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The comparison of prednisolone and honey activities in the experimental corrosive esophagitis model

DeneySEL koroziv özofajit modelinde prednisolon ve balın etkinliklerinin karşılaştırılması

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Abstract

Aim: Honey is well known for its beneficial wound healing-related effects, including anti-edematous effects, stimulation of granulation tissue formation, chemical debridement, and immune system enhancement. In this experimental study, the effects of honey and prednisolone on stricture formation in sodium hydroxide-induced corrosive esophagitis were investigated.

Methods: This study was carried out on Wistar albino rats weighing between 200-250 grams. Rats were divided into four equal groups. Corrosive esophagitis induced by 37.5% sodium hydroxide was formed in three groups. The first group received no specific treatment. The second group was treated with honey via the oral route, and the third group was treated by prednisolone intraperitoneally. The control group underwent a sham laparotomy. All subjects were sacrificed by the end of the 28th day. A 20-mm long segment of the distal esophagus was harvested for histopathological examination. The tissue damage scores and stenosis index scores of the groups were measured and compared.

Results: A total of 32 rats were included in the study, with eight subjects in each group. The mean values of stenosis index score and tissue damage score were significantly lower in the honey-treated group ($P=0.001$).

Conclusion: Oral honey treatment seems to reduce the severity of esophageal strictures associated with corrosive esophagitis, when compared to untreated and prednisolone-treated groups.

Keywords: Caustic esophageal burn, Corrosive esophagitis, Honey, Prednisolone, Stricture, Stenosis index, Tissue damage

Öz

Amaç: Bal antiödem etkisi, granülasyonu hızlandırıcı etkisi, enzimatik debridman ve immün sistemi güçlendirici etkisi bilinen bir doğal gıdadır. Bu deneysel çalışmanın amacı bir alkali ajan olan sodyum hidroksit ile oluşturulan koroziv özofajitte darlık gelişimi üzerine balın ve prednisolonun etkilerini araştırmaktır.

Yöntemler: Bu çalışma, ağırlıkları 200-250 gram arasında değişen Wistar tipi albino sıçanlar üzerinde gerçekleştirildi. Denekler, eşit sayıda dört gruba bölündü. Birinci, ikinci ve üçüncü gruplar özofajit modeli grupları olup, bu gruplardaki tüm deneklerde %37,5'lük sodyum hidroksit ile koroziv özofajit oluşturuldu. Birinci gruba herhangi bir tedavi uygulanmazken, ikinci gruba oral bal tedavisi ve üçüncü gruba intraperitoneal prednisolon tedavisi uygulandı. Kontrol grubunun özofagusuna herhangi bir işlem yapılmadan şam laparotomi uygulandı. Tüm denekler 28. gün sakrifiye edildi ve deneklerin distal özofaguslarından alınan 20 mm uzunluğundaki örnekler histopatolojik incelemeye tabi tutuldu. Grupların doku hasarı skorları ve stenoz indeksi skorları ölçülerek kıyaslandı.

Bulgular: Çalışmaya toplam 32 denek dahil edildi ve her bir grupta sekiz denek mevcuttu. Stenoz indeksi skoru ortalama değeri ve doku hasarı skoru ortalama değeri balla tedavi edilen grupta, prednisolon verilen ve tedavi verilmeyen gruplara kıyasla anlamlı olarak düşüktü ($P=0,001$).

Sonuç: Bal, prednisolona kıyasla, alkali ajanla oluşturulan deneysel koroziv özofajit modelinde gelişen özofagus darlıkları üzerinde daha anlamlı düzeyde olumlu etkiye sahiptir.

Anahtar kelimeler: Kostik özofagus yanığı, Koroziv özofajit, Bal, Prednisolon, Darlık, Darlık indeksi, Doku hasarı

Introduction

Burn injuries in the esophagus caused by drinking strong acid and alkaline substances are generally seen more in pre-school age children and the elderly in developing countries [1]. The scar tissue that develops during the healing process causes a narrowing of the esophagus as with any burn, which leads to severe problems in the patient's quality of life, morbidity, and even mortality [2].

Treatment of strictures related to esophageal burns have been studied since the beginning of last century. A few methods have been proven successful in the studies on clinical treatments, except for dilatation and local steroid injection. Those that are accepted as relatively successful are still a long way from being the ideal treatment method. Therefore, experimental research has started using various substances and materials on animal burn models. Apart from steroids, materials that have been found to be largely successful have not been introduced into practical use in the clinic. The reasons for this are partially due to toxicity, cost, and availability problems, and the main reason is that they have not been proven safe for human use [3].

Since treatment is difficult after the formation of burn strictures, the research on treatment must be aimed at preventing stricture formation following the burn. Stricture development occurs with the development of excessive collagen during the healing process and negative wound healing [4].

Since the ancient times, honey has been used in the treatment of various diseases, especially wound care. It has been advocated as a foodstuff with high nutrient content, having properties that accelerate wound healing, such as high viscosity, acidic pH, high osmolarity and hydrogen peroxide, all of which engage in bacterial growth inhibition [5]. Numerous studies have shown that honey also suppresses free radical production [6]. There are many studies demonstrating that granulation is prevented, and stricture formation is decreased by steroidal components [7-9].

The aim of this experimental study was to investigate the effects of honey and prednisolone on stricture formation in sodium hydroxide-induced corrosive esophagitis in a rat model.

Materials and methods

Study design

This experimental study was conducted in the Experimental Medicine and Research Center of the University after approval was obtained from the Local Animal Research Ethics Committee. All procedures in the study were performed in accordance with the principles of the Guidelines for Animal Research of the Ethics Committee.

A total of 32 female Wistar albino rats, each weighing 200–250 g, were randomly separated into four groups of eight rats. All animals were kept in metal cages at a room temperature of 22°C and a 12-h light-dark cycle. The rats that were to undergo laparotomy were fasted starting on the morning of the procedure.

Forming the model of chemical esophagus burn

Laparotomy was performed after the administration of intraperitoneal anesthesia with 40 mg/kg sodium thiopental. Abdomen was entered with a 2-cm midline incision, and a 20

mm-long segment of the abdominal esophagus was prepared. A 6F catheter, 48 mm in length, was passed through the mouth and placed in the upper segment of the abdominal esophagus. To prevent aspiration of the corrosive agent into the respiratory system, the esophagus was sutured with 2/0 silk immediately proximal to and below the diaphragm. A solution of 1 ml 37.5% NaOH (pH=12) prepared for the 90 sec period after catheter placement was then administered to the esophagus. The burnt segment was irrigated for 60 seconds with distilled water. The proximal 2/0 suture was cut, and catheter was withdrawn from the mouth with negative pressure to prevent aspiration. The distal 2/0 suture was then cut, and laparotomy incision was closed (Gehanno and Gudeon Model) [10,11].

Study groups

Group 1 (Burn, n=8): Corrosive esophagitis was induced. Animals were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Group 2 (Burn +Honey, n=8): Corrosive esophagitis was induced, and the animals were administered honey via gavage once a day starting on postoperative Day 1. The rats were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Group 3 (Burn+Prednisolone, n=8): Corrosive esophagitis was induced, and the animals were administered 1 mg/kg/day intraperitoneal prednisolone daily, starting from postoperative Day 1. The rats were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Group 4 (Sham laparotomy group–control group, n=8): No corrosive esophagitis was induced. Rats were kept under standard laboratory conditions and fed for 28 days with free access to standard pellet food and tap water.

Sample Collection: At the end of the 28-day study period, all rats were euthanized with high-dose anesthetics. A 20 mm-long section of esophageal tissue was removed for histological evaluation. The proximal section of the burnt segment was placed in 10% neutral formaldehyde for histological examination and stored under appropriate conditions until the assay.

Histopathological evaluation

Routine histological methods were applied to tissues fixed in neutral formaldehyde. Four micrometer-thick slices were cut from the tissue embedded in paraffin blocks and stained with hematoxylin and eosin [12].

Stenosis Index (SI): The stenosis index (SI) has been used to determine stricture severity in hollow organs, especially the esophagus. The esophageal wall thickness is measured in two random areas each from 4 separate regions with an ocular micrometer using a scanning lens of 4 x 10 magnification on a light microscope (Olympus BX51, Tokyo, Japan), the average of which is calculated to evaluate SI along with the lumen diameters (Figure 1) ($A_{av}=[A1+A2]/2$). The lumen width is also measured from two separate areas with two separate lines, and the average is calculated ($B_{av}=[B1+B2]/2$). SI is finally calculated as average wall thickness divided by average lumen diameter ($SI = A_{av}/B_{av}$) [13,14].

Tissue damage classification

Submucosal collagen intensity, damage within the muscularis mucosa, and collagen density in the tunica muscularis were evaluated with scoring in three distinct categories. Submucosa is evaluated as 0: no damage, 1: mild, and 2: severe damage. Damage in the muscularis mucosa is scored as 0: absent and 1: present. The tunica muscularis was evaluated as 0: no damage, 1: mild and 2: severe damage. These points were summed up to get a score from 0 to 5 (Figure 2) [15].

Statistical analysis

Statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA). Descriptive statistical methods were used (mean, standard deviation, median, frequency, percentage, minimum, maximum values) in the evaluation of quantitative data, and Kruskal Wallis test was used in the comparison of more than 3 non-normally distributed groups. To determine the origin of the difference and compare two groups, Mann Whitney U test was used. Statistical significance was set at the levels of $P < 0.01$ and $P < 0.05$.

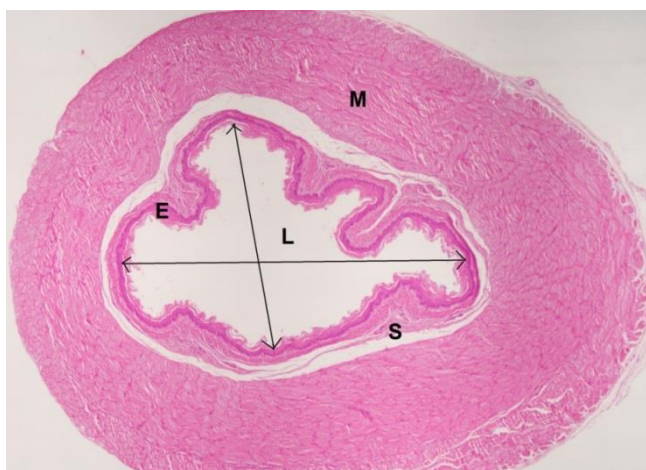


Figure 1: Normal histology of transverse esophageal section in control group (Double arrow depicts lumen width. Lumen (L), epithelium (E), submucosa (S), tunica muscularis (M) (Hematoxylin and eosin $\times 40$))

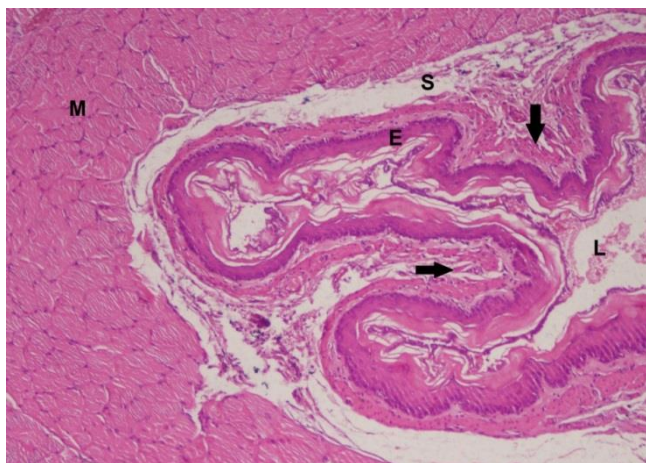


Figure 2: Histology of transverse esophageal section in untreated corrosive burn group (Lumen (L), epithelium (E), submucosa (S), tunica muscularis (M), collagen deposition and inflammation (arrows) (Hematoxylin and eosin $\times 100$))

Results

Tissue Damage (TD) scoring results

A normal histological structure was observed in the morphological images of the control group's slices. In the histological slices of Group 1 (esophageal corrosive burn and no treatment), evident degenerative changes were observed: A significant increase was detected in submucosal collagen as well

as collagen deposited around circular muscle fibers in the inner muscular layer. Also, the muscle fibers in the muscularis mucosa were significantly more irregular and degenerate.

All the groups were scored histopathologically and results were statistically compared (Table 1). As the tissue damage (TD) score of Group 4 was 0, it was not included in the evaluation in Table 1.

A statistically significant difference was found between the TD scores of the groups ($P=0.005$). Evaluations were made to determine from which group the significance originated. A statistically significant difference was determined between Groups 1 and 2 ($P=0.001$).

The difference between Groups 1 and 3 was not statistically significant ($P=0.139$).

The comparison of Groups 2 and 3 revealed that there were significant differences between honey and prednisolone in protecting against the development of esophageal stricture ($P=0.045$).

Stenosis Index (SI) scoring results

The stenosis index (SI) results and statistical comparisons are shown in Table 2.

A statistically significant difference was determined between Groups 2 and 3 with respect to the SI results ($P=0.003$), and between Groups 4, 1 and 3 ($P=0.001$, $P=0.002$, respectively) in terms of mean SI scores. Compared to the control group, the scores of Groups 1 and 3 were significantly low, and that of Groups 2 and 4 were similar ($P=0.674$).

Table 1: Comparisons of the tissue damage scores

Tissue Damage Score	Mean (SD)	Min-Max	Median	P-value
Group 1 (burn)	3.50(0.92)	2-5	3.5	^a 0.005*
Group 2 (burn + honey)	1.00(0.92)	0-3	1	
Group 3 (burn+prednisolone)	2.38(1.51)	0-4	3	
Group 1 (burn)	3.50(0.92)	2-5	3.5	^b 0.001**
Group 2 (burn + honey)	1.00(0.92)	0-3	1	
Group 1 (burn)	3.50(0.92)	2-5	3.5	^b 0.139
Group 3 (burn+prednisolone)	2.38(1.51)	0-4	3	
Group 2 (burn + honey)	1.00(0.92)	0-3	1	^b 0.045*
Group 3 (burn+prednisolone)	2.38(1.51)	0-4	3	

^aKruskal Wallis Test, ^bMann Whitney U test, ** $P < 0.001$, * $P < 0.05$

Table 2: Comparisons of the histopathological stenosis index

Histopathological Stenosis Index	Mean (SD)	Min-Max	Median	P-value
Group 1 (burn)	7.77(2.56)	5.5-13.6	7.25	^a 0.001**
Group 2 (burn + honey)	4.19(0.63)	3.2-5.4	4.1	
Group 3 (burn+prednisolone)	6.09(1.23)	4.9-8.4	5.7	
Group 4 (control)	4.06(0.64)	2.9-5.08	4.07	
Group 1 (burn)	7.77(2.56)	5.5-13.6	7.25	^b 0.001**
Group 2 (burn + honey)	4.19(0.63)	3.2-5.4	4.1	
Group 1 (burn)	7.77(2.56)	5.5-13.6	7.2	^b 0.059
Group 3 (burn+prednisolone)	6.09(1.23)	4.9-8.4	5.7	
Group 1 (burn)	7.77(2.56)	5.5-13.6	7.25	^b 0.001**
Group 4 (control)	4.06(0.64)	2.9-5.08	4.07	
Group 2 (burn + honey)	4.19(0.63)	3.2-5.4	4.1	^b 0.003*
Group 3 (burn+prednisolone)	6.09(1.23)	4.9-8.4	5.7	
Group 2 (burn + honey)	4.19(0.63)	3.2-5.4	4.1	^b 0.647
Group 4 (control)	4.06(0.64)	2.9-5.08	4.07	
Group 3 (burn+prednisolone)	6.09(1.239)	4.9-8.4	5.7	^b 0.002*
Group 4 (control)	4.06(0.64)	2.9-5.08	4.07	

^aKruskal Wallis Test, ^bMann Whitney U test, ** $P < 0.001$, * $P < 0.05$

Discussion

The results of this study showed that in the treatment of esophagitis associated with caustic substances, honey was more successful than prednisolone in decreasing stricture development and reducing TD to a minimum.

Exposure to caustic substances is still a fundamental problem in undeveloped regions of the world [16,17]. Liquefaction necrosis occurs in the esophageal mucosa with the ingestion of alkaline agents. Free oxygen radicals are known to increase with ischemia and TD around these areas, which trigger

lipid peroxidation in intracellular organellar membranes. This continues with an increase in membrane permeability and thereby, an increase in leukocytes starts the inflammatory process, escalating the damage.

In mild cases, esophageal functions can be regained. However, severe cases can result in stricture formation. Several experimental studies have been conducted with the aim of preventing stricture development, with treatments including agents that prevent lipid peroxidase inhibition such as tumor necrosis factor (TNF)-alpha antibodies, ozone therapy, sucralfate, pentoxifylline, and ketotifen [18,19].

The use of corticosteroids to prevent esophageal stricture development after the ingestion of corrosive materials is controversial. Some studies have reported the use of corticosteroids as 0%–25% in first- and second-degree esophageal burns and that stricture developed in 88% of cases when they are not used [19,20]. According to the results of some studies, the use of corticosteroids is of no benefit, and it has been suggested that stricture develops at rates of 20% to 38% despite the selected treatment for esophageal burns [21-23].

In the current experimental study, no statistically significant differences were determined between the prednisolone group (Group 3) and the esophagitis group irrigated with saline only (Group 1) with respect to the SI and TD scores. Prednisolone did not show a protective effect against fibrosis and stricture formation by reducing tissue damage.

According to the comparisons of the histopathological TD scores of Groups 2 and 3 (burn +honey and burn + prednisolone, respectively), honey showed a significantly greater histopathological effect in preventing fibrosis and stricture formation compared to prednisolone.

Honey is used as a strong agent in wound healing due to its anti-bacterial and anti-inflammatory effects [24-26]. Acceleration of epithelialization is necessary for wound healing. It is possible to reduce the inflammation, edema, and exudation formation in the wound with honey [24,27].

Clinical and animal studies have shown that honey reduces gastric acid expression. Honey added to the daily diet has been used to treat gastric ulcers. In a previous study of 600 gastric ulcer patients, it was reported that approximately 80% were treated with oral honey supplementation, and 59% of the patients taking honey recovered from ulcers [28].

Honey has also been proven effective in the treatment of patients with benign oral ulcers [29,30]. In a study of 50 adults with minor oral ulcers by Mohamed and Al-Dour, the ulcers recovered in three days in the group receiving honey, while this improvement was not seen in the control group [29].

In general, the advantages of filling a wet wound or abscess pits with honey are known. This is primarily because the mechanical form of honey forms a chemical barrier thus preventing cross-infection. It also accelerates adaptation of a tissue flap and shortens treatment time. The efficacy of honey against some strains of *Pseudomonas* and *Staphylococcus* has been shown to be superior to some antibacterial agents [30].

The chemical debridement property of honey has been reported to have great advantages in Fournier gangrene and decubitus ulcers. A previous clinical study compared 50 patients using Savlon antiseptic and honey. Recovery was seen in 60% of

the wounds cleaned with honey and in 36% of those cleaned with antiseptic in the same period [26].

Limitations

This experimental research has some limitations. As with all animal experiments, it is imperative to work with a limited number of animals. In addition, our study evaluated the histopathological results only. Since the rats were sacrificed shortly after, we could not examine the esophageal pathologies that may occur in the long term.

Conclusion

The results of this experimental study showed that compared to prednisolone, the effects of honey in preventing stricture and fibrosis formation were histopathologically and significantly greater. Honey can be used in emergency departments, especially for children. Further clinical studies are required to assess honey in the acute treatment of corrosive burns.

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Trends in lung cancer incidence within the last 10 years: An Eastern Anatolian single center experience

Son 10 yıldaki akciğer kanseri insidansındaki eğilimler: Doğu Anadolu'da tek merkez deneyimi

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Abstract

Aim: Lung cancer is the most common cause of cancer-related deaths among men and women, and mortality and morbidity rates vary according to different histological groups. Therefore, histological type determination is extremely important. The purpose of the study is to investigate the histological subtypes of lung cancer cases within the last 10 years in one of the biggest centers of the Eastern Anatolian Region, considering the changes made in the 2015 updates in lung tumors by World Health Organization (WHO), and investigate the relationship between these histological sub-types and distribution according to year, gender and age.

Methods: In this cross-sectional study, patients who were referred for lung biopsy between January 2010 and December 2019 and diagnosed with lung carcinoma were retrospectively analyzed.

Results: Our study shows that the frequency of lung cancer, along with histological subtypes, has increased throughout the years. The most common lung cancer type, regardless of gender, is Squamous Cell Carcinoma (SCC), followed by Small Cell Lung Carcinoma (SCLC) and Adenocarcinoma. Adenocarcinoma and SHC were the most common subtypes among females and males, respectively. A significant relationship was observed between gender and histological type ($P<0.001$).

Conclusion: The data from our study suggest that the incidence of lung cancer increased throughout the years, similar to the data from our country and other developing countries around the world. In terms of subtypes, among developing countries, Adenocarcinoma rate increased while SCC rate decreased. In our study, the most common histological types increased at a similar rate. Adenocarcinoma was the most common lung cancer among females, similar to other developing countries. The most common lung cancer overall remained the same: SCC. This was considered an indication of the unchanged smoking habits of males.

Keywords: Lung cancer, Histopathology, Incidence

Öz

Amaç: Akciğer kanseri kadın ve erkeklerde kansere bağlı ölümlerin en sık nedeni olup farklı histolojik gruplara göre mortalite ve morbidite oranı değişkenlik göstermektedir. Bu nedenle histolojik tip tayini son derece önemlidir. Çalışmamızın amacı, 2015 Dünya Sağlık Örgütü (DSÖ) Akciğer tümörlerinin güncellenmesinde yapılan değişiklikleri temel alarak Doğu Anadolu Bölgesindeki en büyük merkezlerden birisinde son 10 yılda akciğer kanseri tanısı almış vakaların histolojik alt tiplerini ve aynı zamanda bu histolojik alt tiplerin yıl, cinsiyet ve yaş dağılımı arasındaki ilişkisini incelemektir.

Yöntemler: Kesitsel tipteki bu çalışmada, Ocak 2010-Aralık 2019 yılları arasında merkezimizde akciğer biyopsi materyali olarak gönderilmiş ve akciğer karsinomu tanılı olgular retrospektif olarak incelenmiştir.

Bulgular: Çalışmamızda akciğer kanseri sıklığı yıllara göre artmış olup histolojik tipler benzer oranda artmıştır. En fazla görülen akciğer kanseri tipi kadın ve erkeklerin toplamında sırasıyla Skuamöz Hücreli Karsinom (SHK), Küçük Hücreli Akciğer Karsinomu (KHAK) ve Adenokarsinomdur. Kadınlarda en fazla adenokarsinom, erkeklerde ise SHK görülmüş olup istatistiksel olarak cinsiyet ile histolojik tip arasında anlamlı bir ilişki izlenmiştir ($P<0,001$).

Sonuç: Çalışmamızda ülkemizdeki ve gelişmekte olan ülkelerdeki veriler ile benzer şekilde akciğer kanseri sıklığında yıllara göre bir artış izlenmiştir. Gelişmiş ülkelerde adenokarsinom sıklığı artarken SHK sıklığı azalmıştır. Çalışmamızda ise en fazla görülen histolojik tipler benzer oranda artmıştır. Bunun yanı sıra gelişmiş ülkelerle benzer şekilde kadınlarda en fazla görülen akciğer kanseri tipi adenokarsinom olarak bulunmuştur. Tüm popülasyonda ise en sık görülen akciğer kanser tipi değişmemiş olup halen SHK dur. Bu durum erkeklerde sigara içme alışkanlığındaki değişikliklerin olmaması ile ilişkilendirilebilir.

Anahtar kelimeler: Akciğer Kanseri, Histopatoloji, İnsidans

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Introduction

Lung cancer is the most common cause of cancer-related deaths among men and women, and mortality and morbidity rates vary according to different histological groups. In 2019, there were 228,150 new cases only in the United States of America [1]. Lung cancers are clinically separated into two main groups as Small Cell Lung Carcinoma (SCLC) and Non-small Cell Lung Carcinoma (NSCLC) based on differences in treatment. SCLC cases constitute 13% while NSCLC constitutes 83% of the cases; however, histological sub-type of 3% of the lung cancer cases is unknown [1, 2].

SCLC is treated by chemo-radiotherapy instead of surgery, because the tumor is usually at an advanced stage at the time of diagnosis. On the other hand, NSCLC generally has a chance for surgical operation [3]. Due to the differences in treatment, detection of histological type is crucial for lung neoplasia. WHO reclassified lung neoplasia in terms of their pathologies in 2015 and made many changes to the 2004 classification. Epithelial malignancy is the most common one among lung malignancies and they are mainly categorized as follows based on the new classification (Table 1).

Table 1: WHO 2015 lung cancer classification [4]

Adenocarcinoma	Sarcomatoid carcinoma (SC)
Squamous Cell Carcinoma (SCC)	Pleomorphic carcinoma
Neuroendocrine Carcinoma	Fusiform Cell carcinoma
Small Cell Carcinoma (SCLC)	Giant Cell carcinoma
Large Cell Neuroendocrine Carcinoma (LCNC)	Carcinosarcoma
Large Cell Carcinoma (LCC)	Pulmonary blastoma
Adenosquamous Carcinoma (ASC)	Unclassified and Other carcinomas
	Lymphoepithelioma-like Carcinoma
	NUT carcinoma

There are various main categories other than epithelial neoplasia that are less frequent, namely, Mesenchymal Neoplasia, Lymphohistiocytic Tumors, Ectopic Tumors, and Metastatic Tumors [4]. The purpose of the study is to investigate the histological subtypes of lung cancer within the last 10 years in the Medical Pathology Department of one of the biggest centers of Eastern Anatolian Region, considering the changes made with the 2015 updates, and investigate the relationship between these histological sub-types and distribution according to year, gender and age.

Materials and methods

The study involved 1242 lung carcinoma cases that were referred to our center for lung biopsy between January 2010-December 2019. Based on 2015 WHO classification, two pathologists evaluated paraffin blocks, hematoxylin-eosin (H&E) and immunohistochemical slides of each case, and their pathology reports. The cases were divided according to their histological subtypes. The relationship between gender, age, year, and these sub-categories was investigated. Clinical information such as the gender and age of patients, and year of the cases were obtained from the hospital registry. The cases that missed any of the clinical information were excluded from the study. The study was ethically approved by the local ethics committee by the decision numbered B.30.2.ATA.0.01.00/46.

Statistical analysis

Statistical analysis was performed using IBM SPSS20. The data was presented as mean, standard deviation, median, minimum, maximum, percentage, and number. Normality of continuous variables was evaluated by the Shapiro Wilk-W test

when sample size was <50 and the Kolmogorov Smirnov test when sample size >50. Independent Samples t-test was used for comparison of normally distributed independent groups, whereas Mann Whitney U-test was utilized for comparing the non-normally distributed data. Pearson's chi-square test, Chi-square Yates test and Fisher's Exact test were used if the expected value in a 2x2 comparison between categorical values was >5, between 3-5 and <3, respectively. The coherence of the clinical golden standard and newly developed diagnosis test is evaluated by calculating Cohen's Kappa coefficient. A *P*-value <0.05 was considered statistically significant.

Results

The mean age of 1242 cases was 67 years, among which 1085 (87.4%) were males, and 157 (12.6%) were females. The male to female ratio was approximately 10/1. The mean age of the males and females were 65 and 69 years, respectively. There was no significant difference between females and males in terms of age (*P*=0.21).

Evaluation of the frequency of lung cancer throughout the years revealed that the highest and lowest number of diagnoses were made in 2019 and 2010. The number of new diagnoses stayed the same between 2010 and 2014. It escalated in 2015 and increased gradually thereafter (Table 2) (Figure 1).

Table 2: Lung cancer distribution by years

Year	n	%
2010	72	5.8
2011	78	6.28
2012	72	5.8
2013	86	6.92
2014	82	6.6
2015	128	10.31
2016	138	11.11
2017	171	13.77
2018	181	14.57
2019	234	18.84
TOTAL	1242	100

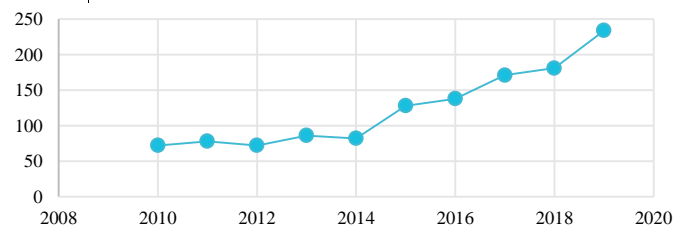


Figure 1: Lung cancer distribution by years

The percentages of the cases in terms of their classification were as follows: 578 cases were SCC (46.5%), 250 were SCLC (20.1%), 221 were adenocarcinoma (17.8%), 66 were Non-classified Carcinoma (NOS) (5.3%), 56 were Metastases (4.5%), 24 were LCNC (1.9%), 17 were Lymphoma (1.4%), 9 were Malign Mesenchymal Neoplasia (MMN) (0.7%), 7 were ASC (0.7%), 7 were LCC (0.7%), 7 were SK (0.7%). According to the pathological diagnosis, the most common one in the group was SCC, followed by SCLC and adenocarcinoma (Table 3). There was a significant relationship between gender and histological type (*P*<0.001). Adenocarcinoma was most common in women, while SCC was most common in men. Evaluation of the most frequent pathological diagnoses revealed that 45 out of 157 lung cancer cases in females were adenocarcinoma (28.6%), 43 were SCC (27.3%) and 31 were SCLC (19.7%). In males, 535 of 1085 lung cancer cases were SCC (49.3%), 219 were SCLC (20.1%), and 176 were (16.2%) adenocarcinoma.

When the distribution of pathological diagnoses was evaluated, it was observed that all pathological diagnoses had increased, but there was no significant relationship between the distribution by years and pathological diagnosis ($P=0.06$) (Table 4). Similarly, no significant relationship was observed between the distribution by years and gender ($P=0.13$) (Figures 2 and 3).

Table 3: The relationship between the three most common histological types and gender

	Adenocarcinoma	SCC	SCLC	P-value
Male	176	535	219	<0.001
Female	45	43	31	

SCC: Squamous Cell Carcinoma, SCLC: Small Cell Carcinoma

Table 4: Pathological diagnosis distribution by years

Year	Adeno carcinoma	SCC	MMN	Metastasis	ASC	LCNC	SCLC	SC	LCC	Lymphoma	NOS
2010	8	38	0	3	0	1	16	1	3	2	0
2011	13	40	0	6	0	4	12	1	1	1	0
2012	8	35	0	3	0	1	22	1	1	1	0
2013	9	43	0	3	2	2	26	0	0	0	1
2014	16	37	1	0	0	3	22	0	0	3	0
2015	15	72	3	3	0	2	23	0	0	3	7
2016	22	64	1	6	0	2	32	2	0	0	9
2017	28	77	1	11	0	2	25	0	0	3	24
2018	42	74	1	12	0	2	31	1	0	0	18
2019	60	98	2	9	5	5	41	1	2	4	7

SCC: Squamous Cell Carcinoma, ASC: Adenosquamous Carcinoma, LCC: Large Cell Carcinoma, SC: Sarcomatoid carcinoma, LCNC: Large Cell Neuroendocrine Carcinoma, SCLC: Small Cell Carcinoma NOS: Non-Classified Carcinoma, MMN: Malign Mesenchymal Neoplasia

Lung cancer is the primary cause of cancer-related deaths worldwide [6]. In the last decade, lung cancer incidence has significantly decreased in industrialized countries. Particularly, the decrease in males' smoking habits reduced lung cancer. Inversely, cultural change in industrialized countries increased the number of smoking females, causing an increase in lung cancer prevalence. The scenario for developing countries is slightly different. The difference is more distinct for females. In industrialized countries, lung cancer is more common in females compared to other countries [7]. In the United States of America and the United Kingdom, incidence and mortality rates of lung cancer have been decreasing since the 1990s. In a study dated 2014, which was conducted on 452,714 lung cancer cases between 1977-2010 in the USA, Lewis et al. [8] stated that lung cancer rate per 100,000 people had decreased after it peaked at the beginning of the 1990s. They particularly emphasized the decrease in the lung cancer rate among males. They underlined the fact that the decrease in SCC was more distinct and they linked this to the decrease in smoking, while also stating that adenocarcinoma had increased among females. On the other hand, the rate of lung cancer did not fluctuate in developing countries, particularly in Brazil, Russia, India, China, and South Africa since the rate of smoking in males and females was still high. According to GLOBOCAN 2012 data, in China, the rate of lung cancer was 21% among all cancers and the rate of lung-cancer related deaths was 27%. Consequently, it is the most common malignancy and the cause of cancer-related mortality [9].

In our study, it is seen that the rate of lung cancer has increased, like the data from other developing countries, and the greatest number of new diagnoses was observed in 2019. The number of cases stayed the same between 2010-2015. The number escalated in 2015 and increased gradually thereafter. The rate increased for both genders, and no significant relationship was observed between the gender of the patient and the increase in lung cancer.

Lung carcinomas are a heterogeneous tumor group with more than 50 subtypes [10]. To be able to benefit from the treatment most efficiently, histological identification and biomarker information should be obtained correctly. Thus, the identification of histological sub-types gains more importance for diagnosis and treatment [11]. Consequently, the WHO prepared a clearer classification of lung neoplasia to enable pathologists and clinicians to speak the same language. Lung cancers have been divided into two main groups for years: SCLC and NSCLC. The most common NSCLCs are adenocarcinoma, SCC and LCC. According to the WHO 2015 classification, SCC and adenocarcinoma have different subtypes, and a more detailed classification of the histological subtype is used in resection materials [11].

The frequency of adenocarcinoma increases gradually, and it is the most common lung cancer in developed countries [12]. Adenocarcinoma constitutes more than 40% of all lung cancers, and 60% of NSCLC. More than 70% of the surgically operated cases are adenocarcinoma [8, 11]. SCC constitutes 20% of lung cancers and its incidence in the developed countries has decreased in recent years. It is strong related to smoking [13]. Survival rate is higher for SCCs than adenocarcinomas. LCC,

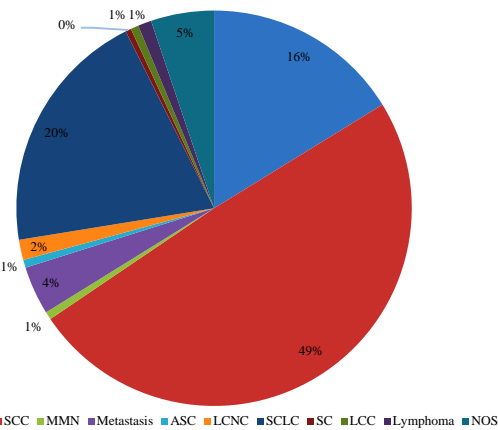


Figure 2: Distribution of pathological diagnoses in men (SCC: Squamous Cell Carcinoma, ASC: Adenosquamous Carcinoma, LCC: Large Cell Carcinoma, SC: Sarcomatoid carcinoma, LCNC: Large Cell Neuroendocrine Carcinoma, SCLC: Small Cell Carcinoma NOS: Non-Classified Carcinoma, MMN: Malign Mesenchymal Neoplasia)

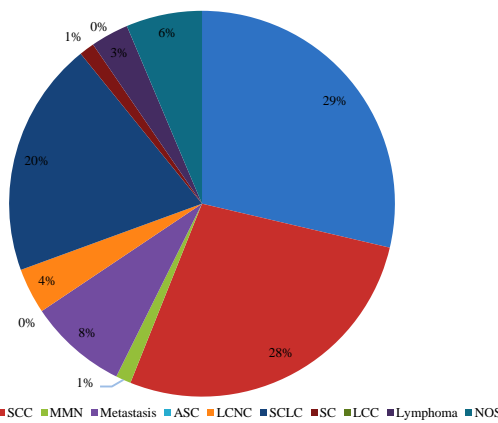


Figure 3: Distribution of pathological diagnoses in women (SCC: Squamous Cell Carcinoma, ASC: Adenosquamous Carcinoma, LCC: Large Cell Carcinoma, SC: Sarcomatoid carcinoma, LCNC: Large Cell Neuroendocrine Carcinoma, SCLC: Small Cell Carcinoma NOS: Non-Classified Carcinoma, MMN: Malign Mesenchymal Neoplasia)

Discussion

The incidence of lung cancer increases in the 6th and 7th decades, and it is most observed between 40-70 years of age. It is more common among males compared to females, the ratio of males to females being 9/1 [5]. In this study, this ratio was 10/1. The mean age of all cases was 67, which were both similar to the literature data.

used for NSCLC, does not specifically differentiate from, or carry the morphological and immunochemical features of adenocarcinoma, SCC, and neuroendocrine carcinoma. The frequency of the LCC is exceptionally low [14]. ASC is a rare lung carcinoma that constitutes 0.4-4% of all lung carcinomas. In 1978, the Japanese Lung Cancer Society reported that to be able to diagnose ASC, components of SCC and adenocarcinoma have to constitute 20% of each tumor [15]. In the last WHO classification, it is required for each component to form 10% of the tumor [16]. Pleomorphic, fusiform cell and giant cell carcinomas constitute less than 3% of lung cancers [11]. SCLC, which is an aggressive malignancy with common metastases, constitutes 10% of all lung cancers. In most cases, recurrence and metastases are observed within the first 2 years and survival rate is less than 10% [8].

Before the 1990s SCC was the most common histological sub-type, especially among males. Later, adenocarcinoma took the lead in the USA, Canada, most of the European countries and in Japan [7]. Among females, adenocarcinoma rates are higher compared to SCC and SCLC rates and its rate increases parallel to the increase in lung cancer incidence [17]. Similarly, in our study, adenocarcinoma was the most common subtype in females.

The frequency of the histological types reported by the studies in our country is different than those from developed countries but comparable to those conducted in developing countries. Goksel et al. [5] reported the SCC, SCLC and adenocarcinoma rates as 45.4%, 20.5% and 20.2%, respectively. Bircan et al. [18] reported the SCC, SCLC, adenocarcinoma and non-classified NCSLC rates as 37.9%, 14.9%, 12.6%, 26.4%, respectively. Yurdakul et al. [19] reported 77.7% of the cases as NCSLC, 15.5% as SCLC and 6.8% as non-classified malign epithelial tumors. In our study, the data were comparable with studies from our country and other developing countries: SCC was the most common subtype, followed by SCLC and adenocarcinoma. Histological diagnoses were significantly different among females and males: Adenocarcinoma was most common among females, whereas SCC was most common among males. Further evaluation revealed that 45 of 157 lung cancer cases in females were adenocarcinoma (28.6%), 43 were SCC (27.3%) and 31 were SCLC (19.7%). In males, 535 of 1085 lung cancer cases were SCC (49.3%), 219 were SCLC (20.1%), and 176 were (16.2%) adenocarcinoma.

Limitations

Since the mortality rate due to lung cancer is high in our region, data such as lifestyle, habit, exposure, and diet of the patients could not be evaluated adequately. Our unit has a significant role in reflecting the data from the region since it is a tertiary center serving most of the Eastern Anatolian Region. We believe that a comprehensive study that presents the epidemiological data is essential and should be conducted in the future.

Conclusion

Our data were similar to studies from our country and other developing countries, as it showed that the frequency of lung cancer increased by years. In developed countries, adenocarcinoma frequency increased, while SCC frequency decreased. The most common histological subtype in our study

increased at a similar rate. Besides, like developed countries, adenocarcinoma was found to be the most frequent lung cancer type among females. In this population, the most common lung cancer type remained the same, SCC. We presume that this finding is in accordance with the continued smoking habit of males.

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Evaluation of galectin-3 in patients with heart failure and its relationship with NT-proBNP levels: A case-control study

Kalp yetersizliği olan hastalarda galektin-3'ün değerlendirilmesi ve NT-proBNP düzeyleri ile ilişkisi: Vaka-kontrol çalışması

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Abstract

Aim: Cardiac fibrosis, a pathological phenomenon in cardiac remodeling, is associated with heart diseases. The aim of this study was to investigate the relationship of Galectin-3 with N-terminal pro B-type natriuretic peptide (NT-pro-BNP) levels in patients with heart failure (HF).

Methods: A total of 50 patients with HF (patient group) and 30 subjects with normal ejection fractions (control group) were enrolled in this study. Serum galectin-3 levels and plasma NT-pro-BNP were measured in all subjects. Demographic and clinical characteristics of the patients were recorded. The Galectin-3 and NT-pro-BNP levels were compared between the groups.

Results: Patients with HF had significantly higher Galectin-3 and NT-pro-BNP levels than control subjects (37.5 (18.0-80.0) versus 12.00 (8.00-14.00), $P<0.001$; 467.0 (1157.5-5107.2) versus 50.0 (35.0-102.0), $P<0.001$, respectively). Galectin-3 was correlated with serum glucose, creatine, left atrial diameter, ejection fraction and NT-pro-BNP in the HF patients. There was a positive and significant correlation between the NT-pro-BNP and Galectin-3 levels ($r=0.742$, $P=0.001$). In addition, there was an inverse and significant correlation between the ejection fraction and Galectin-3 levels ($r=-0.556$, $P=0.001$).

Conclusion: The present study demonstrates that galectin-3 and NT-pro-BNP levels are significantly higher in patients with systolic HF. Galectin-3 was positively and significantly correlated with the NT-pro-BNP and inversely correlated with ejection fraction.

Keywords: Galectin-3, NT-pro-BNP, Heart failure, Ejection fraction

Öz

Amaç: Kardiyak fibroz kardiyak remodelingde patolojik bir durumdur ve kalp hastalıkları ile ilişkilidir. Bu çalışmanın amacı galaktin-3'ün kalp yetmezliği (KY) olan hastalarda N-terminal pro B tipi natriüretik peptid (NT-pro-BNP) düzeyleri ile ilişkisini araştırmaktır.

Yöntemler: Çalışmaya KY tanısı olan toplam 50 hasta (hasta grubu) ve ejeksiyon fraksiyonu normal olan 30 birey (kontrol grubu) dahil edildi. Tüm bireylerde serum galektin-3 ve plazma NT-pro-BNP düzeyleri ölçüldü. Bireylerin demografik ve klinik özellikleri kaydedildi. Galaktin-3 ve NT-pro-BNP düzeyleri gruplar arasında karşılaştırıldı.

Bulgular: KY olan hastalarda galaktin-3 ve NT-pro-BNP düzeyleri kontrol grubundan (37.5 (18.0-80.0), 12.0 (8.0-14.0), $P<0.001$; 467.0 (1157.5-5107.2), 50.0 (35.0-102.0) $P<0.001$, sırasıyla) anlamlı derecede yüksek bulundu. Galaktin-3, KY hastalarında serum glukoz, kreatin, sol atriyal çap, ejeksiyon fraksiyonu ve NT-pro-BNP düzeyleri ile korele olarak bulundu. NT-pro-BNP ve Galaktin-3 düzeyleri arasında pozitif ve anlamlı bir ilişki vardı ($r=0.742$ $P=0.001$). Ayrıca, ejeksiyon fraksiyonu ile Galaktin-3 seviyeleri arasında negatif ve anlamlı bir korelasyon vardı ($r=-0.556$, $P=0.001$).

Sonuç: Sonuç olarak, bu çalışma, sistolik HF hastalarında galektin-3 ve NT-pro-BNP düzeylerinin anlamlı şekilde daha yüksek olduğunu göstermektedir. Galektin-3, NT-pro-BNP ile pozitif ve anlamlı, ejeksiyon fraksiyonu ile negatif korelasyon gösterdi.

Ahahtar kelimeler: Galaktin-3, NT-pro-BNP, Kalp yetmezliği, Ejeksiyon fraksiyonu

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Introduction

Heart failure (HF), the leading cause of hospitalization in patients older than 65 years, is responsible for high mortality rates each year. Cardiac fibrosis is a pathological phenomenon in cardiac remodeling and is associated with heart diseases, including HF and cardiomyopathy [1].

Galectin-3, a member of the galactic family, is a 30 kDa protein. It is expressed intracellularly by inflammatory cells such as macrophages, neutrophils, mast cells, and fibroblasts [2,3]. Fibrosis and inflammation are principal mechanisms in heart failure development and cardiac remodeling [4]. Galectin-3 plays a principal role in fibroblast activation, is reportedly related to the development of cardiac hypertrophy and fibrosis [5,6]. Galectin-3 expression is increased in the remodeling myocardium, and it has been used as a prognostic biomarker in patients with heart failure [7]. Previous studies have shown that high circulating Gal-3 levels are indicative of the severity of heart diseases or related to increased risk of major adverse cardiovascular events including HF, arrhythmias or mortality [8–10].

B-type natriuretic peptides (BNP) are secreted by ventricular cardiomyocytes, and they reflect the severity of hemodynamic overload [11]. BNP levels are closely related to HF severity, and commonly used as a diagnostic and prognostic biomarker for HF [12]. BNP is linked to increased adverse cardiovascular outcomes in heart diseases [13,14]. In addition, NT-proBNP levels are strongly related to survival in HF regardless of ejection fraction [15]. Both BNP and NT-proBNP are established as HF biomarkers and suggested for use by international guidelines [16,17]. We hypothesized that Galectin-3 might be related to NT-proBNP levels in patients with chronic systolic HF. Hence, we aimed to evaluate the galectin-3 and NT-proBNP in systolic HF patients in this study.

Materials and methods

This cross-sectional, prospective observational study included 80 individuals, 50 patients with systolic HF and 30 subjects with normal EFs, who were referred to our Cardiology and Internal Medicine Outpatient Clinics between November 2014 and March 2015. All subjects' histories were taken in detail, and they underwent clinical, biochemical, electrocardiographic, and transthoracic echocardiographic examinations. Inclusion criteria were as follows: Patients >35 years of age with a left ventricular ejection fraction ≤ 0.5 . Exclusion criteria included refusal to participate in the study, acute or chronic pancreatitis, acute coronary syndromes, abnormal thyroid function, uncontrolled hypertension, anemia, chronic lung disease, renal or hepatic dysfunction, severe valvular stenosis or regurgitation, pericardial effusion on transthoracic echocardiography, atrial fibrillation, known malignancy, systemic infection and inflammatory diseases.

Blood samples were collected from the antecubital vein by atraumatic needles and sent to the laboratory for analysis. The blood was collected in tripotassium EDTA (7.2 mg) tubes and analyzed using an automatic blood counter immediately. Hematological parameters were analyzed by LH 780 analyzer (Beckman Coulter Inc, Miami, Florida). Fasting blood glucose,

serum creatinine, alanine transaminase (ALT), aspartate transaminase (AST) levels were recorded.

Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or requirement for the antihypertensive medication [18]. Hyperlipidemia was defined as total cholesterol higher than 220 mg/dl or triglycerides ≥ 150 mg/dl [19]. Type 2 diabetes mellitus was diagnosed according to the American Diabetes Association criteria [20]. Smoking included active or previous (>10 pack-years) tobacco use. 12-lead electrocardiography (ECG) was recorded. Informed consent was obtained from all patients before the study. This study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the local Ethics Committee of the Hospital (Bülent Ecevit University, Number: 171/2014).

Each patient underwent a complete transthoracic echocardiographic examination using the American Society of Echocardiography guidelines of measurement [21]. The transthoracic echocardiography was performed at rest, in the left lateral decubitus position, using an echocardiographic device (Vivid S6, General Electric, Horton, Norway) with a 3.0 MHz transducer, by one experienced cardiologist who was blinded to the patients' clinical data. Echocardiographic images were recorded into a computerized database, and the off-line measurements were performed. Left ventricular end-systolic and end-diastolic diameters (LVESD, LVEDD) were determined by M-mode and left atrium diameter was measured using the biplane from the parasternal long-axis view. Left ventricular ejection fraction (EF) was determined using the biplane modified Simpson's method [22].

Venous blood samples were collected from each patient and centrifuged at 3000 rpm for 15 min after clotting occurred in the serum tubes. After centrifuging, samples were stored at -80°C until analysis. Serum galectin-3 levels were measured by a commercially available Enzyme-linked Immunosorbent Assay Kit (Bioassay Technology Laboratory) according to the manufacturer's protocol, with a detection range of 5 pg/ml-2.000 pg/ml. Biochemical analyses were made by clinicians who were blinded to clinical information and to ensure accurate measurements, all samples were analyzed in duplicates. Plasma NT-pro B-type natriuretic peptide (NT-proBNP) was also measured by an Enzyme-linked Immunosorbent Assay Kit (Bioassay Technology Laboratory).

Statistical analysis

Data were analyzed with SPSS software version 20.0 for Windows (SPSS Inc, Chicago, Illinois). The Kolmogorov-Smirnov test was used to verify that continuous variables were normally distributed, which were expressed as mean \pm standard deviation (SD), while non-normally distributed variables were presented as median with interquartile range (IQR). The categorical variables were presented as percentages. Differences between two groups were evaluated with Student's unpaired t-test or the Mann-Whitney U test for parameters with a normal or non-normal distribution. The frequencies of nominal variables were compared using Fisher's exact test or chi-square test. The Spearman test was used for correlation analysis. With 90% power and a two-sided type 1 error of 5%, we calculated that 50

patients were needed in the HF group. Statistical significance was defined as *P*-value <0.05.

Results

The demographic and clinical data of the study population are presented in Table 1. No difference was found in the demographic characteristics between the groups regarding gender, hypertension, diabetes mellitus, and smoking. The age, hyperlipidemia, and CAD were higher in the HF group. In blood analysis, serum glucose, creatinine, and AST were higher in the HF group, whereas the hemoglobin levels were significantly lower. In the echocardiographic analysis, the ejection fraction and left atrium diameter were higher in the HF group. Figure 1 presents a significant difference in NT-pro-BNP and Galectin-3 values between groups. Tables 2 and 3 show the correlation analyses between NT-pro-BNP, Galectin-3, and clinical parameters. NT-pro-BNP was positively and significantly correlated with glucose, creatine, left atrium diameter, LVEDD, LVESD, and Galectin-3 levels, and inversely and significantly correlated with hemoglobin levels and ejection fraction. Figure 2 shows the positive and significant correlation between the NT-pro-BNP and Galectin-3 levels ($r=0.742, P=0.001$). Correlation analysis between Galectin-3 levels and clinical parameters revealed a positive and significant correlation between Galectin-3 and serum glucose, creatine, left atrium, and NT-pro-BNP levels, and a negative correlation between Galectin-3 and ejection fraction ($r=-0.556, P=0.001$).

Table 1: Demographic and clinical characteristics of the study population

	Control (n=30)	Heart Failure (n=50)	<i>P</i> -value
Age (years)	51.3(6.1)	66.0(12.2)	<0.01
Male n(%)	19(63%)	23(46%)	0.13
Hypertension n(%)	9(20%)	18(36%)	0.13
Diabetes mellitus n(%)	4(13%)	15(30%)	0.09
Hyperlipidemia n(%)	6(20%)	22(44%)	0.02
Smoking n(%)	14(46%)	25(50%)	0.77
CAD n(%)	6(20%)	50(100%)	<0.01
ASA n(%)	6(20%)	50(100%)	<0.01
Beta-blocker n(%)	18(26%)	50(100%)	<0.01
ACE inhibitor n(%)	5(16%)	38(76%)	<0.01
Aldosterone antagonist n(%)	3(10%)	21(42%)	<0.01
Sodium (mEq/L)	139.0(2.3)	139.0(2.3)	0.98
Serum glucose (mg/dl)	109.2(19.0)	136.7(51.9)	<0.01
Creatinine (mg/dl)	0.7(0.6-0.8)	0.9(0.8-1.0)	<0.01
Alanine transaminase (U/l)	16.0(13.0-19.0)	17.5(12.0-21.2)	0.79
Aspartate transaminase (U/l)	18.6(3.1)	22.9(8.9)	0.01
Hemoglobin (g/dL)	13.6(1.9)	12.6(2.1)	0.03
LVEDD (cm)	4.8(4.5-4.8)	5.0(0.5)	0.04
LVESD (cm)	3.2(3.1-3.4)	3.7(0.6)	<0.01
LA (mm)	36.3(2.5)	42.3(4.3)	<0.01
Ejection Fraction (%)	58.1(3.7)	37.7(5.5)	<0.01
NT-pro-BNP (pg/ml)	50.0(35.0-102.0)	467.0(1157.5-5107.2)	<0.01
Galectin3 (pg/ml)	12.0(8.0-14.0)	37.5(18.0-80.0)	<0.01

CAD: Coronary artery disease, ASA: Acetyl salicylic acid, ACE: Angiotensin-converting enzyme, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LA: Left atrium

Table 2: The univariate correlations of the Nt-pro-BNP levels

	<i>r</i>	<i>P</i> -value
Glucose	0.274	0.014
Creatine	0.363	0.001
Hemoglobin	-0.248	0.026
Left atrium	0.460	0.001
LVEDD	0.222	0.048
LVESD	0.230	0.040
Ejection fraction	-0.65	0.001
Galectin-3	0.742	0.001

LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter

Table 3: The univariate correlations of the Galectin-3 levels

	<i>r</i>	<i>P</i> -value
Glucose	0.221	0.049
Creatine	0.283	0.011
Hemoglobin	-0.205	0.069
Left atrium	0.418	0.001
Ejection fraction	-0.556	0.001
NT-pro-BNP	0.742	0.001

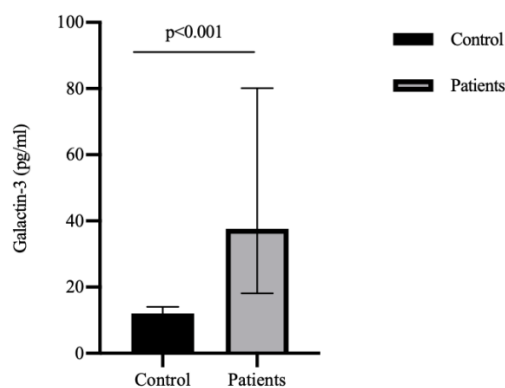


Figure 1: Galectin-3 levels between groups

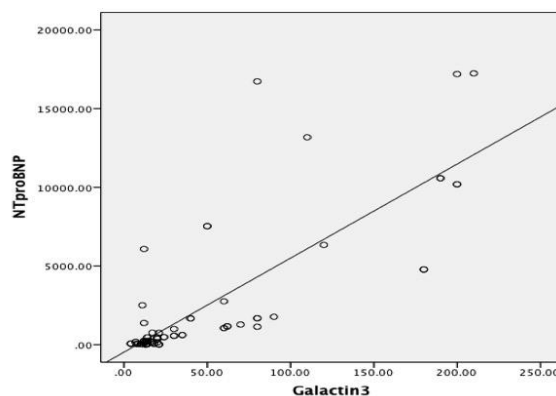


Figure 2: Correlation between NT-pro-BNP and Galectin-3 levels ($r=0.742, P=0.001$)

Discussion

This study demonstrated two significant findings in patients with HF. First, the galectin-3 and NT-pro-BNP levels were significantly higher in the HF group. Second, there was a positive, significant association between galectin-3 and NT-pro-BNP levels. These results suggest increased galectin-3 and NT-pro-BNP levels might be related to remodeling in HF patients.

Systolic heart failure is a clinical syndrome characterized by a loss of pumping capacity. Galectin-3 over-expression by macrophages was observed in heart failure and it is reportedly useful in the diagnosis and prediction of prognosis in HF patients [4,10]. The essential role of galectin-3 in HF was first described by Sharma et al. and they found that even without occult heart failure, galectin-3 over-expression is detectable in macrophages during the early stages of myocardial dysfunction [4]. Galectin-3 induces fibroblast proliferation, leading to loss of systolic cardiac function [4,23]. A previous study showed that galectin-3 was a predictor of ejection fraction and infarct size after myocardial infarction (MI) [24]. Also, elevated galectin-3 levels were associated with post-MI left ventricular remodeling [4,25]. Lisowska et al. [26] evaluated the predictive value of galectin-3 for the occurrence of coronary artery disease (CAD) and prognosis after myocardial infarction to find that galectin-3 was related to severe coronary disease in patients with CAD, and an independent predictor of post-MI mortality. In our study, we found that galectin-3 levels were higher in the HF group compared to the control group. Our findings support the previous studies with higher galectin-3 levels in the HF group and its relation to cardiac fibrosis and remodeling in patients with systolic HF.

BNP and NT-pro-BNP are currently suggested biomarkers for use in patients with HF in several clinical settings [27,28]. They can both be used as an initial diagnostic test in

patients with dyspnea to rule out the possibility of HF [28]. Measurements of BNP and NT-pro-BNP provide independent prognostic information in patients with HF. It was reported that BNP levels were lower in patients with HF with preserved ejection fraction than in those with reduced ejection fraction [29]. NT-pro-BNP was better than BNP in predicting morbidity, mortality, and hospitalization in patients with HF [30]. Linssen et al. [31] evaluated the prognostic performance of BNP versus NT-pro-BNP measurements in a large population of HF patients, and found that BNP and NT-proBNP were strong and independent predictors of all-cause death and HF-related re-hospitalization. In a study that evaluated the galectin-3 levels concentration and its association with the severity of HF, the authors demonstrated that galectin-3 levels showed a progressive increase with increasing severity of HF, and it was positively correlated with the level of plasma NT-pro-BNP. Moreover, a study by Barman et al. showed that galectin-3 levels were positively and significantly correlated with NT-pro-BNP levels [32]. Similar to the literature, we also found that NT-pro-BNP levels were higher in the HF group than the control group. In addition, in our study, left ventricular diameters and left atrial diameter were significantly correlated with NT-pro-BNP levels in patients with HF.

Limitations

This present study has some limitations: This was a single-center study and based on a relatively small group of patients. Single baseline measurements of NT-pro-BNP and galectin-3 were used, and these levels might change in time course, especially with medications. Moreover, patients with preserved ejection fraction and non-ischemic cardiomyopathy were not included in the study.

Conclusion

This study demonstrates that galectin-3 and NT-pro-BNP levels are significantly higher in patients with systolic HF. Galectin-3 was positively and significantly correlated with the NT-pro-BNP and inversely correlated with ejection fraction. From our study, we may suggest that the galectin-3 is a reliable marker of remodeling in patients with systolic HF. Further and large-scale studies are needed to confirm these findings.

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Impact of vitamin D on mobilization, pulmonary function tests, grip strength and functionality in patients with spinal cord injury: A cross-sectional study

D vitamininin omurilik yaralanmalı hastalarda mobilizasyon, solunum fonksiyon testleri, kavrama gücü ve fonksiyonellik üzerine etkisi: Kesitsel bir çalışma

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Abstract

Aim: Since vitamin D deficiency is a growing problem worldwide, insufficient levels of vitamin D were reported in patients with spinal cord injury (SCI). It was stated that levels of vitamin D may be an indirect indicator of functional status in patients with SCI. The aim of this study was to investigate the relationship between vitamin D levels and mobilization, functionality, grip strength, and pulmonary function test parameters in patients with subacute SCI.

Methods: Fifty-eight patients with subacute motor complete thoracic (T) and lumbar SCI injuries [46 males, 12 females; mean age 32.0 (11.2) years] were included. The time to complete the verticalization program on the tilt table without any orthostatic symptoms was considered as the 'time of mobilization.' Grip strength (GS) was measured using a dynamometer, pulmonary function test (PFT) parameters were measured using a spirometer, and functional status was measured using the Functional Independence Measure (FIM). For determining the levels of vitamin D, 25-hydroxy-vitamin D [25(OH)D] was measured and levels below 20 ng/mL were considered as deficiency. The patients were divided into two groups according to 25(OH)D levels, <20 ng/mL and ≥20 ng/mL. The demographic features, mobilization, PFT, GS, and FIM scores were compared according to the levels of 25(OH)D. The patients were divided into two other groups according to neurologic levels: levels between T6-10 and levels T11 and below, and then intragroup comparisons according to the levels of 25(OH)D were performed.

Results: The mean 25(OH)D level of the patients was found as 19.8 (8.3) ng/mL. When all patients were evaluated, time of mobilization was longer and FIM scores were lower in the 25(OH)D deficient group than in the other group ($P<0.001$ and $P=0.038$, respectively). When patients were evaluated separately according to their neurologic levels, time of mobilization was longer in the 25(OH)D deficient group, both in patients with a lesion level between T6-10 and the lesion levels T11 and below ($P<0.001$ and $P=0.009$, respectively). There was no statistically significant difference between the groups in terms of other clinical evaluations according to the neurologic levels of the patients.

Conclusion: Among the patients with SCI, time of mobilization of patients with vitamin D deficiency was longer than those of patients with non-deficient vitamin D levels, regardless of the neurologic level. Although the results of this study showed no statistically significant difference there may also be a relationship between vitamin D levels and pulmonary functions, GS, and FIM scores.

Keywords: Paraplegia, 25-hydroxy-vitamin D, Orthostatic hypotension, Lung function, Functional independence measure

Öz

Amaç: D vitamini eksikliği dünya çapında büyüyen bir problem olduğundan, omurilik yaralanmalı (OY) hastalarda da yetersiz D vitamini seviyeleri bildirilmiştir. D vitamini düzeylerinin, OY hastalarda fonksiyonel durumun dolaylı bir göstergesi olabileceği belirtilmiştir. Bu çalışmanın amacı, subakut dönemdeki OY hastalarda D vitamini düzeyleri ile mobilizasyon, fonksiyonel durum, el kavrama gücü ve solunum fonksiyon testi (SFT) parametreleri arasındaki ilişkiyi araştırmaktır.

Yöntemler: Subakut motor komplet torakal (T) ve lomber OY 58 hasta [46 erkek, 12 kadın; yaş ortalaması 32.0 (11.2) yıl] çalışmaya dahil edildi. Herhangi bir ortostatik semptom olmadan tilt masası ile vertikalizasyon programını tamamlama süresi "mobilizasyon zamanı" olarak değerlendirildi. El kavrama gücü dinamometre ile, SFT spirometre ile, fonksiyonel durum ise Fonksiyonel Bağımsızlık Ölçeği (FBÖ) ile değerlendirildi. D vitamini düzeylerini belirlemek için 25-hidroksi-vitamin D [25(OH)D] ölçümü yapıldı ve 20ng/mL'nin altındaki değerler eksiklik olarak değerlendirildi. Hastalar 25(OH)D seviyeleri <20 ng/mL olan ve 25(OH)D seviyeleri ≥20 ng/mL olan olmak üzere iki gruba ayrıldılar. Demografik özellikler, mobilizasyon, SFT, el kavrama gücü ve FBÖ skorları 25(OH)D düzeylerine göre karşılaştırıldı. Hastalar nörolojik seviyelerine göre de farklı iki gruba ayrıldılar: Seviye T6-T10 arası ve seviye T11 ve altı. Sonrasında 25(OH)D düzeylerine göre grup içi karşılaştırmalar yapıldı.

Bulgular: Hastaların ortalama 25(OH)D düzeyleri 19.8 (8.3) ng/mL olarak bulundu. Tüm hastalar değerlendirildiğinde, 25(OH)D eksikliği olan grupta diğer gruba göre "mobilizasyon zamanı" daha uzundu ve FBÖ skorları daha düşüktü (sırasıyla $P<0.001$ and $P=0.038$). Hastalar nörolojik düzeylerine göre ayrı ayrı değerlendirildiğinde; hem lezyon seviyesi T6-T10 arası olan grupta hem de lezyon seviyesi T11 ve altı olan grupta; 25(OH)D eksikliği olan hastalarda "mobilizasyon zamanı" daha uzundu (sırasıyla $P<0.001$ and $P=0.009$). Hastalar nörolojik düzeylerine göre ayrıldıklarında diğer klinik değerlendirmeleri açısından; gruplar arasında istatistiksel olarak anlamlı fark yoktu.

Sonuç: OY hastalarda; nörolojik seviyeden bağımsız olarak D vitamini eksikliği olan hastaların mobilizasyon süresi olmayan hastalara göre daha uzundur. Bu çalışmanın sonuçları istatistiksel olarak anlamlı bir fark göstermese de, D vitamini düzeyleri ile solunum fonksiyonları, el kavrama gücü ve FBÖ skorları arasında da bir ilişki olabilir.

Anahtar kelimeler: Parapleji, 25-hidroksi-vitamin D, Ortostatik hipotansiyon, Akciğer fonksiyonu, Fonksiyonel bağımsızlık ölçeği

Introduction

Vitamin D is an important factor in bone metabolism and neuromuscular functions. Moreover, its deficiency and insufficiency have been found to be associated with many chronic diseases including common cancers, metabolic syndrome, and cardiovascular, infectious and autoimmune diseases. Serum 25-hydroxyvitamin D [25(OH)D] is considered the best marker for assessing vitamin D status [1]. Determining the accurate thresholds for vitamin D deficiency is still a matter of debate [2]. The Endocrine Society's Clinical Practice Guideline defines vitamin D deficiency, insufficiency, and sufficiency as serum concentrations of 25(OH)D <20 ng/mL (<50 nmol/L), 21-29 ng/mL (51-74 nmol/L), and 30-100 ng/mL (75-250 nmol/L), respectively [3]. Severe vitamin D deficiency with a 25(OH)D <12 ng/mL (or 30 nmol/L) dramatically increases the risk of excess mortality, infections, and many other diseases, and should be avoided whenever possible [1].

Vitamin D deficiency is a growing problem worldwide [2,4]. It has been described as a pandemic in recent years [5]. Insufficient or severely deficient levels of 25(OH)D were reported in patients with spinal cord injury (SCI) [6-8]. Moreover, there are some studies showing that deficiency of 25(OH)D may represent an independent predictor of worsening of physical functions of people with chronic SCI [9,10].

Along with motor and sensory deficits, disturbances of the cardiovascular, bronchopulmonary, gastrointestinal, thermoregulatory, and genitourinary systems are common after an SCI [11]. Cardiovascular complications are mostly associated with dysfunctions of the autonomic nervous system. Orthostatic hypotension, irregularities of the cardiac rhythm, autonomic dysreflexia are common autonomic problems. Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mm Hg, or a reduction in diastolic blood pressure of at least 10 mm Hg, upon a change in body position from a supine position to an upright posture, regardless of the presence of symptoms [12]. There are studies showing the relationship between orthostatic hypotension and vitamin D in some other diseases and in some geriatric groups [13-18]. Orthostatic hypotension seen in patients with spinal cord injury is the most important factor that negatively affects mobilization of patients. To the best of our knowledge, there is no study in the literature examining the relationship between orthostatic hypotension and vitamin D in patients with SCI.

In addition, upper extremities are very important for mobilization in patients with SCI with complete paraplegia. Therefore, in the rehabilitation program of a patient with SCI (especially patients with complete paraplegia), the most important point is to strengthen the upper extremities to the maximal level in the acute period of rehabilitation, because at the end of the acute/subacute phase, strong upper extremities are needed for independent transfers [19]. Skeletal muscle expresses vitamin D receptors and may require vitamin D for its function and there are many studies showing that vitamin D deficiency causes weakness and falls [3]. The effect of vitamin D on the limb muscles of the patients with SCI should be investigated.

However, extremity muscle strength is not the only important factor in a patient with SCI. Respiratory muscles that

affect pulmonary functions are just as important. One of the other important complications of SCI is pulmonary dysfunction. Recent studies have shown that early mobilization plays an important role in the prevention of pulmonary function decline and in the development of muscle strength [19]. Studies on some lung diseases have shown a relationship between vitamin D and pulmonary functions [20-22]. However, in some studies conducted on patients with chronic SCI, there was no association shown between pulmonary functions and vitamin D [23,24].

Thus, the purpose of this study was to investigate the relationship between vitamin D levels and mobilization, pulmonary function tests, grip strength, and the functionality of patients with subacute SCI because these parameters are closely related with each other in the rehabilitation setting.

Materials and methods

Patient selection

Fifty-eight patients with SCI, aged 18-65 years, who were admitted to the inpatient physical therapy and rehabilitation service of Ankara Physical Medicine and Rehabilitation Training and Research Hospital, which is a national tertiary referral center in Turkey, and who agreed to participate were included in the study.

In this study, patients with an SCI that resulted in complete motor paraplegia were included in order to achieve homogenization. The updated classification of the American Spinal Injury Association (ASIA) was used [25]. Patients with ASIA A and ASIA B were included in the study according to this classification. Moreover, only patients with injuries below the level of thoracic (T) 6th vertebrae (T6) were included in the study because some upper extremity functions would be studied, and some measurements should be made in a sitting position. All patients with SCI in the rehabilitation center were included in the verticalization program with the tilt table before achieving the sitting level [19]; only patients who completed the verticalization program with the tilt table were included in the study.

The exclusion criteria were as follows: Patients aged <18 or >65 years; incomplete motor SCI (ASIA C or D) or neurologic level above T6, non-traumatic spinal cord pathologies (e.g. tumor, infection, ischemia), disease duration shorter than 6 weeks or more than 6 months, additional neurologic diseases other than SCI, patients with motor impairment of the upper limbs, history of smoking, patients with pulmonary disease, using drugs that could affect vitamin D metabolism / various medications that deplete vitamin D stores, use of high-potency vitamin D supplements on a regular basis prior to initial assessment, a history of regular sunbathing, previous diagnoses of childhood rickets or history of other adult metabolic bone disorder such as osteoporosis and osteomalacia, presence of any other systemic disease (hematologic, endocrine, rheumatologic, renal, cardiovascular, gastrointestinal, pulmonary disease), presence of chronic medical disorders requiring medical treatments, active infection, history of malignancy, pregnancy/lactation, bleeding diathesis, other complications of SCI (e.g. thromboembolism, heterotopic ossification, pressure ulcers), patients who underwent therapies other than routine (e.g. elastic pressure socks, abdominal pillow, sufficient fluid intake) during verticalization program with the tilt table such as

electrical stimulation and/or medical treatment (e.g. midodrine) for the treatment of orthostatic hypotension, patients with speech disorders, communication disorders, cognitive dysfunction, severe psychological pathologies, and debility.

Before the study, permission was obtained from the local ethics committee. The participants were informed about the aim and method of the study and their written and oral consent was obtained. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Clinical measurement parameters

Demographic features

The age, sex, body mass index (BMI), etiology of SCI, time from SCI, and ASIA Impairment Scale scores of the patients were recorded. The patients were divided into two groups according to neurological levels by means of ASIA classification, because the expected functional status of patients will change according to the level of SCI: levels between T6-10 (group 1) and levels T11 and below (group 2) [19,26].

Clinical evaluation parameters

As the “mobilization time”, the ending time (means of days) of the verticalization program with the tilt table was accepted.

For defining the functionality of the patients, the Functional Independence Measure (FIM) was used [27]. FIM assesses the degree of independence of the individual in basic physical and cognitive activities in daily life. FIM consists of 18 items and basically measures two parameters: motor function and cognitive function. Each item consists of a 7-point scale in which 1 indicates total assistance and 7 shows complete independence. The ‘motor function’ section consists of self-care, sphincter, transfer, and locomotion sub-sections, and the total scoring ranges from 13 to 91. The ‘cognitive function’ section consists of communication and social cognition sub-sections, and the total scores range from 5 to 35. Total scoring of FIM ranges from 18 to 126. High scores in the scale indicate that the patient’s independence is high. The validity and reliability of the FIM is well established [28]. In this study, only the motor function section was used.

In this study, the grip strength (GS) of the upper extremities of all patients with SCI was evaluated using a Jamar® hand dynamometer (Sammons Preston, Inc., Bolingbrook, IL). For the test position, patients were instructed to sit in a wheelchair with their feet flat on the chair, and measurements were performed while the shoulder was in adduction, elbow in 90° flexion, and the forearm in the neutral position between the supine and pronation position. In the GS test, patients were required to increase their grip force smoothly and to maintain the same strength for approximately three seconds at the maximum level. The third range of the dynamometer was used as the standard when measuring and GS was measured in kilograms-force. GS was evaluated three times with one-minute rest intervals, and their averages were calculated. The dominant arm was used for the measurements.

The pulmonary function tests were defined by resting spirometric measurements including forced vital capacity (FVC), vital capacity (VC), forced expiratory volume in one second (FEV1), the ratio of FEV1 to FVC (FEV1/FVC), peak expiratory flow rate (PEF), and maximum voluntary ventilation (MVV),

which were performed using a hand-held spirometer (Vmax29 Sensormedix, Yorba Linda, CA, USA). All studies were performed with the subjects in the sitting position. Each subject performed at least three trials and the best performance was used for analysis. Measurements were expressed as percentages of the predicted values. Eighty percent of predicted maximum or greater was accepted as normal.

Laboratory measurement parameters

Due to the seasonal variation of vitamin D, this study was conducted only between September and December. Blood samples were taken from peripheral venous blood at the same time in the morning after eight hours of fasting. Routine blood tests (hemogram, liver-kidney-thyroid function tests, erythrocyte sedimentation rate, C-reactive protein) were performed in all patients in the Biochemistry Laboratory of Ankara Physical Medicine and Rehabilitation Training and Research Hospital. Patients without abnormalities in routine blood tests were included in the study. For the evaluation of vitamin D levels, serum 25(OH)D levels were determined using an electrochemiluminescence immunoassay.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows 11.5 statistical package program (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Whether the distribution of continuous and discrete numerical variables was close to normal was investigated using the Kolmogorov-Smirnov test. Descriptive statistics are shown as mean (standard deviation) (SD) or median (minimum – maximum) for continuous and discrete numerical variables, and categorical variables as number of cases and percentage (%). The significance of the difference in terms of mean values between the groups was investigated using Student’s t test and the significance of the difference in terms of median values was investigated using the Mann-Whitney U test. Categorical variables were evaluated using Pearson’s Chi-square or Fisher’s exact test. Results of $P < 0.05$ were considered statistically significant.

Results

The mean age of the patients was 32.0 (11.2) years. Some other demographic and clinical characteristics of the patients are shown in Table 1. The mean 25(OH)D level was found as 19.8 (8.3) ng/mL. The patients were divided into two groups according to their 25(OH)D levels: < 20 ng/mL and ≥ 20 ng/mL. The demographic and clinical characteristics of the patients were compared according to 25(OH)D levels (Table 2). A statistically significant difference between the two groups was observed only in ‘time of mobilization’ and ‘FIM-motor subscale ($P < 0.001$ and $P = 0.038$, respectively).

As mentioned in the methods section, the patients were divided into two groups according to neurologic levels by means of the ASIA classification: levels between T6-10 (group 1) and levels T11 and below (group 2). It was evaluated whether there was a difference in demographic and clinical characteristics between the groups according to 25(OH)D levels. In Group 1, a statistically significant difference between the two groups was observed only in time of mobilization ($P < 0.001$) (Table 3). Similarly, in Group 2, a statistically significant difference

between the two groups was observed only in time of mobilization ($P=0.009$) (Table 4). Figure 1 summarizes the relationship between mobilization time and 25(OH)D levels. There was no difference between the groups in terms of other clinical evaluations according to the neurologic levels of the patients.

Table 1: Demographic and clinical characteristics of the patients

	n=58
Age (years) [mean (SD)]	32.0 (11.2) (min:18, max:53)
Sex [n(%)]	
Female	12 (20.7%)
Male	46 (79.3%)
Body mass index (kg/m ²) [mean (SD)]	22.7 (4.0)
Disease duration (months) [median (min-max)]	4 (1.5-6)
Time of mobilization* (days) [median (min-max)]	10 (0-45)
Etiology of the injury [n(%)]	
Falling from high	24 (41.4%)
Traffic accident	27 (46.6%)
Gunshot injury	4 (6.9%)
Cutting tool injury	1 (1.7%)
Earthquake injury	2 (3.4%)
Neurological Level [n(%)]	
Levels between T6-T10	31 (53.4%)
Levels T11 and below	27 (46.6%)
FIM - Motor Subscale [median (min-max)]	53 (27-80)
Grip strength (kg) [mean (SD)]	49.7 (17.5)
25-OH Vitamin D Levels (ng/mL) [mean (SD)]	19.8 (8.3)
Pulmonary Function Tests*** [mean (SD)]	
FVC	82.5 (19.2)
FEV1	83.4 (18.8)
FEV1/FVC	102.3 (12.0)
PEF	66.3 (18.9)
VC	81.0 (18.8)
MVV	98.7 (25.1)

* The time to complete the verticalization program on the tilt table without any orthostatic symptoms was considered as the "time of mobilization", ** FIM: Functional Independence Measure, *** % predictive values of FVC: Forced vital capacity, FEV1: Forced expiratory volume at 1 second, PEF: Peak expiratory flow rate, VC: vital capacity, MVV: Maximum voluntary ventilation, T: thoracic

Table 2: Demographic and clinical characteristics of the patients according to vitamin D levels

	Vitamin D <20 ng/mL (n=28)	Vitamin D ≥20 ng/mL (n=30)	P-value
Age (years) [mean (SD)]	33.6 (11.5)	30.2 (11.1)	0.257
Sex [n(%)]			0.893
Female	6 (21.4%)	6 (20.0%)	
Male	22 (78.6%)	24 (80.0%)	
Body mass index (kg/m ²) [mean (SD)]	23.0 (2.8)	22.8 (4.4)	0.871
Disease duration (months) [median (min-max)]	3.2 (1.5-6.0)	4.5 (2.0-6.0)	0.075
Time of mobilization* (days) [mean (SD)]	18.1 (10.3)	6.1 (4.6)	<0.001
Neurologic level [n(%)]			0.110
Levels between T6-T10	18 (64.3%)	13 (43.3%)	
Levels T11 and below	10 (35.7%)	17 (56.7%)	
FIM** - Motor Subscale [median (min-max)]	51 (27-74)	56 (39-80)	0.038
Grip strength (kg) [mean (SD)]	47.7 (19.8)	51.5 (15.2)	0.432
Pulmonary Function Tests*** [mean (SD)]			
FVC	77.4 (15.8)	86.9 (20.9)	0.117
FEV1	79.6 (14.5)	86.8 (21.6)	0.233
FEV1/FVC	104.4 (12.8)	100.7 (11.7)	0.330
PEF	63.6 (16.3)	68.9 (20.9)	0.383
VC	74.8 (15.6)	85.9 (20.1)	0.062
MVV	96.2 (29.3)	99.5 (22.1)	0.675

* The time to complete the verticalization program on the tilt table without any orthostatic symptoms was considered as the "time of mobilization", ** FIM: Functional Independence Measure, *** % predictive values of FVC: Forced vital capacity, FEV1: Forced expiratory volume at 1 second, PEF: Peak expiratory flow rate, VC: vital capacity, MVV: Maximum voluntary ventilation, T: thoracic

Table 3: Demographic and clinical characteristics of patients with a neurologic lesion levels between T6-T10 (group 1)

	Vitamin D <20 ng/mL (n=18)	Vitamin D ≥20 ng/mL (n=13)	P-value
Age (years) [mean (SD)]	35.1 (12.0)	31.7 (12.3)	0.444
Sex [n(%)]			0.999
Female	4 (22.2%)	2 (15.4%)	
Male	14 (77.8%)	11 (84.6%)	
Body mass index (kg/m ²) [mean (SD)]	23.8 (3.0)	22.1 (2.7)	0.137
Disease duration (months) [median (min-max)]	3 (1.5-6)	6 (2-6)	0.115
Time of mobilization* (days) [mean (SD)]	17.0 (5.9)	8.9 (4.6)	<0.001
FIM** - Motor Subscale [median (min-max)]	47 (27-71)	53 (39-67)	0.211
Grip strength (kg) [mean (SD)]	41.7 (16.5)	47.7 (15.5)	0.326
Pulmonary Function Tests*** [mean (SD)]			
FVC	74.3 (18.3)	79.4 (20.6)	0.542
FEV1	78.5 (16.8)	81.3 (21.5)	0.735
FEV1/FVC	107.5 (12.3)	103.3 (13.1)	0.448
PEF	63.8 (12.1)	65.5 (14.9)	0.765
VC	72.9 (18.1)	78.0 (20.8)	0.547
MVV	91.5 (29.7)	93.7 (27.8)	0.860

* The time to complete the verticalization program on the tilt table without any orthostatic symptoms was considered as the "time of mobilization", ** FIM: Functional Independence Measure, *** % predictive values of FVC: Forced vital capacity, FEV1: Forced expiratory volume at 1 second, PEF: Peak expiratory flow rate, VC: vital capacity, MVV: Maximum voluntary ventilation, T: thoracic

Table 4: Demographic and clinical characteristics of patients with neurologic lesion levels T11 and below (group 2)

	Vitamin D <20 ng/mL (n=10)	Vitamin D ≥20 ng/mL (n=17)	P-value
Age (years) [mean (SD)]	31.0 (10.7)	29.1 (10.4)	0.658
Sex [n(%)]			0.999
Female	2 (20.0%)	4 (23.5%)	
Male	8 (80.0%)	13 (76.5%)	
Body mass index (kg/m ²) [mean (SD)]	21.5 (1.7)	23.4 (5.4)	0.212
Disease duration (months) [median (min-max)]	4 (1.5-5)	4.5 (2-6)	0.711
Time of mobilization* (days) [mean (SD)]	19.9 (15.3)	3.9 (3.2)	0.009
FIM** - Motor Subscale [median (min-max)]	61.5 (40-74)	72 (41-80)	0.223
Grip strength (kg) [mean (SD)]	59.9 (21.2)	54.7 (14.8)	0.484
Pulmonary Function Tests*** [mean (SD)]			
FVC	83.6 (6.8)	92.2 (20.2)	0.332
FEV1	81.8 (9.3)	90.6 (21.6)	0.354
FEV1/FVC	98.3 (12.5)	98.8 (10.6)	0.921
PEF	63.3 (24.1)	71.3 (24.7)	0.515
VC	79.2 (6.6)	91.6 (18.2)	0.159
MVV	105.5 (28.7)	103.7 (16.9)	0.859

* The time to complete the verticalization program on the tilt table without any orthostatic symptoms was considered as the "time of mobilization", ** FIM: Functional Independence Measure, *** % predictive values of FVC: Forced vital capacity, FEV1: Forced expiratory volume at 1 second, PEF: Peak expiratory flow rate, VC: vital capacity, MVV: Maximum voluntary ventilation, T: thoracic

Discussion

Vitamin D insufficiency is common in patients with SCI and the consequences of impaired vitamin D status for patients with SCI can be listed as musculoskeletal health concerning bone health (osteoporosis, fracture risk, and fracture healing), muscle health (muscle weakness, myalgia, impairments of gait and physical performance), and cardiometabolic health, which concerns hypertension, obesity, dyslipidemia, glucose intolerance, and diabetes [7]. The primary result of the present study is that there is a relation between time to mobilization of patients with SCI and vitamin D deficiency. This is another consequence that may be added to the cardiometabolic health list.

Along with motor and sensory deficits, instabilities of the cardiovascular, thermoregulatory, and pulmonary system are common after an SCI. In the acute phase of the SCI, orthostatic hypotension can be seen in 33-74% of cases [11]. In patients with orthostatic hypotension, the verticalization time with the tilt table and thus the mobilization time is prolonged. The results of this study showed that, in patients with vitamin D deficiency,

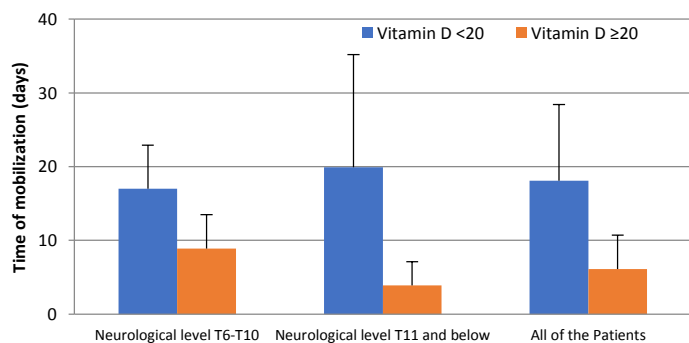


Figure 1: The relationship between mobilization time and 25(OH)D levels according to the neurologic levels of the patients

regardless of the neurologic level, the verticalization time with the tilt table is longer than in those with non-deficient vitamin D levels. In the literature, there are some studies conducted on older people [17, 18], oldest-old people [13], and patients with Parkinson's disease [14], all of which suggest that low vitamin D status is associated with orthostatic hypotension. In a systematic review and meta-analysis about hypovitaminosis D and orthostatic hypotension, it was concluded that hypovitaminosis D was associated with orthostatic hypotension, independent of potential confounders [16]. Although systolic and diastolic blood pressure values are not available in the present study, it can be assumed that the time to complete the verticalization program with the tilt table is an indirect indicator of orthostatic hypotension. In the treatment of orthostatic hypotension of patients with SCI, elastic socks, abdominal pillow, sufficient fluid intake, and gradual verticalization with the tilt table are recommended [26]. Generally, no medical treatment is required. If necessary, salt tablets or midodrine are recommended [29]. According to the results of the present study, in addition to all other beneficial effects, the level of vitamin D in patients with SCI should be checked before starting rehabilitation to prevent orthostatic hypotension, and if there is a deficiency, replacement should be initiated.

Respiratory problems after SCI continue to be the most common cause of morbidity and mortality in this patient population [23, 30]. It is known that the level and severity of injury affects pulmonary function tests in patients with SCI. Patients with high-level SCI have worse pulmonary function tests [31]. According to the results of the present study, although there was no statistical comparison, the pulmonary function test results of patients with neurologic injury levels between T6 and T10 were lower than patients with injury levels of T11 and below. This was not one of the purposes of the present study. However, one of the main aims of the study was to investigate the effects of vitamin D levels on pulmonary function tests. In almost all of the pulmonary function parameters that were studied, it was shown that in all groups with vitamin D deficiency (regardless of the neurologic level), the test results were lower than in the group with non-deficient vitamin D levels. However, these differences were not statistically significant. In some studies among patients with chronic SCI, no significant associations between levels of vitamin D and pulmonary function tests [23] and respiratory symptoms [24] were shown. The findings of the present study show similar results with the literature in patients with SCI.

Among all respiratory function test parameters, MVV has a special feature. This test is an indirect indicator of respiratory muscle strength. The authors of the present study thought a difference might be found both in MVV levels and in GS levels according to the vitamin D levels due to the potential effect of vitamin D on muscle performance. Vitamin D deficiency impairs proximal muscle function, and is thought to predispose falls, especially in the elderly, because skeletal muscle expresses vitamin D receptors and may require vitamin D for maximizing its function [3]. In a study conducted by Flueck et al. [32], athletes with SCI were subjected to vitamin D replacement and its effect on athletic performance was investigated. The authors concluded that the association between

upper body performance or muscle strength and vitamin D status remained unclear. In a cross-sectional study conducted by Barbonetti et al. [10], it was concluded that in people with chronic SCI, a low vitamin D level represented an independent predictor of poor physical function, which was assessed through functional independence in activities of daily living and leisure time physical activity. However, in another longitudinal cohort study that aimed to explore the association of baseline vitamin D levels with one-year changes in physical functional outcomes in people with chronic SCI, it was shown that a low vitamin D level might represent an independent predictor of worsening in physical function outcomes over time [9]. In the present study, functional independence was measured using the motor subscale of FIM. When patients were evaluated without being divided into groups as neurologic impairment levels, a statistically significant relationship was found between vitamin D levels and FIM scores, which showed that those with vitamin D deficiency had lower FIM scores. However, when patients were evaluated according to their neurologic injury levels (between T6 and T10, and T11 and below) there was no statistically significant relationship between vitamin D and FIM scores. The reason for all of the above results (MVV, GS, and FIM scores) may be that the patients included in the study were in the subacute period. When the disease becomes chronic, the likelihood of this effect may well increase.

Limitations

One limitation of this study is that the relationship between vitamin D levels and orthostatic hypotension was examined indirectly. The second limitation of the study is that only patients with motor deficits in their lower extremities were included in the study. Another is that it was performed only in a certain season and patients who were treated in different seasons were not compared. We suggest more comprehensive studies to evaluate blood pressure changes during verticalization programs. We also recommend conducting studies investigating the relationship between vitamin D levels and orthostatic hypotension in patients with high-level SCI because orthostatic hypotension is more common in patients with cervical injuries. There is a need for larger series of studies in which seasonal differences are also examined.

Conclusions

Among patients with SCI, the tilt table verticalization time of patients with vitamin D deficiency is longer than in those with non-deficient vitamin D levels, regardless of the neurologic level. The time to complete the verticalization program with the tilt table is an indirect indicator of orthostatic hypotension. Vitamin D levels should be checked and necessary replacement should be undertaken in patients with SCI in order to help cope with orthostatic hypotension.

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Effect of saline flush on the onset time of sugammadex: A randomized clinical study

Salin yıkamasının sugammadexin başlangıç zamanı üzerine etkisi: Randomize klinik çalışma

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Abstract

Aim: Several methods have been tried out to shorten the onset time of sugammadex. The objective of this study was to examine the effect of 20 mL saline flush administered immediately after sugammadex on its onset time by using train-of-four (TOF) monitoring.

Methods: This study was initiated after obtaining the approval of the institutional Medical Research Ethics Committee. A total of 60 ASA I-II patients aged between 18-65 years scheduled for elective abdominal surgery in our hospital between August 2017 and January 2018, which would last 1-3 hours under general anesthesia, were enrolled in this study. Patients were randomly divided into two groups as Group S (saline flush group, n=30) and Group C (control group, n=30). Saline flush group received 2 mg/kg sugammadex and 20 ml isotonic saline flush immediately after sugammadex administration, while the control group received 2 mg/kg sugammadex only. TOF monitoring was used to assess neuromuscular block. Electrocardiography, oxygen saturation, noninvasive arterial pressure as well as acceleromyography values measured by TOF monitoring device were recorded and compared between the groups. All patients were continuously monitored intraoperatively and 30 minutes postoperatively.

Results: Both groups were similar in terms of basic clinical characteristics and demographics. There was a statistically significant difference between the groups in terms of the time of TOF to reach 0.9 from 0.2. The mean time of TOF to reach 0.9 from 0.2 was lower in Saline flush group than in control group (85.4 vs 130.5 seconds; $P=0.001$).

Conclusion: Our study demonstrated that 20 mL saline flush administered immediately after sugammadex shortened the onset time of sugammadex.

Keywords: Saline solution, Neuromuscular block, Train-of-four monitoring, Sugammadex

Öz

Amaç: Sugammadexin etkisinin başlama süresini kısaltmak için çeşitli yöntemler uygulanmıştır. Bu çalışmanın amacı, sugammadex uygulamasından hemen sonra uygulanan 20 mL serum fizyolojik bolusun, dörtlü uyarı dizisi (TOF) yöntemi ile izlenilerek, etki başlangıç süresini incelemektir.

Yöntemler: Yerel Etik Kurul onamı sonrası Ağustos 2017 ve Ocak 2018 arası genel anestezi altında elektif cerrahi planlanan, ASA I-II statüde, operasyon süresi 1-3 saat sürecek, 18-65 yaş arasında 60 hasta çalışmaya dahil edildi. Hastalar rastgele Grup S (Serum Fizyolojik grubu, n=30) ve Grup C (Kontrol grubu, n=30) olmak üzere iki gruba ayrıldı. Serum Fizyolojik grubuna 2 mg/kg sugammadex uygulamasından hemen sonra 20 cc izotonik serum fizyolojik bolus olarak uygulandı. Kontrol grubuna ise sadece 2 mg/kg sugammadex verildi. Nöromüsküler bloğun izlemi için TOF monitörü kullanıldı. Elektrokardiyografi, oksijen saturasyonu, noninvaziv arteriyel basınç ve TOF izleme cihazı ile ölçülen akseleromyografi değerleri kaydedildi ve gruplar arasında karşılaştırıldı. Tüm hastalar ameliyat sırasında ve ameliyattan 30 dakika sonra monitorize olarak izlendi.

Bulgular: Her iki grupta temel klinik özellikler ve demografik veriler açısından benzerdi. Gruplar arasında TOF'un 0,2'den 0,9'a ulaşması açısından istatistiksel olarak anlamlı bir fark vardı. TOF'un 0,2'den 0,9'a ulaşma süresi Serum Fizyolojik grubunda kontrol grubuna göre anlamlı olarak düşük tespit edildi (85,4'e ve 130,5 saniye; $P=0,001$).

Sonuç: Çalışmamız göstermiştir ki, sugammadex uygulamasından hemen sonra uygulanan 20 ml serum fizyolojinin sugammadexin etki başlangıç zamanını kısalttığını göstermiştir.

Anahtar kelimeler: Serum fizyolojik, Neuromuscular block, Dörtlü uyarı dizisi izlemi, Sugammadex

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Introduction

Neuromuscular blocker (NMB) drugs are commonly used for relaxation of skeletal muscle during surgical operations [1]. Reversal of the neuromuscular block depends upon the usage of the agents that inhibit the activity of acetylcholinesterase. Hereby, the relevant receptors are inactivated and neuromuscular blockers are eliminated from the systemic circulation. Lack of complete reversal of the neuromuscular block at the end of the operation may cause postoperative complications such as hypoxemia, respiratory distress and swallowing difficulty, airway problems, and hypercapnia [2]. In order to avoid these complications, depth of the neuromuscular block is assessed using Train-of-four (TOF) nerve stimulation, and a T4/T1 ratio ≥ 0.9 is recommended for extubation [3]. Anticholinesterases and sugammadex, which have recently become popular, are used for pharmacological antagonism of neuromuscular blockers. Sugammadex is a modified γ -cyclodextrin, binds to neuromuscular blocker agents in steroid form (rocuronium and vecuronium) and forms encapsulation, with which the neuromuscular blocker agent rapidly moves away from neuromuscular junction, providing rapid reversal of the blockage [4].

Various methods and applications have been attempted to shorten onset time of the drugs administered via the intravenous route. Among these are priming principle, timing principle and using high doses [5]. It has been reported in the literature that especially saline flush immediately after intravenous drug administration shortens the onset time [6,7]. Studies in the literature recommend 20 mL saline flush to be administered after adenosine, a drug with a half-life of shorter than 10 seconds and administered via a peripheral vein, to rapidly reach to the heart [6]. Ishigaki et al. [7] have demonstrated that 20 mL saline flush administration immediately after intravenous administration of rocuronium shortens the onset time of the drug. To the best of our knowledge, this is the first study investigating the effect of saline flush administered immediately after sugammadex on the onset time of this drug using TOF monitoring.

Materials and methods

Study population and design

The study was initiated after obtaining the necessary permissions and ethics approval from Bolu Abant İzzet Baysal University Medical Researches Ethics Committee (approval date: March 06, 2017 and decision number: 49). A total of 60 ASA I-II patients aged between 18-65 years scheduled for elective abdominal surgery in our hospital between August 2017 and January 2018, which would last 1-3 hours under general anesthesia, were enrolled in this prospective randomized clinical study. Included patients were informed about the study and written informed consents were obtained. Patients were randomized by using computer-generated random numbers and divided into two groups as Group S (saline flush group, n=30) and Group C (control group, n=30). Patients' basic demographic and clinical features, operation and anesthesia times, perioperative hemodynamic data such as mean arterial pressure and heart rate as well as the reversal times of neuromuscular

block measured by TOF monitoring device were recorded and then compared between the groups. Patients aged under 18 and over 65 years, obese patients (those with a body mass index > 30 kg/m²), patients with hypersensitivity to the drugs used in the study or the agents in their composition, those with severe hepatic, renal, cardiovascular diseases and/or neuromuscular diseases, and patients who had emergency surgery, concomitant surgery and those whose time under general anesthesia exceeded 3 hours were excluded from the study.

Perioperative anesthesia management

Patients taken to the operating room were routinely monitored with electrocardiography (ECG), oxygen saturation (SpO₂) probes, and noninvasive blood pressure arterial monitorization. An acceleromyography device (TOF Watch SX, Organon, Netherlands) was connected to stimulate the ulnar nerve for assessing neuromuscular block. TOF electrodes were placed on the ulnar edge of the distal forearm; a heat probe was placed in the palm, and a transducer to the inner side of the thumb. A signal stabilization of neuromuscular transmission monitoring was performed. Hand and forearm were wrapped with cotton to prevent peripheral temperature to drop below 32°C. Vascular access was achieved with a 20G cannula placed from the forearm on the operating table.

After anesthetic induction of the patients was provided with 2 mg/kg propofol (Propofol Lipuro 1% ampoule, B. Braun, Germany) and 1 mcg/kg Fentanyl (Fentanyl ampul 0.05 mg/mL, Janssen, Belgium), TOF device was calibrated. Rocuronium bromide (Myocron vial 50 mg/mL, Vem Ilac, Turkey) was administered at a dose of 0.6 mg/kg, TOF device was set to automatically read every 16 seconds and measurements began. For train-of-four (TOF) monitoring, four supramaximal stimuli of 2 Hz were given in 0.5 seconds, and ratio of the fourth response to the first was recorded. Block degree was determined according to the number of responses. Patients were intubated when TOF was 0. Maintenance of anesthesia was performed using 50% O₂+N₂O and 4-6% desflurane. At the end of the operation, 10 mg/kg paracetamol (Perfalgan 10 mg/mL vial, Bristol-Myers Squibb, USA) was used for postoperative analgesia. In order to maintain TOF ≤ 0.2 , additional rocuronium was intravenously administered as needed. Group S (saline flush group) received 2 mg/kg sugammadex (Bridion vial 200 mg/2mL, Organon, Oss, Netherlands) intravenously for 3-5 seconds, after which 20 ml of isotonic saline was flushed. Group C (control group) received 2 mg/kg sugammadex intravenously for 3-5 seconds. Inhalation anesthesia was not ended until measurements were completed to prevent patients from feeling pain during TOF measurements. TOF measurement and inhalation anesthesia were terminated when a TOF ratio of 0.9 or higher was observed. Time of TOF ratio to reach 0.9 from 0.2 was recorded. Patients were extubated and transported to the postoperative recovery room. Those with an Aldrete score ≥ 9 were taken to the ward. In addition, heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and SpO₂ were recorded just before anesthetic induction, at the 5th, 10th, 30th and 60th post-induction minutes and 10th and 30th postoperative minutes.

Sample size calculation

Primary endpoint of our study was time of TOF ratio to reach 0.9 after saline flush. Sample size estimation was based on the method described by Filho et al. [8]. In order to detect a 25% change time of TOF ratio to reach 0.9 (120 (40) sec control values in the study by Filho et.), with an α error of 0.05 and a power of 95%, we found that the sample size should be at least 30 patients per group. Estimating an approximate 10% dropout rate, we included 33 patients in each group. The sample size estimation was performed using G Power 3 Calculator.

Statistical analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences for Windows 11.5) package software. Normality of continuous variables was analyzed with Kolmogorov Smirnov test. Descriptive statistics were expressed as mean (standard deviation) for continuous variables, and as number (percentage) for categorical variables. Continuous variables were compared between the groups with “Independent Sample t test” and “Mann-Whitney U test” where appropriate. Chi-square test was used in comparison of the categorical variables. Split Plot Anova Test was used in comparison of changes of heart rate and mean arterial pressure over time between the two groups. A *P*-value <0.05 was considered statistically significant.

Results

The study initially included 66 patients who underwent isolated abdominal surgery from August 2017 to January 2018 in our hospital. Six patients rejected to participate in the study, who were excluded (Figure 1). The two groups were similar in terms of demographics and basic clinical characteristics (Table 1). No significant difference was found between the groups in terms of intraoperative and postoperative heart rate values (Figure 2) or intraoperative and postoperative mean arterial pressure (MAP) values (Figure 3).

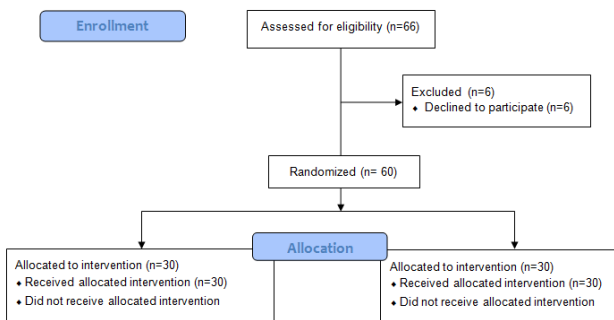


Figure 1: Flow-diagram

There was a statistically significant difference between the groups in terms of the time of TOF to reach 0.9 from 0.2. The mean time of TOF to reach 0.9 from 0.2 was significantly lower in Saline flush group than in control group (Table 2).

Adverse events were not observed in any of the patients and the perioperative period was completed uneventfully.

Table 1: Demographics and basic clinical features of the groups

Variables	Control group (n=30)	Saline flush group (n=30)	<i>P</i> -value
Age (year)	42.5(13.6)	40.3(13.6)	0.536*
Gender - Female	18 (60.0%)	14 (46.7%)	0.084†
Mean Aldrete score	9.7(0.4)	9.5(0.5)	0.118**
Body Mass Index (kg/m ²)	25.7(3.0)	25.8(3.2)	0.955**
ASA ½	10/20	11/19	0.791†
Operation Time (min)	100.4(53.8)	106.7(33.1)	0.629†
Anesthesia Time (min)	109.6(54.6)	117.8(35.3)	0.493*

Data were presented as mean (standard deviation) or number (percentage). Statistical tests for the analysis were as follows: *Mann-Whitney U Test, **Independent Sample T Test, †Chi-Square Test

Table 2: Comparison of mean times of TOF to reach 0.9 from 0.2 between the groups

Variable	Control Group (n=30)	Saline Flush Group (n=30)	<i>P</i> -value
The mean time of TOF 0.2-0.9 (second)	130.5(61.9)	85.4(33.1)	0.001*

Data were presented as mean (standard deviation). Statistical test for the analysis was as follow: *Mann-Whitney U Test

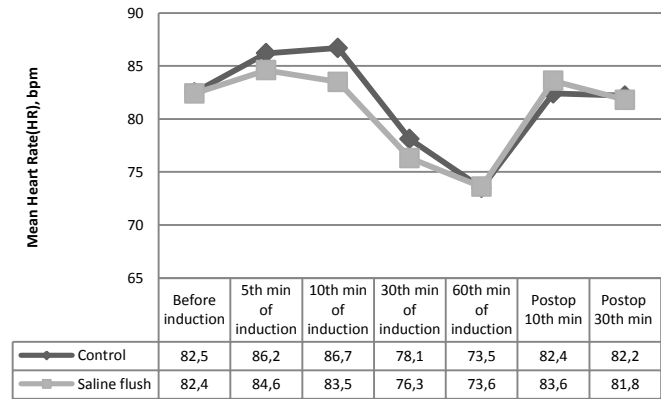


Figure 2: Comparison of heart rates between the groups

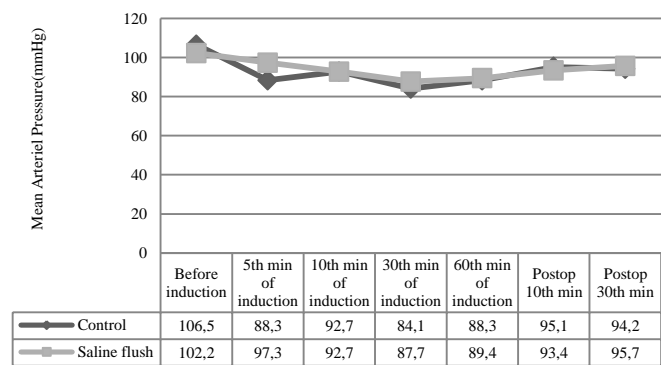


Figure 3: Comparison of mean arterial pressures between the groups

Discussion

This study showed that 20 mL saline flush administered immediately after sugammadex (2 mg/kg) accelerated its time of onset, shortened the time of TOF to reach 0.9 from 0.2, and contributed to rapid reversal of neuromuscular block.

Some pharmacological and non-pharmacological methods are used to decrease the time of onset of drugs, namely, increasing drug dose, elevation of the extremity where the drug is administered and saline flush after administration of drugs from the peripheral vein. Administration of rocuronium at a dose of 0.9-1.2 mg/kg instead of its normal dose 0.6 mg/kg is stated as an appropriate alternative to succinylcholine for neuromuscular block during rapid induction [9,10]. IV drug administration from a peripheral vein is typically followed by a fluid bolus application in many clinic applications. Although saline flush application has been performed via a peripheral vein and its effects have been shown in some studies, we could not find a study about saline flush after sugammadex. Kulkarni et al. [11] have used the saline flush method and extremity elevation together after rocuronium administration, and found that it shortened time of onset of rocuronium. A study conducted in dogs during cardiac arrest concluded that bolus injection of 20 mL saline after dye administration resulted in enhanced dye circulation time and a higher peak levels [12]. American Heart Association (AHA) declared that administration of a resuscitation drug from a peripheral vein during cardiopulmonary resuscitation should be followed by 20 mL fluid bolus to accelerate flow of the drug into the central circulation [6]. In their study with 48 patients, Ishigaki et al. [7]

administered neuromuscular blockade with 0.6 mg/kg rocuronium in patients in the control and saline groups, and found that the onset time of the drug was 90 seconds in the control group and 60 seconds in the saline bolus group. Nitahara et al. [13] investigated the effect of 20 mL saline bolus injection following 0.1 mg/kg vecuronium administered from a peripheral vein with elevation of extremity and found onset time of neuromuscular block as 128.3 seconds in the control and 104.6 seconds in the saline flush group. Iwasaki et al. [14] compared administration of vecuronium from a pulmonary artery catheter to the right atrium, and administration from dorsal vein of the hand, and found the onset time as 82 seconds in dorsal vein administration and 11 seconds in administration to the right atrium. Similarly, in our study we found that onset time of drug effect was 50 seconds shorter in saline flush group than the control group.

Sugammadex is the first relaxant binding agent used in reversal of the block provided by neuromuscular blockers. Decurarization with sugammadex has been a new approach for a rapid and safe reversal of neuromuscular block provided by rocuronium or vecuronium [15,16]. Time required for TOF to reach 0.9 in reversal of deep neuromuscular block under sevoflurane anesthesia was found to be 18 folds shorter with sugammadex compared to neostigmine [17].

In a randomized controlled study by Blobner et al. [18] on 198 patients, 2 mg/kg sugammadex or 50 µg/kg neostigmine were administered when TOF was 0.2 in patients with neuromuscular block provided by rocuronium. Times of TOF ratio to reach 0.9 were measured as 1.4 minutes in the sugammadex group and 17.6 minutes in neostigmine group. Shields et al. [19] investigated the efficacy of different doses of sugammadex in reversal of the neuromuscular block provided by rocuronium. In the study conducted in 30 patients, neuromuscular block was initially provided with 0.6 mg/kg rocuronium, and the time of TOF to reach 0.9 (the time of reversal of neuromuscular block) was found as 150 seconds with 2 mg/kg dose of sugammadex. In our study, we find the mean time of TOF to reach 0.9 from 0.2 was 130.5 (61.9) seconds in the control group, while this duration dropped to 85.4 (33.1) seconds in the group who received saline flush. We think this might be due to saline flush causing sugammadex to rapidly enter the systemic circulation and accelerating its effect. Saline flush of 20 mL administered immediately after sugammadex (2 mg/kg) caused sugammadex to rapidly enter the systemic circulation, shortened its time of onset and the time of TOF to reach 0.9 from 0.2, and contributed to rapid reversal of neuromuscular blockade.

Limitations

The main limitations of the present study were the relatively small sample size, the single-centered design, limited data, and the lack of a long follow-up during the postoperative period. However, further, larger scale studies are needed to confirm this effect and achieve stronger evidence.

Conclusion

We suggest that saline flush administration would be helpful in the cases where a rapid reversal of neuromuscular block is desired.

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The value of heat shock protein (HSP) 60 on in-hospital and short-term prognosis in patients with acute ST segment elevation myocardial infarction

Akut ST elevasyonlu miyokard infarktüsünde ısı şok proteini 60'ın hastane içi ve kısa dönem prognostik değeri

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Introduction

Atherosclerosis is a structural disease of medium-sized and large arteries, which commences as an endothelial dysfunction in the intima and media layers in its early phases, then transforms into true atherosclerotic plaque formations in its further phases. It begins to affect the arteries during the early stages of bodily development, and follows a continuous and uninterrupted pattern through a lifespan [1]. Among the most commonly affected arteries are coronary arteries, aorta, ilio-femoral arteries and carotid arteries. It may also affect, albeit less frequently, the intracranial arteries.

Development of atherosclerosis is multifactorial. Inflammation has been known to play role in every stage of atherosclerosis, as well as plaque rupture and thrombus formation [2]. Inception of the disease relies upon the interaction of the immune mechanisms with metabolic risk factors. Once initiated, the disease shows progression in various rates. Moreover, disrupted endothelial structure contributes further to the progression of the disease.

Cells begin to synthesize some proteins known as heat shock proteins upon exposure to sudden increase in temperature, anoxia, reactive oxygen species and changing glucose levels. The heat shock proteins (HSP) are subgrouped according to their molecular weights (HSP 10, 40, 60, 70, 90, 110, small HSP). HSPs are secreted from cytosol, mitochondria, endoplasmic reticulum and cell nucleus [3-6]. Moreover, importance of the HSPs relies on their ability to interact with other proteins, thereby modifying both their structure and function. HSPs exert strong cytoprotective effect and behave as chaperons for other cellular proteins. They also resist aggregation of the proteins during their folding, disassembly and exposure to stress, like high temperature. Many HSPs are synthesized and secreted into the cytosol in response to stress.

HSP 60 is found in high amounts in the vicinity of atherosclerotic areas, despite their absence in non-atherosclerotic vessel segments within the same vascular lumen. Vascular endothelial cells do not secrete HSP60 under physiological circumstances. Upon encountering any stress induced by classical atherosclerotic risk factors, however, they begin to secrete HSP60 and some other adhesion molecules simultaneously, thus triggering both cellular and humoral immunity which further causes intimal layer of the vessel to be infiltrated by mononuclear cells. This reversible process may convert into an irreversible one, should the atherosclerotic risk factors still persist [7]. Plasma HSP 60 level was found to be elevated in patients with increased carotid intima-media thickness, independently of such other atherosclerotic risk factors as gender and age [8]. HSP 60 and HSP 70 plasma levels were reported to be significantly elevated in patients with borderline hypertension, which was considered to be associated with premature atherosclerosis [9]. Major cardiovascular events were observed in greater frequency in patients with higher plasma level of HSP 65, a member of HSP 60 family. The aforementioned findings led the physicians to extrapolate that plasma HSP 60 level could have a prognostic value on the morbidity and mortality related to atherosclerosis.

In the light of the afore-mentioned premises, we intended to inquire the in-hospital and 30-day prognostic importance of HSP 60 in patients with acute ST-segment elevation myocardial infarction (STEMI).

Materials and methods

Patient selection

Patients older than 18 years of age who were admitted to the emergency department with acute STEMI within 12 hour of the onset of symptoms between 2011 and 2013 were included in the study. Our study was designed as a prospective cohort. After excluding those with any co-existing active infection or inflammation, autoimmune connective tissue disorder and malignancy, which are among the clinical states that may have been implicated in higher baseline HSP60 levels measured on admission, a total of 221 patients were considered to be appropriate for study enrollment. All the patients included in the study were interrogated with regards to age, gender, risk factors for atherosclerosis, any previous history of ischemic diseases, myocardial infarction (MI) or percutaneous coronary intervention, and medications used. Informed consent was obtained from every participants and the local ethics committee (Selçuk University Ethics Committee) approved our study. (Approval Number:2011-50, Date:31.05.2011)

Biochemical analysis

10 ml of blood sample was collected into plain tubes from the patients admitted to the emergency department with acute STEMI within 12 hours from onset of the symptoms. Respective supernatants obtained from the blood samples through centrifugation at 3000 ppm for 5 minutes were transferred to Eppendorf tubes and were frozen at -80°C until the time of assay. The analyses for HSP 60 were performed through Enzyme-Linked Immunosorbent Assay (ELISA) method using commercial kit in Rayto-2100C Microplate Reader (India) and expressed in ng/mL.

Medications and devices used

Patients considered appropriate for percutaneous coronary intervention received 300 mg acetylsalicylic acid and 600 mg loading dose of clopidogrel. The other medications were used in compliance with the relevant guideline of STEMI management [10]. Right femoral artery was selected as the main site of entry for the angiographic procedure. In patients deemed to have high thrombus burden, a loading of 25 µg/kg tirofiban hydrochloride as glycoprotein IIb-IIIa antagonist was administered intracoronarily in 3 minutes, followed by a constant intravenous infusion at a rate of 0.15µg/kg/min for 18 hours. The patients in whom fibrinolytic therapy was performed received 300 mg acetylsalicylic acid and 300 mg loading dose of clopidogrel. However, 75 mg oral clopidogrel was administered without any loading dose in patients older than 75 years of age. Successful reperfusion of myocardium was decided to be achieved if the patient was rendered asymptomatic and there appeared to be 70% or more resolution in relevant ST segments in the ECG strip compared to baseline ECG.

All patients received high dose of statin (atorvastatin 40-80 mg and rosuvastatin 20-40 mg, preferably), beta-blocker treatment (except those with manifest cardiac decompensation and/or with any contraindication for beta blocker use),

angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB), and maintenance doses of 100 mg acetylsalicylic acid and 75 mg clopidogrel. Primary percutaneous coronary interventions were performed by experienced interventional cardiologists (more than 75 PCI cases/year), using standard methods in Toshiba Infinix DFP-8000D interventional angiography system. Echocardiographic evaluations were conducted using Toshiba Aplio XV echocardiography device.

End points

Primary end point: Analysis of predictive value of HSP 60 in in-hospital and 30-day mortality after acute STEMI.

Secondary end point: Analysis of predictive value of HSP 60 in in-hospital development of cardiogenic shock and heart failure, and length of hospital stay.

In-Hospital and short-term follow-up of the patients

Data regarding in-hospital end-points of the patients was obtained either through interview with the patients or through interrogation of their hospital records. In order to gather data regarding first-month follow-up, on the other hand, the patients were summoned to out-patient clinic via phone call. For those unable to attend to out-patient clinic visit, relevant data was obtained via direct phone call either with the patients themselves or one of his/her relatives. Furthermore, hospital records of the patients, if any, who presented to the hospital within one month after hospital discharge were also utilized in this regard.

Statistical analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 software was utilized in the statistical analysis of the study findings. Numbers, percentage, mean (SD), median, minimum (min), maximum (max) and 25-75 percentiles were used for the descriptive statistics. Z test and Kruskal-Wallis tests were used for the comparison of quantitative data. Chi-square test, on the other hand, was used for the comparison of qualitative data. The parameters found to be significant were further assessed using logistic-regression analysis so as to determine the predictors of mortality. In this regard, such variables as age, length of hospital stay, HSP 60 value and development of cardiogenic shock were involved in the logistic regression model as independent predictor, as they provided significant contribution to the model in the univariate analysis ($P < 0.05$). The other variables lacking any significant contribution ($P > 0.05$), on the other hand, were not included in the logistic regression model. Furthermore, cut-off value of HSP60 level was determined by using ROC curve analysis. P -values < 0.05 was regarded as statistically significant.

Results

Clinical and demographic characteristics of the patients

The ages of all 221 patients ranged between 25 and 89 years. Mean age was found to be 59.8(4.6) years. Of all patients, 176 (80%) were male, while 45 (20%) were female. The mean ages of the males and the females were 57.69 and 68.57 years, respectively. Respective incidences of hypertension, diabetes mellitus, hyperlipidemia and history of smoking were 40.5%, 18.6%, 13.2% and 70.9%. 85% of the patients was admitted with

Killip class 1. GpIIb/IIIa antagonistic agent (tirofiban) was used in 33.2% of the patients.

There was no relationship between HSP60 value and such personal demographic characteristics as gender, hypertension, hyperlipidemia, diabetes mellitus and smoking (Table 1).

Primary end-point was observed in 30 (13.6%) out of all 221 patients included in the study, most of which occurring as in-hospital mortality (21 patients) (Table 2).HSP60 value was measured to be greater in patients in whom in-hospital or one-month mortality occurred (for one-Month mortality $P = 0.020$ and for In-Hospital mortality $P = 0.004$).

Logistic regression analysis revealed that mortality was associated with age, length of hospitalization, development of cardiogenic shock and HSP60 value ($P < 0.05$).Accordingly, age, development of cardiogenic shock and greater HSP60 value were found to be positively correlated with mortality, while length of hospital stay being found to be negatively correlated with mortality. Furthermore, on the basis of odd ratios, every increase of 1 year of age was related to 1.16 time increased risk of death (Table 3).

HSP60 value was significantly increased in patients developing cardiogenic shock and in those with in-hospital heart failure (Table 4).

Table 1: The relationship between HSP60 value and risk factors of coronary arterial disease

Risk factors of coronary arterial disease	(n)	HSP60 Median (IQR 25-75)	Statistical analysis Z	P-value	
Gender	Female	176	6.075 (4.455-8.665)	1.811	0.070
	Male	45	7.110 (4.820-11.710)		
Hypertension	No	131	6.360 (4.510-9.360)	0.124	0.901
	Yes	90	6.450 (4.660-9.080)		
Hyperlipidemia	No	192	6.450 (4.510-9.360)	0.159	0.874
	Yes	29	6.230 (4.890-8.800)		
Diabetes Mellitus	No	179	6.540 (4.660-9.360)	-1.193	0.233
	Yes	42	5.770 (4.220-8.420)		
Smoking	No	65	6.590 (4.660-10.370)	-0.412	0.680
	Yes	156	6.185 (4.530-9.165)		

Table 2: Relationship between mortality and HSP60 value

Mortality	(n)	Median HSP60 (ng/mL) (IQR 25-75)	Statistical analysis Z	P-value	
In-Hospital Mortality	No	200	6.230 (4.510-8.690)	2.853	0.004
	Yes	21	8.720 (5.750-20.820)		
One-Month Mortality	No	185	6.140 (4.510-8.580)	2.325	0.020
	Yes	9	21.880 (6.590-45.070)		

Table 3: Depiction of the results from the logistic regression analysis

Variables	B	Wald	P-value	Odds	95 % Confidence Interval for Odds Minimum	Maximum
Age	0.149	23.116	<0.001	1.161	1.093	1.234
Length of Hospital Stay	-0.457	5.479	0.019	0.633	0.432	0.928
HSP60 value	0.055	8.750	0.003	1.056	1.019	1.095
Development of Cardiogenic Shock	4.865	12.712	<0.001	129.719	8.943	1881.658
Constant	-11.549	23.352	<0.001	0.000		

Table 4: Relationship between HSP60 value and in-hospital cardiogenic shock or in-hospital heart failure

	(n)	Median HSP60 value (ng/mL) (IQR 25-75)	Statistical analysis Z	P-value	
In-Hospital Cardiogenic Shock	No	211	6.270 (4.510-9.250)	1.637	0.021
	Yes	10	7.650 (5.750-22.100)		
In-Hospital Heart Failure	No	131	6.450 (4.330-9.080)	1.101	0.033
	Yes	90	6.405 (4.890-10.370)		

Determination of HSP60 cut-off point

ROC curve analysis was utilized in an attempt to define any potential cut-off point of HSP60 in the determination of mortality, which yielded a cut-off point >7.325 ng/mL value with sensitivity of 67.7% and specificity of 66.8% (AUC: 0.70; $P<0.001$) (Figure 1). In addition, this cut-off was analyzed through Chi-Square test to evaluate further its accuracy which showed that HSP60 in 127 out of 191 patients in whom mortality did not occur was lower than the cut-off value. The HSP60 value in 20 out of 30 patients in whom mortality occurred, on the other hand, can be seen to be greater than the cut-off value. Chi-square test also yielded a significant relationship between HSP60 cut-off value and mortality ($P<0.001$). The accuracy of predicting patients in whom mortality did not occur was 97.4% and that of the patients in whom mortality occurred was 56.7%. Overall accuracy of prediction was 91.8%.

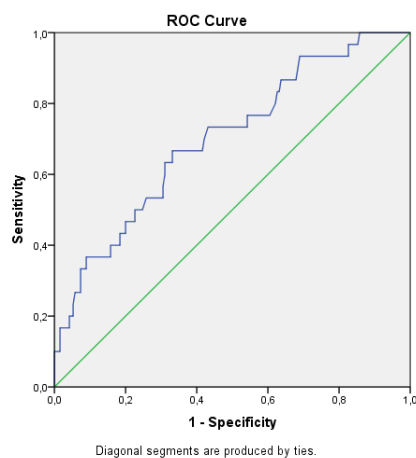


Figure 1: ROC curve analysis for HSP60 values in the determination of mortality (a cut-off point >7.325 ng/mL value with sensitivity of 67.7% and specificity of 66.8%, AUC: 0.70; $P<0.001$)

Discussion

HSP60 is a nuclear-encoded protein which is predominantly found in the mitochondria. In addition to the widely accepted definition that it is an intracellular molecule, HSP60 has also been known to be secreted from cells and can be present in the peripheral blood of healthy individuals [11,12]. Extra cellular HSPs are one of the most powerful ways of sending a “danger signal” to the immune system and thereby triggering an immune response [13,14]. HSPs function in cell cycle control, cell proliferation, development, organization of the cyto-architecture, and regulation of cell death and survival [15,16]. It is not surprising therefore that HSPs possess a pivotal role in the development of atherosclerosis [17].

Seroepidemiologic studies also point out to the role of circulating HSP60s in the development and progression of atherosclerosis [8,9]. Atherosclerosis has been accepted as an inflammatory process and previous studies reported a significant relationship between atherosclerosis and the inflammation markers (such as CRP) and infections with *Chlamydia pneumoniae*, *cytomegalovirus (CMV)* and *Helicobacter pylori* [18]. Minor relationship was reported between the inflammation markers of CRP and HSP60 in a study by Xiao et al [19].

Compatible with the findings by Xiao et al. [12] study by Zhang et al. reported no correlation between CRP and HSP60. The findings from these studies might translate into the possibility that CRP and HSP60 may exert their atherosclerosis-

triggering effect through distinct mechanisms. Previous studies reported that high levels of HSP60 could stimulate the expression and release of respective pro-inflammatory mediators and vascular adhesion molecules from the myeloid cells and the endothelial cells. Accordingly, these secreted molecules, together with the immune responses they initiated, were reported to have been implicated directly in the pathogenesis of atherosclerosis [20,21].

A prospective study in 2008 by Zhang et al. [14] which compared the risk of coronary arterial(CAD) disease development between individuals with very high level of HSP 60 (> 1000 ng/ml) and those with low level of HSP60 reported a positive and strong correlation between high levels of HSP60 and risk of CAD development, independently of such traditional risk factors of CAD development as age, gender, smoking status, body-mass index, hypertension, diabetes mellitus and positive family history of premature coronary arterial disease AMI was also shown to induce the secretion of HSP60.

It was reported in previous studies that human HSP60 (hHSP60) and HSP60 secreted from *C.pneumoniae* were co-localized in the atherosclerotic plaques and both play a pivotal role chronic bacterial and viral infection of the plaques [22]. Many other studies conducted on cardiovascular diseases reported the presence of antibodies against HSP60 and such pathogens as *C.pneumoniae*, *H. pylori* and *CMV* along with microbial/human HSP60 [23].

Biasucci et al. [24] suggested *C.pneumoniae*-HSP60 antibodies as specific markers in acute coronary syndromes. Burian et al. [25] reported that high level of antibodies against hHSP60 and *C.pneumoniae* were independent risk factors for CAD. Considering such a relationship between CAD development and anti-HSP60 antibody level, it would be rational to assume that high levels of HSP60 together with high levels of anti-HSP60 antibody might reflect a over-activated immunity and exacerbated atherosclerotic process [18,26]. Addition of HSP60 and anti-HSP60 levels to such well-known CAD risk factors as smoking, hypertension and diabetes mellitus act as a booster in the development of CAD. In a prospective study, HSP60 level was reported to show a transient increase in blood circulation following STEMI, the reason for which was proposed to be cardiomyocyte necrosis and accompanying endothelial dysfunction [27]. In this regard, Schett et al. [28] also reported abundant HSP60 secretion into circulation as a result of experimentally-induced myocardial ischemia and necrosis in rat models. Shear-stress related to STEMI is also likely to be another contributor of high levels of HSP60 [29].

In a study conducted on 826 patients and investigating the relationship between HSP60 level and carotid atherosclerosis, serum HSP60 level was found to be elevated in patients with increased carotid intima-media thickness, independently of other traditional atherosclerosis risk factors [10]. Similarly, in a study by Pockley et al. [11] comparing HSP60 and HSP70 levels between healthy individuals those with borderline hypertension, HSP60 and HSP70 levels were found to be significantly increased in the individuals with borderline hypertension and this was considered to have a possible relationship with early atherosclerosis.

In another study including 79 patients with documented history of CAD, incidence of major cardiovascular event development was increased in patients with high level of HSP65, a member of HSP60 family. All these findings direct clinicians to infer that increased serum HSP60 level may have a prognostic importance on morbidity and mortality in patients with atherosclerosis.

In a recent prospective study conducted by Bonnad et al. [30] patients presenting with acute heart failure were assigned into 3 groups according to the HSP60 levels on admission and followed-up for 7 months. The incidence of death and re-admission to the hospital for acute cardiac decompensation was statistically higher in the group of high HSP60 level. Therefore, HSP60 level was suggested to have a prognostic significance on patients with heart failure

Our study showed that HSP60 level had a prognostic significance in the prediction of mortality. Especially the cut-off value in our study was found to possess a high accuracy in the prediction of mortality. We believe that patients at high risk of in-hospital mortality may be successfully predicted by measuring HSP60 level on admission so that these high-risk patients can be closely followed-up to abate further the mortality rates. As for the secondary end point of our study, we also found a significant relationship between admission HSP60 level and in-hospital development of heart failure or cardiogenic shock. To the best of our knowledge, our study is the first in this regard.

Limitations

Our study should be assessed together with some limitations. First, our study population is relatively small and studies conducted on larger groups are warranted to verify our results. Secondly, although our in-hospital and 30-day mortality rates (9.5% and 13.6%, respectively) seems higher than expected, we consider that this relatively greater mortality rates could be attributable to the fact that our hospital operates as a tertiary center and hence receive a great number of patients in diverse clinical conditions.

Conclusion

Our study showed that HSP60 possess a prognostic significance in the prediction of in-hospital and 30-day mortality in patients presenting with acute STEMI within 12 hours of onset symptom onset. However, the fact that our study recruited a relatively small group of patients may hinder true interpretation of our findings. Hence, future studies including larger groups of patients are needed to confirm our results.

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Prognostic factors affecting survival in third-line treatment of advanced non-small cell lung cancer: Retrospective cohort study

İleri evre küçük hücre dışı akciğer kanserinde üçüncü basamak tedavide sağ kalımı etkileyen prognostik faktörler: Retrospektif kohort çalışma

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Abstract

Aim: In patients who have reached third-line treatment, survival times are short and response to treatment is poor. However, in some patients, survival times and treatment responses are good despite advanced treatment lines. The present study investigates the prognostic factors that affect survival among patients who have undergone third-line treatment for non-small cell lung cancer (NSCLC).

Methods: Among the 1,150 patients who were treated for and followed-up with a diagnosis of NSCLC between January 2008 and December 2015, 102 (8%) who had received third-line treatment were included in this retrospective cohort study.

Results: The mean patient age was 56 years (SD: 10.1), and 70.6% were male. The third-line treatment provided a median PFS of 2.36 (range: 1.15–36.1) months and an OS of 4.2 (range: 1.28–38.1) months. Cox hazard-model analyses indicated significant associations between prolonged survival and gender, smoking, non-squamous histology, age below 45 years, the presence of EGFR mutations and the use of EGFR tyrosine kinase inhibitors.

Conclusion: The prognosis may be better for some patients who have reached third-line treatments, namely, young patients, females, non-smokers, and those with a non-squamous histology. In these patients, physicians should be alert in terms of driver mutations, such as EGFR mutation.

Keywords: Third-line treatment, Anti-EGFR, Treatment, Prognosis, Non-small cell lung cancer

Öz

Amaç: Üçüncü basamak tedaviye ulaşmış hastalarda sağkalım süreleri kısa ve tedaviye yanıtları kötüdür. Ancak bazı hastalarda sağkalım süreleri ve tedavi yanıtları ilerlemiş tedavi basamağına rağmen iyidir. Bu çalışmadaki amacımız, küçük hücreli dışı akciğer kanserinde (KHDAK) üçüncü basamak tedaviye ulaşmış olan hastaların sağkalımlarını etkileyen prognostik faktörleri saptamaktır.

Yöntemler: Ocak 2008-Aralık 2015 tarihleri arasında KHDAK tanısı ile tedavi edilen ve takip edilen 1.150 hastadan üçüncü basamak tedavi alan 102 (%8) hasta bu retrospektif kohort çalışmada değerlendirildi.

Bulgular: Hastaların ortalama yaşı 54 (Standart sapma: 10,1) ve %70,6 sı erkekti. Üçüncü basamakta ortalama progresyonsuz sağkalım süresi ortalama 2.36 (Aralık: 1,15-36,1) ve ortalama toplam sağkalım 4.2 (1,28-38,1) aydı. Cox hazard modeli analizinde uzun sağkalımı etkileyen temel faktörler; cinsiyet, sigara, skuamöz dışı histoloji, 45 yaş altında olmak, EGFR mutasyon durumu ve Anti-EGFR tedavi almış olarak saptandı.

Sonuç: Kadın, sigara içmeyen, skuamöz dışı histolojisi olan, genç olan üçüncü basamak tedaviye ulaşmış hastalarda prognozun daha iyi olabileceği ve bu hastalarda EGFR mutasyonu gibi driver mutasyonları açısından hassas olunması gerektiği bilinmelidir.

Anahtar kelimeler: Üçüncü basamak tedavi, Anti-EGFR, Tedavi, Prognoz, Küçük hücre dışı akciğer kanseri

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Introduction

The five-year overall survival (OS) rate associated with all lung cancers was previously reported as 16.8% [1-3]. At the time of diagnosis, 57% of all patients present with metastatic disease and the five-year OS rate for metastatic disease was reported as 4.2% [3,4].

Epidermal growth factor receptor (EGFR) exon 19 deletion and exon 21 L858 mutations are valuable predictors of benefit from EGFR tyrosine kinase inhibitor (TKI) therapy, while rearrangements in the Anaplastic lymphoma kinase (ALK) gene predict benefit from ALK TKI agents [5,6]. The currently available second and third-line treatment options include targeted therapies for patients with driver mutations, and immunotherapies and chemotherapeutic agents for patients without mutations [7-12].

This study investigates the prognostic factors that affect survival among patients who received third-line treatment for non-small cell lung cancer (NSCLC).

Materials and methods

The study sample was formed after reviewing the medical files of 1,150 patients who were treated for and followed-up with a diagnosis of stage IV NSCLC at two separate centers between January 2008 and December 2015. Of those patients, 980 (85%) were screened in the Health Sciences University Dr Abdurrahman Yurtaslan Ankara Oncology Hospital, and 170 (15.6%) were screened at the Health Sciences University Ankara Atatürk Chest Diseases Hospital.

Patients aged 18 years and above, with a pathologically confirmed diagnosis of stage IV metastatic non-small cell lung cancer and a history of receiving at least one cycle of third-line treatment, were evaluated in this study. Of all the screened patients, 102 (8%) had received third-line treatment for metastatic disease. Patients were stratified based on gender, smoking status, age below or above 45 years, the presence of EGFR mutations, use of anti-EGFR treatment and histology. Data on the response evaluations were collected from the medical records of the patients.

Statistical analysis

The SPSS 17.0 program was used to estimate survival rate, and descriptive data were calculated through the use of the same program. Kaplan-Meier curves and a Long-rank test were used to analyze the survival data, and a Cox Regression analysis was performed to identify factors that affect survival. *P*-values of <0.05 were considered statistically significant.

Results

The mean age of 102 evaluated patients was 54 years (SD 10.1), 72 (70.6%) patients were male and 70 (68.1%) were smokers. Histopathological examinations confirmed non-squamous histology in 68 (66.6%) patients, and EGFR mutations were detected in 24 (23.5%) patients, of whom 21 (20.5%) were female, 23(22.5%) had non-squamous histology, and 21 (20.5%) had no history of smoking (Table 1).

All patients underwent platinum-doublet chemotherapy as the first-line treatment. The median number of first-line treatment cycles was five, and the disease control rate was 68%.

The most commonly preferred agents for second-line treatment were docetaxel 40 patients (39.2%), a platinum-doublet regimen 27 patients (26.4%) and pemetrexed 16 patients (15.7%). The median number of first-line treatment cycles was four, and the disease control rate was 58.6%. The most frequently used third-line treatments were vinorelbine in 26 patients (28.3%), docetaxel in 19 patients (18.6%), gemcitabine in 17 patients (16.7%) and erlotinib in 14 patients (13.7%). The median number of cycles was three and the disease control rate was 40.8% (Table 2).

Table 1: Patient demographics and clinical characteristics

Characteristics	n	%
Age-year mean (SD)	102	100
Age, years	54 (10.1)	
≥45	n	%
<45	84	82.4
18	18	17.6
Sex		
Female	30	29.4
Male	72	70.6
Smoking status		
Yes	70	70.6
No	32	29.4
Histology		
SCC	34	33.3
Adenocarcinoma	60	58.8
Large cell	4	3.9
Others	4	3.9
EGFR mutation		
Male	3	2.9
Female	21	20.5
Squamous	1	0.9
Non squamous	23	20.5
Smoker	3	2.9
Non smokers	21	20.5
ALK rearrangement	4	3.9
Died	102	100

EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, SCC: Squamous cell carcinoma

Table 2: Treatment characteristics

Treatment	First-line		Second-line		Third-line	
	n	%	n	%	n	%
Doublet platin based	102	100	27	26.4	6	5.8
Docetaxel	-	-	40	39.2	19	18.6
Gemcitabine	-	-	7	6.9	17	16.7
Pemetrexed	-	-	16	15.7	10	9.8
Vinorelbine	-	-	2	2	26	28.3
Erlotinib	-	-	8	7.8	14	13.7
Crizotinib	-	-	2	2	2	2
Others	-	-	-	-	5	4.9
Treatment Response						
Complete response	1	1	-	-	-	-
Partial response	33	32.4	18	17.4	11	10.4
Stabil disease	35	34.3	42	41.2	31	30.4
Progression	33	32.4	42	41.2	60	58.8
Number of cycle(Median)	5		4		3	
Number of drug						
Single agent	-	-	75	73.5	96	94.1
Doublet	102	100	27	26.5	6	5.9
Overall Survival Month	25	12.8			4.2	
Median (Range)	(9-63.7)		(4.5-46.1)		(1.28-38.1)	
Progression free survival-Month						
Median (range)	7.2 (2.63-24.25)		5.25 (1.4-34.79)		2.36 (1.15-36.1)	

Irrespective of the agent used, the median PFS with first-line treatment was 7.2 months (range: 2.6–24.2), and the median OS was 25 months (range: 9–63.7). The median PFS and OS with second-line treatment were 5.25 (range: 1.4–34.79) and 12.8 (range: 4.5–46.1) months, respectively. The median PFS and OS with third-line treatment were 2.36 (range: 1.15–36.1) and 4.2 (range: 1.28–38.1) months, respectively (Table 2).

In a univariate analysis of the sub-groups of patients receiving third-line treatment, overall survival was found to be better among women, non-smokers, patients with non-squamous histology, patients younger than 45 years, EGFR mutant patients and those treated with anti-EGFR agents. Multivariate analyses indicated that non-squamous histology, the presence of EGFR

mutations and the use of anti-EGFR treatments were associated with better survival (Table 3).

Table 3: Univariate and multivariate analysis of prognostic factors-associated overall survival

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95 % CI	P-value	HR	95% CI	P-value
Histology						
Non-squamous	0.46	0.3-0.72	0.001	0.62	0.3-0.98	0.041
Squamous						
Sex						
Female	0.36	0.22-0.59	<0.001			
Male						
Smoking status						
Non-smokers	0.34	0.21-0.57	<0.001			
Smokers						
EGFR mutation						
Mutant	0.26	0.15-0.45	<0.001	0.48	0.25-0.93	0.032
Wild						
Anti- EGFR treatment						
Yes	0.20	0.09-0.44	0.001	0.35	0.14-0.87	0.025
No						
Age						
<45 years	0.51	0.3-0.86	0.013			
>45 years						

HR: Hazard ratio, EGFR: Epidermal growth factor receptor

Among the EGFR-mutant patients, PFS was 12.45 months [95%CI, 9.06 to 15.83] in patients who received anti-EGFR, and 2.33 months [95%CI, 2.15 to 2.5] in patients who received conventional therapies as third-line treatment ($P=0.001$). The OS in these patient groups was 21.02 months [95%CI, 12.8 to 29.16] and 3.64 months [95%CI, 2.85 to 4.4], respectively ($P<0.001$) (Figure 1). PFS and OS did not significantly differ with anti-EGFR treatment as a second- or third-line treatment (Figure 2).

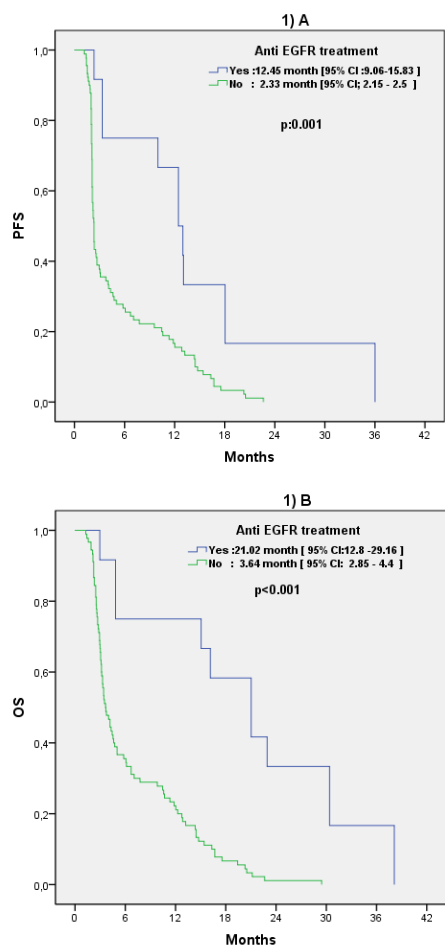


Figure 1: A) Comparison of progression free survival (PFS) rate of Anti-EGFR treatment status B) Comparison of overall survival (OS) rate of Anti-EGFR treatment status

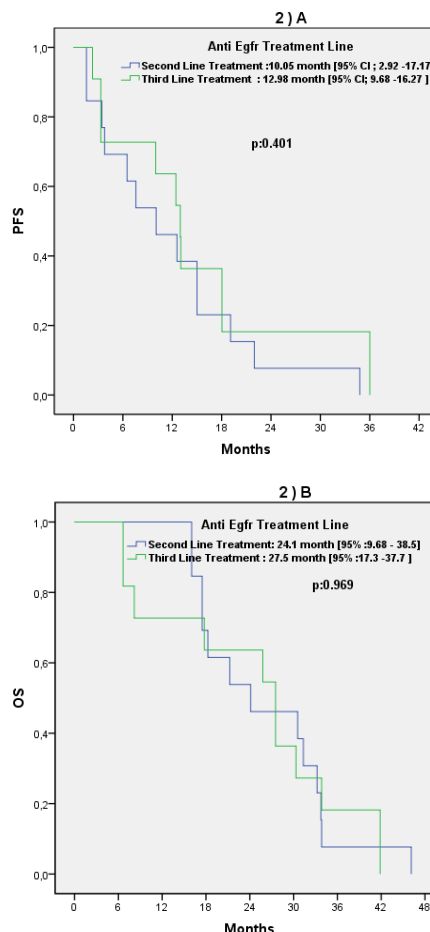


Figure 2: A) Comparison of progression free survival (PFS) rate of Anti-EGFR treatment line B) Comparison of overall survival (OS) rate of Anti-EGFR treatment line

Discussion

The use of EGFR-TKIs such as erlotinib, gefitinib, afatinib in first-line treatment in EGFR mutant patients has been shown in many studies [13-18]. In recent years, Osimertinib has proven to be more effective than other Anti EGFR-TKIs in first-line treatment in EGFR mutant patients, taking its place in the guidelines [18]. In the progression after EGFR-TKI, in the second-line treatment, the efficacy of osimertinib was proven if the T790M mutation was shown in the new biopsy [20].

Patients who were evaluated retrospectively were selected between 2008 and 2015. In the present study, we retrospectively evaluated the data of 102 patients who had received third-line treatment in two different centers.

In the years shown, chemotherapy agents were recommended as monotherapy in second and third-line therapy. EGFR-TKIs allowed national healthcare institutions to be given in second-line and third-line in our country. Although we have limitations in this retrospective study, the main issue we try to emphasize is to address factors that may be prognostic in patients who come to third-line treatment. The results of the present study showed that the female gender, being a non-smoker, younger than 45 years of age, the presence of EGFR mutations and the use of EGFR-TKIs were significant prognostic factors for third-line treatment.

While 8% of the patients screened in this study received third-line treatment for NSCLC, 172 patients (14%) received third-line treatment following a previously reported Austrian study [21]. In both the present and Australian studies, monotherapy was more commonly preferred as the second and

third-line treatments for metastatic NSCLC due to its low toxicity and the better tolerability profile seen with monotherapy regimens [21].

In a retrospective analysis performed by Kaira et al. [22] on 124 patients with metastatic NSCLC, patients who survived for more than five years were found to have adenocarcinoma histology and a good PS. In the present study, analyses of patients according to pathologic sub-types indicated that non-squamous histology was a prognostic factor that was associated with better survival. In a previous study, Kawaguchi et al. [23] reported that PS (Performance status) and smoking were independent prognostic factors, while non-smoking was found to be a prognostic factor in the present study. Zhen et al. [24] previously reported that non-smoking, adenocarcinoma histology, good PS and use of EGFR-TKIs were associated with a better OS in the third-line treatment of metastatic NSCLC.

A DELTA study that evaluated second and third-line regimens in an EGFR-wild patient group compared erlotinib with docetaxel and reported superior response rates and PFS with docetaxel than with erlotinib [25]. In a study that evaluated 503 Asian patients, female gender, the presence of EGFR mutations, use of EGFR-TKIs, adenocarcinoma histology, non-smoking and PS 0–1 were associated with statistically significant survival benefits [26].

Limitations

The limitations of the present study include its retrospective design, in addition to the limited number of patients and study centers.

Conclusion

EGFR mutations were found to be more common in non-smokers, younger population, the female gender and non-squamous histology in the present study. The use of EGFR-TKIs for the third-line treatment of NSCLC in EGFR-mutant patients provided better survival outcomes when compared to conventional chemotherapy regimens.

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Evaluation of postpartum depression scores of elective and emergency cesarean section patients

Planlı ve acil sezaryen olanlarda depresyon skorlarının değerlendirilmesi

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Abstract

Aim: One of the factors affecting postpartum depression is anxiety during pregnancy. This study aims to provide early diagnosis of postpartum depression by investigating the impact of pre-operative anxiety of women, who had an elective or emergency cesarean, on postpartum depression.

Methods: This case-control study was conducted on 103 patients (51 elective, 52 emergency cesarean section cases). Before the surgery, the patients filled State-Trait Anxiety Inventory (STAI) and a form surveying the descriptive properties and obstetric histories. Edinburg Postpartum Depression Scale (EPDS) was applied 6 weeks after delivery. The impact of these results and the anxiety levels in the preoperative period on postoperative depression were analyzed.

Results: The mean value of STAI-1 in the emergency and elective cesarean section groups were 41.31 and 43.61, respectively. Both groups had higher than average (>41) anxiety levels. The mean values of the STAI-2 were equal (48.35) and the anxiety level was above average. As per EPDS, the mean scores of the emergency and elective cesarean section groups were 6.98 and 5.31, respectively. The difference of postpartum rates between two groups was statistically significant ($P=0.050$). Postpartum depression was observed in 11.53% of the emergency group and 3.92% of the elective group.

Conclusion: Both groups had high state and trait anxiety, however, the postpartum depression rate in emergency patients was higher. It is significant to provide psychological support to the patients with high pre-operative anxiety and early treatment to the ones with a higher tendency of depression in the postpartum period.

Keywords: Cesarean, Emergency, Elective, State-trait anxiety, Postpartum depression

Öz

Amaç: Postpartum depresyonu etkileyen önemli etmenlerden biri hamilelik dönemindeki kaygıdır. Elektif şartlarda sezaryene alınan kadınlarda acil şartlarda sezaryene alınanların operasyon öncesindeki kaygılarının postpartum depresyon gelişiminde etkili olup olmadığı değerlendirilerek postpartum depresyonu erkenden tanımak amaçlanmıştır.

Yöntemler: Bu vaka kontrol çalışmasında 51 planlı ve 52 acil olmak üzere 103 kişiyle gerçekleştirildi. Sezaryenden önce hastaların tanımlayıcı ve obstetrik özelliklerini içeren anket formu ile Durumluk Sürekli Kaygı Envanteri (STAI) doldurularak kaygı düzeyleri belirlendi. Doğumdan 6 hafta sonra Edinburg Postpartum Depresyon Ölçeği (EPDS) uygulandı. Elde edilen sonuçlarla preoperatif devredeki kaygı durumunun postoperatif depresyon gelişmesine etkili olup olmadığı analiz edildi.

Bulgular: Acil gruptaki hastaların STAI-1 ortalaması 41,31, planlı gruptaki hastaların 43,61'di. Her iki grupta da kaygı seviyeleri ortalamının üzerindeydi (>41). STAI-2 ortalamaları her iki grupta eşitti (48,35) ve kaygı seviyesi ortalamının üzerindeydi. EPDS'de acil hastaların puan ortalaması 6,98, planlı hastaların puan ortalaması 5,31 olarak tespit edildi. Bu sonuç istatistikî olarak anlamlıydı ($P=0,050$). Buna göre acil grubun %11,53'ü, planlı grubun %3,92'sinde postpartum dönemde depresyon tespit edildi.

Sonuç: Her iki grubun durumluk ve sürekli kaygıları yüksek olmakla birlikte acil sezaryen yapılanlarda postpartum depresyon daha yüksekti. Bu nedenle preoperatif yüksek kaygısı olan hastalara gerekli psikolojik desteğin sağlanması ve postpartum dönemde depresyon eğilimi olanların erken tedaviye alınmaları önemlidir.

Anahtar kelimeler: Sezaryen, Acil, Elektif, Durumluk-sürekli kaygı, Postpartum depresyon

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Introduction

During the postpartum period, the mother tries to adapt to the physical, biological, social, and emotional changes and get used to her newborn. Psychosocial factors, as well as the hormonal changes, cause various fluctuations in moods during the postpartum period [1,2]. A patient that is unable to internalize her new role as a mother and to cope with baby-care may have psychiatric problems. One year following the delivery is a risky period for anxiety disorders, obsessive-compulsive disorder, depression, and sometimes psychosis [3]. Within a couple of days following delivery, postpartum blues are common and it may be confused with postpartum depression [4]. Postpartum blues, which can be seen as mild nervousness, sadness, fatigue, frequent crying, feelings of loss and sorrow, getting attached to the ones around herself, is observed in 60-70% of the women that had delivery [5]. Postpartum blues develop within 1-2 days following delivery and lasts for 1-2 weeks. It does not prevent the mother from caring for her baby but it has a 20% chance of transforming into major depression within 1 year [6].

On the other hand, depression is a complicated psychological disorder, which is a syndrome composed of several symptoms and indications [7]. Depression symptoms include -but are not limited to- fatigue, sleeping and appetite disorders, anhedonia, and agitation. Diagnostic and Statistical Manual of Mental Disorders describes postpartum depression as a non-psychotic major depression that occurs within four weeks following delivery.

This study aims to show that early diagnosis and meticulous treatment of postpartum depression is crucial. The study investigates the moods of women, who had elective and emergency cesarean section, as well as the relationship between urgency and the pre-operative anxiety, and their impact on postpartum depression.

Materials and methods

This study was a single-centered and descriptive case-control study. Initially, 58 elective cesarean section and 60 emergency cesarean section patients, which were randomly selected from a maternity hospital between October 2018 and March 2019, were included in the study. However, the study was finally conducted on 103 patients among which 51 were elective and 52 were emergency cesarean section patients. Visual and hearing-impaired patients, patients who were already diagnosed with psychiatric disorders, patients with speech disorder or depression history in the family, and those that were under 18 years of age were not included in the study. The emergency cesarean cases such as cord prolapse, placenta decollement, actively bleeding placenta previa that would threaten the lives of the mother or the baby were excluded. The cases that are elective only because of the patient's choice and those that lack medical indication were also excluded since this might have affected the anxiety levels. Permission of the University of Health Sciences, Erzurum Regional Training and Research Hospital Ethics Committee (No: 37732058-514.10-2018/10-66) and informed consent of all participants were obtained for the study.

Data collection

For the collection of data, questionnaire forms including descriptive and obstetric properties of the patients, namely, State-Trait Anxiety Inventory (STAI) and Edinburgh Postpartum Depression Scale (EPDS) were used [8, 9]. Patients were asked to fill the STAI state (STAI-1) and STAI trait (STAI-2) forms before the operation and their anxiety levels were evaluated.

STAI-1 is a state anxiety scale that measures the subjective fear of the individual in the present situation. STAI-2 is a trait anxiety scale and measures the tendency of the individual towards anxiety. Such individuals almost always perceive the situations in which they are in as stressful [10]. STAI-1 and STAI-2 forms have 20 questions each. They include some expressions that individuals use to express their emotions. The patients are asked to select the choice that best fits their current feelings without spending a lot of time thinking. In both scales, answer choices are in 4 groups and if the patient does not select 3 or more choices, the answer is considered invalid. Oner and Le Compte measured the validity and reliability of this inventory. The alpha reliability of the scale is 0.83-0.87 and the retest reliability is 0.71-0.86. They reported that the item reliability may fluctuate between 0.34 and 0.72. Low scores indicate a low level of anxiety and high scores indicate a high level of anxiety. They reported the average score to be between 36 and 41 [11].

In our study, we waited for at least 6 weeks as required by the postpartum period depressive episode diagnosis criteria. Six weeks after delivery, EPDS was applied to the patients. EPDS, which was defined by Cox et al. in 1987, is a scale that is used by clinicians for early diagnosis of postpartum depression [12]. EPDS is a self-evaluation scale consisting of 10 questions. All questions are scored from 0 to 3. The maximum available score for this scale is 30. Questions 1, 2 and 4 from the scale are scored as 0-1-2-3 and the others are scored as 3-2-1-0. The total value is calculated by adding the scores from these questions. Engindeniz measured the reliability and validity of the scale. The internal consistency coefficient was 0.79, split-half reliability was 0.80, and the cut-off point was 12 or 13. Consequently, sensitivity was 0.84, specificity was 0.88, positive predictive value was 0.69, and the negative predictive value was 0.94 [13]. Medical assistance is suggested if the mother scores more than 12 or 13, which indicates a higher possibility of depression [12]. The results of the study were analyzed to determine whether the anxiety level during the pre-operative period had any impact on postoperative depression.

Statistical analysis

The IBM SPSS 20 statistical analysis program was used for the statistics. Mean, median, standard deviation, minimum, maximum, percentage, and numbers were used to present the data. Shapiro Wilk-W and Kolmogorov Smirnov tests were used when sample sizes were under 50 and equal to or greater than 50, respectively, to examine the normal distribution of continuous variables.

For the comparison of two independent normally and non-normally distributed groups, Independent Samples t-test and Mann Whitney-U test were used, respectively.

Pearson Chi-square, chi-square and Fisher's Exact tests were used for 2x2 comparisons between categorical variables

when the expected count was >5, between 3-5 and <3, respectively. The statistical significance level was $P < 0.05$.

G*Power 3.1.9.2 software was used for power analysis. The power of this data was $1-\beta=0.99$ with elective group $n=51$, emergency group $n=52$, $\alpha=0.05$ and an effect size of $d=1.0$.

Results

The two groups were similar in terms of age, weight, gestational weeks, and socioeconomic levels. This indicates the homogeneity and normal distribution of the study. The mean ages of 52 patients in the emergency cesarean group and 51 patients in the elective cesarean section group were 27.88 (5.35) and 28.94 (5.35) years, respectively. The mean weights of the emergency and elective groups were 74.42 (12.35) and 75.63 (13.92) kg, respectively. There was no difference between the socioeconomic levels of the patients ($P=0.384$) (Table 1).

Table 1: Descriptive properties

	Emergency		Elective		P-value
	n	Mean (SD)	n	Mean (SD)	
Age	52	27.88 (5.35)	51	28.94 (5.35)	0.305
Weight	52	74.42 (12.35)	51	75.63 (13.92)	0.643
Socioeconomic level					
Low	27		23		0.384
Middle	22		23		
High	3		5		
Number of household members	52	4.10 (1.81)	51	4.31 (1.63)	0.492
Smoking					
Yes	3		4		0.444
No	49		46		

* The cells are shaded in gray, if the value or calculation is not available for the particular category.

It was the first cesarean for 44.2% of the emergency group and 66.5% of the elective group; thus, number of first cesarean was higher for the elective group. The mean number of gestational weeks in the emergency and elective groups were 38.29 (1.68) and 38.18 (1.77), respectively. The mean weight of the newborn was 3148.37 (549.11) g in the emergency group, and 3238.31 (551.77) g in the elective group. General conditions of 78.8 % of the newborns from the emergency group were good, whereas this rate was 94.1% for the elective group (Apgar scores > 8-10) ($P=0.009$) (Table 2).

The mean values of STAI-1 in the emergency and elective groups were 41.31 and 43.61, respectively, which were both higher than the average anxiety level (>41). Development of postpartum depression between the two groups was statistically significant ($P=0.003$). The groups had different minimum and maximum values. The mean values of STAI-2 were equal (48.35) and the anxiety level was above average. There was a significant correlation between STAI-1 and STAI-2 values ($P=0.01$). When the mean values are evaluated, it was seen that patients with high trait anxiety also had a high level of state anxiety.

The cut-off point in EPDS was calculated as 13. The rate of patients in the elective group that were above cut-off point was 3.92%, whereas this rate was 11.53% for the emergency cesarean group. As per EPDS, the mean scores of the emergency and elective groups were 6.98 and 5.31, respectively ($P=0.050$). Postpartum depression was observed in 11.53% of the emergency group and 3.92% of the elective group (Figure 1) (Table 3).

Table 2: Obstetric history

	Emergency		Elective		Chi-square	P-value	
	Mean (SD)	Min	Max	Mean			Min
Number of pregnancy (n)	3.65 (1.34)	2.00	8.00	3.63 (1.17)	1.00	7.00	0.932
Number of previous cesarean section	1.81 (1.05)	1.00	5.00	2.06 (0.76)	0.00	3.00	0.044
Number of living children	2.52 (1.34)	1.00	7.00	2.53 (0.83)	1.00	5.00	0.741
Number of abortion	0.27 (0.60)	0.00	3.00	0.27 (0.63)	0.00	3.00	0.892
Week in pregnancy at delivery (w)	38.29 (1.68)	34.00	41.00	38.18 (1.77)	32.00	41.00	0.743
Weight of newborn (g)	3148.37 (549.11)	1500.00	4110.00	3238.31 (551.77)	2000.00	4800.00	0.729
Problems during pregnancy							
Yes	30			23			1.635
No	22			28			0.201
General condition of the newborn*							
Apgar score 8-10	41			48			6.745
Apgar score 4-7	11			2			0.009
Apgar score 1-3	0			0			
Indication of cesarean							
Previous cesarean	23			35			6.229
Other	29			16			0.013
Previous problematic pregnancy							
Yes	8			12			0.810
No	41			39			0.201
Chronic illness							
Yes	11			3			5.113
No	41			48			0.024

* Apgar score indicates the general condition of the newborn (Apgar score 8-10 (good), 4-6 (has to be observed), 1-3 (needs intensive care)), ** The cells are shaded in gray, if the value or calculation is not available for the particular category

Table 3: Scale values

	Emergency		Elective		t, Z	P-value		
	Mean (SD)	Minimum	Maximum	Mean			Minimum	Maximum
STAI-1	41.31 (6.44)	26.00	70.00	43.61 (3.64)	36.00	52.00	-2.992	.003
STAI-2	48.35 (5.49)	36.00	62.00	48.35 (4.91)	35.00	59.00	-.007	.995
EPDS	6.98 (4.35)	0.00	21.00	5.31 (4.32)	0.00	24.00	1.949	.050

STAI: State Trait Anxiety Inventory, EPDS: Edinburgh Postpartum Depression Scale

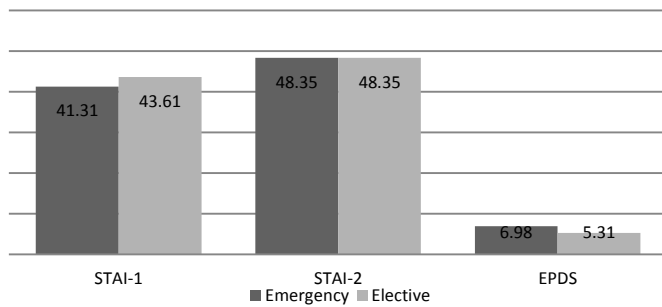


Figure 1: Mean of scale values

Discussion

Postpartum depression affects the health and life quality of the newborn and the mother [14]. Therefore, its early diagnosis, prevention, and treatment are crucial. The present study investigated the existing anxiety in elective and emergency cesarean section patients, their anxiety during cesarean section and the impact of a high level of anxiety on postpartum depression. In this study, both groups had very high STAI-1 and STAI-2 anxiety levels. Jokić-Begić et al. [15] stated that the fear of labor significantly increased antenatal anxiety. Another study reported that the trait and state anxiety levels increased as the time for delivery got closer [16]. In a study by Hepp et al. [17], it is stated that the labor pain and postoperative pain increased the anxiety level.

STAI-1 scale was higher in elective cesarean patients compared to emergency cesarean patients. Although it was statistically insignificant, the rate of previous cesarean sections and number of children > 2 were higher in the elective cesarean group compared to the emergency cesarean group. The studies state that increased responsibility with more children, and the mother's exposure to psychological and biological changes increases the possibility of depression [18]. In the literature, pre-operative anxiety and depression levels of patients who underwent cesarean section were reportedly high [19]. High state anxiety of elective cesarean patients is due to increased responsibility regarding their families and their previous operation experiences that caused developing fear against pain.

In a study by Hepp et al. [17], it was reported that subjective anxiety levels before elective cesarean were high, and the feeling of pain increased the perioperative anxiety but did not affect postpartum depression. In this study, STAI-2 was also applied to the patients before the operation to determine if they had existing anxiety and whether such a state of anxiety had any impact on the progression of postpartum depression. Both groups had same STAI-2 levels. Their anxiety levels were equal because of similar demographic properties of the patients. This indicated that the anxiety of the patients was not only related to delivery but also due to an elevated level of anxiety in their daily lives. In another study, women that had little social support, poor health and a history of stressful life events were found to be at risk of poor mental health [20].

Similarly, we concluded that the middle and low socioeconomic status increased concerns about living standards. The majority of the patients in both groups indicated their socioeconomic levels as either middle or low. The number of patients, who indicated their socioeconomic level as high, was very little. This data suggests that socioeconomic level affects anxiety due to the concerns in life. In a prevalence study by

Ayvaz et al. [21], the incidence of postpartum depression in lower-income societies was found to be high. In a study by Hein et al. [22], socioeconomic status was reported to be effective in the progression of depression after pregnancy.

Postpartum depression develops at least 2 weeks after delivery and this period may extend up to 1 year [23]. Thus, to optimize the study, EPDS was applied 6 weeks after the delivery to detect postpartum depression in patients. Depression ratings of the emergency cesarean patients were higher than the elective cesarean patients and the results were statistically significant. According to the STAI-1 scale, the anxiety level of the emergency group was lower than the elective group; even though the postpartum depression rate was higher for the emergency group. This conflict may be explained by the obstetric histories of the patients. In the emergency group, the number of weeks in pregnancy was lower, there were more newborns in a bad general condition and the number of patients who were faced with problems during pregnancy was higher. Therefore, the postpartum depression rate was higher in the emergency group despite the lower anxiety level.

Previous studies reported that the rate of postpartum depression increased if there were problems with the newborn or the newborn was kept in the intensive care unit [23]. Consequently, the patients, who had newborns with bad general conditions, were excluded from this study to maintain the normal distribution of the patients.

The low anxiety level in the emergency group may also be explained by the time restriction. The patients possibly did not comprehend the urgency of the situation to develop state anxiety. However, if they had had complications after the delivery due to operation, if they had received their newborn later than they expected or if their newborns were held under intensive care longer, they may also have shown increased postpartum depression rates.

The elective group had a lower rate of postpartum depression despite the higher state anxiety level. This is probably related to the feeling of relief and being able to return to their routine after birth.

Limitations

The limitation of the study was that we were unable to reach some of the mothers in 6th postpartum week and they were excluded from the study. Consequently, this reduced the sample size of the study. It is suggested for future studies to measure and investigate depression scores of the patients with high pre-operative anxiety.

Conclusion

Both groups had prominent levels of trait anxiety, however, the postpartum depression rates of the emergency group were higher. For the sake of mothers' mental health and the newborns' psychological progression, we believe that it is crucial to provide necessary psychological support to patients with high pre-operative anxiety, particularly to emergency cesarean patients, determine the patients with high-risk of postpartum depression during the postpartum period, and treat them at an early stage as necessary.

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Sleep quality & prevalence of restless legs syndrome among healthcare professionals

Sağlık çalışanlarında uyku kalitesi ve huzursuz bacaklar sendromu sıklığı

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Abstract

Aim: Healthcare professionals constitute a high-risk group for occupational stress as a consequence of difficult working conditions and therefore, they are prone to sleep disorders. The present study aimed to determine the prevalence of poor sleep quality and restless legs syndrome among healthcare professionals working daytime duty at a tertiary center, and to identify potential factors influencing sleep quality.

Methods: A total of 150 participants including physicians, nurses and other health professionals were included in this questionnaire-based cross-sectional study. All participants completed a self-administered questionnaire comprised of the Pittsburgh Sleep Quality Index (PSQI), Beck Depression Inventory (BDI) and Restless Legs Syndrome (RLS) Study Group Diagnostic Criteria, as well as demographic characteristics.

Results: Global PSQI score was 6.8 and the mean BDI score was 11.8. A PSQI score of >5, which indicates poor sleep quality, was noted in 69 participants (46%), while Restless legs syndrome was found in 31 (21%) and depression in 40 (26%) of the participants. Workplace violence, working at an intensive care unit, working in the operating room, and BDI scores were found to be factors that independently contributed to poor sleep quality. Furthermore, age, occupational experience, working at intensive care unit, work environment unrest and BDI scores were predictors of RLS.

Conclusions: In a substantial proportion of healthcare professionals, sleep quality is somewhat impaired and RLS and depressive symptoms are also frequent in this population. Work environment unrest, working conditions and intensity of depressive symptoms are determinants of sleep disorders in healthcare professionals. Healthcare professionals should be regularly screened for the presence of sleep disorders to recognize and treat the underlying causative conditions.

Keywords: Healthcare professional, Sleep quality, Restless legs syndrome, Depression, Occupational stress

Öz

Amaç: Sağlık çalışanları, zor çalışma koşullarının bir sonucu olarak mesleki stres için yüksek riskli bir grup oluşturmaktadır ve bu nedenle uyku bozukluklarına eğilimlidir. Bu çalışma, üçüncü basamak bir merkezde gündüz hizmet veren sağlık çalışanları arasında kötü uyku kalitesi ve huzursuz bacaklar sendromu prevalansını belirlemeyi ve uyku kalitesini etkileyen potansiyel faktörleri belirlemeyi amaçlamıştır.

Yöntemler: Anket tabanlı kesitsel özellikte olan bu çalışmaya hekimler, hemşireler ve diğer sağlık profesyonelleri dahil toplam 150 katılımcı dahil edildi. Tüm katılımcılar, Pittsburgh Uyku Kalitesi İndeksi (PSQI), Beck Depresyon Envanteri (BDI) ve Huzursuz Bacaklar Sendromu (RLS) Çalışma Grubu Tanı Kriterleri ve demografik özelliklerden oluşan kendi kendine uygulanan bir anket doldurdu.

Bulgular: Global PSQI skoru 6,8 ve ortalama BDI skoru 11,8 idi. 69 hastada (%46) kötü uyku kalitesini gösteren, >5 PSQI skoru, 31 hastada Huzursuz bacaklar sendromu saptandı (%21) ve depresyon katılımcılarının 40'ında (%26). İşyerinde şiddet, yoğun bakım ünitesinde çalışma, ameliyathanede çalışma ve BDI skorları bağımsız olarak düşük uyku kalitesine katkıda bulunan faktörler olarak bulundu. Ayrıca yaş, mesleki deneyim, yoğun bakım ünitesinde çalışma, çalışma ortamı huzursuzluğu ve BDI skorları RLS'nin prediktörleridir.

Sonuçlar: Sağlık çalışanlarının önemli bir kısmında uyku kalitesi bir miktar bozulmakta ve bu popülasyonda RLS ve depresif belirtiler de sık görülmektedir. Çalışma ortamındaki huzursuzluk, çalışma koşulları ve depresif belirtilerin yoğunluğu sağlık uzmanlarında uyku bozukluklarının belirleyicisidir. Sağlık uzmanları, alta yatan nedensel durumları tanımak ve tedavi etmek için uyku bozukluklarının varlığı açısından düzenli olarak taranmalıdır.

Anahtar kelimeler: Sağlık uzmanı, Uyku kalitesi, Huzursuz bacaklar sendromu, Depresyon, Mesleki stres

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Introduction

Sleep is a temporary and superficial state of unconsciousness with distinctive electrophysiological features, in which the response to external stimuli level is elevated. Sleep disorders are a common problem; however, a high proportion of these disorders remain undiagnosed, which is largely due to underestimation of the problem by those who suffer these conditions [1]. Restorative sleep is closely related to day-time performance, psychological stress and social interactions; therefore, they may adversely affect mental and physical health [2].

Healthcare professionals constitute a high-risk group for occupational stress as a consequence of working conditions; often translating into development of adverse results such as, loss of personal accomplishment at work, burnout and depression [3]. Sleep disorders may play an important role in the emergence of such problems, as healthcare workers are known to have high frequency of sleep disorders [4,5]. When a healthcare worker is exposed to excessive occupational stress for a long period of time, a wide variety of psychological problems including anxiety, depression and sleep disorders might occur [6]. Moreover, sleep disorders and other problems existing in healthcare professionals not only influence their physical and mental health, but may also affect their work efficiency and could endanger the quality of healthcare provided to patients. Other factors such as working in demanding positions (such as the intensive care unit and operating room), being subject to violence by patients and patient relatives, and having psychiatric problems or chronic diseases may also contribute to sleep disorders. Thus, sleep quality and sleep disorders in healthcare professionals should not be underestimated in order to improve healthcare professionals' physical and mental health in addition to preventing low performance at work.

The purpose of the present study was to determine the prevalence of poor sleep quality and restless legs syndrome among healthcare professionals working daytime duty at a tertiary center, and to identify potential factors influencing sleep quality.

Materials and methods

This study was conducted on healthcare professionals working in a tertiary center in İstanbul, Turkey, in November 2019. In the study, the population of the research is 850 health personnel working in the hospital. By taking 95% confidence level and 8% sample error, the minimum sample number was determined as 128. In this context, taking into consideration that there may be incorrect data, a survey was conducted with 150 health personnel. A total of 150 participants including physicians, nurses and other health professionals who responded to the self-administered questionnaire consisting of questions regarding demographic data, sleep quality, RLS and depression were included in the study. Those with known sleep disturbances, RLS and depression, or those receiving treatment for these conditions were excluded. Ethics committee approval and necessary permissions were obtained for the study.

To assess sleep quality, we used the Pittsburgh Sleep Quality Index (PSQI) which is a reliable, valid and standardized

measure of sleep quality [7]. The PSQI consists of seven components scored from 1 to 3 including the following: 1) subjective sleep quality (very good to very bad); 2) sleep latency (≤ 15 minutes to > 60 minutes); 3) sleep duration (≥ 7 hours to < 5 hours); 4) sleep efficiency ($\geq 85\%$ to $< 65\%$ ratio of hours of sleep/hours in bed); 5) sleep disturbances (from 'none during the past month' to ' ≥ 3 times per week'); 6) use of sleeping medications (none to ≥ 3 times a week); and 7) daytime dysfunction ('not a problem' to 'a very big problem'). Scores for all components are summed to provide a global score ranging between 0 and 21 points. It is widely accepted that a PSQI score > 5 indicates poor sleeping quality and a PSQI score < 5 indicates good sleeping quality [8].

Presence of RLS was based on the International Restless Legs Syndrome Study Group Diagnostic Criteria consisting of the following 4 criteria: 1) having an urge to move the legs, generally accompanied by unpleased sensation in the legs, 2) RLS symptoms activated by rest, 3) RLS symptoms alleviated by moving, in particular, by walking; 4) RLS symptoms being worse in the evening or night, either currently or in the past. Patients fulfilling these 4 criteria were diagnosed with RLS [9].

Depressive symptoms were assessed using the Beck depression inventory (BDI), which is an instrument used for the purpose of diagnosing depression consisting of 21 items on symptoms and attitudes, with intensities ranging between 0-3 [10]. The items refer to sadness, pessimism, sense of failure, lack of satisfaction, guilt, feeling of punishment, self-deprecation, self-accusation, suicidal ideation, crying spells, irritability, social withdrawal, indecisiveness, distortion of body image, inhibition to work, sleep disorder, fatigue, loss of appetite, weight loss, somatic concern, and decreased libido. Depression was defined as having a BDI score of ≥ 16 .

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess normality of distribution in continuous variables. Continuous variables were presented as mean (standard deviation, while categorical variables were presented as frequency (n) and percentage (%). Correlation analyses were performed to investigate the association between PSQI scores and selected variables. Logistic regression analyses were carried out to identify the predictors of poor sleep quality and RLS. Two-sided P -value ≤ 0.05 was accepted to show statistical significance.

Results

A hundred and fifty participants (mean age: 33.5 (10.2) years) who responded to the questionnaire and met the inclusion criteria were recruited in this study. Among these, 103 (68%) were female and 47 (32%) were male; 66 (44%) were single, 73 (49%) were married and 11 (7%) were divorced. There were 30 (20%) physicians and 33 (22%) nurses enrolled in the study. 44 (29%) of the participants had a chronic disease. The mean coffee and tea consumption per day was 3.5 (2.4) cups and alcohol consumption and smoking were recorded in 53 (35%) and 51 (34%) individuals of the study group, respectively. A PSQI score of > 5 , indicating poor sleep quality, was noted in 69 (46%) participants. Global mean PSQI score was 6.8 (4.7) and the mean

BDI score was 11.8 (8.3). Restless legs syndrome was noted in 31 (21%) and a BDI score ≥ 16 , indicating depression, was noted in 40 (26%) of the participants (Table 1). The BDI score was correlated positively with the PSQI score ($r = 0.546$, $P < 0.001$, Figure 1). Logistic regression analysis revealed that work environment unrest (OR:0.217, 95% CI: 0.057-0.830, $P = 0.026$), working at an intensive care unit (OR:0.047, 95% CI:0.004-0.527, $P = 0.013$), working in operating room (OR:0.091, 95% CI:0.013-0.614, $P = 0.014$), and BDI scores (OR:1.159, 95% CI:1.053-1.275, $P = 0.003$) were independently predictive for poor sleep quality (Table 2). Independent predictors for presence of RLS were age (OR:1.072, 95% CI:1.016-1.132, $P = 0.012$), occupational experience (OR:1.148, 95% CI:1.007-1.309, $P = 0.039$), working at an intensive care unit (OR:0.246, 95% CI:0.074-0.819, $P = 0.022$), work environment unrest (OR:5.520, 95% CI:1.697-17.957, $P = 0.005$) and BDI scores (OR:1.084, 95% CI:1.009-1.165, $P = 0.026$), as determined by logistic regression analysis (Table 3).

Table 1: Demographics, occupational features and sleep quality of the study population

	n=150
Gender	
Male, n (%)	47 (32 %)
Female, n (%)	103 (68 %)
Age	33.5 (10.2)
Marriage	
Single, n (%)	66 (44 %)
Married, n (%)	73 (49 %)
Divorced, n (%)	11 (7 %)
Working unit	
Radiology Unit, n (%)	2 (1.5 %)
Intensive Care Unit, n (%)	20 (13 %)
Operating Room, n (%)	11 (7.5 %)
Other n (%)	38 (25 %)
Unit below ground level, n (%)	71 (47.3 %)
Unit over ground level, n (%)	79 (52.7 %)
Experience (years)	11 (10.5)
Position	
Physician, n (%)	30 (20 %)
Nurse, n (%)	33 (22 %)
Technician, n (%)	19 (12.7 %)
Other, n (%)	68 (44 %)
Presence of chronic diseases, n (%)	44 (29 %)
Daily tea and coffee consumption (cups)	3.5 (2.4)
Alcohol consumption, n (%)	53 (35 %)
Smoking, n (%)	51 (34 %)
Work environment unrest, n (%)	94 (63 %)
Global PSQI score	6.8 (4.7)
PSQI > 5 points, n (%)	69 (46 %)
Mean BDI score	11.8 (8.3)
BDI > 16 points, n (%)	40 (26 %)
Restless Leg Syndrome, n (%)	31 (21 %)

BDI: Beck depression inventory, PSQI: Pittsburgh sleep quality index

Table 2: Predictors of poor sleep quality in healthcare professionals

	OR	95 % CI	P-value
Age	0.989	0.909-1.077	0.799
Gender	1.105	0.492-2.480	0.809
Marriage	0.855	0.207-3.526	0.828
Tea/coffee consumption	1.620	1.140-2.301	0.007
Chronic diseases	1.642	0.424-6.361	0.473
Occupational experience	0.978	0.842-1.137	0.774
Alcohol consumption	0.902	0.271-3.002	0.866
Smoking	0.370	0.110-1.239	0.107
Workplace violence	0.217	0.057-0.830	0.026
Intensive care unit staff	0.047	0.004-0.527	0.013
Operating room staff	0.091	0.013-0.614	0.014
BDI score	1.159	1.053-1.275	0.003

BDI: Beck depression inventory

Table 3: Predictors of restless legs syndrome in healthcare professionals

	OR	95 % CI	P-value
Age	1.072	1.016-1.132	0.012
Gender	0.930	0.287-3.014	0.903
Marriage	1.280	0.412-3.981	0.670
Tea/coffee consumption	1.132	0.864-1.483	0.370
Occupational experience	1.148	1.007-1.309	0.039
Alcohol consumption	0.974	0.338-2.805	0.961
Smoking	0.755	0.275-2.078	0.587
Workplace violence	5.520	1.697-17.957	0.005
Operating room staff	1.159	0.314-4.271	0.825
Intensive care unit staff	0.246	0.074-0.819	0.022
BDI score	1.084	1.009-1.165	0.026

BDI: Beck depression inventory

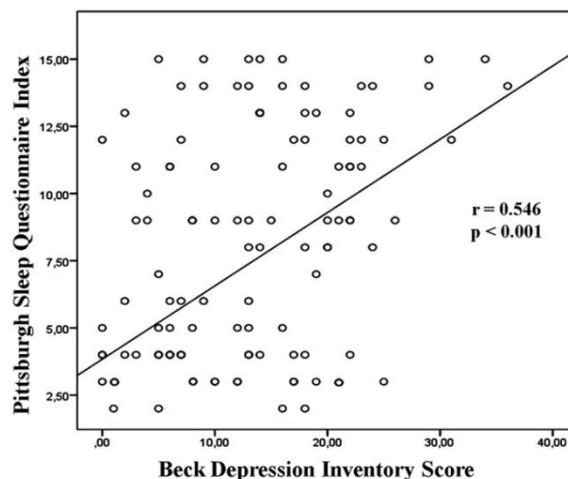


Figure 1: The BDI score was correlated positively with the PSQI score

Discussion

Poor sleep quality occurs in a wide spectrum including narcolepsy, restless legs syndrome and insomnia, and drowsiness occurring during the day causes various malfunctions. This is an important public health problem that reduces physical capacity, cognitive functions and mental capacity, and can often progress to impaired concentration, weakness, anxiety and even depression [8]. Considering the individual effort of the healthcare worker in the provision of healthcare, it is obvious that the sleep problems that will arise in this population will adversely affect both the healthcare provided and the patient group benefiting from this service [9]. Therefore, the sleep problems that may arise in healthcare professionals should be approached seriously and their causes should be investigated, and measures to be taken in order to ensure the quality of sleep should be implemented quickly.

In this study, the prevalence of poor sleep quality of healthcare professionals was 46% and this result is generally in compliance with previous studies performed on nurses and doctors. Ghalichi et al. administered Pittsburgh Sleep Quality scale to 925 healthcare workers, and sleep quality was found poor in 43.1% of the participants [10]. In the study conducted by Yasin et al. on a group of young doctors, the frequency of sleep withdrawal, intense insomnia findings during the day, weakness and insufficient sleep sensation were present in almost half of the participants [11]. In a study conducted on nurses, the prevalence of sleep disorder was 50% in nurses working in daytime, while this rate reached 66% in nurses working at night [12]. In another study conducted on the intensive care unit nurses, 62.9% of the participants reported that their sleep quality was bad [13].

Tough working conditions and troubles showing up at work make health workers vulnerable for sleep disorders [14]. On the other hand, impaired sleep quality may also be associated with decreased compassion satisfaction, increased burnout and secondary traumatic stress in the healthcare worker [15]. In summary, poor sleep quality reduces the satisfaction of the healthcare worker working with devotion. Female gender, divorce, shift work, and age may be taken among the other factors that impair sleep quality [16]. In a conducted study, a significant positive correlation was found interestingly between the sleep quality level and spiritual health scores of 170 intensive care nurses [17]. When we look at the results of our study,

depressive symptoms are closely related to sleep quality. This relationship has also been shown in previous studies conducted on military personnel, nurses and caregivers who take care of dementia and Alzheimer's patients [18-20]. These findings suggest that there is a two-way relationship between depression and sleep quality. To put it in different way, sleep disorders can cause depressive symptoms, and vice versa also occurs frequently. Considering that depressive symptoms are also present often in healthcare professionals, it would not be wrong to claim that depression is directly related to poor sleep quality. In the light of all these data, our results show that high BDI scores, which are indicators of depression, are an independent marker for poor sleep quality in healthcare workers. In addition, smoking, working in the intensive care unit or operating room and work environment unrest have emerged as independent indicators of poor sleep quality in our study. These findings reveal how workplace troubles and depressive symptoms have an impact on sleep quality as shown in the study conducted by Sun et al. [21]. The possible explanation for this is that pressure on healthcare professionals working in critical units and anxiety cause depression over time, and intense depressive symptoms also result in insomnia.

In this study we conducted, the frequency of restless legs syndrome, which we evaluated according to four criteria, was also determined in 21% of healthcare professionals. In another study conducted previously in healthcare professionals, Civi et al. [22] found the frequency of restless leg syndrome at a rate of 15%. In a study conducted in our country with a methodology similar to ours, this rate was found to be 12.8% [23]. In our study, the reason for the higher frequency of restless leg syndrome in healthcare workers may be that our working environment trouble rates are high. Civi et al. [22] found that age and gender are not important markers for restless leg syndrome. Contrary to these findings, our results show that age, professional experience are independent markers for the presence of RLS. According to the results of our study, working in the intensive care unit, working environment troubles and intensity of depressive symptoms are also independent markers for the presence of RLS.

Limitations

The present study has some limitations to be mentioned. The cross-sectional design of this study is not adequate to reach a causal relationship between poor sleep quality and several demographic features and working conditions of the healthcare professionals. However, the strong and independent relation between sleep quality and working conditions, as presented here, give rise to the consideration that some occupational risk factors might be a reason for poor sleep quality. Additionally, data regarding the safety outcomes and medical service quality (which might be adversely affected by sleep disorders) were not assessed. Lastly, we did not question the severity of RLS in this study. Although our results indicate that RLS presence is associated with several important factors studied here, future studies may benefit from assessing the relationship between these factors and the severity of RLS.

Conclusion

In summary, the results of the present study provide significant data regarding the relationships between sleep quality,

RLS and depressive symptoms in healthcare professionals. In this study, we demonstrated that sleep quality was impaired in a substantial proportion of healthcare professionals and RLS and depressive symptoms are also frequent in this population. We also identified workplace, work environment unrest and intensity of depressive symptoms as determinants of poor sleep quality. With this background in mind, we suggest that healthcare professionals should be regularly screened for the presence of poor sleep quality to recognize and treat the underlying causative conditions. Measures to improve sleep quality should also be taken to enhance their health-related quality of life and occupational productivity, in order to preserve the quality of medical care provided to the public.

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Predictive value of plateletcrit in the diagnosis of lower extremity deep vein thrombosis

Alt ekstremitte derin ven trombozu tanısında plateletcritin prediktif değeri

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Abstract

Aim: Deep vein thrombosis (DVT) is a prevalent cause of mortality and morbidity mostly seen in the lower extremities. Early diagnosis is important in terms of the usability of mechanical thrombolysis methods. In this study, we aimed to investigate the diagnostic value of Plateletcrit (PCT) values in patients with suspected DVT.

Methods: Patients who were admitted to our clinic with suspected DVT between January 10, 2017-January 10, 2020 were included in this retrospective cohort study. As a result of their examination with a preliminary diagnosis of DVT, patients who were not diagnosed with DVT were recorded as Group 1, and those with DVT were recorded as Group 2. Univariate and multivariate logistic regression analyses were performed to reveal parameters supporting the diagnosis of DVT.

Results: A total of 139 patients were included in the study. The mean ages of patients in Group 1 (n=33) and Group 2 (n=106) were 45.7 (11.3) years and 53.9 (12.8) years, respectively. Age, body mass index (BMI) and trauma history rates were significantly higher in Group 2 (P values: $P=0.019$, $P=0.038$, $P=0.015$, respectively). The mean platelet volume (MPV), C-reactive protein (CRP), D-Dimer and PCT values were significantly higher in group 2 (P values; $P=0.001$, $P=0.018$, $P<0.001$, $P<0.001$, respectively). In the ROC analysis, the cut-off value for PCT was 0.1989 (AUC=0.732, $P<0.001$, 70.8% sensitivity, 66.7% specificity)

Conclusion: In this study, we found that PCT value, which can be obtained easily and cheaply from routine blood parameters, may be a predictor in patients with suspected DVT.

Keywords: Venous thrombosis, Platelets, Blood cells, Blood vessels

Öz

Amaç: Derin ven trombozu (DVT), çoğunlukla alt ekstremitelerde görülen önemli bir mortalite ve morbidite nedenidir. Günümüzde kullanılan mekanik tromboliz yöntemlerinin kullanılabilirliği açısından erken tanı önemlidir. Bu çalışmada derin ven trombozu (DVT) şüphesi olan hastalarda plateletcrit (PCT)'in tanılma değerini araştırmayı amaçladık.

Yöntemler: Çalışmaya 10 Ocak 2017- 10 Ocak 2020 tarihleri arasında kliniğimize şüpheli DVT kliniği ile başvuran hastalar bu retrospektif kohort çalışmasına dahil edildi. Kliniğimize DVT ön tanısıyla başvurup yapılan tetkikleri sonucunda DVT saptanmayan hastalar Grup 1, DVT saptanan hastalar ise Grup 2 olarak kaydedildi. DVT tanısını destekleyen parametreleri ortaya çıkarmak için tek değişkenli analizler ve çok değişkenli lojistik regresyon analizi yapıldı.

Bulgular: Çalışmaya 139 hasta dahil edildi. Grup 1'de 33 hasta olup ortalama yaşları 45,7 (11,3)'di, Grup 2 de ise 106 hasta olup ortalama yaşları 53,9 (12,8)'di. Yaş, beden kitle indeksi (BMI) ve travma hikayesi oranları Grup 2'de anlamlı olarak yüksekti (Sırasıyla P değerleri; $P=0,019$, $P=0,038$, $P=0,015$). Grup 2'de ortalama trombosit hacmi (MPV), C- reaktif protein (CRP), d-dimer ve PCT değerleri anlamlı olarak yüksek bulundu (Sırasıyla P değerleri; $P=0,001$, $P=0,018$, $P<0,001$, $P<0,001$). Yapılan ROC analizinde, PCT için kesme değeri 0,198 (AUC= 0,732, $P<0,001$, %70,8 sensitivite, %66,7 spesifite) olarak tespit edildi.

Sonuç: Bu güncel çalışmada rutin kan parametrelerinden kolay ve ucuz olarak elde edilebilen PCT değerinin şüpheli DVT kliniği olan hastalarda prediktör olabileceğini tespit ettik.

Anahtar kelimeler: Venöz tromboz, Trombositler, Kan hücreleri, Kan damarları

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Introduction

Deep vein thrombosis (DVT) is a prevalent cause of mortality and morbidity mostly seen in the lower extremities. Although this condition is sometimes asymptomatic, it usually presents with sudden onset of swelling and pain in the extremity. Although its global annual incidence is 50-124/100,000, its frequency is gradually increasing [1]. DVT may result in mortality due to a possible sudden pulmonary embolism but may also cause post-thrombotic syndrome in patients [2]. Although Doppler ultrasonography is the gold standard diagnostic method in its diagnosis, various blood parameters (D-dimer) can also provide diagnostic support. Early diagnosis is important in terms of the usability of mechanical thrombolysis methods that are used today.

Platelets play a significant role in the pathogenesis of thromboembolism. Larger size platelets are more active metabolically and enzymatically than small ones. In other words, increase in mean platelet volume (MPV) increases the risk of thrombosis. Numerous studies have investigated the roles of platelet and MPV in the pathogenesis and progression of vascular diseases [3-5]. Plateletcrit (PCT) is a parameter obtained by multiplying MPV with platelet count. In a recent study, PCT value was reportedly higher in patients with retinal vein thrombosis compared to the control group [6].

In this study, we aimed to investigate the diagnostic value of PCT in patients with DVT.

Materials and methods

Patients who were admitted to our clinic with a suspected DVT clinic between January 10, 2017-January 10, 2020 were included in the study retrospectively. The study was ethically approved by the local ethics committee by the decision numbered 17.01.2010/774035. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration. The data of patients were accessed from the hospital registry and patient registration files. Demographic data (age, gender, etc.), doppler ultrasonography (DUSG) results and routine hemogram and biochemistry parameters were recorded. Those with known systemic inflammatory disease, hematological disease, cancer patients, those receiving antiplatelet therapy, patients with previous DVT, and bed-dependent patients due to chronic diseases were excluded from the study. After exclusion criteria, 139 patients were included in the study. Patients with a preliminary diagnosis of DVT who were not diagnosed with DVT after examination were included in Group 1 (33 patients), and patients with a definite diagnosis of DVT were included in Group 2 (106 patients).

Hemogram and biochemical parameters were measured with automatic analyzers. Plateletcrit calculation was made according to the formula:

$$\text{PCT} = \text{Platelet count (} 10^3/\mu\text{L)} \times (\text{MPV}/10,000)$$

Statistical analysis

Statistical analysis was performed by using the SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program. Student's t-test was used for numerical values with normal distribution, and

Mann-Whitney U test was used for non-normally distributed numerical data. Numerical values were expressed as mean \pm standard deviation. Chi-square test was used to compare categorical variables. $P < 0.05$ was considered statistically significant. Multivariate logistic regression analysis was performed to evaluate significant parameters in the univariate analysis for predicting DVT. Receiver Operating Characteristic (ROC) analysis was performed to evaluate the predictive value of PCT for DVT and the area under the curve was calculated.

Results

A total of 139 patients were included in the study. The mean ages of patients in Group 1 (n=33) and Group 2 (n=106) were 45.7 (11.3) years and 53.9 (12.8) years, respectively. There was no statistically significant difference between the groups in terms of gender, smoking, hypertension, hyperlipidemia, diabetes mellitus or history of cerebrovascular events ($P=0.712$, $P=0.695$, $P=0.747$, $P=0.661$, $P=0.618$, $P=0.269$, respectively). Age, body mass index (BMI) and trauma history rates were significantly higher in Group 2 ($P=0.019$, $P=0.038$, $P=0.015$, respectively) (Table 1).

Laboratory parameter data of the patients are presented in Table 2. There was no difference between the groups in terms of hematocrit, white blood cells, lymphocyte, platelet and albumin values. The mean platelet volume (MPV), C-reactive protein (CRP), D-dimer and PCT values were significantly higher in Group 2 ($P=0.001$, $P=0.018$, $P < 0.001$, $P < 0.001$, respectively).

Table 1: Demographic features of the patients

Characteristics	Group 1 N=33	Group 2 N=106	P-value
Age(years), mean (SD)	45.7 (11.3)	53.9 (12.8)	0.019
Female gender, n (%)	20 (60.6)	68 (66)	0.712
Smoking, n (%)	10 (30.3)	36 (33.9)	0.695
BMI (kg/m ²), mean (SD)	25.4 (4.2)	29.7 (7.8)	0.038
Hypertension, n (%)	9 (27.2)	32 (30.1)	0.747
Hyperlipidemia, n (%)	6 (18.1)	23 (21.6)	0.661
Diabetes mellitus, n (%)	3 (9)	13 (12.2)	0.618
History of stroke, n (%)	3 (9)	18 (16.9)	0.269
History of trauma, n (%)	6(18.1)	43 (40.5)	0.015

BMI: Body mass index

Table 2: Laboratory variables of the patients

Variables	Group 1 N=33 mean (SD)	Group 2 N=106 mean (SD)	P-value
Hematocrit (%)	42.9 (5.3)	45.2 (6.1)	0.297
WBC ($10^3/\mu\text{L}$)	7.9 (2.7)	8.4 (3.1)	0.272
Platelet ($10^3/\mu\text{L}$)	252.8 (69.2)	269.5 (76.7)	0.156
MPV (fL)	7.9 (1.3)	8.6 (1.4)	0.001
CRP (mg/dL)	4.8 (7.9)	9.7 (11.3)	0.018
Albumin (g /dL)	3.9 (0.8)	3.6 (0.7)	0.427
D-dimer ($\mu\text{g/mL}$)	1.98 (2.87)	7.28 (11.96)	<0.001
PCT	0.176 (0.43)	0.219 (0.57)	<0.001

WBC: White blood Cell, MPV: Mean platelet volume, CRP: C Reactive protein, PCT: Plateletcrit

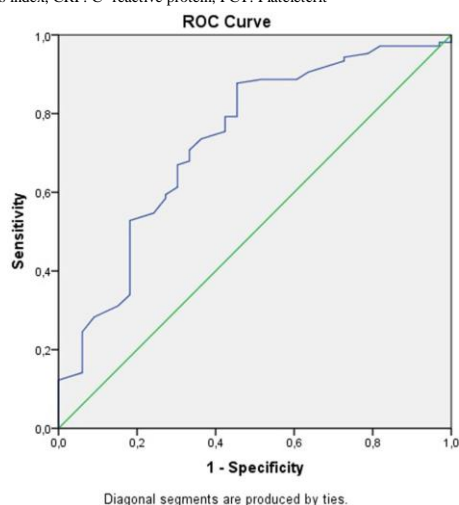
Multivariate logistic regression analysis was performed to reveal parameters supporting the diagnosis of deep vein thrombosis (Table 3). In the evaluation, high D-dimer values (OR: 3.645, CI 95%: 2.384-5.776, $P < 0.001$), presence of trauma history (OR: 0.774, CI 95%: 0.594-0.996, $P=0.033$) and PCT (OR: 1.116, CI 95%: 1.090-1.227, $P=0.005$) were determined as independent predictors for showing deep vein thrombosis.

ROC analysis revealed that the cut-off value for PCT was 0.198 (AUC=0.732, $P < 0.001$, 70.8% sensitivity, 66.7% specificity) (Figure 1).

Table 3: Multivariate logistic regression analysis to identify predictors of deep venous thrombosis

Variables	P-value	Exp(B) Odds Ratio	95% C.I.	
			Lower	Upper
Age	0.077	0.986	0.874-	1.112
BMI	0.217	1.019	0.976-	1.312
CRP	0.116	0.679	0.456-	1.647
D-dimer	<0.001	3.645	2.384-	5.776
History of trauma	0.033	0.774	0.594-	0.996
PCT	0.005	1.116	1.090-	1.227

BMI: Body mass index, CRP: C- reactive protein, PCT: Plateletcrit



Diagonal segments are produced by ties.

Figure 1: Receiver operating characteristic curve analysis figure for Plateletcrit (cut-off= 0.198, AUC=0.732, $P<0.001$, 70.8% sensitivity, 66.7% specificity)

Discussion

Deep venous thrombosis is the third most common disease among all cardiovascular diseases. This can lead to catastrophic outcomes such as pulmonary embolism as well as clinical conditions such as post-thrombotic syndrome [7, 8]. Therefore, early diagnosis of DVT and initiation of the necessary treatment is extremely important. In this study, we determined that PCT value was an independent predictor in the diagnosis of DVT as well as the D-dimer test, which has been proven useful in the diagnosis of DVT (OR: 1.116, CI 95%: 1.090-1.227, $P=0.005$).

Platelets play a role in important tasks in the human body, such as hemostasis and tissue regeneration. Depending on the increasing number of platelets and activity in the blood, thromboxane synthesis and synthesis of adhesion molecules increase, so that susceptibility to thrombosis occurs [9]. These causes have been the subject of research in the pathogenesis of cardiovascular diseases and their prognosis after treatment. A study by Jahangiri et al. [10] investigated the effect of platelets on stent thrombosis in patients with ilio caval stents. In this study, baseline platelet counts were found to be effective on early stent thrombosis. In a study conducted by Yuksel et al. [11] on the severity of coronary artery disease, high platelet counts were also associated with diffuse atherosclerosis. There are also studies showing that the number of platelets is effective in studies between patients with and without deep vein thrombosis. In a study by Caliskan et al. [12] platelet counts were found to be higher in patients diagnosed with DVT than the control group. In another study constructed similarly to this study, platelet counts were shown in relation to DVT [13].

Mean platelet volume (MPV) is an important indicator for platelet functions showing platelet size. Large platelets contain a higher number of granular structures. These granular structures also contribute to thrombosis by secreting various prothrombotic factors [14]. Therefore, increased MPV values are

an important indicator of platelet functions [15]. Therefore, MPV value has been extensively investigated in cardiovascular diseases. The effect of MPV on restenosis after carotid artery stenting was investigated by Dai et al. [16]. In this study, patients were followed for 12.1 (16.1) months and high MPV values before the procedure were found to be associated with restenosis. In another study by Dundar et al. [17], the prognostic significance of MPV was shown in patients with subarachnoid hemorrhage. Cil et al. [18] found that MPV value was significantly associated with DVT and was found to be an independent predictor in demonstrating intra-hospital DVT. A study of the locations of MPV and D-dimer parameters in the diagnosis of DVT by Canan et al. [19] included 256 patients with suspected lower extremity DVT. The authors found high MPV values in relation to DVT in this study. They also suggested that MPV values may have a specificity-enhancing effect in the diagnostic approach with D-dimer values.

Plateletcrit (PCT) value is a parameter obtained by multiplying the number of platelets and MPV and it shows the total platelet mass in the blood. In a study by Akpınar et al. [20] increased PCT values were found effective in the development of saphenous vein disease after coronary bypass operations. In another study, PCT values were found to be higher in patients with central retinal vein occlusion than in healthy individuals [6]. The relationship of recurrent pregnancy loss with thrombosis is known. Accordingly, the relationship between PCT value and recurrent abortion was investigated by Aydınoglu et al. [21] The authors found that at the end of the study, the cheap and easily available PCT parameter could predict possible recurrent pregnancy losses. In the study conducted in 2017, the relationship between DVT and PCT was investigated. In this study, authors found a significant relationship with the PCT value in female patients with DVT [22].

DVT developing in trauma patients and pulmonary embolism that may occur due to this is the third most common cause of death in trauma patients [23]. The predisposition to post-traumatic thrombosis leads to DVT. Accordingly, in our study, we found the history of trauma in patients with DVT as a predictive predictor for DVT.

Limitations

The most important limitations of our study include its retrospective nature, single-centeredness, and small number of the patients. In addition, although iliac compression syndrome is rarely seen, it has not been possible to distinguish patients with it that may lead to DVT [24]. It is quite difficult to discuss these clinical conditions due to the retrospective nature.

Conclusions

As a result, although thrombosis parameters have been extensively investigated in the diagnosis of DVT, the study investigating the relationship between PCT and DVT has been limited. In this study, we found that PCT value, which can be obtained easily and cheaply from routine blood parameters, may be a predictor in patients with suspected DVT. Multicenter future studies are needed in this regard.

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High basal LH levels are associated with improved cycle outcomes of assisted reproduction

Yüksek bazal LH seviyeleri daha iyi yardımcı üreme siklus sonuçları ile ilişkilidir

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Abstract

Aim: Several parameters are used to observe the ovarian responsiveness to gonadotropin stimulation. Basal LH levels have been suggested on ovarian response as well as basal FSH levels. This study was aimed to evaluate the correlation of basal LH levels with cycle and pregnancy outcomes in patients who underwent GnRH-antagonist IVF (in-vitro fertilization) cycles.

Methods: This retrospective cohort study recruited a total of 317 cycles with values of FSH <10 IU/L. Basal hormonal parameters (FSH, LH, estradiol) were recorded prior to ovarian stimulation. Patients were treated with GnRH antagonist protocols and stimulated with recombinant FSH. The patients were categorized according to designated threshold levels for LH values (Group 1: LH <4.1 IU/L and Group 2: LH ≥4.1). The number of total retrieved oocytes and mature oocytes, implantation rate, clinical pregnancy rate and ongoing pregnancy rate were analyzed between study groups.

Results: Group 2 had a higher number of retrieved oocytes and mature oocytes compared to Group 1 ($P=0.006$ and $P=0.03$, respectively). Although not statistically significant, there was a trend towards higher rates of pregnancy on high LH levels. Clinical and ongoing pregnancy rates were insignificantly lower in Group 1 (38.3% vs. 48.5%, $P=0.162$ and 29.4% vs. 34.0%, $P=0.535$; respectively). The basal LH levels positively correlated with the number of oocytes, and the combination with low FSH levels was also found to be associated with higher number of retrieved oocytes and peak estradiol levels.

Conclusions: Elevated basal LH levels provide a beneficial effect on cycle outcome such as number of retrieved oocytes. However, clinical pregnancy rates were found to be similar between below and above the threshold of LH levels.

Keywords: Luteinizing hormone, IVF (in-vitro fertilization), Infertility, Oocyte number, Pregnancy rate

Öz

Amaç: Gonadotropin stimülasyonuna over yanıtını değerlendirmek için birçok parametre bulunmaktadır. Basal LH seviyeleri FSH seviyelerine ek olarak over yanıtında önerilmektedir. Bu çalışma ile GnRH-antagonist IVF (in-vitro fertilizasyon) siklusu uygulanan hastalarda bazal LH seviyelerinin siklus ve gebelik sonuçları ile ilişkisini değerlendirmek amaçlanmıştır.

Yöntemler: Retrospektif kohort çalışmaya FSH değeri 10 IU/L'den daha düşük olan 317 siklus dahil edilmiştir. Bazal hormonal bulgular (FSH, LH, estradiol) ovaryan stimülasyon başlamadan önce kaydedildi. Hastalara GnRH-antagonist protokol ve rekombinant FSH tedavisi uygulandı. Hastalar; LH değeri için belirlenmiş olan eşik değerlere göre kategorize edilmişlerdir (Grup 1: LH <4,1 IU/L ve Grup 2: LH ≥4,1). Elde edilen toplam oosit sayısı, matür oosit sayısı, implantasyon oranı, klinik gebelik ve devam eden gebelik oranı çalışma grupları arasında analiz edilerek karşılaştırıldı.

Bulgular: Grup 2 hastalarda, Grup 1 ile karşılaştırıldığında daha fazla oosit sayısı ve matür oosit sayısı tespit edilmiştir ($P=0,006$ ve $P=0,03$). İstatistiksel olarak anlamlı olmasa dahi, yüksek LH seviyelerinde daha yüksek gebelik oranları lehine bir eğilim saptandı. Klinik gebelik ve devam eden gebelik oranları Grup 1'de daha düşüktü ancak bu farklılık istatistiksel olarak anlamlı değildi (Klinik ve devam eden gebelik için sırasıyla %38,3'e karşı %48,5, $P=0,162$ ve %29,4'e karşı %34,0, $P=0,535$). Bazal LH seviyeleri oosit sayısı ile pozitif olarak korele olarak saptandı ve düşük FSH seviyeleri ile kombinasyonu da daha fazla oosit sayısı ve pik östrojen düzeyleri ile ilişkili bulundu.

Sonuç: Artmış bazal LH seviyeleri toplam elde edilen oosit sayısı gibi siklus sonuçları üzerinde faydalı etki sağlayabilir. Bununla birlikte klinik gebelik oranları LH seviyesi eşik değerinin altında ve üstünde olanlar arasında benzer olarak tespit edildi.

Anahtar kelimeler: Luteinize edici hormon, IVF (in-vitro fertilizasyon), İnfertilite, Oosit sayısı, Gebelik oranı

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Introduction

Optimal ovarian responsiveness and normal follicular growth are essential especially in assisted reproductive techniques (ART). The main aim of ovarian stimulation is to provide a higher number of mature oocytes for in-vitro fertilization (IVF) cycles which results in obtaining high-quality embryos [1]. Several parameters have been reported to predict the response of ovarian stimulation. Age is the most important variable that affects fertility potential. The baseline predictors of ovarian response are female's age, day-3 FSH (follicle-stimulating hormone), LH (luteinizing hormone), estradiol, and anti-Mullerian hormone (AMH) [2-5]. The most commonly used marker is day-3 FSH level and it may reflect the ovarian reserve concerning female age [2,6,7]. Baseline LH levels are also used to assess infertile women prior to ART cycles [8]. Normal follicular growth and maturation require the contribution of both FSH and LH stimulation according to the two-cell theory, however the main role had been attributed to FSH value until now [9]. Endogenous LH activity is necessary to get optimal development of follicles, while low LH levels may be an indicator of poor activity for the hypothalamus-pituitary-ovarian axis [10]. LH levels may have an impact on ovarian response especially on normal FSH levels [10,11]. Several studies evaluated the efficacy of LH to predict the response to ovarian stimulation and the association between LH levels and treatment outcomes [11-14], but the results are still controversial about the precise role of LH. The purpose of this study was to determine the relationship between baseline LH levels and ovarian response and treatment outcomes in ART cycles. The primary outcomes were correlation of LH levels with the total dose of gonadotropins used and the number of retrieved oocytes. The secondary outcome was to evaluate pregnancy outcomes.

Materials and methods

This retrospective cohort study was carried out at a reproductive endocrinology and infertility unit of a university-based hospital between 2017 and 2019. The study was approved by the local Ethics Committee of Eskisehir Osmangazi University Faculty of Medicine and conducted in accordance with the principles of Helsinki Declaration (2020/ Ref. No: E.7215-2020/43). All the patients who underwent IVF/ICSI cycles were evaluated. Inclusion criteria were age <45 years at the cycle initiation, and basal FSH <10 IU/L. Patients who underwent fresh embryo transfer cycles were included in the study population. A total of 978 cycles were evaluated and cycles with characteristics including basal FSH \geq 10 IU/L, endocrine abnormalities such as thyroid disorders and hyperprolactinemia, high ovarian response such as polycystic ovarian syndrome, long agonist protocols and frozen-thaw embryo transfers were excluded from the study. In this regard, we excluded low and high response cycles, and selected homogeneous group to assess only the normoresponders.

Demographic characteristics and basal (cycle day-2 or 3) parameters were evaluated. Basal hormone levels such as FSH (follicle-stimulating hormone), LH (luteinizing hormone), estradiol, AMH (anti-Mullerian hormone), were determined on day-2 or 3 of the menstrual cycle prior to ovarian stimulation.

The patient's serum samples were measured for FSH, LH by electrochemiluminescent immunometric assay using commercial kits. We analyzed the data and determined the cut-off values for FSH and LH levels to discriminate the successful and unsuccessful pregnancy outcome. The cut-off levels for FSH and LH levels were determined as 6.2 and 4.1, respectively. According to the cut-off level for LH levels, the study population was divided into two groups as below and above the threshold levels. We compared the outcomes between the study groups.

All patients underwent GnRH-antagonist protocol for ovarian stimulation with a daily injection of recombinant FSH (Gonal-f, Merck, Germany) starting on cycle day-2 or 3. The doses of gonadotropins were customized according to the patient's age, BMI and basal antral follicle count. GnRH antagonist (Cetrorelix, Merck, Germany) was administered depending on the size of the leading follicle as 14 mm or serum estradiol level exceeding 300 pg/mL and continued until the hCG administration. Triggering of ovulation was achieved with recombinant hCG (Ovitrelle 250 μ g; Merck, Germany) when at least three follicles reached 18 mm in diameter. Transvaginal-guided oocyte retrieval was carried out 36 hours after triggering. The retrieved oocytes were fertilized by standard IVF or ICSI procedure. Embryo development was observed and embryo quality was determined according to guidelines [15,16]. Embryo transfers were performed under ultrasound guidance after assessing the embryo quality on day-3 (cleavage stage) or day-5 (blastocyst stage) of the fertilization. Cycle outcomes such as stimulation parameters (dose of gonadotropins, number of follicles), number of oocytes and fertilization rate were also recorded. Vaginal progesterone gel (Crinone 8% gel, Merck, Germany) was administered as a luteal phase support until the 9th of gestational week.

Serum beta-hCG levels were measured to determine the cycle outcome as the implantation rate, 12 days after embryo transfer. Clinical pregnancy was defined as the presence of a gestational sac and fetal heartbeat after 6-7 weeks of gestation. Ongoing pregnancy was defined as pregnancies that reached 25 weeks gestation or more.

Statistical analysis

Statistical evaluation was performed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Descriptive parameters and cycle outcomes were reported as mean standard deviation and median values according to the distribution of the data. Normal or abnormal distribution was determined using the Kolmogorov-Smirnov test. The Student's t-test was used to compare normally distributed data. In cases of non-parametric continuous and categorical data, the differences were observed with Mann-Whitney U and Kruskal-Wallis tests. The Pearson chi-square test or Fisher Exact test was carried out to analyze categorical data. Spearman correlation analysis was performed to establish the correlation between basal LH levels and cycle outcomes. We performed the receiver operating characteristics (ROC) curve analysis to determine the most efficient threshold values for serum LH and FSH levels to discriminate between successful and unsuccessful cycle outcomes. A *P*-value of <0.05 was considered statistically significant.

Results

A total of 978 IVF/ICSI cycles were evaluated for the study population. We included the GnRH antagonist protocol and fresh embryo transfer cycles in patients with FSH<10 IU/L. Six hundred and sixty-one cycles which did not meet the inclusion criteria were excluded from the study. Eventually, the present study included 317 cycles to analyze. The mean age was 31.9(4.6) years, basal FSH and LH levels were 6.9 (1.5) IU/L and 6.4 (3.0) IU/L for overall study population, respectively. The implantation, clinical pregnancy and ongoing pregnancy rates were reported as 55.9%, 46.4% and 33.1%, respectively. We determined a cut-off value for LH levels as 4.1 to distinguish the highest and lowest pregnancy rates. Patients in Group 1 with basal LH <4.1 IU/L reported 64 women, while Group 2 of patients with basal LH ≥4.1 IU/L reported 253 women. There were no differences between the study groups with regards to mean age and the duration of infertility. Table 1 shows baseline demographic and hormonal characteristics. The antral follicle count on the day-2 or 3 was slightly higher in Group 2. The basal LH and AMH levels were also significantly higher in the high LH group ($P<0.001$ and $P=0.027$, respectively). The ovarian stimulation results and cycle outcomes of the groups are shown in Table 2. We did not find any significant differences between the study groups for the starting dose of gonadotropins, duration of infertility and the total dose of gonadotropins. The mean total dose of gonadotropins was found lower in favor of Group 2 compared to Group 1, but did not reach significance (1930.1 IU vs. 2031.8 IU, $P=0.157$; respectively). Although the total dose of gonadotropins was lower in Group 2, the peak estradiol levels on the day of hCG were found to be significantly higher in Group 2 compared to Group 1 ($P=0.001$). Moreover, we observed that the total number of retrieved oocytes and mature oocytes were also significantly higher in the group with LH ≥4.1 IU/L (Table 2). We also analyzed the correlation of LH levels with the cycle outcomes. A significantly positive correlation was present between LH levels and cycle outcomes such as the number of retrieved oocytes and mature oocytes (Figure 1). We also found a negative correlation with LH levels for the total dose of gonadotropins, which means that the dose of gonadotropins decreases with increase in LH levels (Figure 1). FSH value is as important as LH levels to achieve effective IVF outcomes. However, we have also identified a cut-off value for FSH values as 6.2 IU/L and we think that the higher levels may indicate poorer outcomes. Therefore, we categorized patients into four groups with these cut-off values for both FSH and LH levels as Low LH-Low FSH, Low LH-High FSH, High LH-Low FSH and High LH-High FSH. Figure 2 shows the cycle outcomes in terms of FSH and LH categorization. The results were found to have significantly improved in the ‘High LH-Low FSH’ group of patients (Figure 2) ($P<0.001$). Although there was a trend toward a higher rate of implantation, clinical pregnancy, and ongoing pregnancy rates in the high LH group, we did not find any significant differences between Groups 1 and 2 regarding the pregnancy outcomes (Table 3).

Table 1: Demographic and basal parameters of the patients

	Group 1 (LH <4.1) (n=64)	Group 2 (LH ≥4.1) (n=253)	P-value
Age (years)	31.2 (4.3)	32.1 (4.7)	0.165
BMI (kg/m ²)	27.3 (5.7)	24.7 (4.7)	0.001
Duration of infertility (years)	5.3 (3.6)	5.2 (3.8)	0.501
Baseline AFC	10.4 (5.2)	11.9 (5.5)	0.027
Baseline FSH (IU/L)	6.2 (1.8)	7.1 (1.4)	0.001
Baseline LH (IU/L)	3.4 (0.7)	7.2 (2.8)	<0.001
Baseline FSH/LH ratio	1.9 (0.6)	1.1 (0.4)	<0.001
AMH (U/L)	2.2 (1.8)	3.2 (2.5)	0.001

Values are defined as Mean (SD), LH: luteinizing hormone, BMI: body mass index, AFC: antral follicle count, FSH: follicle-stimulating hormone, AMH: anti-Mullerian hormone

Table 2: The ovarian stimulation and cycle outcomes

	Group 1 (LH <4.1) (n=64)	Group 2 (LH ≥4.1) (n=253)	P-value
Starting dose of gonadotropins (IU)	230.7 (56.1)	218.1 (54.4)	0.069
Antagonist starting day	7.0 (0.9)	7.2 (1.1)	0.658
Duration of stimulation (days)	8.9 (1.3)	8.8 (1.5)	0.477
Total dose of gonadotropins (IU)	2031.8 (624.5)	1930.1 (642.1)	0.157
Serum P on the day of hCG (ng/mL)	0.66 (0.38)	0.74 (0.44)	0.217
Serum estradiol on the day of hCG (pg/mL)	1680.9 (1160.5)	2025.4 (1030.9)	0.001
Endometrial thickness on the day of hCG (mm)	9.1 (1.6)	9.3 (1.5)	0.067
Total follicle number >15 mm	4.8 (2.6)	5.1 (2.6)	0.379
Number of total retrieved oocytes	7.1 (3.7)	8.5 (3.8)	0.006
Number of Total mature oocytes	4.8 (2.7)	5.8 (3.3)	0.030
Fertilization rate (%)	92.4 (18.1)	94.2 (14.9)	0.686

Values are defined as Mean (SD), LH: luteinizing hormone, P: progesterone, hCG: human chorionic gonadotropin

Table 3: The pregnancy outcomes

	Groups 1 (LH <4.1) (n=64)	Group 2 (LH ≥4.1) (n=253)	P-value
Implantation rate (%)	46.7	58.2	0.108
Clinical Pregnancy rate (%)	38.3	48.5	0.162
Ongoing pregnancy rate (%)	29.4	34.0	0.535

LH: luteinizing hormone

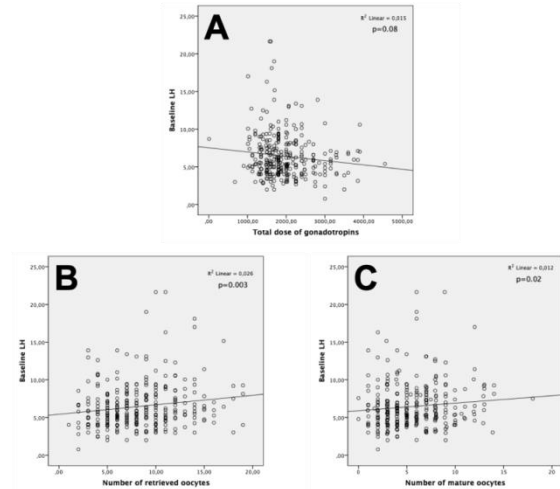


Figure 1: The correlation analysis of basal LH levels with; A: Total dose of gonadotropins B: The number of retrieved oocytes C: The number of mature oocytes

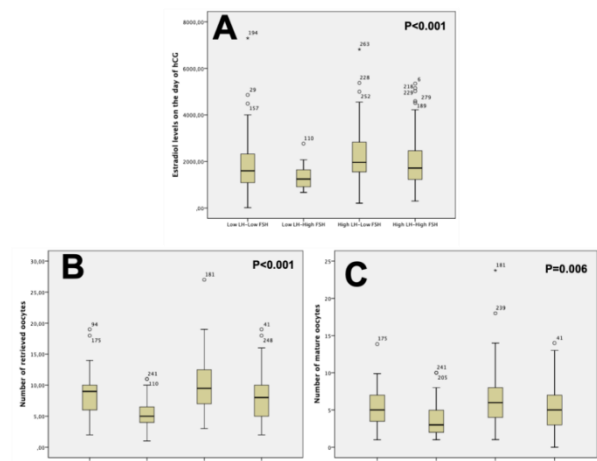


Figure 2: The combination analysis of basal FSH and LH levels according to the cut-off levels A: Estradiol on the day of hCG B: The number of retrieved oocytes C: The number of mature oocytes

Discussion

In this study, we investigated the effect of basal LH levels on IVF cycle outcomes and the correlation between LH levels and the number of retrieved oocytes. We established that higher LH values positively correlated with the number of retrieved oocytes and mature oocytes, although there were no significant differences regarding the pregnancy results. We also observed a trend toward the higher pregnancy outcomes in patients with higher LH values, but no statistical differences. The basal FSH and LH levels were also found to be associated with the cycle outcomes in ART cycles, however optimal combination for successful outcomes such as peak estradiol levels and the number of retrieved oocytes was found to be low FSH and high LH levels in patients with FSH <10 IU/L.

Mukherjee et al. [11] suggested that low LH levels (<3 IU/L) were predictive in determining poor response to ovarian stimulation. Several studies investigated whether high LH levels had a positive impact on ART outcome [17-20]. Barroso et al. [12] demonstrated that a higher number of retrieved oocytes was obtained in patients with high LH values, with a borderline significance. In an observational study, LH levels were divided into three groups and the number of oocytes was found to be significantly higher in the LH ≥ 8 IU/L group [17]. The authors did not find any significance regarding clinical pregnancy and live birth rates between the different basal LH levels. A prospective observational study suggested that the significantly higher number of oocytes was retrieved in the LH >3 IU/L group of patients than in the LH ≤ 3 IU/L group [18]. They showed similar total gonadotropin doses used for ovarian stimulation among study groups. There were higher pregnancy rates in favor of the high LH subgroup, although there were no significant differences between the high and low LH subgroups (30.6% vs. 18.5%, $P=0.17$). In a recent retrospective data analysis, Sun et al. [20] observed that the number of retrieved oocytes, mature oocytes were significantly greater in the group with LH ≥ 10 IU/L than in the groups with LH <10 IU/L. The total dose of gonadotropins and duration of stimulation were also lower in the high LH subgroup than the low LH cases. They also demonstrated that more total embryos, more top quality embryos and high peak estradiol levels were significantly in the group with basal LH ≥ 10 IU/L than the group with lower LH levels. However, these improved results did not have an effect on pregnancy outcomes. Similar to current literature, we also found that the number of oocytes and peak estradiol levels were significantly higher in the high LH group. The pregnancy rates did not differ significantly between the high and low LH groups, although there was a trend toward higher LH levels. It has been speculated that LH may have an influence on cytoplasmic maturation and embryo quality and may lead to an improvement in the implantation potential [21,22]. However, the effect of basal LH on fertility potential is still controversial. Some investigators established that high exposure to LH may have a deleterious effect on ART cycles especially in polycystic ovarian syndrome and it may cause early pregnancy loss [23].

Noci et al. [10] suggested that intra-ovarian regulators may be decreased with LH levels below 3 IU/L and the responsiveness to gonadotropins is reduced due to low LH levels.

In a retrospective study, Tas et al. [24] evaluated the effect of myo-inositol on ovarian stimulation and the LH levels were found to be higher in the study group. They did not find any significant improvement in the study group in terms of ovarian response. It was suggested that the low basal LH levels may be associated with reduced ovarian responsiveness to ovarian stimulation in ART cycles [10,11,25]. Noci et al. [26] suggested that some women presenting low LH levels had some impairment of follicular growth and differentiation in GnRH analog suppressed cycles and the higher dose of gonadotropins might overcome these undesirable results. In GnRH analog suppressed cycles, the ovarian response to FSH is regulated independently of basal serum LH levels [26-28]. The low LH levels were not the only factor that was associated with a negative impact on IVF cycle outcome, although there was also a higher ovarian response to FSH stimulation in favor of high LH levels for cycles with a combination of GnRH-agonist and pure FSH [12]. We found >15 mm similar follicle numbers on the day of hCG administration between groups. Moreover, the total number of retrieved oocytes and mature oocytes were significantly higher above the LH threshold. We demonstrated that the total dose of gonadotropin used was higher in patients with low LH levels but this difference did not attain any significance. Similar to the recent studies, we observed that patients having low basal LH levels had a lower response to ovarian stimulation and a lower number of oocytes in ART cycles.

We used only recombinant FSH for ovarian stimulation in the GnRH-antagonist cycles, however there were controversial results about using hMG (human menopausal gonadotropin) or only FSH for ovarian stimulation in GnRH-agonist IVF/ICSI cycles [29]. Theoretically, the addition of LH may be beneficial in cases with low LH levels. The requirement of LH may have a threshold during folliculogenesis, and it may affect follicle growth and oocyte quality. On the contrary, Kolibianakis et al. [30] demonstrated that the addition of recombinant LH did not increase live birth rates in patients treated with GnRH analogs and FSH for IVF cycles. In a large retrospective study, Lyu et al. [19] also concluded that the supplementation of recombinant LH did not improve cycle outcome in the GnRH antagonist cycles. Most of the studies were performed especially in GnRH analogue suppressed cycles with ovarian stimulation. Lyu et al. [19] included both GnRH agonist and antagonist cycles to the study population similar to our study. They demonstrated that the pregnancy rates were not significantly different between FSH/LH ratio above and below the threshold in patients with FSH <10 IU/L, although these rates were different within GnRH antagonist cycles between study groups.

The effect of basal LH levels may be put forward with the ratio of FSH/LH like in the study of Lyu et al. [19]. It was speculated that a high FSH/LH ratio may lead to low ovarian responsiveness, low oocyte quality and low embryo quality [12]. Prasad et al. [18] evaluated the basal LH level and FSH/LH ratio for predicting IVF cycle outcomes. The number of oocytes and pregnancy rates were found to be significantly higher in the FSH/LH <2 group compared to FSH/LH ≥ 2 . It was demonstrated that the FSH/LH ratio increased based on lower LH levels, and was not associated with FSH levels [12,14]. A retrospective

study also established that the total number of oocytes, mature oocytes, number of top quality embryos were significantly higher in the FSH/LH <2 group than the FSH/LH \geq 2 group [19]. Ho et al. [1] also observed that increased FHS/LH ratio was related to the lower number of retrieved oocytes and lower peak estradiol levels. The elevated FSH/LH ratio was shown as a predictor for poor ovarian response in patients with normal FSH levels [11,12]. On the other hand, some authors suggested using individual FSH, LH levels and combinations instead of using ratios, to estimate the ovarian response to the gonadotropin stimulation [31]. Brodin et al. [31] reported a significantly higher number of oocytes, higher pregnancy rates and lower doses of FSH in the high LH and low FSH combinations according to the thresholds of their study in the GnRH-agonist IVF cycles. We also demonstrated a higher number of oocytes and lower doses of gonadotropins in the high LH and low FSH combinations, but did not find any significant differences regarding pregnancy rates. We also suggested that the pregnancy rates may have been affected not only by hormonal values but also by multi-factorial parameters, consequently it is more adequate to evaluate the association of hormonal levels with ovarian stimulation results. Bansal et al. [32] also found similar cycle outcomes, however they showed the lowest dose of gonadotropins in the lower levels of both FSH and LH group.

Limitations

The present study has some limitations. The most important limitation of our study is its retrospective nature. On the other hand, the strengths of our study were that the study consisted of a study population with homogeneous patients who were normoresponders and performing only GnRH-antagonist protocol to determine the efficacy of basal LH levels. Additional large prospective studies are required to confirm our findings.

Conclusion

We established that higher basal LH levels were associated with improved cycle outcomes. However, it was not a useful parameter for predicting successful pregnancies. The cut-off values of FSH and LH levels may vary according to local laboratory variations, so each center should determine their own threshold for these values. The unexpected low ovarian response may be encountered especially in young patients with normal FSH levels. In these patients, basal LH levels may be beneficial to determine appropriate ovarian stimulation dose and protocol.

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Risk factors, clinical characteristics and mortality of candidemia in non-neutropenic, critically ill patients in a tertiary care hospital

Üçüncü basamak bir hastanede nötrojenik olmayan yoğun bakım hastalarında kandidemi risk faktörleri, klinik özellikleri ve mortalitesi

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Abstract

Aim: In recent years candida species have emerged as important nosocomial pathogens leading to increased mortality and prolonged hospitalization. In this study, we aimed to determine the distribution of *Candida* species in the intensive care unit (ICU) and to investigate the risk factors and mortality rates in *Candida albicans* (CA) and non-*albicans Candida* infections (NAC).

Methods: This retrospective cohort study was conducted between January 2018 and January 2019. 134 patients hospitalized in the intensive care units with *Candida* reproduction in their blood cultures were included in the study. Blood cultures were processed, and strain distribution was performed according to routine practice using the automated blood culture system BACTEC 9240 (Becton Dickinson, Maryland, USA).

Results: *Candida* growth was detected in the blood culture of 134 patients, among which 54.5% consisted of CA and 45.5% of NAC. NAC was most commonly followed by *C. parapsilosis* (17.2%), and *C. glabrata* (13.4%). Mortality rate of patients aged ≥ 60 years was significantly higher in all three candida species ($P=0.003$). NAC was seen at an insignificantly higher rate in patients with solid-organ malignancy ($P=0.09$). Although mortality was higher in CA than NAC strain (53.6% and 43.4%, respectively), this was not statistically significant ($P=0.83$).

Conclusion: Although CA is still the most common strain in ICU patients, the incidence of NAC is increasing. Candidemia has high mortality rates in ICU patients. Especially elderly patients with underlying diseases should be followed carefully.

Keywords: Bloodstream infections, *Candida albicans*, Non-*albicans Candida*, Risk assessment, Mortality

Öz

Amaç: Son yıllarda kandida türleri mortalitenin artmasına ve hastanede kalış süresinin uzamasına neden olan önemli nozokomiyal patojenler olarak ortaya çıkmıştır. Bu çalışmada yoğun bakım ünitesinde yatan hastalarda *Candida* türlerinin dağılımını belirlemek ve *Candida albicans* (CA) ve non-*albicans Candida* (NAC) risk faktörlerini ve mortalite oranlarını belirlemeyi amaçladık.

Yöntemler: Bu retrospektif kohort çalışma, Ocak 2018 ve Aralık 2018 tarihleri arasında gerçekleştirildi. Yoğun bakım ünitelerinde kan kültürlerinde *Candida* üremesi olan 134 hasta çalışmaya dahil edildi. Kan kültürleri, otomatik kan kültür sistemi BACTEC 9240 (Becton Dickinson, Maryland, ABD) kullanılarak rutin uygulamalara göre işlendi ve tür dağılımı otomatik sistem tarafından gerçekleştirildi.

Bulgular: Toplam 134 hastanın kan kültüründe *Candida* üremesi saptandı. Bu üremelerin %54,5'i CA ve %45,5'i NAC'den oluşuyordu. NAC'yi en sık %17,2 *C. parapsilosis* ve %13,4 ile *C. glabrata* izledi. Her üç tür için de ≥ 60 yaş yıllık ölüm oranı anlamlı olarak daha yüksekti ($P=0,003$). Solid organ malignitesi olan hastalarda NAC daha yüksek oranda görüldü, ancak bu istatistiksel olarak anlamlı değildi ($P=0,09$). CA şüphesinde mortalite NAC şüphesinden daha yüksek olmasına rağmen (sırasıyla %53,6 ve %43,4), bu istatistiksel olarak anlamlı değildi ($P=0,83$).

Sonuç: YBÜ hastalarında CA hala en sık görülen tür olmasına rağmen, NAC insidansı artmaktadır. Yoğun bakım hastalarında kandidemi yüksek mortalite oranlarına sahiptir. Özellikle alta yatan hastalıkları olan yaşlı hastalar dikkatle takip edilmelidir.

Anahtar kelimeler: Kan dolaşımı enfeksiyonları, *Candida albicans*, Non-*albicans candida*, Risk faktörleri, Mortalite

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Introduction

In the last two decades, the incidence of candidemia has been increasing despite advances in diagnostic methods, the emergence of new antifungal drugs, and the implementation of candida prevention strategies [1]. Candidemia is the 4th most common cause of bloodstream infections in the United States and the 7th most common cause in Europe [2-3]. According to data reported by the European Center for Disease Prevention and Control in 2013, *Candida* spp. is the fifth microorganism causing sepsis in patients admitted to intensive care unit (ICU). Recently, the increase in the incidence of candidemia has been associated with complex medical and surgical procedures that ensure the survival of critical patients [4].

Important risk factors for invasive candidiasis include age, underlying disease, exposure to broad spectrum antibiotics and cancer chemotherapy, advanced care of premature newborns, major abdominal surgery, organ transplantation, prolonged stay in intensive care, vascular catheters, implanted medical devices such as prosthetic heart valves, and parenteral nutrition [5]. While *Candida albicans* (CA) is the most commonly isolated strain from hospitalized patients, non-*albicans Candida* (NAC) strains have been reported with increasing frequency in recent years. *Candida glabrata* strains are found in 15-20% of Candida infections [6]. The mortality of NAC infections is higher than that of CA infections [7-8]. Therefore, early diagnosis of candida infections and early appropriate empirical treatment for CA and NAC species are of immense importance, especially in patients with NAC [6].

The epidemiology of candidemia varies by geographical region. Therefore, surveillance studies are mandatory [4]. In this study, we aimed to investigate the distribution of species, risk factors and mortality rates in candidemia developing in the intensive care unit and thus to make prognosis analysis of CA and NAC infections. This study will guide clinicians in empirical treatment options.

Materials and methods

The hospital in which the study was conducted is a tertiary hospital with 442 beds and receives intensive patients not only from the province it's located in, but also from the surrounding provinces. It is a branch hospital where even specific operations such as lung, kidney, heart, and liver transplantations are performed. 105 of these 442 beds are intensive care beds. This is a retrospective, single-center, observational cohort study. The records of patients between 1 January 2018 and 30 January 2019 in our intensive care unit were reviewed retrospectively. Patients with candida growth in blood culture were included in the study. Candidemia is defined as the detection of a single candida strain in the blood culture. Samples where more than one strain was detected were excluded from the study.

Blood cultures and strain distribution were processed according to routine practice using the automated blood culture system BACTEC 9240 (Becton Dickinson, Maryland, USA). Blood cultures were incubated for 14 days. For isolation of *Candida*, blood cultures were transferred onto blood and Endo agars, and incubated at 37⁰ C for 24-48 hours. Gram staining was

performed on the colonies. The germ tube test was performed for those in which yeast cells were detected by microscopy. The positive isolates from the germ tube test were identified as *Candida albicans*. Colonies with negative germ tube test were identified at the species level with identification kits (API 20C AUX; BioMérieux, France).

Following the approval of the study protocol by the local Ethics Committee (SBÜ Ankara Yuksek Ihtisas Training and Research Hospital, approval number:22.10.2018-58/29620911-929), the medical records, clinical features and risk factors of all patients between 1 January 2018 and 30 January 2019 were retrospectively analyzed. *Candida* growth was detected in blood cultures of 134 patients. The age, gender, previous operation status, presence of solid organ malignancy, antibiotic use, dialysis status, TPN use, ventilator use, breeding candida genus and mortality rates developed within 30 days after reproduction were compared for each patient.

Statistical analysis

Fisher Exact test or Pearson Chi-square tests were used for categorical data analysis by groups. *P*-value of <0.05 was considered statistically significant. Data analysis was performed with SPSS 17.0 (SPSS Ver. 17.0, Chicago IL, USA) program.

Results

Candida growth was detected in the blood culture of 134 patients within the specified period. Among them, 49 were female (36.6%) and 85 were male (63.4%). The patients ranged in age from 1 to 96 years with the mean ages of females and males being 50 (24.3) years and 51 (25.7) years, respectively.

Among 134 patients, 73 (54.5%) had *C. albicans* and 61 (45.5%) had non-*albicans candida*. Out of the non-*albicans candidas*, there were 23 *C. parapsilosis* (17.2%), 18 *C. glabrata* (13.4%), 7 *C. tropicalis* (5.2%), 3 *C. lusitaniae* (2.2%), 2 *C. lipolytica* (1.5%) and 8 other species (6%). The growth of *Candida* took between 0-8 days in blood culture samples with an average reproduction time of 2-3 days. *C. albicans*, was the most commonly detected strain with a rate of 54.5%. This was followed by *C. parapsilosis* (17.2%) and *C. glabrata* (13.4%). Malignancy was present in 23.9% of total patients. The rate of surgery among these patients were 71.6%. Around 90.3% of the patients had used antibiotics before the development of candida, and 58.2% had prolonged intubation and 32.8%, chronic renal failure (Table 1). When the 3 most common candida species and mortality rates were analyzed according to age distribution (Table 2), among patients between 0-20 years of age (n=24), 54.2% (n=13) were seen to have CA growth.

While 46.2% (n=6) of these Candidemias were mortal, patients who were ≥60 years of age (n=35) suffered a CA-related mortality rate of 62.9% (n=22) (n=35). *C. parapsilosis* was equally distributed in all age groups, and mortality due to *C. parapsilosis* was 25% between 0-20 years and 60% in ≥ 60 years. *C. glabrata* was not seen in the 0-20 age group, it was similarly detected in other age groups. Total mortality rates of the 3 most common candida species were similar between 0-20 years and 21-59 years of age (29.2% and 30.8%, respectively). The overall mortality rate in the age group of ≥60 years was found to be 56.9%, which was significant (*P*=0.003). No statistically significant difference was found in terms of the

distribution of candida species between the age groups ($P=0.057$), or in terms of mortality ($P=0.347$). When CA and NAC types were compared, there was no statistically significant difference between mortality rates ($P=0.864$). There was no statistically significant difference between the distribution of the three most common candida species (*C.albicans*, *C.parapsilosis* and *C. glabrata*) ($P=0.84$) according to age groups, and between their mortality rates ($P=0.989$).

Table 1: Characterization of patients with *C.albicans* and non-*albicans* *Candida* infection

Profile		<i>C. albicans</i> (n=73)	Non- <i>albicans</i> <i>Candida</i> (n=61)	P-value
Age	≥60	34 (57.6%)	25 (42.4%)	0.516
	<60	39 (52%)	36 (48%)	
Gender	Male	52 (61.2%)	33 (38.8%)	0.04
	Female	21 (42.9%)	28 (57.1%)	
Solid tumor	Yes	11 (34.4%)	21 (65.6%)	0.09
	No	62 (60.8%)	40 (39.2%)	
Surgery	Yes	49 (50.5%)	48 (49.5%)	0.136
	No	24 (64.9%)	13 (35.1%)	
Mechanical ventilation	Yes	41 (52.6%)	37 (47.4%)	0.600
	No	32 (57.1%)	24 (42.9%)	
Chronic renal insufficiency	Yes	27 (61.4%)	17 (38.6%)	0.263
	No	46 (51.1%)	44 (48.9%)	
Total parenteral nutrition	Yes	8 (42.1%)	11 (57.9%)	0.242
	No	65 (56.5%)	50 (43.5%)	
Broad spectrum antibiotic exposure	Yes	64 (52.9%)	57 (47.1%)	0.261
	No	9 (69.2%)	4 (30.8%)	
All-cause in- hospital mortality	Yes	37 (53.6%)	32 (46.4%)	0.838
	No	36 (55.4%)	29 (44.6%)	

Table 2: Mortality and age distribution between three most common *Candida* species

Age	<i>C. albicans</i>		<i>C. parapsilosis</i>		<i>C. glabrata</i>		Total Ex (n) (%)
	(n) (%)	(ex) (%)	(n) (%)	(ex) (%)	(n) (%)	(ex) (%)	
0-20 (n=24)	13 (54.2)	6 (46.2)	4 (16.7)	1 (25)	0 (0)	0 (0)	7/17 (41.2)
21-59 (n=52)	26 (50)	9 (32.1)	9 (17.3)	3 (33.3)	10 (19.2)	4 (40)	16/45 (35.5)
≥60 (n=58)	34 (58.6)	22 (62.9)	10 (17.2)	6 (60)	8 (13.8)	5 (55.6)	33/52 (63.5)
Mortality	37/73	(50.7)	10/23	(43.5)	9/18	(50)	

Discussion

Candida is an important cause of bloodstream infections in critical patients hospitalized in Intensive Care Units [9]. Longer survival of patients with serious and complex problems as a result of advances in medicine has led to a population of individuals susceptible to infection. *Candida* is the most common fungal pathogen in intensive care patients and its main clinical form is blood circulation infection, followed by peritonitis and other abdominal infections, and endocarditis. There has been a shift in the distribution of agents among candida species reported in many hospitals over the last two decades. While almost all of the candidemia strains reported in the past are CA, increasing candidemia rates have been reported with NAC species in recent years [10]. The incidence of NAC infection varies widely between regions and the reason for this is unclear [11]. This may be due to different patient populations and health care standards [12]. The most commonly reported NAC species were *C.parapsilosis* or *C. glabrata*, followed by *C. tropicalis* and *C. crusei* [10-11]. Although the frequency of detection varies, pathogens have been identified as *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* in 95% of the infections in the last 20-30 years [13]. Their distribution varies according to the studies conducted in different geographical regions. CA is the most common species, but significant regional differences have been found between the number of cases caused by *C. glabrata* and *C. parapsilosis*. In studies from Northern Europe and the United States, numerous cases of *C. glabrata* have been reported, whereas in Spain and Brazil, the number of cases caused by *C. glabrata* is less and most of the cases are attributed to *C. parapsilosis* [2]. While the incidence of CA decreases globally, *C. glabrata* and *C. krusei* are stable and *C. parapsilosis* and *C.*

tropicalis rates have been increasing [1]. In our study, we determined that 54.5% of the cases were CA. The most common causative agent after CA was *C.parapsilosis* with 17.2%. This result was consistent with other studies conducted in Turkey [14-17]. In our study, the third most common strain was *C. glabrata* (13.4%). We could not find any relationship between any candida species and mortality. Some previous studies have reported the association of *C. glabrata* with high age and high mortality rates [18-20]. Again, studies showing a high mortality relationship with CA have been reported [20]. In the study conducted by Das et al. there was no significant relationship between *C. glabrata* and mortality [21]. In another study in the literature, it was reported that candida species do not affect mortality [22]. In our study, no difference was found between CA and NAC in terms of age, gender, underlying disease and mortality rates among patients with candidemia. Although CA mortality rate was higher in our study than NAC (53.6% and 43.4%, respectively), this was not statistically significant. When the three most common types of candida were compared, total mortality among ≥60 years of age was significantly higher in *C. albicans*, *C. parapsilosis* and *C. glabrata* compared to other age groups ($P=0.003$). In a study by Karadağ et al. mortality was reported to be significantly higher in patients aged 50 years and older [23]. We did not find any difference between the development of CA and NAC infection with total parenteral nutrition [24] or mechanical ventilation 2 weeks prior to diagnosis, which was reported as a risk factor for NAC infection. Similar results have been reported in the study conducted by Gong et al [6]. In our study, there was no difference between the presence of solid organ malignancy and the development of CA or NAC. This may be due to the lack of neutropenic patients because we don't offer chemotherapy in the hospital. There was no significant correlation between the distribution of candida species among surgical and non-surgical patients. Aliskan et al. reported similar results in their study [14]. Candidemia has been reported to be the cause of mortality at a rate of 30-60% [25,10]. In our study, there was no statistical difference between CA and NAC mortality considering all causes. We found that the crude mortality rate of CA was 53.6% and NAC was 43.4%. In a study conducted in Europe, the 30-day mortality rate in intensive care patients was 53.6% [20]. In another study performed by Marriott et al. in non-neutropenic intensive care patients, they reported a 30-day mortality rate of 56% in patients with Candidemia [26].

Limitations

There were some limitations of this study. *Candida* index and APACHE II score could not be obtained for each patient due to the retrospective nature of the study. Prospective multi-center studies with large sample sizes should be performed, which could provide more relevant epidemiology information.

Conclusion

Candidemia has high mortality rates, especially in patients in the ICU. CA was found to be the most common pathogen. Especially patients over 60 years of age should be followed up more closely in terms of mortality. Knowledge of local epidemiological trends in candida species will guide clinicians in early diagnosis and therapeutic choices.

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Neurofeedback improves EEG complexity and social interaction in a boy with autism: A case report

Otizml bir çocukta, nörogeribildirim EEG karmaşıklığı ve sosyal etkileşimi artırdı: Olgu raporu

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Abstract

Autism is an interhemispheric connectivity disorder, and intracortical circuits are also likely to be disturbed. Autism is characterized by impairments in communication with restricted interest and repetitive behaviors. Auto Train Brain is a neurofeedback-enabled mobile phone software application designed in Sabancı University laboratory for improving the cognitive functions of dyslexic children. Applying Auto Train Brain for 14 channels to an autistic boy created complexity improvements at lower temporal scales. After neurofeedback therapy, the patient began to use eight different single words, and his social responsiveness became significantly better. As a result of these, his CARS score improved from 39 to 34. He demonstrated an increased ability to follow instructions, and his attention span increased. Therefore, his FACT score increased from 21 to 30.

Keywords: Autism, Auto Train Brain, Neurofeedback

Öz

Otizm her iki hemisfer arasında oluşan bağlantısızlık sendromudur, aynı hemisferdeki kısa bağlantıların da etkilenmesi muhtemeldir. Otizmde dar ilgi alanı ile iletişimde bozukluk ve tekrarlayıcı davranışlar bulunur. Auto Train Brain, Sabancı Üniversitesi laboratuvarlarında tasarlanmış, nörogeribildirime dayalı ve disleksik çocukların bilişsel performanslarını artıran bir cep telefonu uygulamasıdır. Otistik bir çocukta, AutoTrain Brain 14 kanaldan uygulanmış ve düşük geçici ölçekte EEG karmaşıklığının arttığı gözlenmiştir. Nörogeribildirim terapisinden sonra çocuk, 8 farklı kelime kullanmış, sosyal tepkileri önemli ölçüde düzelmiştir. CARS puanı 39'dan 34'e ilerleme kaydetmiştir. Komutları yerine getirme becerisi artmış, dikkat süresi uzamıştır. FACT puanı 21'den 30'a yükselmiştir.

Anahtar kelimeler: Otizm, Auto Train Brain, Nörogeribildirim

Introduction

Impairments in communication with restricted interest and repetitive behaviors characterize the autism spectrum disorders (ASDs), which may affect up to 1% of children. Autism is a polygenetic developmental neurobiological disorder with multiorgan system involvement (neocortical and cerebellar system, immune system, and gastrointestinal system), though it predominantly involves central nervous system dysfunction. It is an interhemispheric connectivity disorder, and intracortical circuits are also likely to be disturbed [1,2].

Auto Train Brain is a neurofeedback-enabled mobile phone software application designed in Sabancı University laboratory for improving the cognitive functions of dyslexic children. The software reads electroencephalography (EEG) signals from 14 channels of eMotiv EPOC+ and processes these signals to provide neurofeedback to a person to improve the brain signals with visual and auditory cues in real-time [3]. With its patented novel approach, Auto Train Brain improves the intracortical circuits and improves functional connectivity for people with dyslexia.

In this report, we have examined the positive outcomes of applying Auto Train Brain to a boy with autism.

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Informed Consent: The authors stated that the written consent was obtained from the parents' of the patient presented with images in the study.

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Case presentation

The patient was thirty months old when he was diagnosed with autism spectrum disorder according to DSM V criteria. He was six years and ten months old at our initial evaluation. He was non- verbal but could sustain brief eye contact and could follow simple commands.

The childhood autism rating scale score (CARS) and Frankfurt Adaptive Concentration Test (FACT) was used to determine autism severity and attention performance, respectively. His CARS score was 39 (The cutoff score for the diagnosis of autism is 30), and FACT score was 21 (the average score is 32). Visual analysis of sleep electroencephalography (EEG) did not reveal any epileptic discharge. The quantitative analysis of EEG data showed lower complexity in the lower temporal scales and higher complexity in the higher temporal scales.

The treatment plan was to apply Auto Train Brain at home, 3 times a week, at least 100 times with the provision and help of his parents. The main goal of the experiment was to reduce the slow brain waves if the recorded ones were above the TD norm age group's average slow waves, and improve the fast brain waves if the recorded ones were below the TD norm group's average fast waves. Visual and auditory feedback was provided online in real-time via the Android Java program after processing the EEG data gathered from the subject's head. For all analyses in this report, Theta (4-8 Hz), Alpha (8-12 Hz), Beta-1 (12-16 Hz), Beta-2(16-25 Hz), and Gamma (25-45 Hz) band data were recorded for 14 channels. Throughout the experiments, an eMotiv EPOC+ headset was used. The internal sampling rate in the headset is 2048 Hz per channel. The EEG data were filtered to remove artifacts and alias frequencies, then downsampled to 128 Hz per channel. There were 14 EEG channels plus two references. Electrodes were placed according to the 10-20 system. Before training with MyEmotiv mobile application, the calibration of the eMotiv headset on the subject's scalp was achieved, ensuring that each electrode transfers EEG data with high quality.

To measure the success of this training, at the start and end of the training, the "sleep" state raw EEG data was measured with eMotiv PRO software and eMotiv EPOC+ headset, and multiscale entropy was calculated [3]. The sampling rate of the EEG data was 128 Hz. The raw data were filtered by using a bandPass FIR filter (1-50Hz). The artifacts were removed manually by using EEGLAB's data rejection options. The independent component analysis was performed. MSE was calculated for one continuous 60-s epoch for each experimental and control EEG reading. The number of samples(N) is set to $N=128*60$ (7680). Sample entropy parameters were set to ($m=2$, $r=0.25*$ standard deviation of EEG signal), which have proven to be effective in other studies [4]. We have created 40 temporal scales to analyze the complexity. The expected outcome of the experiment was to increase in the EEG complexity and increase in social responsiveness.

After neurofeedback therapy, the patient began to use eight different single words, and his social responsiveness became significantly better. As a result of these, his CARS score improved to 34. He demonstrated an increased ability to follow

instructions, and his attention span increased. Therefore, his FACT score increased to 30.

Applying Auto Train Brain for 14 channels created complexity improvements at lower temporal scales. The results show that low complexity at lower temporal scales has improved after 120 sessions of Auto Train Brain training (Figure 1) in all channel locations. The power band values pre- and post-treatment were also included for the sake of completeness of analysis (Figure 2 and Figure 3). These figures demonstrate that the slow brain waves were reduced, and the left-brain dominance was increased.

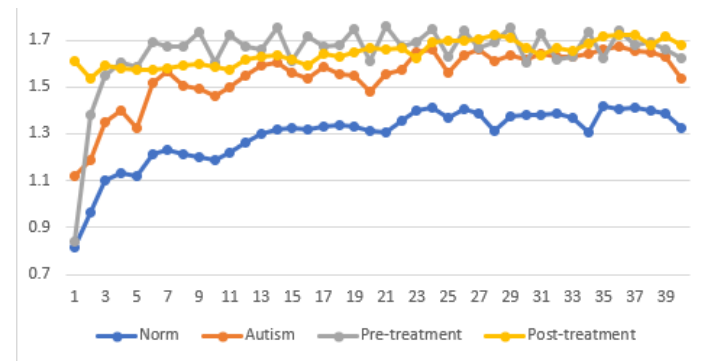


Figure 1: MSE

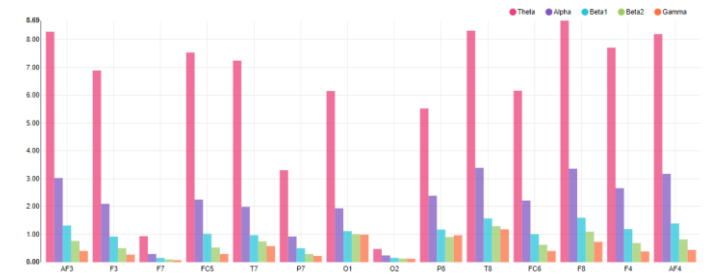


Figure 2: Frequency band values pre- treatment

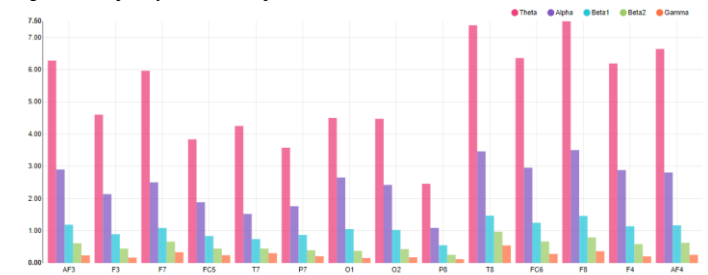


Figure 3: Frequency band values post- treatment

Discussion

This report was the first attempt to apply Auto Train Brain to ASD, as the neurofeedback protocols in Auto Train Brain were initially designed to improve the cognitive abilities of people with dyslexia. In dyslexia, the interhemispheric connections are usually developed, whereas there is "disconnection syndrome" in intracortical circuits (mainly between Broca and Wernicke area). From this perspective, autism and dyslexia seem to be reverse conditions [5,6]. However, they share similarities in gamma band abnormalities (gamma bands are too low or too high in both conditions).

In the literature, neurofeedback has previously been applied to autism with success (at C4 reward 10-13 Hz, at F7 reward 15-18 Hz, at T3-T4 reward 9-12 Hz, at F3-F4 reward 7-10 Hz and 14.5-17.5 Hz, inhibit 2-7 Hz, 22-30 Hz) [7]. Auto Train Brain provides a novel neurofeedback method such that the process is personalized according to each individual's needs, and

the algorithm is bound by age-grouped norm data. These features make it easy to apply at home without any side effects.

Auto Train Brain successfully improves the intracortical circuits and improves the EEG complexity in people with dyslexia with its particular neurofeedback protocols. Applying the same protocols to a boy with autism indeed solved the problems at short cortical connections, whereas the long-distance temporal connections were not affected much. This remaining problem creates the necessity to adapt the neurofeedback protocols of Auto Train Brain for ASD to improve the long temporal connections as well. The new protocol to improve interhemispheric connections was added to Auto Train Brain, but not tested on ASD yet.

The patient was able to wear the headset during the training sessions. In most cases of ASD, the subjects cannot wear the headset for 20 minutes because many ASD subjects find the headset irritating. Although the neurofeedback protocol was useful for solving the functional connectivity issues, a specialized headband for ASD subjects to read EEG signals more comfortably should be developed.

Conclusion

Auto Train Brain, which was initially developed to improve the cognitive abilities of dyslexics, was applied to a boy with autism successfully. According to the multiscale entropy measures pre- and post-experiment, improvements in the intracortical circuits have been determined. There is a need to address the interhemispheric connections at Auto Train Brain protocols which will be enhanced shortly.

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An idiopathic aorta-right atrial fistula: A rare case

İdiopatik aorta-sağ atrial fistül: Nadir bir olgu

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Abstract

Atrial fistulas are the non-natural and rarely seen connections between the left atrium and ascending aorta. This pathological connection can be classified as anterior or posterior according to its location. It can be distinguished angiographically by the absence of myocardial branches. With the effect of systemic pressure, a tunnel occurs from the congenitally weak area in the aortic structure to the low-pressure atrium. There may be no symptoms in the patients, or serious clinical findings, including those related to congestive heart failure may be seen. Even if aorto-atrial fistulas are asymptomatic or hemodynamically insignificant, they should be treated to prevent possible complications. Closure can be performed with the catheterization method or open-heart surgery when appropriate. In this case report, we would like to share the treatment approach of a 49-year-old male patient who was admitted to our hospital with chest pain and whose angiographic and echocardiographic examinations revealed a tunnel from the aorta to the atrium. An informed consent was obtained from the patient.

Keywords: Aorta-atrial fistula

Öz

Aorta atriyal fistüller nadir olarak görülen sol atriyum ile asendan aorta arasındaki doğal olmayan bağlantılardır. Bu patolojik bağlantı yerleşim yerine göre anterior veya posterior olarak sınıflandırılabilir. Miyokardiyal dalların olmaması ile anjiyografide ayırt edilebilir. Sistemik basıncın etkisi ile aort yapısındaki konjenital zayıf olan bir bölgeden düşük basınçlı atriyuma tüne açılması durumudur. Hastalarda semptom olmayacağı gibi konjestif kalp yetmezliğine bağlı semptomlar dahil olmak üzere ciddi klinik yansımaları olabilir. Asemptomatik veya hemodinamik açıdan önemsiz olsa bile olası komplikasyonları nedeniyle tedavi edilmeleri gerekmektedir. Kateterizasyon yöntemi ile yapılabileceği gibi uygun hastalarda açık kalp cerrahisi ile kapama işlemi yapılabilmektedir. Burada 49 yaşında olan, göğüs ağrısı ile hastanemize başvuran, yapılan anjiyografik inceleme ve ekokardiyografik değerlendirmede aortadan atriyuma geçiş tespit edilen hasta için yaptığımız tedavi yaklaşımını kendisinin onayı alındıktan sonra paylaşmak istedik.

Anahtar kelimeler: Aorta-atriyal fistül

Introduction

Tunneling from the aorta to the right atrium is a very rare vascular pathology. In this pathology, there is a shunt arising from the aortic root and terminating in the right atrium. It may occur as a complication of infective endocarditis, mitral valve insufficiency, aortic valve insufficiency, transeptal catheterization, connective tissue diseases, and aortic dissection [1,2]. It is usually detected incidentally during an imaging process and no spontaneous closure was reported [2]. In the period from diagnosis to treatment, it requires a multidisciplinary approach and cardiovascular team co-operation.

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Case presentation

A 49-year-old male patient was admitted to our hospital with long-standing chest pain. The patient had no diagnosis of chronic illness in his medical history. There was no risk factor other than smoking. Physical examination of the cardiovascular system revealed no other pathological finding except a precordial murmur. Other system examinations were normal. In two-dimensional echocardiographic examination of the patient with normal sinus rhythm, the presence of an anteriorly located tunnel from the aortic root to the right atrium was detected (Figure 1a-1b).

maneuvers, the patient was separated from pump with no problem, and the cross clamp was removed. After the rhythm was back to normal, echocardiography was performed intraoperatively, and the absence of aorta-atrial transition was confirmed. Then, decannulation was performed with routine surgical procedures and surgery was completed. The patient, who was observed in the intensive care unit for 24 hours, had an uneventful postoperative period and he was discharged on the 5th postoperative day. No aorta-atrial transition was observed with echocardiographic examination performed at 3rd month.

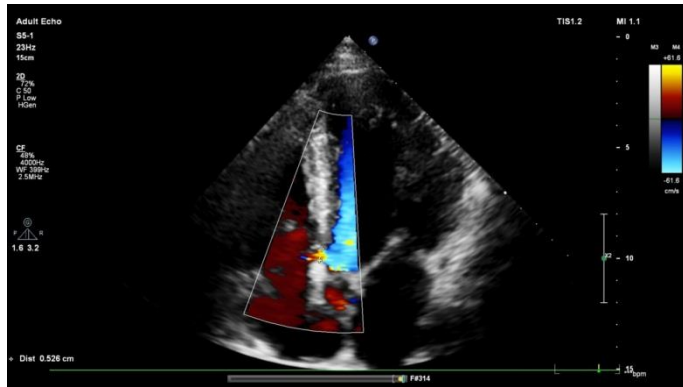


Figure 1a: Two-dimensional echocardiographic image

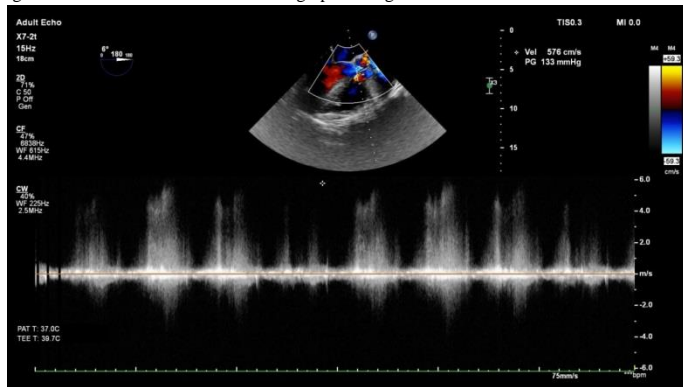


Figure 1b: Two-dimensional echocardiographic image

Transesophageal echocardiography was performed for a clearer evaluation of the tunnel in the patient whose ejection fraction was 60%, and the shunt from the right sinus of Valsalva to the right atrium was observed. His biochemical parameters were within normal range. Coronary angiography via the right radial artery was performed to evaluate coronary vascularization. No pathology was detected in the main vascular structures. The tunnel structure did not contain myocardial branches. After the joint evaluation with the cardiology clinic, the decision to surgically intervene was made, and routine cardiac surgery preparations were started. After pre-operative preparations, the surgery was performed. The mediastinum was reached by median sternotomy. Cardiopulmonary bypass (CPB) was established after aorto-bicaval cannulation. After retrograde aortotomy, cardiac arrest was achieved with cold blood selective and antegrade cardioplegia from the coronary ostium, and it was continued intermittently. The tunnel structure extending from the right coronary sinus to the atrium was observed (Figure 2a, 2b).

The fistula mouth was closed with Teflon supported suture passing from the external aorta and the coronary sinus. Atriotomy was performed and the other end of the fistula was seen. The fistula mouth adjacent to the tricuspid valve was closed with teflon-pledget supported sutures. After venting

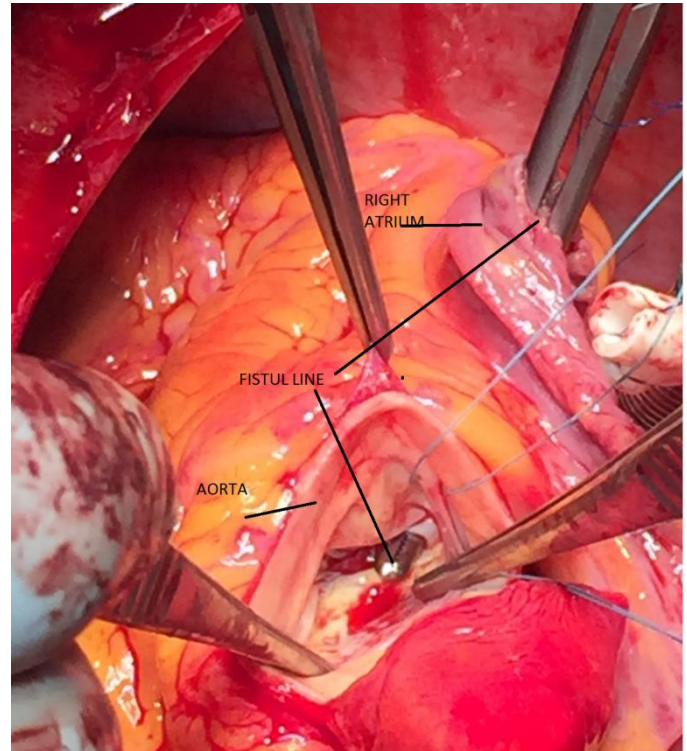


Figure 2a: Intraoperative views of aorta-atrial tunneling

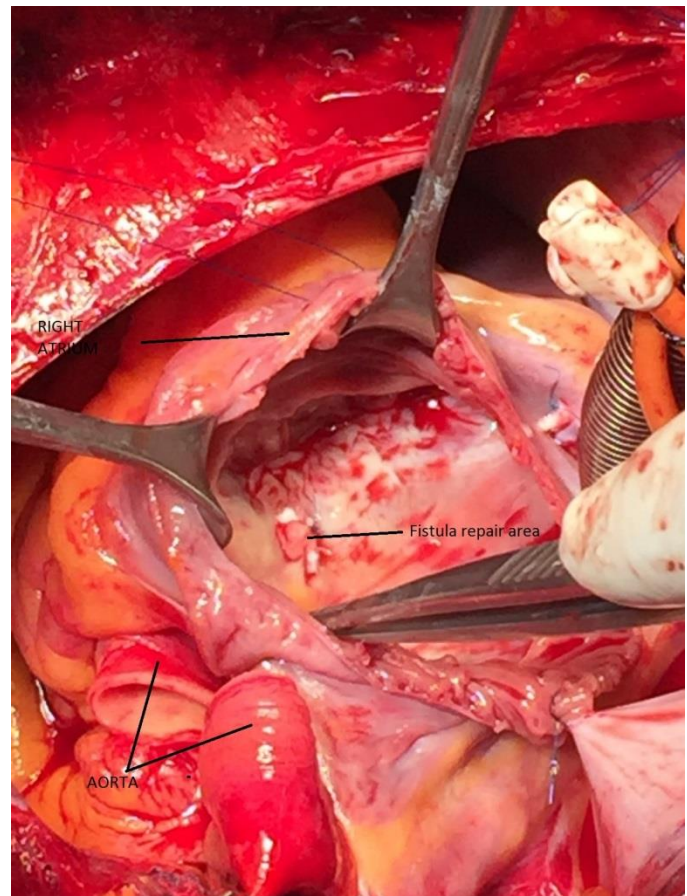


Figure 2b: Intraoperative views of aorta-atrial tunneling

Discussion

This pathology, which was first described by Coto et al. [3] and evaluated as a tunnel extending from the aortic root to the right atrium, is quite rarely seen. It frequently originates from the left sinus, and rarely from the right sinus [4]. In this case, the pathological structure extended from the right sinus to the right atrium. It was argued that a tunnel from congenitally weak area in the tunica media of aorta to low pressure right atrium may occur due to high pressure in the aorta [5]. It may occur due to the presence of an aneurysm in the sinus Valsalva, surgical interventions in the region, infections, aortic dissection, trauma, or idiopathically. The pathology in our case was evaluated as idiopathic since there were no other factors that might play a role in its etiology.

Since some patients can be asymptomatic, this pathology can be detected incidentally by imaging procedures. It can also be detected by the acute form with chest pain, or by the chronic form with congestive heart failure symptoms. Although transthoracic echocardiography is an important guide for the detection of this pathology in patients, the diagnosis becomes clearer with a rate of 97% by transesophageal echocardiography [6]. Coronary angiography and aortography are especially important for the definitive diagnosis and the evaluation of coronary vascular structures [7].

In the treatment options, catheter-supported closure methods and surgical closure are available according to the location and size of the lesion. In our case, since the tunnel in the right atrium was very close to the tricuspid valve, the surgical closure was considered appropriate after evaluation with the cardiology team. Even if the closure procedure is controversial in asymptomatic patients, it was reported that closure procedure is recommended to prevent the development of heart failure in these patients [8].

Conclusion

Aorto-atrial fistulas are rarely seen and important pathologies that can lead to heart failure if it is detected late or not treated. All facilities of the cardiology team should be used in diagnosis. In addition to transthoracic and transesophageal echocardiography, the coronary angiography and aortography should be performed to detect accompanying vascular pathologies. We hereby presented our case of fistula, which is quite rarely seen and extends from right sinus to the right atrium, and our treatment approach.

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A rare cause of precocious puberty: Juvenile granulosa cell tumor

Puberte prekoksun nadir bir nedeni: Juvenil granuloza hücreli tümör

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Abstract

Ovarian sex cord-stromal tumors, including granulosa cell tumors are rare, especially in children. They are classified into juvenile and adult types. Juvenile granulosa cell tumors (JGCT) comprise 5% of all granulosa cell tumors. Precocious pseudo-puberty is a common presentation of these tumors, associated with hormonal changes. We report a rare case of JGCT of the ovary in a 4-year-old girl who presented with breast enlargement and alveolar pigmentation for two months. At her examination she had also an abdominal mass. Based on imaging features and laboratory findings, the diagnosis of the mass was unclear. After surgery, histopathological examination revealed JGCT of the left ovary. Although in most of girls with precocious puberty, the etiology is idiopathic, important causes, such as ovarian tumors like JGCTs must be considered.

Keywords: Juvenile granulosa cell tumor, Ovary, Puberty

Öz

Granuloza hücreli tümörleri içeren over seks kord stromal tümörleri, özellikle çocuklarda nadir görülen tümörlerdir. Juvenil ve yetişkin tip olarak iki gruba ayrılırlar. Juvenil granuloza hücreli tümörler (JGHT) tüm granuloza hücreli tümörlerin %5'ini içerir. Yalancı puberte prekoks, hormonal değişiklikler ile ilişkili bu tümörlerin en sık görülen bulgusudur. Biz burada 2 aydır meme büyümesi ve alveoler pigmentasyon şikayeti ile başvuran, 4 yaşındaki bir kız çocuğunda görülen nadir bir JGHT olgusunu bildirdik. Muayenesinde abdominal kitlesi de mevcuttu. Görüntüleme ve laboratuvar bulguları ile kitlenin tanısı belirsizdi. Operasyon sonrası histopatolojik tanı sol overin JGHT' ü olarak konuldu. Puberte prekoks olan kızların çoğunda etyoloji idiyopatik olsa da JGHT de içeren bazı over tümörleri gibi önemli nedenler göz önünde bulundurulmalıdır.

Anahtar kelimeler: Juvenil granuloza hücreli tümör, Over, Puberte

Introduction

Granulosa cell tumors are the most common malignant sex-cord stromal tumors, and they are classified into juvenile and adult types [1]. Juvenile types constitute only 5% of the granulosa cell tumors [1]. JGCTs most commonly occur in peripubertal girls and in women younger than 30 years of age, at the mean age of 13 years [2]. Precocious pseudo-puberty, a common presentation of these tumors, is related to hormonal changes [3]. We herein present a rare case of JGCT in a 4-year-old girl with isosexual precocity as premature thelarche.

Case presentation

A girl, at the age of 4 years and 4 months, with no significant past medical history, presented with breast enlargement and alveolar pigmentation for the last 2 months (Figure 1). On physical examination, her pubertal stage was Tanner 3 for breast development and Tanner 1 for pubic and axillary hair growth. Anthropometric evaluation revealed 110 cm height (within the 90th percentile), 22 kg weight (within the 90th to 97th percentile), and a body mass index of 18.2 kg/m². She had no headaches or visual complaints. Her bone age was advanced (6 years old). She had a large abdominal mass. She was referred to the Pediatric Endocrinology Clinic in our medical center. Her serum hormonal profile was consistent with peripheral precocious puberty: Estradiol 65 pg/ml; follicle-stimulating hormone (FSH):0.23 mIU/ml, luteinizing hormone (LH):0.29 mIU/ml, dehydroepiandrosterone sulphate: 0.7 ug/dl, testosterone: 0.0 ng/ml. Her thyroid functions were normal. Cancer antigen-125 (CA-125) was high, with 213 U/ml (normal values:0-35 U/ml), but other tumor markers such as alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) were within normal limits. Luteinizing hormone-releasing hormone (LHRH) stimulation test was performed without an increase in LH and FSH. Radiological examination revealed a large, cystic and solid lesion (12x9cm) in the umbilical and infraumbilical regions. The origin of the mass was not detected ultrasonographically (Figure 2). The size of uterus was big for the patient's age, and there was free pelvic fluid. Subsequently, magnetic resonance imaging (MRI) of the abdomen and pelvis showed a huge, 12x9x5 cm (APxTRxCC) lesion of fluid consistency arising from the pelvis (Figure 3 and 4). The ovaries were not visualized, possibly due to this huge mass. Thorax contrast-enhanced computed tomography was performed for staging and there was no sign of metastasis. Positron emission tomography was obtained, and no distant metastases were shown. MRI of the brain and hypothalamic-pituitary region was normal. Based on imaging features and laboratory findings, the diagnosis of the mass was unclear. So, we recommended diagnostic and therapeutic laparotomy. Laparotomy was performed under general anesthesia. An ovarian mass on the left, with a diameter of 12x9 cm, was detected and completely resected along with the left ovary. The right ovary was normal. On gross examination, the tumor was seen to originate from the left ovary, which now consisted of a gray mass with solid and cystic components (Figure 5). Pelvic fluid was aspirated and sent to cytology. No lymphadenopathy was detected in the pelvic area. The mass was sent for histopathological examination. Grossly, a large, intact ovarian tumor with a grey-white fibrous capsule, measuring 14x8x6 cm and weighing 560 grams, was resected. The sagittal surface was heterogeneous, showing creamy nodular areas and small cystic structures. The microscopic appearance was characterized by a proliferation of the sex-cord stromal cells with high mitotic activity (7-8 mitosis per 10 high power fields) and high-grade cell atypia. Immunohistochemical staining was positive for inhibin, calretinin, cluster of differentiation (CD)99 and smooth muscle actin (SMA). The cells were focally positive for pancytokeratin. The tumor was negative for CEBP2, CD10, EMA, AFP and

hCG. No Call-Exner bodies were identified. The ovarian capsule had ruptured, and malignant cells resided within the pelvic fluid. The final diagnosis was a juvenile granulosa cell tumor. The tumor was allocated as FIGO (International Federation of Gynecology and Obstetrics) stage IC and she was treated with bleomycin, etoposide, cisplatin (BEP) chemotherapy for four cycles. Response to treatment was good after 18 months after the surgery with regression in breast size and decrease in serum CA-125 levels. There were no signs of re-occurrence of tumor and control ultrasonography was normal. Informed consent was obtained from the parents.



Figure 1: Breast enlargement and alveolar pigmentation



Figure 2: Ultrasonographic imaging

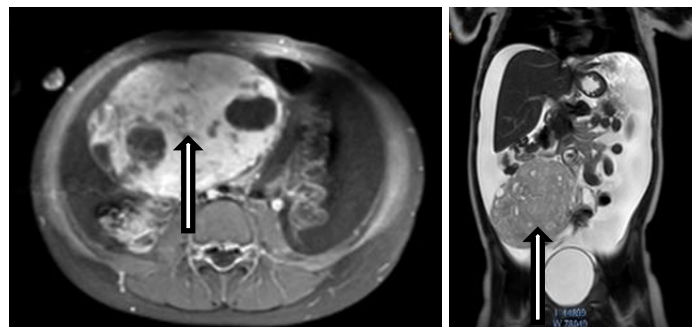


Figure 3: The axial view of an abdominal MRI (Arrow: mass) Figure 4: The coronal view of an abdominal MRI (Arrow: mass)



Figure 5: Intraoperative view of the ovarian tumor

Discussion

Precocious puberty in girls is generally defined as appearance of secondary sexual characteristics before eight years of age. Precocious puberty is divided in two as central precocious puberty (CPP) and peripheral precocious puberty (PPP). CPP results from premature activation of the hypothalamus- pituitary-gonadal axis. The majority (74%) of

girls have idiopathic CPP, but it can be secondary to an underlying disorder [4]. PPP results from sex steroid exposure by a process other than activation of the hypothalamus-pituitary-gonadal axis. It is much less common than CPP [5].

Ovarian tumors are uncommon in the pediatric population, with an estimated incidence of 2.6 cases per 100,000 girls per year. Ovarian tumors in children and adolescents are reported in 10-20% of all ovarian masses or neoplasms and comprises approximately 1-2% of all childhood malignancies [6].

Granulosa cell tumors are rare sex cord stromal tumors, encompassing 1-5% of all ovarian tumors [7]. They are classified into juvenile and adult types [1]. The adult type of GCTs is the more common type, accounting for nearly 95% of all GCTs. They usually present in women over 40 years of age [2]. Juvenile types constitute only 5% of GCTs and occur in prepubertal girls and in women younger than 30 years, with a mean age of 13 years [2,8]. JGCTs can be hormonally active, secreting estrogen and causing 10% of all cases of precocious puberty in premenstrual females [2,7].

We herein describe a rare case of JGCT in a 4-year-old girl presenting with isosexual precocity as premature thelarche. She had an abdomino-pelvic mass without abdominal pain. Her serum laboratory findings were consistent with peripheral precocious puberty, with high estradiol levels. CA-125 was also high. Since we did not know the exact histopathology at the time of diagnosis, we did not measure inhibin levels. On the third postoperative day, inhibin A was normal (1 pg/ml), along with other sex hormones and tumor markers, which were all within normal range.

Patients with recurrent or persistent ovarian cysts, especially with a significant solid component beyond three months, should alert the clinician to the possibility of an ovarian tumor, and JGCT [9]. In our case, it was the patient's first visit and she had no past medical history. The abdomino-pelvic ultrasound showed a huge cystic and solid lesion of 12 cm in diameter. The left and right ovaries were not visualized. The uterus was oversized for the patient's age. MRI of the abdomen and pelvis confirmed ultrasonographic findings. With high levels of CA-125, our preliminary diagnosis was an ovarian tumor.

Imaging characteristics of adult and juvenile GCTs are non-specific and these tumors cannot be reliably distinguished from other ovarian tumors on imaging alone [10]. The evaluation of sex hormones and serum tumor markers can be useful for the differential diagnosis in pediatric ovarian masses. In our patient, laboratory findings were more helpful for the diagnosis compared to imaging. Our patient presented with alveolar pigmentation, breast enlargement, advanced bone age and accelerated height and weight gain. These were seen due to tumor-derived estradiol.

At presentation, 90% of JGCTs are FIGO stage I, confined to the ovary, and have a good prognosis with a 5-year survival rate of 90%. They are curable with conservative surgery alone. However, patients with advanced disease or tumors with high mitotic activity have poorer prognosis and maybe treated with chemotherapy [11].

Precocious puberty has been previously reported in some girls with JGCTs. Abdominopelvic ultrasonography should

be performed in all females with PP. After detecting ovarian tumor, serum tumor markers should be evaluated along with serum sex hormones.

Ovarian tumors at all ages are treated by oophorectomy or salpingo-oophorectomy and surgical staging. The prognosis of ovarian tumors in children is excellent if they are detected in early stages [12].

Outcomes tend to be less favorable in the presence of a large tumor size (10-15cm) or tumor rupture [13]. Other unfavorable prognostic factors may include nuclear atypia, high mitotic rate, extra-capsular extension of tumor within the ovary, and presence of residual disease after surgery [7]. The median time to relapse is approximately four to six years after initial diagnosis [14]. Tumor markers such as inhibin can also be used to assess for recurrence [15].

Conclusion

JGCTs are rare causes of peripheral precocious puberty. In initial stages, survival time is long and fertility sparing surgery can be safely preferred since most of the patients are young. Serum sex hormones, tumor markers, and inhibin can be used to assess diagnosis and recurrence.

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Intermammary pilonidal sinus: A case report of a 23-year-old girl

İntermammarian pilonidal sinus: 23 yaşında bir kadında olgu sunumu

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Abstract

Pilonidal sinus is a chronic inflammatory disease of the skin and subcutaneous tissue, a cyst filled with a ball of hair, characterized by a discharging sinus and abscess. The disease is typically seen in the sacrococcygeal region. However, it can occur in other areas, such as the occiput, nose, neck, intermammary (sternal) area, axilla, finger (interdigital area), groin or external genital area. In this case report, an intermammary (sternal) pilonidal sinus, which is rarely seen, was presented along with the literature.

Keywords: Intermammary, Pilonidal sinus, Inflammation, Excision

Öz

Pilonidal sinüs cilt ve cilt altı dokusunun kronik inflamatuvar bir hastalığı olup, akıntılı bir sinüs ağzı ve apse ile karakterize, içi kıl yumağı dolu bir kisttir. Hastalık tipik olarak sakrokoksigeal bölgede görülür. Ancak nadiren saçlı deride, burunda, boyunda, intermammarian (sternal) alanda, aksillada, parmak arasında (interdijital bölge), kasıkta ve dış genital bölgede görülebilir. Çalışmamızda çok nadir olarak rastlanılan intermammarian (sternal) pilonidal sinüs olgusu, literatür eşliğinde sunuldu.

Anahtar kelimeler: İntermammarian, Pilonidal sinüs, İnflamasyon, Eksizyon

Introduction

Pilonidal sinus was first described by Mayo as a hair containing sinus in 1833 and as a hair containing wound by Anderson in 1847(1). It is a chronic infection of hairy skin in the skin fold, and the cleft where the anus opens between the two gluteal regions is the most common localization. It constitutes 15% of the perianal diseases with an incidence of 0.07% (2,3). Men are affected two to four times more often than women (4).

In contrast to the cases of pilonidal sinus occurring in most other body regions, cases of intermammary pilonidal sinus are rarer but occur more frequently in women. Here we present a 23-year-old female with an intermammary pilonidal sinus characterized by a painful sinus with purulent discharge.

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Case presentation

A 23-year-old female patient presented with a history of itchy and painful pilonidal sinus with purulent discharge in the intermammary region. On clinical examination, the patient showed a discharging pilonidal sinus with multiple pits. At the interview, she stated no personal history of additional disease or previous operations.

Ultrasonographic examination revealed an 11x26 mm cystic mass with dense particulate material in the subcutaneous adipose tissue in lower part of the sternum. In Doppler examination, an increase in vascularization was observed in the cystic mass wall and the surrounding soft tissues, consistent with subcutaneous abscess. In advanced examination with magnetic resonance imaging (MRI), a lesion measuring approximately 2 cm was detected. MRI of the mass revealed hyperintensity in T2A and hypointensity in T1A sequences (Figure 1a, 1b).

The sinus tract and cystic cavity were all excised (Figure 2) and the defect was closed primarily.

The diagnosis of pilonidal sinus was confirmed by histopathological examination (Figure 3).

The patient was discharged on the same day after the operation. Postoperatively, the patient had excellent cosmetic outcome.

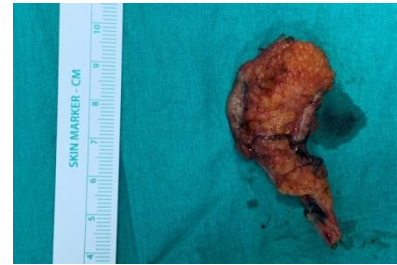


Figure 2: Material excised during the operation was measured with a sterile ruler (6x2,5 cm)

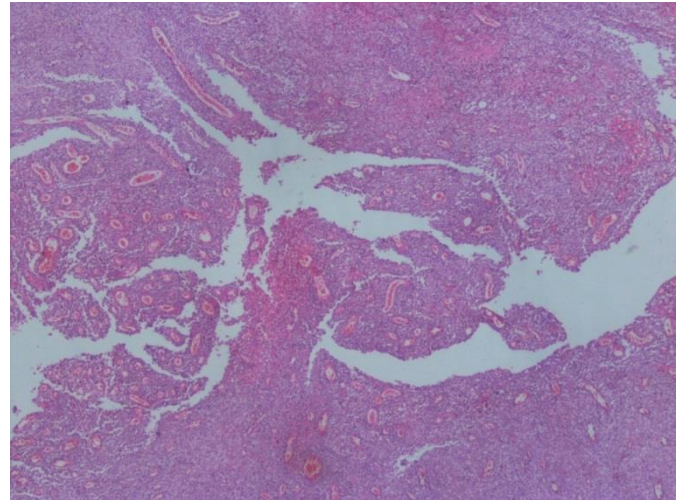


Figure 3: Inflammatory granulation tissue and mixed inflammatory cell infiltration around the tract (hematoxylin and eosin, magnification ×100)

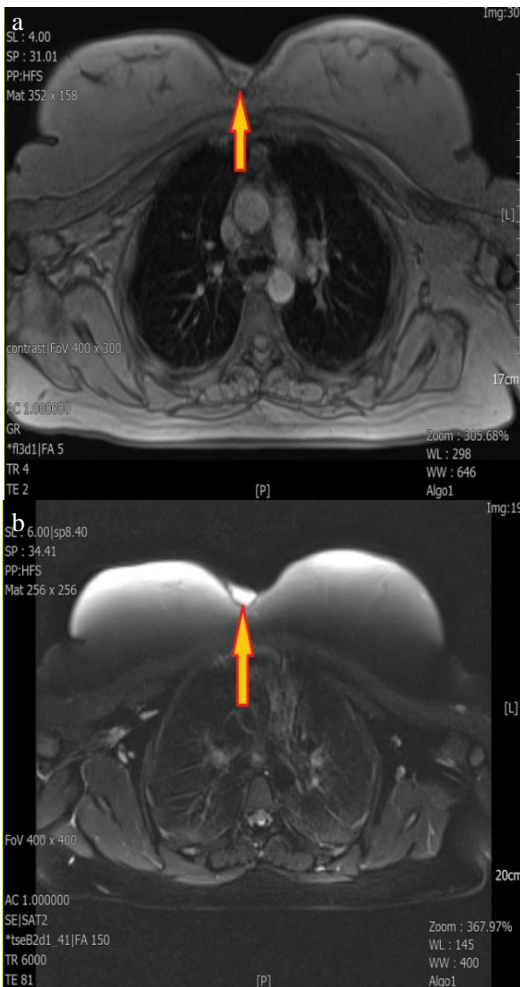


Figure 1a, 1b: 1. MRI scan in axial plane, T1 weighted. 2. MRI scan in axial plane, T2 weighted. MRI of the mass revealed hyperintensity in the T2A, and hypointensity in the T1A sequences

Discussion

There have been many theories about the development of pilonidal sinus. The idea that pilonidal sinus, which was previously thought to be congenital, is acquired is now widely accepted. Despite the complete removal of the sinus tract, the recurrence of the disease and the formation of the disease in the body parts where the local trauma is more intense, distances us from the theory that the disease is congenital. There are two most popular theories: 1) Hair is embedded beneath the dermis in areas where friction and pressure are too high, and the skin is too sensitive. 2) Excess bacteria and debris clog the mouth and hair follicles grow inwards. In another similar theory, the normal movement and tension in the dermis expands the hair follicles, which rupture and grow inside (5, 6).

Pilonidal sinus disease is usually observed within the 10-40 age range, and it is less frequent in children and adults older than 40 years (7). Our case was a 23-year-old female patient in accordance with the usual age range of the disease. There are many factors predisposing to pilonidal sinus: 1) A hairy body with an increased amount of daily spilled hair, 2) Spilled hair residing for a long time in the narrow and deep groove as a result of narrow and deep natal cleft (intergluteal cleft), 3) The skin remaining moist for a long time, 4) Having a crack, wound or scar tissue in the natal cleft, 5) Establishing local trauma based on sedentary lifestyle and prolonged sitting, 6) Poor hygiene, 7) Family history, 8) Obesity/overweight (8, 9, 10). However, in cases where none of these risk factors are present, pilonidal sinus disease may still occur. In our case, there were risk factors such as hairy body, moist skin and bad hygiene. The incidence of reported intermammary pilonidal sinus is very low. There are a few case reports and only one case series consisting of 12 patients reported by Shareef et al. (11).

In patients with pilonidal sinus disease, the clinical presentation may show a spectrum ranging from acute infection to chronic disease and may sometimes be asymptomatic. Patients with acute pilonidal disease present with pain, intermittent mucous, purulent or bloody discharge, fever and weakness in the case of abscesses. Patients with chronic pilonidal disease present with recurrent and persistent pain and discharge as in our case. The diagnosis is usually made by physical and imaging examinations. After diagnosis, the prognosis of pilonidal sinus is usually good. Cases of squamous cell carcinoma developed on chronic pilonidal disease are also rarely reported [12,13]. Pilonidal diseases may be difficult to differentiate from other similar or accompanying diseases, and require detailed physical examination. Folliculitis, hidradenitis suppurativa and some systemic diseases mimicking pilonidal diseases are distinguished from pilonidal diseases by their localization and lack of a sinus tract [14,15].

Histopathological examination of the sinus wall often includes foreign body giant cells, polymorphonuclear leukocytes and lymphocytes. Inflammation leads to the formation of secondary sinus mouths by progressing in the cephalic and lateral directions [7]. The pilonidal sinus cavity walls are not epithelized, therefore they are not true cysts, but secondary sinus tracts can be epithelized.

Antibiotic therapy is insufficient in the presence of pilonidal abscess and drainage is performed with appropriate incision. Antibiotic treatment can be used only in the presence of cellulite without abscess. According to the patient's discomfort or the severity of the symptoms, surgical decision is taken. Although there are various techniques used in pilonidal sinus surgery, primary closure is often performed and in case of wide excision, it can be left for secondary healing and various plastic surgery techniques can be used [16]. In our case, primary closure technique was used due to the absence of wide tissue excision and non-tensioned approach of the skin edges.

High recurrence rates are unavoidable especially after incomplete and incorrect surgical treatment, thus limiting the patient's daily life activities as well as causing discomfort to the patient and extending the time of return to work. In our case, the patient was discharged on the same day after the surgical excision. In the postoperative first week and first month follow-up, excellent results were obtained in terms of wound healing and cosmetics. Although excision and primary repair is the main surgical treatment, residual tissue should not be left behind to prevent recurrence of the disease.

Conclusions

Intermammary pilonidal sinus, although uncommon, may occur in intermammary area especially in young, obese, female patients with hairy bodies. Surgery is the most often used treatment method.

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