısa ve kapsamlı gelişim envanterlerine ait maddeleri kapsamaktaydı.

Bulgular: Çalışmaya toplam 103 kişi katıldı (ortanca, en düşük-en yüksekyaş = 33 (18-57) (erkek/kadın = 33/70). Erkeklerin ve kadınların sosyal ağ çeşitliliği, algılanan sosyal destek, ve gelişim puanları arasında anlamlı fark saptanmadı. Kısa gelişim envanterine göre 38 yaş üzerindeki sağlık çalışanları, 27 yaşından genç olanlara kıyasla daha yüksek gelişim puanları gösterdi (p=0.001). Kapsamlı gelişim envanterine göre aidiyet (p=0.032), beceriler (p=0.006), öz değer (p=0.048), anlam ve amaç (p<0.001), iyimserlik (p=0.009), yaşam doyumu (p=0.012) ve olumlu duygular (p=0.042) alt ölçekleri yaş grupları arasında farklılık gösterdi. Sosyal ağ çeşitliliği (r=.56, p<0.001) ve algılanan sosyal destek (r = .53, p<0.001) gelişimle pozitif yönde ilişkiliydi. Olası karıştırıcılar kontrol edildikten sonra, sosyal ağ çeşitliliği, algılanan sosyal destek ve yaş, gelişim üzerindeki toplam etkinin % 46' sını oluşturmaktaydı.

Sonuç: Çalışmamız sosyal ağ çeşitliliğini arttırarak ve alınan sosyal desteğin niteliğini ve işlevselliğini geliştirerek, sağlık çalışanlarının refahı üzerinde anlamlı ve olumlu bir etki yaratılabileceği bulgularıyla literatüre katkı sağlamaktadır.

Anahtar sözcükler: sosyal ağlar, psikolojik refah, sağlık çalışanları, sosyal destek, mutlulukçuluk, gelişim

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INTRODUCTION

The parameters of health and well-being and their connections to individuals' social interactions have been investigated for many years [1]. Diversified social networks have been shown to relate to greater resistance to communicable diseases [2]. A large prospective cohort study indicated that mortality risk is higher for people with fewer strong and weak ties [3]. The mechanisms of these relations are thought to be connected to evidence that social networks are linked to a greater amygdala volume [4] and myelin integrity in the brain, which may explain why social networks impact so many different areas of health [5]. Aside from the structural aspects of social networks, the content of support received from these networks has a considerable impact on well-being [6]. Supportive relationships are deemed to be among the personal factors affecting the well-being of healthcare workers (HCWs) as well [7].

Researchers have defined well-being in the light of two major views: the hedonic view and the eudaimonic view. The first view includes subjective satisfaction, the sensation of pleasure against displeasure, and all assessments of the good/bad components of life. The second one focuses on positive functioning, which includes such elements as recognition of one's qualities and abilities, enlightened self-awareness, actualizing oneself, purpose, and meaning in life [8]. Sue and colleagues combined the hedonic and eudaimonic views, thus including the subjective and psychological well-being into a holistic and positive approach. They defined this construct as "thriving"—the condition of social, mental, and physical positive functioning at its peak. The thriving measures, the comprehensive inventory of thriving (CIT), and the brief inventory of thriving (BIT) outperformed current scales in forecasting a wide range of health outcomes, including objective and self-reported health status, health behaviors, and physical functioning [9]. Arslan and colleagues found that university students who had more severe psychological symptoms had fewer positive psychological domains in CIT and BIT [10]. These scales have been used to compare positive psychological health across different cultures [11].

The well-being of HCWs is a critical quality indicator in the provision of high-quality healthcare [12]. Unfortunately, there is a scarcity of information on HCWs' well-being, social network, and social support. Researchers have stressed the importance of factors in shaping eudaimonic well-being in employees of the mental health care system in the Netherlands; however, this study did not examine the relationships between well-being and social networks or social support [13]. In another study examining HCWs' well-being, the experience of eudaimonic feelings during patient-provider interactions, rather than simply experiencing increases in happy emotions and decreasing negative ones, was found to be important for the well-being of HCWs [14]. Several studies sought to determine the effects of work-related social support from co-workers and supervisors, in contrast to the social support from close ties [15]. Another heavy focus in this literature has been on COVID-19 and resilience [7].

In light of the scarcity of relevant data, we conducted this study to explore the relationship between social network diversity (SND), perceived social support, and thriving in HCWs. We hypothesized that thriving is positively influenced by both SND and perceived social support. By identifying the role and extent of these relationships, scalable prevention and intervention studies can be developed to address the overall well-being of HCWs.

MATERIAL AND METHODS

Study design and setting

This cross-sectional study focused on doctors, nurses, and auxiliary staff of a prominent university hospital. A convenience sampling method was used to recruit participants. Anonymous data were collected once with a Qualtrics link (https://www.qualtrics.com) to a self-administered online survey; the link was sent to the institutional email addresses via the general e-mail group of the hospital. No exclusion criteria were used. No incentives were provided. Participants gave their informed consent before the questionnaire was administered. The study was carried out per good scientific standards and was approved by the university's ethics committee (2019.149.

IRB3.088).

Measures and study variables

Besides the established questionnaires and scales, the survey consists of questions on sociodemographic information and medical diseases.

Social network index (SNI)

The SNI evaluates a social network's diversity and size. In this study, we examined the diversity dimension of the SNI, which included roles in 12 types of social interactions: spouses, parents, in-laws, children, other close relatives, close neighbors, friends, co-workers, schoolmates, volunteers, members of non-religious groups, and religious groups. Each relationship was awarded a score, with the highest possible score set at 12 [2]. As for a network's diversity, three or fewer social roles are classified as limited, four or five social roles correspond to medium, and six or more social roles are counted as a diverse social network. The SNI was first translated into Turkish by two members of the study group and then translated back to English by another member, who was fluent in English and who was not part of the first translation. The index was completed by two other people who were not part of the study. Inconsistencies in expressions and misunderstandings were resolved until the final version was reached. As it was an index, no reliability or validity study was needed to verify its characteristics.

Multidimensional Scale of Perceived Social Support (MSPSS)

MSPSS determines the perceived sufficiency of social support from three different sources. We use 12 items to assess three different types of support: i) family (items 3, 4, 8, and 11), ii) significant others (items 1, 2, 5, and 10), and iii) friends (items 6, 7, 9, and 12). Each item is graded between 1 (very strongly disagree) and 7 points (very strongly agree). The scale's overall score was calculated by adding the sub-dimension scores. The sub-dimensions of the scale have scores ranging from 4 to 28, while the overall scale score is between 12 and 84. Higher ratings imply a greater sense of social support. Eker and colleagues have demonstrated the reliability, validity, and factorial structure of the Turkish version of the revised MSPSS [16].

The comprehensive and brief inventory of thriving scale (CIT)

The CIT is a versatile well-being scale consisting of 54 questions. It measures 18 areas of psychological functioning: support, community, trust, respect, loneliness, belonging, engagement, skills, learning, control, accomplishment, self-efficacy, self-worth, meaning, purpose, optimism, and life satisfaction. The development of this scale was motivated by the fact that most earlier measures of psychological well-being focus on only a few positive dimensions. In contrast, CIT measures psychological well-being across a wide range and is useful to researchers and health practitioners, due to its ability to predict important health outcomes, given its holistic approach [9]. A shorter scale with 10 key psychological well-being factors was derived from CIT, namely, the Brief Inventory of Thriving (BIT). BIT is a quick-to-complete tool that may be utilized in initial patient assessments as a brief screening tool to inform on mental health and provide actionable guidance. The validity and reliability of CIT and BIT were tested with data collected from 11 distinct cultures (the United States, Turkey, Spain, Singapore, Russia, Mexico, India, Germany, China, Australia, and Argentina). Turkish adaptation and validation have been carried out by Arslan [10]. We chose the BIT score as the primary outcome, as the mono-dimensional scale was recommended over the multidimensional scale of the CIT; this, in turn, is because of the BIT's superior psychometric properties in the original and successive validations [17], and the fit indices of its single-factor solution were observed to be sufficient for all cultures [11].

Statistical Analysis: We used IBM's Software Package for Social Sciences Statistics for Windows, Version 26.0 (SPSS, Armonk, NY, USA), to examine the data we had collected. The Shapiro Wilk test was used to check the normality of the variables. Descriptive statistics of the categorical variables are reported as frequencies and percentages. When reporting descriptives of continuous variables, median, minimum, maximum,

and percentiles were used. Missing data were removed on an analysis-by-analysis basis, and only valid percentages were given. Categorical variables were compared using the Chi-Square test and Fisher's Exact test. The Mann-Whitney U test was performed to compare medians of two non-normally distributed continuous variables; for medians of more than two, the Kruskal Wallis test was used. Correlations between the variables were examined with Spearman correlation coefficients. The associations between multiple independent variables and the BIT score were first examined using univariate analysis. Then, those with p-values of less than 0.25 were further explored with multivariate general linear models. Statistical significance is defined as a p-value of less than 0.05 (two-tailed). We carried out a priori sample size calculation to perform a simple correlation r (r=0.5) of N observations. The needed sample size was 29 (n=29), calculated using a two-sided test with a 5% significance level (α =0.05) and an 80% power (β =0.2). For the generalized linear model, a sample size of a minimum of 60 people in total, with an increase of 0.10 (6 variables) for each variable was computed.

RESULTS

A total of 153 participants replied to the invitation, 50 surveys were excluded due to missing data; thus, we analyzed data from 103 participants.

Demographics of the participants

Table 1 summarizes the overall characteristics of the participants. Most participants were females with undergraduate or higher degrees. Approximately one-third of the participants had high levels of income. Each of the HCWs had a diverse social network (median, min.–max.) 8 (6–11).

Comparison of BIT and subscales of CIT by gender and age

Median, minimum-maximum, 25th, and 75th percentile values of the CIT and BIT, by gender and by age, are summarized in Tables 2 and 3, respectively. The CIT and BIT scores did not differ between genders (Table 2). Age groups were formed according to quartiles. The BIT demonstrated healthcare workers older than 38 years exhibited higher scores in thriving compared to those younger than 27 years (p=0.001). The domains of CIT, support, community, trust, respect, loneliness, engagement, learning, control, accomplishment, self-efficacy, and negative emotions did not differ by age group (Table 3). However, the domains of belonging (p=0.032), skills (p=0.006), self-worth (p=0.048), meaning and purpose (p<0.001), optimism (p=0.009), life satisfaction (p=0.012), and positive feelings (p=0.042) significantly differed between age groups (Table 3).

Table 1. General characteristics of the participants by gender

	Men (n = 33)		Women (n = 70)		p	X^2
Age (yr) (median) (min-max)	35 (18-47)		30.5 (23-57)		0.449	
	n	%	n	%		
Educational status					0.004	11.13
Elementary-high school	6	18.2	1	1.4		
Bachelor	13	39.4	42	60.0		
Graduate and over	14	42.4	27	38.6		
Marital status					0.002	0.977
Single	19	57.6	40	57.1		
Married	14	42.4	30	42.9		
Monthly income level					0.069	5.353
Low	16	48.5	31	44.3		
Medium	2	6.1	17	24.3		
High	15	45.5	22	31.4		
At least one medical disorder	8	24.2	19	27.1	0.755	0.098
	median (min-max)		median (min-max)		p	
Social network diversity	8 (6-11)		8 (6-11)		0.859	
Perceived social support	62 (12-82)		69 (23-84)		0.156	
BIT	3.7 (1.0-4.6)		3.6 (2.2-5.0)		0.879	

BIT: Brief inventory of thriving, Yr: years, min: minimum, max: maximum

Factors that affect thriving

In univariate analysis, the BIT and SND (r=.56, p<0.001) scores and the BIT and perceived social support (r=.53, p<0.001) scores were moderately and positively correlated (Table 4). Univariate analysis was also applied to explore the associations of the BIT with age, gender, education level, income level, marital status, SND, perceived social support, and status of having at least one medical disorder. The following factors had p

Table 2. CIT subscale scores ad BIT scores by gender

						Percentiles			p
	Gender	N	Median	Min.	Max.	25	50	75	
Support	Male	33	4.67	1.00	5.67	4.00	4.67	5.00	0.487
	Female	70	4.50	2.00	5.67	4.00	4.50	5.00	
Community	Male	33	3.67	1.00	5.00	3.00	3.67	4.00	0.051
	Female	70	4.00	2.00	5.00	3.33	4.00	4.33	
Trust	Male	33	3.00	1.00	4.33	2.50	3.00	3.33	0.784
	Female	70	3.00	1.00	5.00	2.33	3.00	3.33	
Respect	Male	33	3.67	1.00	4.67	3.00	3.67	4.00	0.179
	Female	70	4.00	1.00	5.00	3.58	4.00	4.00	
Loneliness	Male	33	3.67	1.33	5.00	3.33	3.67	4.33	0.615
	Female	70	4.00	1.33	5.00	3.00	4.00	4.33	
Belonging	Male	33	2.67	1.00	4.00	2.17	2.67	3.33	0.067
	Female	70	3.00	1.00	5.00	2.33	3.00	3.75	
Engagement	Male	33	3.67	1.00	5.00	3.00	3.67	4.00	0.314
	Female	70	4.00	1.67	5.00	3.33	4.00	4.33	
Skills	Male	33	3.67	1.00	5.00	3.33	3.67	4.33	0.409
	Female	70	3.67	1.00	5.00	3.00	3.67	4.00	
Learning	Male	33	4.00	1.00	5.00	3.33	4.00	4.67	0.966
	Female	70	4.00	2.33	5.00	3.67	4.00	4.33	
Control	Male	33	4.00	2.67	5.00	3.50	4.00	4.33	0.742
	Female	70	4.00	1.00	5.00	3.67	4.00	4.42	
Accomplishment	Male	33	3.33	1.00	5.00	2.50	3.33	4.00	0.589
	Female	70	3.33	2.00	5.00	3.00	3.33	4.00	
Self-efficacy	Male	33	4.00	1.00	5.00	3.50	4.00	4.33	0.415
	Female	70	4.00	3.00	5.00	3.67	4.00	4.67	
Self-worth	Male	33	4.00	1.00	5.00	3.33	4.00	4.67	0.423
	Female	70	4.00	1.33	5.00	4.00	4.00	4.67	
Meaning and purpose	Male	33	4.00	1.00	5.00	3.00	4.00	4.33	0.396
	Female	70	3.67	1.00	5.00	3.00	3.67	4.00	
Optimism	Male	33	4.00	1.00	5.00	3.33	4.00	4.33	0.114
	Female	70	3.67	1.00	5.00	2.67	3.67	4.00	
Life satisfaction	Male	33	3.67	1.00	5.00	3.00	3.67	4.00	0.450
	Female	70	3.33	1.00	5.00	2.67	3.33	4.00	
Positive emotions	Male	33	3.67	1.00	5.00	3.00	3.67	4.00	0.549
	Female	70	3.67	1.00	5.00	2.92	3.67	4.00	
Negative emotions	Male	33	3.33	1.00	5.00	2.67	3.33	4.00	0.974
	Female	70	3.33	1.00	5.00	2.33	3.33	4.00	
BIT	Male	33	3.70	1.00	4.60	3.30	3.70	3.90	0.879
	Female	70	3.60	2.20	5.00	3.20	3.60	4.00	

Min: minimum; max: maximum

Table 3. CIT subscale scores and BIT scores by age groups

	Age groups					Percentiles				
		N	Median	Min.	Max.	25	50	75	H	p
Support	≤27	28	4.00	1.00	5.00	3.33	4.00	4.92	7.568	0.056
	28-33	24	4.67	2.00	5.00	4.00	4.67	5.00		
	34-38	29	4.33	2.67	5.00	4.00	4.33	5.00		
	>38	22	5.00	1.67	5.00	4.25	5.00	5.00		
Community	≤27	28	3.83	1.00	5.00	3.08	3.83	4.33	6.557	0.087
	28-33	24	4.00	2.33	5.00	3.33	4.00	4.33		
	34-38	29	3.33	2.00	5.00	3.00	3.33	4.00		
	>38	22	4.00	2.33	5.00	3.58	4.00	4.33		
Trust	27	28	3.00	1.00	4.33	2.00	3.00	3.25	7.493	0.058
	28-33	24	3.00	1.00	5.00	2.67	3.00	3.33		
	34-38	29	2.67	1.67	4.33	2.33	2.67	3.33		
	>38	22	3.33	1.67	4.33	2.92	3.33	3.75		
Respect	≤27	28	4.00	1.00	4.67	3.33	4.00	4.00	0.402	0.940
	28-33	24	3.83	1.00	5.00	3.00	3.83	4.00		
	34-38	29	3.67	2.67	5.00	3.33	3.67	4.33		
	>38	22	3.67	3.00	5.00	3.58	3.67	4.00		
Loneliness	≤27	28	3.67	1.33	5.00	2.67	3.67	4.00	1.482	0.686
	28-33	24	4.00	1.33	5.00	3.00	4.00	4.33		
	34-38	29	3.67	1.33	5.00	3.17	3.67	4.33		
	>38	22	4.00	1.67	5.00	3.25	4.00	4.67		
Belonging	≤27	28	2.67	1.00	5.00	2.00	2.67	3.67	8.878	0.032
	28-33	24	3.00	1.00	4.33	2.33	3.00	3.58		
	34-38	29	3.00	1.00	4.67	1.83	3.00	3.33		
	>38	22	3.67	2.33	5.00	3.00	3.67	4.00		
Engagement	27	28	3.67	1.00	5.00	3.08	3.67	4.00	7.65	0.054
	28-33	24	4.00	3.00	5.00	3.33	4.00	4.33		
	34-38	29	4.00	1.67	5.00	3.00	4.00	4.33		
	>38	22	4.00	3.33	5.00	3.67	4.00	4.67		
Skills	≤27	28	3.33	1.00	4.67	2.67	3.33	4.00	12.43	0.006
	28-33	24	4.00	2.67	5.00	3.33	4.00	4.00		
	34-38	29	3.33	1.00	5.00	3.00	3.33	4.50		
	>38	22	4.00	3.00	5.00	3.67	4.00	4.67		
Learning	≤27	28	4.00	1.00	5.00	3.08	4.00	4.25	1.403	0.705
	28-33	24	4.00	2.67	5.00	3.67	4.00	4.33		
	34-38	29	4.00	2.33	5.00	3.33	4.00	4.67		
	>38	22	4.00	2.67	5.00	3.67	4.00	4.33		
Control	≤27	28	4.00	1.67	5.00	3.00	4.00	4.58	1.016	0.797
	28-33	24	4.17	1.00	5.00	3.42	4.17	4.67		
	34-38	29	4.00	2.00	5.00	3.67	4.00	4.50		
	>38	22	4.00	3.00	5.00	3.67	4.00	4.00		
Accomplishment	≤27	28	3.00	1.00	5.00	2.75	3.00	3.33	6.237	0.101
	28-33	24	3.33	2.00	5.00	3.00	3.33	4.00		
	34-38	29	3.33	2.00	5.00	2.50	3.33	4.00		
	>38	22	3.83	2.00	5.00	3.00	3.83	4.00		
Self-efficacy	≤27	28	4.00	1.00	5.00	3.42	4.00	4.33	2.434	0.487
	28-33	24	4.00	3.00	5.00	3.67	4.00	4.67		
	34-38	29	4.00	3.00	5.00	3.67	4.00	4.33		
	>38	22	4.00	2.67	5.00	3.67	4.00	4.75		

Continues on next page

Table 3. CIT subscale scores and BIT scores by age groups (Continue)

	Age groups					Percentiles				
		N	Median	Min.	Max.	25	50	75	H	p
Self-worth	≤27	28	4.00	1.00	5.00	3.08	4.00	4.00	7.901	0.048
	28-33	24	4.00	3.00	5.00	3.67	4.00	4.67		
	34-38	29	4.00	1.33	5.00	3.33	4.00	5.00		
	>38	22	4.00	3.67	5.00	4.00	4.00	4.67		
Meaning and purpose	≤27	28	3.00	1.00	4.67	2.33	3.00	3.33	21.61	<0.001
	28-33	24	4.00	2.00	5.00	3.08	4.00	4.25		
	34-38	29	3.67	1.00	5.00	2.83	3.67	4.50		
	>38	22	4.00	2.67	5.00	3.58	4.00	4.33		
Optimism	≤27	28	3.17	1.00	5.00	2.33	3.17	4.00	11.67	0.009
	28-33	24	3.83	2.00	5.00	3.00	3.83	4.25		
	34-38	29	3.33	2.00	5.00	2.67	3.33	4.33		
	>38	22	4.00	2.33	5.00	3.67	4.00	4.33		
Life satisfaction	≤27	28	2.67	1.00	5.00	2.08	2.67	3.67	11.04	0.012
	28-33	24	3.33	2.00	5.00	3.00	3.33	4.00		
	34-38	29	3.00	1.33	5.00	2.67	3.00	4.00		
	>38	22	3.83	2.00	5.00	3.00	3.83	4.00		
Positive emotions	≤27	28	3.00	1.00	5.00	2.33	3.00	4.00	8.215	0.042
	28-33	24	4.00	1.67	5.00	2.75	4.00	4.00		
	34-38	29	3.67	1.67	5.00	3.00	3.67	4.00		
	>38	22	4.00	2.00	5.00	3.33	4.00	4.00		
Negative emotions	≤27	28	3.00	1.00	5.00	2.00	3.00	4.00	6.767	0.08
	28-33	24	3.50	2.00	5.00	2.75	3.50	4.25		
	34-38	29	3.33	2.00	5.00	2.67	3.33	4.00		
		22	4.00	1.67	5.00	3.33	4.00	4.00		
BIT	≤27	28	3.25	1.00	4.60	2.85	3.25	3.68	6.024	<0.001
	28-33	24	3.65	2.80	4.90	3.40	3.65	4.00		
	34-38	29	3.70	2.20	4.90	3.30	3.70	3.90		
	>38	22	3.90	3.20	5.00	3.45	3.90	4.03		

levels of 0.25 or lower: income level, education level, marital status, age, social diversity, and perceived social support. These were further explored in the general linear model (GLM). Age, SND, and perceived social support are seen to significantly and positively influence thriving, once we adjust for the potential confounding variables of gender, marital status, education level, and income level. The explanatory power of the model was 46% (R2=0.46) (Table 5).

DISCUSSION

We analyzed the relationships between the thriving of HCWs, on the one hand, and SND and perceived social support, on the other. Our study was motivated by the limited eudaimonic views in the literature regarding evaluations of HCWs' well-being. We believe this gap needs to be filled in order to better promote HCWs' well-being. Our major findings were: i) SND and perceived social support positively influence thriving, ii) SND, perceived social support, and age account for 46% of the total effects on thriving, and iii) men and women did not differ in BIT scores or 18 of the subscale scores of the CIT, iv) Healthcare workers older than 38 years exhibited higher scores in BIT compared to those younger than 27 years.

The positive influence of SND on thriving aligns with a prior study's finding that adults with a diverse social network enjoy greater subjective well-being [18]. Depressive symptomatology is lower for older adults with diverse networks and higher for those with limited networks [19]. Regarding mechanisms, researchers have proposed linking diverse social networks with myelin integrity [5]

and greater amygdala volume [4]. The former mechanism may help explain why social networks impact so many different areas of health [5] and why greater amygdala volume translates to fewer psychiatric symptoms [20] and better social skills [21]. We could not locate any study on SND and thriving in HCWs in the literature. Therefore, we believe these findings will provide an avenue to inform the development of interventions aiming to promote the eudaimonic well-being of HCWs.

Table 4. Correlations between social network diversity perceived social support and thriving

	1	2	3.
1. Social network diversity	1		
2. Perceived social support	0.37**	1	
3. Brief inventory of thriving	0.56**	0.53**	1

**= Significant at 0.001 level (p < 0.001)

Table 5. General linear model for thriving

					95% CI	
	B	SE	t	p	Lower Bound	Upper Bound
Intercept	0.530	0.447	1,186	0.239	-0.357	1,418
Monthly income level						
Low	-0.006	0.147	-0.039	0.969	-0.297	0.286
Medium	0.054	0.152	0.356	0.722	-0.248	0.357
High	reference					
Education level						
Elementary-high	-0.320	0.207	-1.545	0.126	-0.731	0.091
Bachelor	0.147	0.129	1,140	0.257	-0.109	0.402
Graduate and higher	reference					
Marital status	-0.085	0.107	-0.799	0.426	-0.297	0.127
Age	0.026	0.008	3,287	0.001	0.010	0.042
Social network diversity	0.169	0.043	3,955	< 0.001	0.084	0.253
Perceived social support	0.013	0.003	4,278	< 0.001	0.007	0.018

CI: Confidence interval; Adjusted R^2 = 0.46

Perceived social support positively affecting well-being is corroborated by the literature [7, 22]. Supportive relationships are counted among the personal factors affecting HCWs' well-being [7]. The social support HCWs may receive from friends, significant others, and family within a diverse social network may provide them with the emotional strength that is often crucial to adapting to challenging working conditions, such as long working hours, on calls, and extended periods away from their families. These factors may play roles in accord with a main direct-effect model or a buffering model, i.e., by a process of support that protects people from potentially negative consequences of stressful circumstances [22].

From the sociodemographic factors, only age positively influenced BIT scores in HCWs. This finding differs from the original validation study, as it indicated that different age groups in the general population did not differ in BIT scores [9]. The reason for this finding may be that HCWs in their early careers, such as those in our study, learn new knowledge and gain experience while working tight schedules. This, in turn, may leave less time for self-awareness, recognizing one's qualities and abilities, actualizing oneself, and finding purpose and meaning in life, which are fundamental parts of thriving. As they grow older, a more stable work environment and other contextual factors may be secured and could contribute to thriving. Moreover, those older HCWs who stayed on the job longer may be the ones who are more resilient and have higher well-being [7].

No difference by age on CIT subscales - support, community, and engagement was in line however, differences found according to age in belonging, skills, self-worth, meaning and purpose, optimism, and positive emotions were not in line with the study by Su and colleagues. We found no differences by age in trust, respect, loneliness, control, learning, and negative feelings contrary to their study which demonstrated older people in the general population trusted others more, were respected by others, felt less lonely, perceived themselves as having more control over their lives and had fewer negative feelings, but also had less of a desire to learn new things. These discrepancies may reflect differences due to their community sample representing older adults than our study. Cultural differences may be another explanation as their sample was derived from the United States of America [9].Besides, Sorgente and colleagues explained the inconsistency between the CIT findings of some studies in the literature by alleging low validity and generalizability on the part of the CIT. They have drawn attention to the overlap between dimensions of the CIT. This overlap purportedly contradicts the confirmatory factor

analysis framework's theoretical assumptions, which state that each item should be explained by just one latent component [17].

We found no significant difference by gender in the CIT subscales and the BIT. Our findings on the BIT support the findings by Su and colleagues but are not consistent with their findings on the CIT subscales of Trust and Loneliness. They indicated that males are more likely than females to trust others and less likely to feel lonely [9]. These differences can be attributed to the fact that our sample is a homogeneous group consisting of HCWs with relatively diverse social networks, higher levels of education, and relatively higher incomes. Other studies that utilized the CIT and the BIT recruited participants with lower educations and moderate-income levels from the general population [9, 11, 17, 23] or university students [10]. However, the comparisons with the literature could not be made, as these validations [9-11, 17, 23] and review studies [17] do not explicitly examine the effects of income or educational level on well-being.

Our finding that thriving is unaffected by having at least one medical disorder is not in line with Su and colleagues' study. They indicated that individuals with a higher number of diseases reported considerably lower levels of psychological well-being on the majority of CIT subscales and the BIT, compared to those with few or no medical diseases [9]. This discrepancy might be due to their participants' older ages and higher numbers of medical illnesses, while our sample consisted of younger HCWs with very few medical diseases.

Recent literature on physician wellness, burnout, and resilience-focused heavily on COVID-19 [7]. A broader eudaimonic view of well-being with sufficient control-measured outcomes—not only in crisis times but in the longer term and consistently—will foster HCWs' well-being [7]. Given the vastly improved access to the internet and mobile phones, one implication of these findings could be the potential for low-cost web-based interventions which aim at SND and can be scaled up for greater use [24]. Another avenue for a further study could be investigating the organizational factors that affect HCWs' well-being, in contrast to the personal factors, so that the interventions in different contexts may have meaningful additional impacts [25].

Limitations and strengths: Our findings should be judged in light of some limitations. Firstly, this sample was composed of HCWs who had relatively high levels of well-being, favorable socioeconomic profiles, and relatively diverse social networks. They work in a similar work environment of a single hospital therefore the findings may not be representative of all HCWs, especially those who work in remote or frontline settings or those in otherwise challenging circumstances with little organizational support. Cross-sectional design hampered the possibility of inferences regarding causality. Exploring the quality of the work provided by the participants would have provided interesting insights. Despite these limitations, this study expands on prior research by providing insights into the eudaimonic well-being and social networks of HCWs, and allowing readers to better understand their connections.

Conclusion: Our findings imply that a diverse social network, social support from significant others, family, and friends, together with increasing age, account for nearly half of the total effects on thriving in HCWs. Males and females did not differ in domains of psychological functioning in the CIT—support, community, trust, respect, loneliness, belonging, engagement, skills, learning, control, accomplishment, self-efficacy, self-worth, meaning and purpose, optimism, life satisfaction, positive feelings, and negative feelings. HCWs receiving social support from friends, significant others, and family within a diverse social network may gain emotional strength, so that they may adapt to challenging conditions, long working hours, and time spent away from their families. By increasing the diversity of social networks and/or improving the quality and the functionality of social support, a significant and positive impact on HCWs' well-being may be achieved.

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RESEARCH ARTICLE

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The relationship between frontal QRS-T angle and premature ventricular contraction burden in ambulatory 24-hour Holter

Frontal QRS-T Açısı İle Ambulatuar 24 Saat Holterde Prematür Ventriküler Kontraksiyon Yükü Arasındaki İlişki

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ABSTRACT

Aim: Frequent premature ventricular contractions (PVCs) can cause impaired ventricular function or dilatation of ventricular cavities. The frontal plane QRS-T [f(QRS-T)] angle is an indicator of instability in the electrophysiological properties of the myocardium and is associated with arrhythmias. The present study aimed to investigate whether f(QRS-T) angle, as a marker of ventricular repolarization heterogeneity, predicts premature ventricular contraction burden in ambulatory 24-hour Holter.

Methods: The study included 100 patients. The patients were divided into two groups as 'frequent PVC' and 'seldom PVC' according to their PVC burden in 24-hour Holter monitoring. Laboratory and some ambulatory electrocardiography parameters, including frontal plane QRS-T angle, were compared between the two groups.

Results: Frontal QRS-T angle (63.34±37.86° vs 23.46±14.29° p<0.001) was found to be wider in the Frequent PVC group. F(QRS-T) angle of ≥ 34° had a sensitivity of 82.2% and a specificity of 80% in indicating PVC load (AUC: 0.887 (0.824-0.950). In addition, a positive correlation was found between PVC burden and f(QRS-T) angle (r:0.429 p<0.001).

Conclusion: The widening of f(QRS-T) angle could perhaps be considered as a surrogate marker of increased PVC burden in 24-hour Holter monitoring. Measuring f(QRS-T) angle in 12-lead ECG in patients with PVC may be a warning sign for increased PVC burden.

Keywords: premature ventricular contraction, electrocardiography, frontal QRS-T angle

ÖZ

Amaç: Sık prematür ventriküler kontraksiyonlar (PVK), ventriküler fonksiyonun bozulmasına veya ventriküler kavitelerin genişlemesine neden olabilir. Frontal düzlem QRS-T [f(QRS-T)] açısı, miyokardın elektrofizyolojik özelliklerindeki kararsızlığın bir göstergesidir ve aritmilerle ilişkilidir. Bu çalışma, ventriküler repolarizasyon heterojenitesinin bir belirteci olarak f(QRS-T) açısının, ambulatuar 24 saatlik holterde prematüre ventriküler kasılma yükünü tahmin edip etmediğini araştırmayı amaçlamıştır.

Yöntem: Çalışmada 100 hasta mevcuttu. Hastalar 24 saatlik Holter izleminde PVK yüklerine göre "sık PVK" ve "nadir PVK" olarak iki gruba ayrıldı. Laboratuar ve frontal plan QRS-T açısı dahil olmak üzere bazı ambulatuar elektrokardiyografi parametreleri iki grup arasında karşılaştırıldı.

Bulgular: Frontal QRS-T açısı (63.34±37.86°'ye karşı 23.46±14.29° p<0.001) Sık PVK grubunda daha geniş bulundu. F(QRS-T) açısının ≥ 34° olması; PVK yükünü göstermede %82.2 duyarlılığa ve %80 özgüllüğe sahipti (AUC: 0.887 (0.824-0.950). Ayrıca PVK yükü ile f(QRS-T) açısı arasında pozitif korelasyon bulundu (r:0.429 p<0.001).

Sonuç: F(QRS-T) açısının genişlemesi, 24 saatlik Holter izleminde artmış PVK yükünün bir göstergesi olarak düşünülebilir. 12 derivasyonlu EKG'de PVK'sı olan hastalarda f(QRS-T) açısının ölçülmesi, artmış PVK yükü için uyarıcı bir bulgu olabilir.

Anahtar Sözcükler: prematür ventriküler kontraksiyon, elektrokardiyografi, frontal QRS-T açısı

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INTRODUCTION

Premature ventricular contractions (PVCs) are found in 40 to 75 percent of routine 24 to 48-hour Holter monitoring in healthy populations [1]. In the past, frequent PVCs were believed to have a benign clinical course in individuals without underlying structural heart disease [2]. Moreover, it was frequently advised to avoid beginning treatment unless the patient had symptoms or PVCs occurred frequently. However, recent evidence has revealed that frequent PVCs may cause impaired ventricular function or dilatation of ventricular cavities in some patients [3-5]. Indeed, some studies have found that frequent idiopathic PVCs are linked to an increased risk of death, whether the patient has structural heart disease or not [6-7].

A new indicator of ventricular repolarization heterogeneity known as the frontal QRS-T [f(QRS-T)] angle is defined as the angle between the directions of ventricular depolarization and repolarization [8]. It also possesses an important advantage in that it can be quickly determined from an automated electrocardiogram (ECG) interpretation. The prognostic value of the f(QRS-T) angle has been demonstrated in various populations [9,10]. Additionally, according to earlier studies, the abnormal widening of this angle has been linked to sudden cardiac death (SCD) in specific patient populations [11]. An increased f(QRST) angle is a sign of electrophysiological instability in the myocardium and is linked to a worsening cardiac prognosis and mortality [12,13].

In this study, we aimed to examine the correlation between the f(QRS-T) angle in surface ECG and PVC burden estimated from ambulatory 24-hour Holter monitoring.

MATERIAL AND METHODS

Study population

We retrospectively evaluated one hundred patients who underwent 24-hour rhythm Holter monitoring for palpitations. ECG and rhythm Holter recordings were acquired and baseline demographic and clinical characteristics were examined. Exclusion criteria included severe valvular heart disease, prior myocardial infarction, thyroid disorder, permanent pacemaker therapy, heart failure, hypertrophic cardiomyopathy, bundle branch block, electrolyte disturbance, atrial fibrillation and any medication usage that might affect the ECG such as Beta blockers, antiarrhythmics or proarrhythmic drugs. The local ethics committee granted approval for the study (Antalya Education and Research Hospital, Protocol No:2022/23 Decision No:2/8, January 20, 2022).

Holter monitoring

Holter recordings were performed using a three-channel digital recorder (DMS 300-3A Holter ECG Recorders). During the Holter monitoring, all patients were informed to carry on with their ordinary routine and to refrain from drinking coffee or smoking. The Holter recordings were manually edited and analyzed for PVCs, and the number of PVCs was recorded. The PVC burden was calculated as the total number of PVCs divided by the number of all QRS complexes, during 24-hour Holter monitoring. Previous research has reported that the lowest PVC burden linked to reversible cardiomyopathy was 10% [14]; therefore, patients with a frequency of > 10% PVCs/24 h were classified as 'frequent PVC' (n = 50), while those with a frequency of < 10% PVCs/24 h were classified as 'seldom PVC' (n = 50).

The modified Simpson's technique was used to calculate the ejection fraction (EF). A board-certified cardiologist performed the echocardiographic studies.

Electrocardiography

ECGs of the patients were taken just before the rhythm Holter. In the supine position, a 12-lead surface ECG (Nihon Kohden Corporation, Cardiofax M Model ECG-1250) was recorded at a voltage of 10 mm/s and a paper speed of 25 mm/s. The intervals, axis and heart rates were evaluated from the standard ECG. Furthermore, all ECGs were uploaded to a computer and analyzed with x400 percent magnification using the Adobe Photoshop software to reduce incorrect measurements. The P and QRS durations were transcribed from the computer interpretation of the ECG. All the measurements were validated by an investigator. The QT interval was measured from the beginning of the QRS complex to the end

of the T wave and adjusted for heart rate using the Bazett formula: cQT=QT√ (R-R interval). Tp-e intervals were evaluated from precordial leads and described as the interval from the peak of the T wave to the end of the T wave. This data was used to compute the Tp-e/QTc ratio. The QRS axis and T-wave axis were identified in the automatic analysis of the ECG device. The absolute difference between the frontal plane QRS axis and T axis was used to calculate the f(QRS-T) angle (Figure 1). If the angle was more than 180°, it was subtracted from 360° [15].

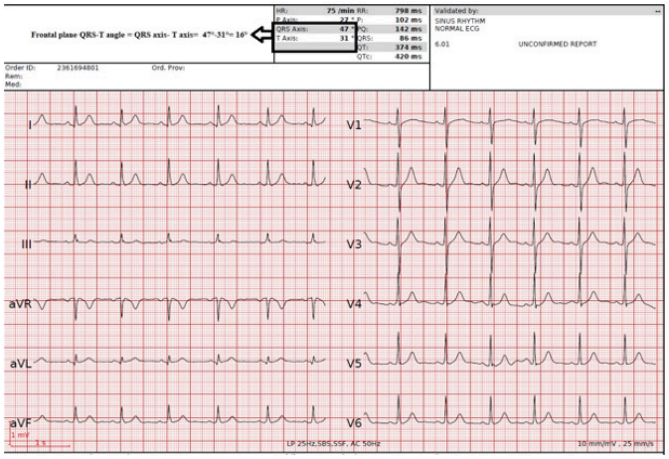

Figure 1: An example of the illustration and measurement of frontal plane QRS -T angle

STATISTICAL ANALYSIS

We evaluate statistical analysis with the SPSS software v27.0.1 (SPSS, Inc., Chicago, Illinois). The descriptive data was summarized as percentage frequencies for categorical variables and mean standard deviation (SD) for continuous variables. The variables were analyzed using analytical (Shapiro-Wilk test) and visual methods to determine whether they were normally distributed. Student's t-test was used to compare normally distributed measurements for independent samples, and Mann Whitney's U-test was used for comparisons of medians.

We obtained the optimal Youden index cut-off for best sensitivity and specificity by performing receiver operating characteristic (ROC) curve analysis, to assess whether the f(QRS-T) angle is useful to predict that PVC exposure; the corresponding area under the curve (AUC) was calculated. In addition, Pearson correlations were used to explore binary relationships between PVC exposure and frontal QRS-T angles. P < 0.05 was taken as the cut-off for significance, accompanied by a 95% confidence interval (CI).

RESULTS

This study included one hundred patients who underwent 24-hour rhythm Holter monitoring due to palpitation. The patients were divided into two groups based on their PVC burden in Holter monitoring: 'frequent PVC' and 'seldom PVC'. The mean PVC burden was 20.37±9.01% in the Frequent PVC group, and 2.04±1.34% in the Seldom PVC group. The study population's baseline demographics, laboratory results and echocardiographic characteristics are described in Table 1. There was no statistical difference between the groups.

Table 1: Comparisons of demographic characteristics, laboratory findings, and echocardiography parameters

	Seldom PVC	Frequent PVC	P value
Age, years	53.22±17.81	55.50±13.81	0.704
Gender			
-Male, n (%)	24 (48)	28 (56)	0.423
Diabetes mellitus n (%)	19 (38)	26 (52)	0.159
Hypertension, n (%)	26 (52)	31 (62)	0.313
Smoking, n (%)	19 (38)	25 (50)	0.227
Coronary artery disease, n (%)	16 (32)	21 (42)	0.300
Hemoglobin, g/dl	13.75±3.23	16.45±2.32	0.319
WBC, (K/ µl)x 103	8.49±2.73	7.45±2.41	0.198
Platelet , (K/ µl)x 103	278.68±56.14	273.06±67.22	0.080
Neutrophil to lymphocyte ratio	2.59±2.41	1.93±0.68	0.579
Fasting blood glucose, mg/dL	116.18±55.29	104.14±41.16	0.187
Creatinine, mg/dL	0.93±0.16	1.05±0.48	0.084
Sodium, mmol/L	139.66±2.71	140.14±3.39	0.494
Potassium, mmol/L	4.86±4.08	6.89±1.44	0.354
HDL, mg/dl	51.64±11.65	53.92±12.48	0.785
LDL, mg/dl	114.58±35.19	105.90±34.81	0.140
Triglyceride, mg/dl	145.63±64.76	154.50±75.47	0.899
TSH, mU/L	1.83 (2)	1.46 (2)	0.825
LVEF,%	60.70±4.28	59.10±5.01	0.090
Heart Rate, bpm	79.58±15.81	75.16±12.67	0.262

(PVC: premature ventricular contractions WBC: White blood cell, HDL: High-density lipoprotein cholesterol, LDL: Low- density lipoprotein cholesterol, TSH: Thyroid Stimulating Hormone, LVEF: left ventricular ejection fraction)

Table 2 shows the ambulatory ECG parameters of both groups. The Frequent PVC group had longer QRS duration (p=0.001), QT interval (p=0.001) and

QTc intervals (p=0.012). Moreover, Tp-e interval (75.84±14.84 vs 86.50±14.29, p= 0.001) and Tp-e/QTc ratio (0.18±0.03 vs 0.20±0.03 p = 0.016) were significantly increased in the Frequent PVC group. The frequency of fragmented QRS was considerably higher in the Frequent PVC group (28% vs 36%, p =0.043). Regarding to HRV time domain indices (SDNN, SDNN, RMSSD, pNN50), there was no noticeable differences across the groups.

Table 2: Ambulatory electrocardiography parameters of patients

	Seldom PVC	Frequent PVC	P value
P duration, msec	108.24±18.08	115.30±24.11	0.15
QRS duration, msec	91.56±13.96	99.48±11.49	0.001
QT interval, msec	368.20±31.97	395.68±46.68	0.001
cQT interval, msec	418.78±25.14	438.04±36.03	0.012
Tp-e, msec	75.84±14.84	86.50±14.29	0.001
Tp-e/cQT ratio	0.18±0.03	0.20±0.03	0.020
Presence of fragmented QRS, n (%)	9 (28)	18 (36)	0.043
Frontal QRS-T angle, (°) degrees	23.46±14.29	63.34±37.86	<0.001
PVC (%)	2.04±1.34	20.37±9.01	<0.001
HRV time domain indices			
SDNN ms	121.94±30.96	119.76±33.47	0.756
SDANN ms	120.14±37.87	118.88±46.69	0.749
RMSSD ms	34.24±18.96	34.22±19.09	0.882
pNN50 %	10.36±9.34	9.68±12.27	0.498

(PVC: premature ventricular contractions, cQT: corrected QT, Tp-e: T wave peak-to-end interval, HRV: heart rate variability, SDNN: standard deviation of all normal-to-normal RR intervals, SDANN: standard deviation of 5-min mean RR intervals, RMSSD: the square root of the mean of the squares of the differences between successive normal-to-normal RR intervals, pNN50: percentage of successive normal RR intervals exceeding 50 ms)

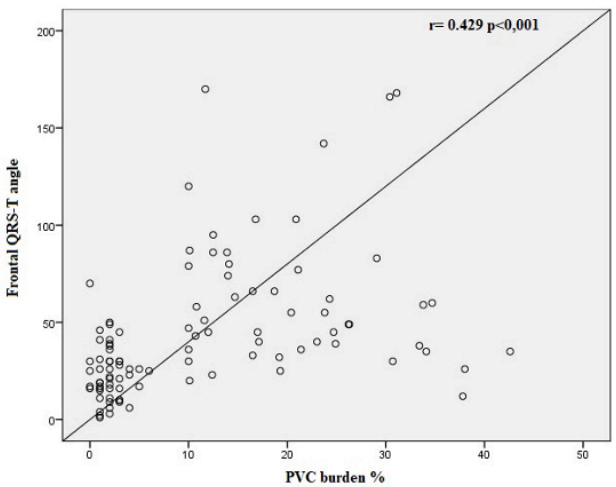

Figure 2: Correlation between PVC burden and Frontal QRS-T angle.

Frontal QRS-T angle (63.34±37.86° vs 23.46±14.29° p<0.001) was found to be wider in the Frequent PVC group. A positive correlation was found between PVC burden and f(QRS-T) angle (r:0.429 p<0.001) (Figure 2). ROC curve analysis was performed to determine the best cut-off value for detecting the PVC burden of the frontal QRS-T angle. An f(QRS-T) angle of ≥ 34° had a sensitivity of 82.2% and a specificity of 80% in indicating PVC burden (AUC: 0.887 (0.824-0.950) (Figure 3).

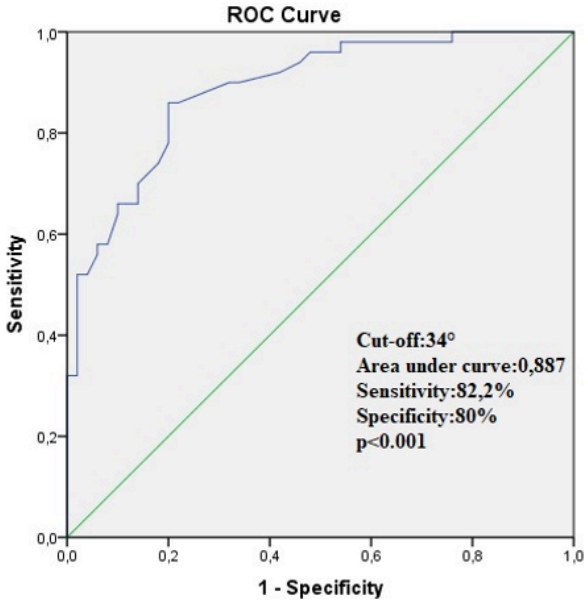

Figure 3: Receiver operating characteristics curve analysis of frontal plane QRS-T angle to predict PVC burden

DISCUSSION

This study demonstrated that the f(QRS-T) angle calculated from surface ECG is a predictor of increased PVC burden. Furthermore, Tp-e intervals and Tp-e/QTc ratio were significantly higher in patients with frequent PVC burden. However, HRV domain indexes were similar between the groups.

Even though it has been traditionally considered that frequent PVCs were associated with a good prognosis in patients without structural heart disease [2], this has not always been demonstrated to be the case. There have been studies that show the presence of PVC is linked to a higher risk of cardiac events and mortality in people that have not been assessed for structural heart disease [16]. The increased daily total burden of PVCs can cause severe cardiac problems, such as syncope,

heart failure and angina.

PVCs are the most common ventricular arrhythmias and despite the high prevalence, in most patients, no cause can be identified. Although PVCs are more common in the elderly and in men, they can also occur in healthy individuals. There are a number of mechanisms responsible for PVC and although some of the underlying mechanisms have been clarified, it is still unclear why some people have a higher frequency of PVC than others, or why some people notice the symptoms, but others do not. PVCs may be felt as palpitations or dizziness. They can also cause chest pain, fainting, fatigue, presyncope, dyspnea or hyperventilation following exercise. Despite there being a number of symptoms associated with PVCs, on occasion they do not cause any symptoms at all and the absence of symptoms is not always a good prognosis. Even in cases where no symptoms are present, it is unquestionably necessary to evaluate using rhythm Holter monitoring if PVCs are found in the surface ECG of the patients, or if the ejection fraction is low in the transthoracic echocardiography. Treatment should be started if the PVC percentage is found to be high in 24-hour rhythm Holter monitoring, even if the patient is asymptomatic. However, 24-hour Holter monitoring may not always be sufficient to show the actual PVC burden. It might be necessary to use some ECG parameters that demonstrate the patient's PVC burden and localization.

PVCs are thought to contribute to the development of malignant arrhythmias. They may transform into ventricular arrhythmias due to a variety of factors that impair the myocardial electrical stability, such as electrolyte disturbance or increased sympathetic activity. In addition, frequent PVCs may cause left ventricular dysfunction and dilatation, leading to the development of ventricular arrhythmia, with mechanisms such as increased automaticity, re-entry and triggered activity [17]. While many studies cannot provide an absolute limit to identify patients at risk of developing PVC induced cardiomyopathy (PIC), at least a 10% PVC burden are at sufficient risk for development of PIC [14]. Regular follow-ups should be performed to assess of ejection fraction and LV dimensions, as well as to prevent future arrhythmic events.

Changes in the repolarization potential of the myocardium may cause predisposition to malignant ventricular arrhythmias and may lead to SCD. Even though the QT interval has traditionally been used to assess myocardial repolarization, correct calculation of the QT interval is challenging, and the measurement's reproducibility is poor [18]. Although QT dispersion is used to measure ventricular refractoriness dispersion, it does not directly reflect the regional heterogeneity of cardiac repolarization [19]. The Tp-e interval is now regarded as a ventricular repolarization marker. Furthermore, it was discovered that patients with Brugada syndrome had a higher risk of mortality if their Tp-e interval was prolonged. [20]. Yayla et al. found significant reductions in the Tp-e/QTc ratio and Tp-e interval after successful radiofrequency ablation (RFA) ($p<0.001$) in patients with a PVC burden >5% at 24-hour Holter follow-ups. [21]. In light of this data, the longer Tp-e interval in patients with frequent PVCs suggests a higher risk of malignant arrhythmia. Nevertheless, the Tp-e interval is an unreliable parameter as it is affected by changes in heart rate and body weight [22]. The Tp-e/QTc ratio has recently been proposed as a more accurate predictor of repolarization and it is unaffected by changes in heart rate [22]. In our study, the Tp-e/QTc ratio was significantly higher in the Frequent PVC group, which is consistent with the literature. However, it is challenging to calculate the Tp-e/QTc ratio accurately, and sophisticated software programs as well as specific tools such as rulers and magnifiers are required.

Recently, some new ECG parameters have been used to evaluate myocardial repolarization. F(QRS-T) angle, which shows ventricular conduction heterogeneity, is one of these parameters. [8,9]. According to some studies, myocardial repolarization parameters, such as QTc interval and T wave inversion, were found to be less accurate and repeatable than this novel parameter [11]. Moreover, the abnormal widening of this angle may in fact be a sign of a number of cardiac events [23].

The QRS-T angle can be calculated with two different methods: spatial and frontal QRS-T angle. Spatial angle is more challenging to calculate and necessitates sophisticated computer programs;

furthermore, it cannot be measured routinely from surface ECG. On the other hand, the automatic report section of ECG devices makes it simple to calculate the frontal QRS-T angle. In our study, we preferred the f(QRS-T) angle, since it has been shown in various studies that it can be used instead of spatial QRS-T angle for risk assessment [24].

Although 24-hour rhythm monitoring is considered the gold standard method for assessing PVC frequency, recent evidence has shown that there may be significant daily variation and that at least six days of rhythm monitoring may be required to determine the maximum daily PVC frequency [25]. This situation reveals the necessity for long-term monitoring to determine the true frequency of PVC in patients, however not every clinic has the required supplies of Holter devices that can be used for long-term monitoring of every patient. In this study, it was found that patients with a high PVC burden had a significantly higher f(QRS-T) angle. It was also determined that f(QRS-T) angle ≥34° predicted the presence of increased PVC burden, with 82.2% sensitivity and 80% specificity. According to this finding, the presence of f(QRS-T) angle of ≥34° in the surface ECGs of patients who are compliant with palpitations and have at least one PVC on their surface ECG is significant and may indicate an increased PVC burden. In these patients, long-term and more frequent Holter monitoring may be considered to determine the accurate PVC burden.

Limitations: The comparatively small number of registered patients is the study's most important limitation. If the sample size of the study had been larger, more consistent results could be obtained. The center where the study was conducted was a tertiary care facility, with many patients presenting in the heart clinic, however it would have required much time and resources to enrol select patients who were neither taking medication or presenting structural heart diseases. Another major limitation was the retrospective design of the study. Owing to the observational nature of the design, only associations can be drawn and no causal relationships can be established. One point not assessed in the study is that the patients' serious cardiac events, such as cardiac mortality and arrhythmias, were not monitored. Therefore, since patients could not be followed up for prospective arrhythmic events, the correlation between f(QRS-T) angle and cardiac events could not be assessed. If long-term follow-ups could be done with more patients, the long-term cardiac events could be evaluated more clearly. In addition, this single center study in a tertiary heart center where many patients apply should have its findings validated in multicentre studies, involving greater patient populations and longer follow-ups. Despite these limitations, this research has raised a number of questions that require further investigation.

Conclusion: Frequent PVCs have a negative effect on myocardial repolarization parameters and may predispose these patients to malignant arrhythmias. As a simple and easily obtained ECG parameter, f(QRS-T) angle may be used in predicting PVC burden. Measuring the f(QRS-T) angle in the 12-lead ECG in patients with PVC may be a warning sign for increased PVC burden and will encourage increased frequency and duration of Holter monitoring, and a review of treatment regimens.

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RESEARCH ARTICLE

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The relationship of learning and memory disfunction with NEURL1 and RGS14 genes in patients with autism spectrum disorders

Otizm Spektrum Bozukluğu Olan Hastalarda Öğrenme ve Hafıza Bozukluklarının NEURL1 ve RGS14 Genleri ile İlişkisi

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ABSTRACT

Aim: We aimed to evaluate the relationship between learning-memory difficulties and NEURL1 and RGS14 genes in patients with autism spectrum disorders (ASD).
Method: Forty children with ASD (20 ASD, 20 high functioning autism (HFA)) and 20 healthy controls were enrolled in this study. NEURL1 and RGS14 gene expressions in blood samples of volunteers were assessed by quantitative Real-Time PCR (qRT-PCR). The clinical and demographical findings in patients were determined and examined in relation to the gene expressions.
Results: According to our findings, NEURL1 gene expression was decreased in both patient groups compared to the control ($p<0.05$). No significant difference between the groups in terms of the RGS14 gene ($p>0.05$). A statistically significant correlation was found between learning and memory difficulties and RGS14 gene expression in HFA patients ($p=0.045$). A positive correlation was observed between NEURL1 and RGS14 gene expressions of ASD patients ($p=0.032$, $r=0,59$).
Conclusion: In this study, we showed that the NEURL1 gene may affect learning and memory difficulties in ASD patients. Nonetheless, we recommend that both genes be studied with more patients and preferably with brain tissues. These genes were evaluated for the first time in a clinical study on autism, and we believe that they will contribute to the literature in this respect.

Keywords: Autism, Neuralized1, RGS14, Learning, Memory

ÖZ

Amaç: Bu çalışmada OSB hastalarında öğrenme ve hafıza güçlükleri ile NEURL1 ve RGS14 genleri arasındaki ilişkiyi değerlendirmeyi amaçladık.
Yöntem: Bu çalışmaya OSB'li 40 çocuk (20 OSB, 20 yüksek fonksiyonlu otizm (HFA)) ve 20 sağlıklı kontrol dahil edildi. Gönüllülerin kan örneklerinde NEURL1 ve RGS14 genlerinin ekspresyonları kantitatif Real-Time PCR (qRT-PCR) yöntemi ile değerlendirildi. Hastalardaki klinik ve demografik bulgular belirlenerek gen ekspresyonları ile ilişkisi incelendi.
Bulgular: Bulgularımıza göre her iki hasta grubunda da kontrol grubuna göre NEURL1 gen ekspresyonu azaldı ($p<0.05$). RGS14 geni açısından gruplar arasında anlamlı fark yoktu ($p>0.05$). HFA hastalarında öğrenme ve bellek güçlükleri ile RGS14 gen ekspresyonu arasında istatistiksel olarak anlamlı bir ilişki bulundu ($p = 0.045$). OSB hastalarının NEURL1 ve RGS14 gen ekspresyonları arasında pozitif korelasyon görüldü ($p=0.032$, $r=0,59$).
Sonuç: Bu çalışmada NEURL1 geninin OSB hastalarında öğrenme ve hafıza güçlüğünü etkileyebileceğini gösterdik. Ancak, her iki genin daha fazla hasta ve tercihen beyin dokuları ile çalışılmasını öneriyoruz. Bu genler ilk kez otizmle ilgili bir klinik çalışmada değerlendirilmiştir, bu açıdan literatüre katkı sağlayacağına inanıyoruz.

Anahtar Sözcükler: Otizm, NEURL1, RGS14, Öğrenme, Hafıza

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Introduction

Autism Spectrum Disorders (ASD) is a neurodevelopmental disorder characterized by cognitive and behavioural disorders that show its effect from an early age [1, 2]. There is wide clinical variability and heterogeneity in ASD. In this context, in addition to typical autism patients, a group of patients that have social interaction deficiencies and an Intelligence Quotient (IQ) of 70 and above, although they fulfil their cognitive functions, are defined as High Functioning Autism (HFA) [1, 4].

At present, the diagnosis of the disease is made based on the diagnostic criteria of the American Psychiatric Association DSM-V (5th edition) [3, 5]. It is known that individuals with ASD have abnormal cognitive episodic memory, difficulties with future planning, relatively weak memory and some learning disorders [6-8]. It is widely recognized that environmental factors, genetic and epigenetic factors are effective in the etiology of ASD. Although various genes associated with ASD have been identified in several studies, the risk genes that cause learning and memory disabilities in ASD have not been clear [1, 7].

The basic mechanism that regulates learning and memory is intercellular synaptic plasticity, which is characterized by a series of biochemical and physiological changes in neuronal synapses in the brain [9-11]. In recent years, it has been shown that Cytoplasmic Polyadenylation Element-Binding Proteins (CPEBs) regulate synaptic plasticity by modulating the poly-A tails of specific mRNAs, and accordingly, it is one of the regulatory elements of learning and memory [10-12]. An important point is that CPEB3 activity is regulated by Neuralized1 (NEURL1), which is an E3 ubiquitin ligase [13, 14]. It has been shown that CPEB3 and NEURL1 can be effective on learning and memory, through the study of post-mortem tissues of patients with ASD as well as in in vivo ASD models [11, 14-16]. CPEB3 is a negative regulator of Glu A1 and GluA2 are receptor of NMDA (N-metil-D-aspartat), although it has been demonstrated that NEURL1-mediated monoubiquitination of CPEB3 increases the translation levels of GluA1 and GluA2, and as a result, enhance learning and memory by increasing synaptic plasticity [11, 14, 17]. It is emphasized that this effect occurs because of overexpression of NEURL1. Therefore, the role of the NEURL1 gene in the pathogenesis of ASD may be significant [14].

On the other hand, it has been shown in previous studies that Regulator of G Protein Signaling 14 (RGS14), which is a member of the Regulators of G Protein Signaling (RGS) proteins gene family, is a suppressor of memory and hippocampal-based learning [18, 19]. In experimental studies, it has been shown that RGS14 regulates Long-Term Potentiation (LTP) and synaptic plasticity in the hippocampal area CA2, and this information has also been confirmed in human studies. The pre- and2 post-synaptic regulatory functions of RGS14 variants show that they have important roles in human neurophysiology and various neurological diseases. However, more studies are needed to fully elucidate the role of RGS14 [20].

In the present study, we aimed to examine whether there were differences in the expression levels of NEURL1 and RGS14 genes in blood samples of ASD, HFA patients and control groups. In our study, we expected that the NEURL1 gene would be downregulated and the RGS14 gene would be upregulated in ASD patients. We evaluated our results in terms of the relationship between learning and memory disorders and these genes. The NEURL1 and RGS14 genes were examined for the first time with ASD patients in this study.

Subjects and methods

Patient selection

Patients between the ages of two and sixteen diagnosed with ASD and HFA at the Child-Adolescent Psychiatry Clinic (Erciyes University) between 2013 and 2014, were included in this study. The sociodemographic data form and the Ankara Developmental Screening Inventory (ADSI) were used in patient selection by specialist psychiatrists, in accordance with DSM-V diagnostic criteria.

Patients using ASD-related drugs and patients with syndromic disorders were excluded. The patients who were included in the study were collected into two groups, ASD and HFA. Healthy individuals compatible with the age and gender of

the patients were selected for the control group. The number of the patients and control, therefore, consisted of sixty individuals in three groups of twenty.

RNA isolation and cDNA synthesis

The genetic examinations were conducted at Erciyes University Genome and Stem Cell Center (GENKOK). RNA extraction was performed using the High Pure RNA Isolation Kit (Roche Diagnostic, Version 12, Germany) from peripheral blood samples taken from participants in the study. The quality and quantity of the RNA were measured with nanodrop (Thermo Scientific, USA). The RNA samples were stored - 80^{0}C.

Complementary DNA (cDNA) synthesis was performed from the obtained RNAs using the Transcriptor High Fidelity cDNA Synthesis kit (Roche Diagnostics, GmbH, Mannheim). According to the manufacturer's instructions, the cDNA was synthesized by incubating for 10 minutes at 29ºC, 60 minutes at 48°C and 5 minutes at 85ºC (LabCycler Sensoquest, Göttingen, Germany). The PCR product was stored at -20^{0}C.

Gene expression analysis

Preamplification was performed to see the blood levels of target genes. For this step and in accordance with the manufacturer's guidelines, we used the Real Time Ready cDNA preamplification master mix (Roche Diagnostics, GmbH, Mannheim).

Neuralized1 and RGS14 mRNA expression levels were determined using the LightCycler®480 Real Time Ready Assay Master Probe Kit (Roche Diagnostics, GmbH, Mannheim) with the Semiquantitative Real-Time PCR (qRT-PCR) method. The protocol was performed in accordance with the manufacturer's guidelines. The primers sequences of the genes were as follows:

NEURL1, 5'-GACTCGGCTGTTATGCTGTTC-3' (F) and 5'-GAGCACCAGCTCGCTATCA-3' (R); RGS14 5'-AGGTCTACCTGGTGGGCAAT-3' (F) and 5'-GCACGGTGCAGTCCTGAT-3' (R); ACTB, 5'-TCCTCCCTGGAGAAGAGCTA-3' (F) and 5'-CGTGGATGCCACAGGACT-3' (R).

All samples were run in duplicate and means were used for statistics. Target genes were normalized with ACTB. The 2-ΔΔCT method was used to compare gene expression relative to quantification.

Statistical analysis

To compare the differences between the groups, either one-way analysis of variance (ANOVA) or the Kruskal-Wallis H test was used for continuous variables, according to the results of the normality test (Shapiro-Wilk Test); a chi-square analysis and frequency analysis was used for categorical variables. Spearman's test was used for correlation analysis and some variables, the list-based deletion method was used. The results were evaluated using the "SPSS 21.0 for Windows." A result of $p<0.05$ was considered statistically significant.

Results

The study included sixty individuals and of these, forty were patients (20 ASDs, 20 HFAs) and twenty were controls. In the study groups, there were 13 (65%) male and 7 (35%) female patients who were diagnosed with ASD, and of the patients who were diagnosed with HFA, 19 (95%) were male and 1 (5%) was female. The control group was comprised of 9 (45%) males and 11 (55%) females. There was a significant difference in terms of gender between the patient groups ($p=0.003$). The mean age of the patients with ASD diagnosis was 4.5±1.83 and the mean age of the patients diagnosed with HFA was 4.02±1.48, whereas the mean age of the control group was 4.2±1.8; there was a homogeneous distribution among the groups ($p=0.259$). When the patient groups were compared in terms of having an intellectual disability (ID), it was observed that 6 (30%) of the patients with ASD and 1 (5%) of the patients with HFA had ID, respectively ($p=0.037$). In addition, it was also determined that 5 (25%) of the parents of ASD patients who were included in the study had consanguinity. There was no sanguinity among the parents of the HFA patients ($p=0.017$). The relatives of 10 (50%) patients with ASD and 11 (55%) patients with HFA were found to have neurological diseases ($p=0.752$). The ADSI test was performed on each patient group and the result was observed to be abnormal in all ASD patients and in 11 (55%) of the HFA patients.

There was a statistically significant difference among the groups (p=0.001; p<0.05) (Table 1).

Table-1. The clinical and demographical findings in the study groups.

Variables	ASD (N=20)	HFA (N=20)	Control (N=20)	p value
Age (years)	4,5 ± 1,83	4,02 ± 1,48	4,22± 1,80	0.682
Gender				
Male	13 (65%)	19 (95%)	11(55%)	0.003*
Female	7 (35%)	1(5%)	9 (45%)	
ID	6 (30%)	1 (5%)	-	0.037*
Consanguinity	5 (25%)	0 (0%)	-	0.017*
Presence of Neurological Disease in Relatives	10 (50%)	11 (55%)	-	0.752
ADSI				
Abnormal	20(100(%)	11 (55%)	-	0.001*
Normal	0(%)	9(45%)	-	

ID: intellectual disability, ADSI: Ankara Developmental Screening Inventory, *p<0.05. (Mean ± SD).

Table-2. The gene expression results of the groups (Mean ± SD).

Groups	NEURL1	RGS14
Control	0,77±1,031	1,39±1,48
ASD	0,395±0,504	1,51±0,81
HFA	0,22±0,221	1,07±0,52
p Value	0,027*	0,219

*There is statistically significant (p < 0.05) difference between groups.

The gene expression results of the groups and the p values of the genes are shown in Table 2. NEURL1 gene expressions were significantly different between the groups (p<0.05). When NEURL1 gene expression was compared between the HFA and control groups (Figure 1a), NEURL1 gene expression was significantly decreased in the HFA group (p=0.006). However, no significant differences were detected between ASD and other groups in the NEURL1 gene expressions. The p value between the ASD and HFA groups was 0.526 (p>0.05), whereas the p value between the ASD and the control groups was 0.85. No significant differences were detected between the groups in the RGS14 gene expressions (Figure 1b): the p value between ASD and HFA was 0.077, the p value between ASD and control groups was 0.219, whereas the p-value between the HFA and control groups was 0.790.

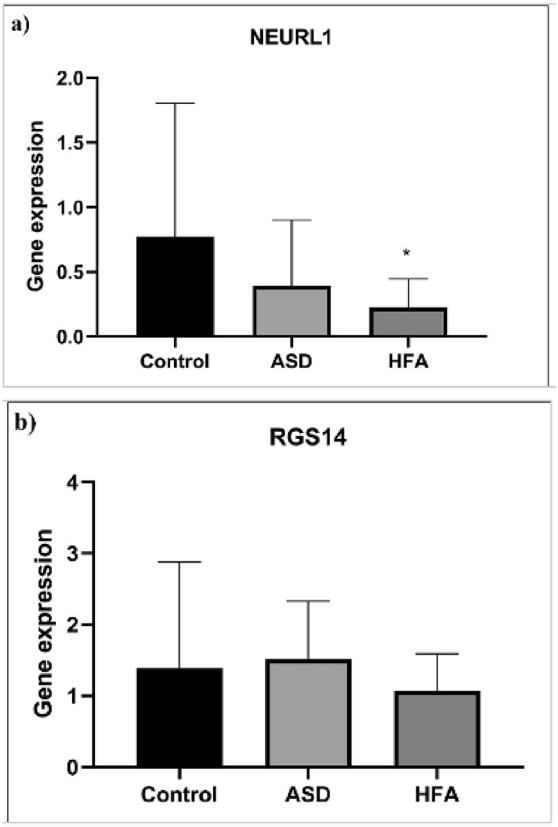

Fig. 1 Real-time RT-PCR results of putative genes associated with learning and memory. The data are given as means±SD *p<0.05 vs. control. a) NEURL1 gene expression comparison between groups. b) RGS14 gene expression comparison between groups.

In addition, the relationship between the NEURL1 and RGS14 genes was evaluated among the patient groups. In the ASD group, the Spearman correlation coefficients between NEURL1 and RGS14 expression levels were found to be 0.65 (p=0.008). However, it was found to be 0.344 (p=0.274) in the HFA group. A strong positive correlation was observed between the NEURL1 and RGS14 genes in the ASD group. When the gene expressions were compared with demographic features, we found a negative correlation between the learning and memory problems and RGS14 gene expression (Table 3).

Discussion

ASD is a complex neurodevelopmental disease. With ASD patients, there are disorders in cognitive episodic memory, future planning and learning difficulties [7, 8, 21]. Molecular and genetic studies suggest that the pathologic changes involved in ASD are likely to alter synapse formation and function, therefore affecting hippocampal-based learning and memory [7, 22]. Overexpression of

Table-3. Correlations of gene expressions and demographical findings.

	Genes	NEURL1	RGS14	Age	ID	NDR	Cons.	Learning and Memory Dif.
ASD	NEURL1							
	Spearman Correlation	-	0,594*	0,014	0,098	-0,077	0,136	0,174
	Sig. (2-tailed)	-	0,032	0,959	0,364	0,392	0,314	0,268
	RGS14							
	Spearman Correlation	0,594*	-	-0,243	0,377	-0,031	0,192	0,318
	Sig. (2-tailed)	0,032	-	0,382	0,083	0,456	0,246	0,124
HFA	NEURL1							
	Spearman Correlation	-	-0,344	0,087	-	-0,097	-	0,231
	Sig. (2-tailed)	-	0,274	0,788	-	0,382	-	0,235
	RGS14							
	Spearman Correlation	-0,344	-	0,384	-	-0,107	-	-0,471*
	Sig. (2-tailed)	0,274	-	0,175	-	0,357	-	0,045

Statistically significant correlations are shaded. *Correlation is significant at the 0.05 level (2-tailed). NDR: Neurological Disease in Relatives, Cons: Consanguinity, Learning and Memory Dif: Learning and Memory Difficulties.

the NEURL1 gene and its related mechanisms have been shown to be effective in learning and memory in animal ASD models [11, 12, 14, 17]. In addition, the RGS14 gene has been shown to be a natural suppressor of synaptic plasticity, memory and hippocampal-based learning [18, 19, 23]. However, the effectiveness of these genes on learning and memory is not yet clear and has not been studied before in patients with ASD. In our study, we investigated the differences in mRNA expression levels of NEURL1 and RGS14 genes in blood samples of ASD and HFA patients and control groups, and we evaluated the role of these genes in the pathogenesis of ASD in terms of its effects on learning and memory problems.

Several studies have shown that the NEURL1 gene suppresses the CPEB3 and, accordingly, increases synaptic plasticity and enhanced hippocampal-based learning and memory as well [14, 16]. Vogler et al. showed that human CPEB3 (activated by monoubiquitination NEURL1) plays a role in human episodic memory [24]. Pavlopolus et al. (2008) showed that overexpression of NEURL1 in the peripheral neurons of the adult Drosophila results in a dosage-dependent enhancement of long-term memory (LTM) [25]. Pavlopolus et al. (2011) showed that the number of synapses and synaptic plasticity increased in the hippocampus as a result of over-expression of NEURL1 in mice with ASD, and stated that this gene is also effective in learning and memory in mammals [14]. Studies on humans about this subject are very limited, therefore it is imperative that this gene be studied in patient groups following animal experiments. Our results are consistent with earlier studies in models of ASD. According to the results of our study, NEURL1 gene expression was decreased in both patient groups compared to the control. However, when evaluated clinically, NEURL1 gene expression did not correlate with ID, learning and memory, therefore we suggest repeating this relationship examination with a larger number of patients. Although this study will guide further research, we suspect that gene expressions in peripheral blood may be inaccurate, therefore studying NEURL1 gene expression from human brain tissues may be a more preferable option.

Despite the fact that RGS14 plays a basic immunological role in tissues like the spleen, thymus and lymphocytes, it is one of the negative regulator genes of the hippocampal-based learning and memory in the brain [19, 23]. Studies in this area mostly focus on experimental mouse models. For instance, it was observed that the cells of the RGS14 gene knockout (RGS14-KO) mice, obtained from the hippocampus CA2 region, respond to various electrochemical stimuli faster, making neuronal connections stronger and forming more complex synapses [19]. Lee et al. showed that RGS14 knockout mice showed a manifest increase in spatial learning and object recognition memory compared to wild-type mice, but that there was no difference in their performance in non-hippocampal behaviour tests.

This gene is therefore predicted to be effective in hippocampus-mediated learning and memory [18]. In our study, mRNA expression levels of the RGS14 gene were evaluated in ASD and HFA patients. No significant differences were detected between groups in the RGS14 gene expressions, although there was a negative correlation between learning and memory difficulties and the RGS14 gene in HFA patients. We believe meaningful data can be obtained with additional patients and more comprehensive studies on this subject. In addition, in order to establish a clear relationship with autism, it is recommended these results be supported by studies using brain tissue in experimental models.

Conclusion

In the present study, we examined the relationship of the NEURL1 and RGS14 genes expressed in the hippocampus, with learning and memory disorders in ASD and HFA patients. We showed that the NEURL1 gene may affect learning and memory in ASD. Moreover, it has also been shown that the RGS14 gene has a relationship with the clinical features of ASD, however, aside from this, we suspect that gene expressions will yield clinically significant results in studies with additional patients and brain tissue analyses. This study was the first to examine the NEURL1 and RGS14 genes in patients with ASD and in this respect, we expect it will make important contributions to the literature.

Conflict of Interest: The authors declare no conflict of interest related to this article.

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The role of fatty acids in attention deficit hyperactivity disorder

Dikkat Eksikliği ve Hiperaktivite Bozukluğunda Yağ Asitlerinin Rolü

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a childhood-onset disorder that affects 5% to 12% of children worldwide. Etiological factors, including nutrition, contribute to this disease, which is characterized by inattention, impulsivity and hyperactivity symptoms. Fats, which form an important part of the daily diet, can have effects on ADHD and its symptoms. In the literature, it is stated that omega-3 fatty acids are low in children with ADHD, and supplementation studies may be effective in improving symptoms. In addition, high omega-6/omega-3 fatty acids ratio in the diet and diets rich in saturated and trans fatty acids are associated with ADHD. In this review, the relationship between ADHD and dietary fatty acids was evaluated.

Keywords: ADHD, saturated fatty acids, trans-fatty acids, omega-3 fatty acids, omega-6/omega-3 ratio

ÖZ

Dikkat eksikliği hiperaktivite bozukluğu (DEHB), çocukluk çağında başlayan ve dünya çapındaki çocukların %5 ile %12'sini etkileyen bir hastalıktır. Dikkatsizlik, dürtüsellik ve hiperaktivite semptomları bozukluklarıyla seyreden DEHB'de beslenmenin de içerisinde bulunduğu etiyolojik faktörler yer almaktadır. Günlük diyetin önemli bir parçasını oluşturan yağlar, DEHB ve semptomları üzerine etkileri olabilmektedir. Literatürde DEHB tanılı çocuklarda omega-3 yağ asitlerinin düşük olduğu ve takviye araştırmalarının semptomları iyileştirmede etkili olabileceği belirtilmektedir. Ayrıca diyetteki yüksek omega-6/omega-3 yağ asitleri oranı ile doymuş ve trans yağ asitlerinden zengin beslenme düzenleri DEHB ile ilişkilendirilmektedir. Bu derlemede DEHB ile diyetle alınan yağ asitleri arasındaki ilişki değerlendirilecektir.

Anahtar kelimeler: DEHB, doymuş yağ asitleri, trans yağ asitleri, omega-3 yağ asitleri, omega-6/omega-3 oranı

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders in children. It affects between 5% and 12% of all children globally and is a syndrome characterized by inattention, lack of focus, restless overactivity, impulsivity and deficiencies in executive functions [1]. ADHD is an illness with a complex etiology, influenced by genetic and environmental components. Genetic predisposition has an essential place in the etiology of ADHD and pathogenic processes for gene expression are linked to a variety of environmental factors, including physical, chemical, dietary, familial and social impacts [1]. ADHD is thought to be a multifactorial disorder, but its pathophysiology has not yet been fully demonstrated [2].

Fatty acids, one of the nutritional factors, play an essential role in maintaining the normal function of the brain and nervous system. The nervous system is the second organ with lipid concentration after adipose tissue: nearly 35% consists of long-chain polyunsaturated fatty acids (LC-PUFAs) [3]. Humans cannot produce linoleic acid, an omega-6 fatty acid, nor alpha-linolenic acid which is an omega-3 fatty acid,and must consume both with nutrition. Linoleic acid and alpha linolenic acid undergo desaturation and elongation by several enzymes; LC-PUFAs are then formed, which are involved in neurodevelopmental processes [4]. Studies have shown that LC-PUFA, Eicosapentaenoic (EPA, n-3) and docosahexaenoic acids (DHA, n-3), may play a role in ADHD. Insufficient omega-3 fatty acid consumption can disrupt serotonin pathway function and impact impulse control, sensory gating and behaviour, resulting in ADHD [5]. Trans fatty acids, in addition to inadequate dietary omega-3 fatty acid intake, can disrupt the body's omega-3 balance [6]. Aside from fatty acid types, the link between a high-fat diet and ADHD has also been investigated: evidence from animal experiments reports that high-fat and saturated-fat diet models may increase to the risk of ADHD through neuroinflammation [7,8].

According to other studies, children with ADHD have atypical fatty acid profiles and these changes may be linked to symptoms [9,10]. In addition, there are cohort studies showing that maternal fatty acid consumption during pregnancy may also have an effect on children's behavior. [11–13]. For this reason, studies on fatty acid supplementation in both pregnancy and childhood continue to be the subject of current study in the literature.

In this review, the properties of dietary fatty acids, the effects of fatty acid intake during pregnancy on children's behavior, the status of fatty acids in children with ADHD and the end points of supplementation studies in the literature, was evaluated.

This research was a literature review of peer-reviewed journal articles that study long-chain fatty acids, saturated fatty acids and trans fatty acids' role in ADHD. The journal articles were found using the following search engines: Google Scholar, National Library of Medicine (Pubmed.gov). Most of the searches were narrowed only to include studies from the past ten years, 2012-2022. The following search keywords were used for relevant articles: “ADHD and fatty acids” and “ADHD and diet.” "Maternal nutrition and ADHD", "ADHD fatty acids RCT", "DHA and ADHD", "EPA and ADHD", "trans fatty acids and ADHD". Articles were also found by reviewing the references of previous literature reviews.

2. Dietary fatty acids

The most important class of dietary fats is triglycerides. The triglycerides' properties are determined by the double bonds, the number and location of the double bonds and their cis-trans forms [14].

Saturated fatty acids (SFA): Fatty acids without double bonds in their side chains. Dairy products, meat, coconut and palm oil are foods rich in SFAs [14] (Figure 1).

Monounsaturated fatty acids (MUFA): Fatty acids with one double bond in their side chains. Olive oil is one of the foods rich in MUFAs [14] (Figure 1).

Polyunsaturated fatty acids (PUFAs): Fatty acids with more than one double bond in their side chains [14]. This fatty acid is referred to as a long-chain acids polyunsaturated fatty acid (LC PUFA) if it is made up of more than 20 carbon atoms. Omega-3 (n-3) and omega-6 are the most common forms

of PUFA (n-6). These include alpha-linolenic acid (ALA: n-3) and linoleic acid (LA: n-6), which are essential nutrients to humans and thus must be obtained via nutrition. Humans are capable of synthesizing arachidonic acid (AA: LC-n-6 fatty acids) from LA and eicosapentaenoic (EPA: long-chain n-3 fatty acids) and docosahexaenoic acid (DHA: long-chain n-3 fatty acids) from AL. Fish and flaxseed oil are rich in n-3 fatty acids, and sunflower, corn and soybean oil are rich in n-6 fatty acids [14] (Figure 1).

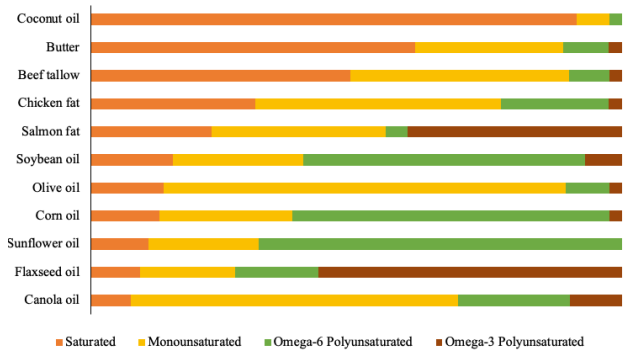

Figure 1: Composition of dietary fats [14]

Trans fatty acids (TFA): Chemically, these are classified as an unsaturated fatty acid but show a saturated fatty acid role in the human metabolism. Trans fatty acids are found in animal fats, milk and dairy products, and vegetable oils saturated with hydrogenation [6]. In vegetable oils, conversion to trans bonds is used to boost oil stability [15].

Dietary cholesterol: It is exclusively found in food of animal origin, such as meat and dairy products [14].

Plant sterols/ Phytosterols: Phytosterols are naturally occurring chemicals found in vegetable oils and nuts [16]. It is commercially added to margarine, mayonnaise, yogurt, cheese and some sauces [17,18].

Dietary fats are macronutrients, one of the main components (35 to 40%) of daily energy [19]. Fatty acids differ according to dietary patterns: while the Mediterranean diet, which is shown as the healthiest diet [20], is rich in PUFAs, SFAs are consumed in excess in the Western diet, which is associated with the increased disease [21] (Figure 2) [14]. Studies investigating the dietary patterns of patients with ADHD show that the Western diet is more readily espoused whereas compliance with the Mediterranean diet is low [22,23]. It has also been reported that the mother's diet contributes to the child's ADHD symptoms [24,25].

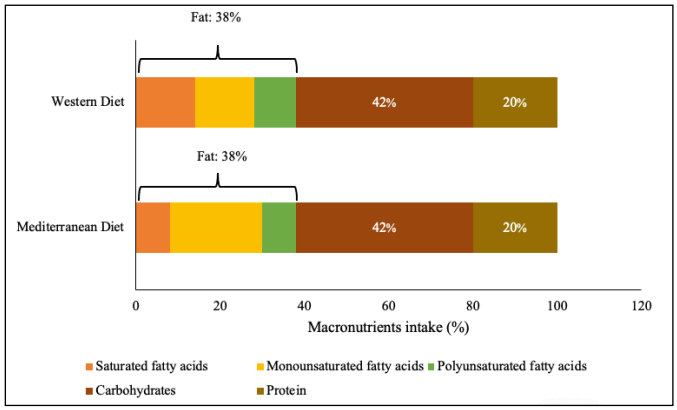

Figure 2: Contribution of fatty acid intake to total energy intake in Mediterranean and Western diets [14]

3. The function of fatty acids in ADHD

Omega-3 and omega-6 fatty acids are abundant in the central nervous system. DHA regulates the synthesis, release and transport of neurotransmitters and plays an important function in neuron development, membrane permeability, endothelial activity, neuronal survival and neurodegeneration prevention [9]. The function of the serotonin receptor, a neurotransmitter, depends on cell fluidity. DHA regulates the serotonin receptor by increasing cell fluidity. EPA and DHA levels regulate serotonin synthesis, storage, release and receptor function during neurodevelopment in the maternal period [26]. The decrease in brain serotonin levels can lead to disorders in social behaviours, such as learning and memory disorders and impulsive behaviours. Therefore, low serotonin levels are one of the underlying mechanisms of ADHD [24]. It has been shown in animal experiments that deprivation of omega-3 fatty acids causes behavioural abnormalities, but behavior returns to normal when DHA supplementation is administered [27].

The brain signalling system is mediated by highly unsaturated fatty acids (HUFAs) along with dopaminergic and serotonergic pathways [28]. N-6 fatty acids are required in the structure of the membrane and the synthesis of eicosanoids [14]. Eicosanoids involve several physiological processes in the brain with the inclusion of

synaptic plasticity, release of neurotransmitters, temporal summation, membrane excitability and apoptosis [29].

Nowadays, the intake of n-3 fatty acids in diets has declined and in western diets, the n-6/n-3 ratios have risen from 1:1 in conventional diets, to around 16:1 [30]. This changed rate can lead to inflammation, vasoconstriction and thrombosis [9]. A low n-6/n-3 ratio is desirable because it reduces the risk of a high prevalence of chronic diseases [30]. Furthermore, a high n-6/n-3 ratio can affect the activity of neurons by limiting the supply of LC n-3 in the brain [31].

4. Maternal diet and ADHD

The placenta delivers long-chain fatty acids to the fetus, and breast milk delivers them to the newborn [32]. According to the examined studies, decreased DHA levels in newborns can lead to mental and behavioural dysfunction, such as poor reading ability, low memory performance, opposing behaviours and emotional disturbances [32]. Hibbel et al. conducted observational cohort research on the seafood intake of 11.875 pregnant women. In the regression analysis, it was seen that the risk of low verbal intelligence scores was approximately 1.5 times higher in the children of those who consumed below 340 grams of seafood each week. They were also shown to be at risk in terms of social behavior, fine motor abilities, communication and social development [11]. DHA, a fatty acid present in seafood, helps to sustain the structure and function of the growing brain. DHA deficiency can impair attention by affecting monoaminergic systems [33]. An Italian cohort study investigated the effect of mothers' seafood consumption during early pregnancy on their children. High seafood consumption has been linked to greater child attentiveness: analyses were made when children reached 8 years of age and were examined independently of seafood consumption and cognitive functions [12]. In another randomized controlled experiment including 1 094 pregnant women, DHA supplementation was administered. Children were assessed when they were 5 years old and improved attention scores were observed in those given the supplement over the placebo [13].

5. Fatty acids status of patients with ADHD

Wang et al., in their study on 216 ADHD and 216 controls, found that serum SFA and n-6/n-3 ratio were higher and MUFA were lower than the control [34]. A cross-sectional study by Montgomery et al., related low DHA levels to decreased reading and memory performance, increased opposing behaviours and emotional disturbances [35]. Parletta et al. showed that children with autism and ADHD have low degrees of EPA, DHA and AA in the blood, and a high n-6/n-3 fatty acids ratio, and these values are associated with ADHD symptoms [9]. However, while omega-3 supplementation trials for ADHD have been successful in the literature, no effect has been observed for autism [36]. Similar to Parletta et al. study, in the Italian sample, it was found that children with ADHD had low DHA levels, n-3 index, and MUFA, and these findings were associated with behaviours but not with cognition [10]. Hawkey et al. published a meta-analysis including 9 studies evaluating blood fatty acid levels in patients with ADHD [37]. In these cross-sectional studies, the levels of fatty acids analyzed from plasma or erythrocyte and dietary intake of fatty acids were evaluated. According to the meta-analysis results, fatty acid levels were found to be low in ADHD patients.

On another viewpoint, there are studies evaluating the effect of excessive consumption of saturated and trans fatty acids on ADHD. The principal part of the Western diet is SFAs, and the Western diet is linked with ADHD and its symptoms [7,8]. Evidence from experimental animal studies reports that a maternal high-fat diet has structural and functional effects on offspring brain development. A high-fat diet may lead to increased proliferation in the hypothalamus, decreased apoptosis in brain regions and neural differentiation. It can also cause neuroinflammation in the serotonergic nervous system, which increases the probability of behavioural problems like ADHD [38].

The omega-3 level in the body can also be regulated by the intake of trans fatty acids [6]. Trans fats are known to raise the risk of cardiovascular disease [39]. In addition, studies are showing that it can affect brain functions [40]. Trans fatty acids may have an impact on ADHD by lowering DHA levels or by inhibiting the conversion of linolenic acid

to DHA [41,42]. Studies in experimental animals have shown that trans fatty acid reduces DHA levels in plasma, liver and brain [43,44]. Few studies, however, have examined the effect of trans fatty acid intake in patients with ADHD. Kim et al. showed that female adolescents with ADHD consumed more dietary trans fatty acids than controls [45]. Similarly, Colter et al. found that people with ADHD consumed more trans-fatty acids than healthy controls [46]. In a study in which fatty acids from erythrocytes of children with ADHD were examined, it was observed that there was a high level of trans fatty acids, and a lower level of DHA compared to the control group. Furthermore, trans fatty acids have been linked to ADHD symptoms. This study had some limitations, as it has was not examined whether dietary fatty acid intake affects blood levels. Children with ADHD who receive treatment are not excluded, so treatment improves the disease and this may be reflected in their fatty acid levels [47].

6. PUFA's supplementation effect on ADHD

Because of PUFAs on the brain and nervous system, n-3/6 supplementation studies in the treatment of ADHD have been the area of research. Children with ADHD received EPA and DHA for seventeen weeks in a randomized controlled trial. In children with learning difficulties that may progress with ADHD, with the increase in DHA level, progress in reading and spelling, a decrease in oppositional behavior, hyperactivity and anxiety symptoms have occurred [48]. Similarly, Gustafsson et al. showed improvement in behavior and oppositional symptoms in a randomized, placebo-controlled study with ADHD who were given EPA supplements for fifteen weeks [49]. A randomized, placebo-controlled supplement of n-3 fatty acids containing EPA and DHA was administered to children with ADHD in a study by Widenhorn-Müller et al. for sixteen weeks. The memory function of children with ADHD has improved, but no impact on other mental measures [50].

However, in another randomized, placebo-controlled study carried out by Matsudaira et al., adolescents with ADHD were given LC-PUFA supplements for twelve weeks, and it was observed that the treated group did not have any superiority over the placebo [27]. In this study, a power analysis was not performed while determining the number of participants and for this reason, the expected effect may not have been observed. Methylphenidate is a drug that is frequently used in the treatment of ADHD [1]. In a double-blinded randomized controlled study of 40 children, the administration of methylphenidate in combination with PUFA supplements resulted in a further reduction in the severity of symptoms than placebo [51].

Chang et al. revealed in a comprehensive review and meta-analysis that supplementation might enhance clinical symptoms and cognitive function in ADHD individuals with low n-3 fatty acid levels [52]. However, it is controversial whether n-3 supplements should be used in children with normal blood levels [7]. Studies must be methodologically consistent for n-3 supplements to be recommended in the treatment of ADHD. For this, accurate ADHD diagnosis criteria, measuring fatty acid levels of patients before supplementing, a double-blind controlled design, consistency of symptom scales and nonpharmacological intervention studies are required [28].

Limitations: There is a limitation in this review. There are studies in the literature in which teacher scales are lacking in assessments for ADHD symptoms. This prevents establishing an exact symptomatic connection. Therefore, a complete relationship could not be established.

Conclusion: Children with ADHD have low levels of n-3 fatty acids, and when children with low n-3 fatty acid levels took the n-3 supplement, improvements in clinical symptoms were seen. Moreover, dietary patterns with a high n-6/n-3 ratio, rich in saturated and trans-fatty acids, may worsen ADHD symptoms. However, long-term randomized controlled double-blind studies are needed to demonstrate the effect of supplementation. In addition, it is not clear how fatty acids affect ADHD.

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LETTER TO EDITOR

EDİTÖRE MEKTUP

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Has the Covid-19 pandemic affected the practice of Orthopedics and Traumatology?

Covid-19 pandemisi, Ortopedi ve Travmatoloji pratiğini etkiledi mi?

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Dear Editor;

The covid-19 pandemic has not only affected infectious or chest disease clinics but also all services and nearly all researchers [1]. To search the rate of affection through orthopedic surgeons in Turkey, we conducted a survey virtually via Turk-Ortopod mailing group. Among all group members, 300 participated in our survey. We want to share our interesting results to point out that the covid-19 pandemic had major changes in many aspects of orthopedic practice like other countries.

Most of the participants were young (72% between 25-44 years old) specialists (48,8%) or residents (20,4%) actively working in daily duties, 60% in training or university hospitals at least for 10 years (45,8% 5-15 years), 83.7% with no chronic comorbidity. 88.3% of these facilities also served covid-19 infected patients, so 64.4% were working in units with risk of covid-19 transmission like emergency departments. Most were living with family members (57% 2-3, 24% 4), and 89% were concerned about the disease being transmitted to the home, while 54% were concerned about self-infection. 26.2% thought there were deficiencies in protective equipment and precautions, 48.7% found it nearly sufficient as advised [2]. So 59.2% wanted to stay away from their home during this period, but only 26.5% had other places to stay. Furthermore 34.7% worried about the risk of income-loss, 41.7% concerned about its impact on social life, as 45.3% experienced changes in their work patterns; 39.1% served only control patients, 86.3% performed only emergent operations, while 39.9% had had nearly 10 elective patients on their waiting lists. Not only psychosocial health of orthopedic surgeons [3], but this situation also negatively impacted waiting patients [4]. However, 70.8% reported that they would operate a covid-19 infected patient only if urgent and necessary precautions were taken. The use of guiding principles for resuming elective orthopedic surgery seems to be safe [5]. Thus patient selection and

surgical timing has been advised to categorize in certain groups by Turkish Society of Orthopaedics and Traumatology [6]. But nevertheless surgeon decides the timing on his own experience [7].

On the other hand, 62.8% found their knowledge about the covid-19 partially sufficient, because 54.2% received their information from scientific sources, 30.8% from social media. While 28.3% thought it was a serious problem, 33.7% believed it needed much more attention. 59.1% believed that the national orthopedic specialty association had sufficient information and guidance through the pandemic period. When this survey was conducted, 46.8% of participants believed they would return to their normal routine within 2 to 5 months. The pandemic had also an effect on the delivery of education, with face to face teaching being replaced by webinar-based teaching. Nevertheless Turkish residents had psychological distress [8], and concerns about their training program, like their colleagues worldwide.

We want to mention that many orthopedic surgeons are concerned about the current situation with a lot of uncertainty, and this impacted the orthopedic surgical practice during this pandemic [9]. Working under directions of the World Health Organization and national associations will provide a safe working environment for orthopedic surgeons till the pandemic ends [10].

With our best regards.

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