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Prognostic significance of metastasis-suppressor gene NM23 in gastric carcinoma

Metastaz supressör genlerden NM23'ün mide kanserindeki prognostik önemi

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Abstract

Aim: Metastasis is critical in the prognosis of gastric cancer patients and in deciding on treatment strategies. Therefore, studies have concentrated on metastasis suppressor genes. This study aimed to identify the characteristics of NM23 expression in gastric cancer and to investigate its anti-metastatic and prognostic significance.

Methods: Ninety patients who underwent surgery for gastric cancer between January 1, 2009 and January 1, 2010 were included in this study. Immunohistochemical staining was applied to specimen sections. The results of the immunohistochemical staining were evaluated with the normal gastric mucosa adjacent to the tumor. The degree of NM23 staining of tumor cell compared to the normal tissue was evaluated in two groups of "negative-weak staining" and "strong staining". Both groups were analyzed for lymph node metastasis, vascular invasion, perineural invasion, degree of tumor differentiation, tumor stage and distant metastasis.

Results: Among 58 patients with lymph node metastasis, 70.7% showed negative-weak staining and 29.3% showed strong staining. Among 32 patients with no lymph node metastasis, 40.6% had negative-weak staining and 59.4% had strong staining. Decrease in NM23 expression was shown to cause an increase in lymph node metastasis (P=0.01). Furthermore, while there was no statistical significance, the rates of distant metastasis, degree of poor differentiation, tumors in stage III and stage IV were apparently higher in the negative-weak staining group. These results were in line with the anti-metastatic property of NM23.

Conclusion: This study showed that NM23 expression had anti-metastatic properties for lymph node metastasis in gastric cancer patients.

Keywords: Gastric carcinoma, Immunohistochemical staining, NM23

Öz

Amaç: Metastaz, mide kanserli hastaların prognozunda ve tedavi stratejilerinin belirlenmesinde kritik öneme sahiptir. Bu nedenle metastaz baskılayıcı genler üzerine çalışmalar yoğunlaşmıştır. Bu çalışmada da, mide kanserlerinde NM23 ekspresyonunun özelliklerinin belirlenmesi, anti-metastatik ve prognostik öneminin araştırılması amaçlanmıştır.

Yöntemler: 1 Ocak 2009 - 1 Ocak 2010 tarihleri arasında mide kanseri nedeniyle opere edilen 90 hasta çalışmaya alındı. Spesmen kesitlere immünohistokimyasal boyama uygulandı. İmmünohistokimyasal boyama sonuçları, tümöre bitişik normal gastrik mukoza ile beraber değerlendirildi. Normal dokuya göre tümör hücresinin NM23 ile boyanma derecesi: "negatif-zayıf boyanma" ve "kuvvetli boyanma" olmak üzere iki grup olarak değerlendirildi. Her iki grup, lenf nodu metastazı, vasküler invazyon, perinöral invazyon, tümör diferesiasyon derecesi, tümör evresi ve uzak metastaz için değerlendirildi.

Bulgular: Lenf nodu metastazı bulunan 58 hastanın %70,7'si negatif –zayıf boyanma gösterirken %29,3'ü kuvvetli boyanma özelliği gösterdi. Lenf nodu metastazı bulunmayan 32 hastanın ise %40,6'sı negatif-zayıf boyanma özelliğine, %59,4'ü kuvvetli boyanma özelliğine sahipti. NM23 ekspresyonundaki azalmanın, lenf nodu metastazındaki artışa neden olduğu gösterildi (P=0,01). Ayrıca istatistiksel anlamlılık bulunmamakla beraber, negatif-zayıf boyanma gösteren grupta, uzak metastaz, kötü diferesiasyon derecesi, evre III ve evre IV tümörlerin oranı belirgin olarak daha yüksekti. Bu bulgularda NM23'ün anti-metastatik özelliğini destekledi.

Sonuç: Bu çalışma NM23 ekspresyonunun, mide kanserli hastalarda, lenf nodu metastazı için anti-metastatik özelliğe sahip olduğunu gösterdi.

Anahtar kelimeler: Mide kanseri, İmmünohistokimyasal boyama, NM23

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Introduction

Gastric carcinoma is aggressive, and one of the most common gastrointestinal cancers [1]. Its incidence varies geographically, and its prevalence is not uniform. The frequency of gastric carcinoma is particularly higher in Japan and Colombia [2,3]. Despite increasing resectability rates and decreasing incidence in Western societies starting from the second half of the twentieth century, gastric carcinoma remains the second globa leading cause of the cancer-related deaths [4].

Metastasis is a critical factor in the prognosis of cancer patients and plays an important role in mortality. Studies have focused on this area to define novel therapeutic strategies. The discovery of a new class of genes, which are metastasis-suppressor genes, has attracted a lot of attention. The first identified metastasis suppressor gene is NM23 [5]. Murine NM23 cDNA was discovered using differential colony hybridization in murine K1735 melanoma cell lines. mRNA and protein levels of NM23 were studied in numerous model systems and its decreased expression was detected in highly metastatic samples [6]. In humans, NM23 gene family (also known as NME genes) comprises 10 genes. It is located at 17q21, and encodes nucleoside diphosphate kinase A. So far, it was clearly shown that NM23-H1 is a critical regulator of the signaling networks that play a role in local invasion and the adhesion of cancer cells in primary tumors [7]. However, the mechanism by which NM23 suppresses tumor metastasis is still not understood. Despite studies indicating that NM23 is anti-metastatic, there are other studies reporting contradictory results. A definitive conclusion is yet to be reached.

In the light of previous research, we thought that the NM23 gene expression can help with the prediction of metastatic diseases. If metastatic disease can be predicted through NM23, patients with a high risk of metastasis can undergo neoadjuvant chemotherapy to decrease recurrence and improve survival rates. For this purpose, the study aims to investigate the antimetastatic properties of NM23.

Materials and methods

This study was approved by the Ethics Committee of Erciyes University School of Medicine. This cohort consists of ninety patients (male 67, female 23) who were diagnosed with gastric carcinoma and operated at Department of General Surgery of Erciyes University School of Medicine between January 1, 2009 and January 1, 2010. The demographic data of patients, i.e. gender, age and tumor localization, tumor size, operation, surgical margin, TNM stage and differentiation, presence of local, vascular and perineural invasion, lymph node involvement, distant and local organ metastasis were recorded.

Patient selection

Based on the pathology, those who are positive for lymph node metastasis were included in the metastasis group, and those who are negative for lymph node metastasis were included in the non-metastatic group. Although paraffin samples obtained from distant metastatic sites such as the liver or lymph nodes were stained with NM23, immunohistochemical staining was performed on the gastric tumor to evaluate prognostic factor (lymph node metastasis, vascular invasion, perineural invasion, local invasion, degree of differentiation and distant metastasis).

Immunohistochemistry (IHC)

General IHC Protocols database was used for NM23 expression analysis in pathological samples. Samples were fixed with 10% formaline, prepared with routine processing, cut in 3 to 5-micron slices and embedded in paraffin. Endogen peroxidase activity was blocked with hydrogen peroxide to minimize non-specific staining and ground dyeing. The samples were washed for 10 minutes in phosphate buffered saline solution. As the primary antibody, NM23-H1 (1/50 dilution) (37.60) (sc-56928, lot#L2107 mouse IgG2a supernatant stored at -20^{o}C, 250 microliters Santa Cruz Biotechnology) was used. This antibody is similar to the NM23-H1 gene product and it increases when NM23-H1/NDP kinase A is present.

Streptavidin-biotin peroxidase method was used for immunohistochemical staining (SPlink HRP Detection Bulk Kit for Mouse and rabbit antibodies streptavidin-biotin kit). Results of immunohistochemical staining were evaluated together with the normal gastric mucosa adjacent to the tumor. Depending on the degree of staining of the tumor cell with NM23 compared to the normal tissue, immune staining was classified into two groups: “negative-weak staining” and “strong staining” (Figure 1).

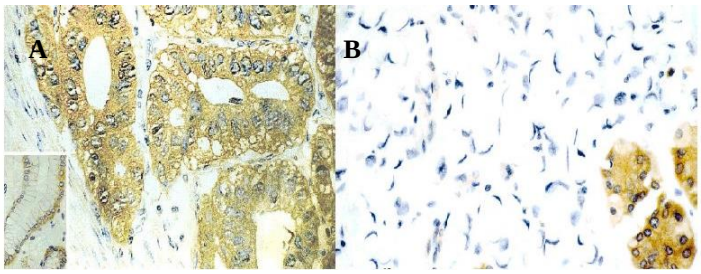

Figure 1: Immunohistochemical staining with NM23 (A: Normal gastric mucosa, strong cytoplasmic staining with NM23, B: Signet cell gastric cancer, Negative staining with NM23)

Statistical analysis

Statistical analyses were performed using SPSS version 15 software. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. In descriptive analyses, variables with normal and non-normal distribution were expressed as mean and median, respectively. To assess the prognostic significance and anti-metastatic properties of NM23 in gastric carcinomas, those with no NM23 staining (negative) and with focal or diffuse weak staining were included in the “negative-weak staining group” (Group 1), and those with focal or diffuse strong staining with NM23 were included in the “strong staining group” (Group 2). The statistical significance of differences between Groups 1 and 2 in terms of lymph node metastasis, vascular invasion, perineural invasion, degree of tumor differentiation, tumor stage and distant metastasis was determined by Chi-square or Fisher tests. A *P*-value less than 0.05 was considered statistically significant.

Results

Table 1 presents the demographic data of the patients. 67 patients are male and 23 are female. Male/female ratio was 2.88 and the median age of the patients was 63 (range, 32-83)

years. No statistically significant difference was found between the groups in terms of age and gender (Table 1).

Table 1: The distribution of general characteristics based on patient and tumor

	n	%
Gender		
Male	67	74.4
Female	23	25.6
Tumor location		
Antrum	63	70
corpus	13	14.5
Cardia	8	8.9
Linitis plastica	6	6.6
Tumor size (cm)		
0-5	29	32.2
5-10	46	51.1
>10	15	16.7
Operation		
Radical subtotal gastrectomy	26	28.9
Total radical gastrectomy	64	71.1

70.7% of 58 patients with lymph node metastasis showed negative-weak staining and 29.3% showed strong staining. 40.6% of 32 patients with no lymph node metastasis had negative-weak staining and 59.4% had strong staining. Group 1 had more lymph node metastasis than group 2 (P=0.01). No statistically significant difference was found between the two groups regarding vascular invasion (P=0.23), perineural invasion (P=0.36), degree of tumor differentiation (P=0.54), distant metastasis (P=0.39) and tumor stage (P=0.24) (Table 2).

Table 2: Evaluation of prognostic variables with NM23 according to staining intensity

		Negative-weak staining group (Group 1) n	Strong staining group (Group 2) n	*P*-value
Lymph node metastasis	Positive	41	17	0.01
	Negative	13	19	
Vascular invasion	Positive	35	18	0.23
	Negative	19	18	
Perineural invasion	Positive	26	13	0.36
	Negative	28	23	
Degree of tumor differentiation	Well-differentiated	12	11	0.54
	Moderately-differentiated	15	11	
	Poorly-differentiated	27	14	
Stage	I	11	12	
	II	9	9	
	III	9	3	0.24
	IV	25	12	
Distant metastasis	Positive	17	8	0.39
	Negative	36	29	

While there was no significant difference between degree of tumor differentiation and groups (P=0.54), NM23 staining in poorly differentiated tumors was observed to be 65.9% and 34.1% for Group 1 and Group 2, respectively. Rate of negative-weak staining was significantly higher in poorly differentiated tumors. These rates supported the anti-metastatic property of NM23. There was no statistically significant difference between Group 1 and Group 2 in terms of distant metastasis. However, our findings supported the anti-metastatic property of NM23. Negative-weak staining was observed in 68% of the patients with distant metastasis, and 32% of the patients showed strong staining. Likewise, negative-weak staining was at 64.6%, and strong staining was at 32.4% in stage IV tumors. In stage III tumors, these ratios were 75% and 25%, respectively. These findings were deemed to be supporting the anti-metastatic property of NM23 expression (Table 2).

Discussion

Although there has been a decrease in mortality in the last 60 years, gastric carcinomas are still the most common cancers and the most common causes of mortality [8]. Metastasis is a critical factor in the prognosis of cancer patients [9]. The first identified metastasis suppressor gene is NM23. Decreased NM23 expression has been associated with potentially increased metastasis in various cancers, i.e. breast cancer, gastric cancer, melanoma [10-14]. In lung and pancreatic cancer, increased NM23 expression is associated with poor prognosis [15]. In the literature, NM23 is thought to play different roles in different tissues. Some studies show that NM23 expression in gastric carcinoma doesn't predict survival and liver or lymph node metastasis [16-18]. In this study, we found that the decrease in NM23 expression caused an increase in lymph node metastasis.

Lee et al. [19] have retrospectively analyzed 841 patients who underwent gastrectomy due to gastric carcinoma. Contrary to our results, it was shown that increased NM23 expression is correlated with poor prognosis. Consistent with the results of Lee et al. [19], Müller et al. [20] have reported that there is a positive correlation between increased NM23 expression and poor prognosis and lymphatic vessel invasion.

We observed that the decrease in NM23 expression led to increased lymph node metastasis. Consistent with our study, Kodera et al. [21] showed that decreased NM23 expression was associated with increased lymph node metastasis. They found no clinically significant correlation between decreased NM23 expression and distant metastasis.

In their study on NM23 expression, Liu et al. [22] have reported that decreased NM23 expression is associated with increased lymph node involvement. On this subject, Yu et al. [23] have noted that there is a correlation between decreased NM23 expression and increased distant metastasis. Our research results coincide with the study of Liu et al. [22]. We could not observe statistical significance with regards to distant metastasis. However, our findings support the argument of Yu et al. [23] that decreased NM23 expression in gastric cancers may lead to increased distant metastases.

No result concerning the anti-metastatic property of NM23 could be reached in some studies on NM23 in gastric cancer. Monig et al. [24], who investigated the correlation between NM23 and prognosis, could not detect any correlation between NM23 expression and distant metastasis, lymph node involvement or prognosis in gastric carcinomas. Similar results were obtained by Radovic et al. [4] who suggested that there was no significant correlation between clinicopathologic variables and NM23 expression. The study by Yang [25] also corroborated these results and concluded that there was no correlation between NM23 expression and metastases, also noting that NM23 can play a role in tumor pathogenesis.

Limitations

The number of patients and the fact that it was a single-center study proved to be the limitations of our study.

Conclusion

This study demonstrated that NM23 expression had anti-metastatic properties for lymph node metastasis. In addition, findings supporting the anti-metastatic property of NM23 expression were obtained in terms of distant metastasis, degree of tumor differentiation and tumor stage. Nevertheless, there are still conflicting findings regarding the anti-metastatic properties of NM23 gene expression. It is therefore thought that further research is needed.

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Association between platelet indices and missed abortion

Missed abortus ile platelet indekslerinin ilişkisi

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Abstract

Aim: The incidence of missed abortion is around 15% of clinically diagnosed pregnancies, and the etiology is uncertain. Limited studies in the literature report increased platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT). The number of cases in these studies is low and results are inconsistent. There is no study that investigates all platelet indices. This study has the largest series in the literature and investigates all platelet indices in missed abortion.

Methods: In this retrospective case-control study, the complete blood count parameters of patients who were diagnosed with missed abortion were examined. Among 500 cases, 228 women with missed abortion constituted the study group, and 272 healthy pregnant women constituted the control group. Women who were 18–45 years of age and 6–14 weeks of gestational age were included.

Results: In the missed abortion group, PDW value was higher (P=0.007), while platelet MPV and PCT values were lower (respectively P<0.001 and P=0.008) than the control group.

Conclusion: Platelet indices parameters in missed abortion are inconsistent.

Keywords: Missed abortion, Platelet indices, Mean platelet volume, Platelet distribution width

Öz

Amaç: Klinik olarak tanı almış gebeliklerin %15'i missed abortus ile sonuçlanmaktadır. Missed abortusun etyolojisi kesin olarak bilinmemektedir. Literatürde sınırlı sayıda çalışmada ortalama platelet hacmi (MPV), platelet dağılım genişliği (PDW), plateletrikt (PCT)'in missed abortusta arttığı bildirilmiştir. Çalışmalardaki olgu sayısı az ve sonuçları tutarsızdır. Literatürde, missed abortusta tüm platelet indekslerini değerlendiren bir çalışma bulunmamaktadır. Bu çalışma missed abortusta tüm platelet indekslerini değerlendiren literatürdeki en geniş seridir.

Yöntemler: Bu retrospektif olgu-kontrol çalışmasında, missed abortus tanısı alan hastaların tam kan sayımı parametreleri karşılaştırıldı. Çalışmada toplam 500 olgunun missed abortus tanısı alan 228'i çalışma grubu, 272 sağlıklı gebe olanı kontrol grubu belirlendi. Çalışmaya 18-45 yaş aralığında, 6-14 gebelik haftasındaki tekil gebeler dahil edildi.

Bulgular: Missed abortus grubunda PDW değeri kontrol grubuna göre yüksek bulunurken (P=0,007); MPV ve PCT değerleri düşük bulundu (sırasıyla P<0,001 ve P=0,008).

Sonuç: Missed abortusta platelet indeksi parametreleri tutarsızdır.

Anahtar kelimeler: Missed abortus, Platelet indeksleri, Ortalama platelet hacmi, Platelet dağılım genişliği

Introduction

The term "missed abortion" refers to a clinical abortion in which the products of conception are not spontaneously expelled from the uterus. The incidence of missed abortion is reported as around 15% of clinically diagnosed pregnancies [1].

Genetic, anatomic, endocrine factors and thrombophilia are responsible for the etiology of missed abortion. Several studies have demonstrated that thrombophilia may cause pregnancy loss and missed abortion [2-4]. The prevalence of thrombophilia in the etiology of missed abortion is not clearly understood.

In thrombophiles, the risk of thrombosis increases [5]. Some studies have shown that MPV was significantly increased in subjects with arterial thrombotic events, i.e. acute myocardial infarction (MI) [6]. Platelet Distribution Width (PDW) and plateletcrit (PCT) values were found high in MI patients [7].

In the literature, there are limited studies that investigate platelet indices such as MPV, PLT and PCT in missed abortion [8,9]. The number of cases in these studies is small and the results are inconsistent. Up to this day, there is no study which investigates all platelet indices regarding this subject. This study has the largest series and investigates all platelet indices in missed abortion.

Materials and methods

Bursa Yüksek Ihtisas Hospital ethics committee approval (2011-KAEK-25 2018/05-13) was obtained for this retrospective case-control study. The medical records of patients who underwent curettage with a diagnosis of missed abortion between January 2014 and January 2018 at Bursa Karacabey, Bursa Mustafakemalpaşa and Muş State Hospital, were reached. Among 500 cases, 228 women with missed abortion constituted the study group and 272 healthy pregnant women constituted the control group. The control group was selected among healthy pregnant women with no complicating conditions for pregnancy and no systemic illness that could affect a complete blood count. Missed abortion was defined as an absence of fetal heart tone that was detected between the 6^{th} and 20^{th} gestational weeks. Gestational age was determined according to the last menstrual period and was confirmed using ultrasonographic findings. If the last menstrual period date was unknown, gestational age estimation was based on ultrasonography. Age, gravida, parity, current age, currently living child, height and history of surgical operations and laboratory values, i.e. hemoglobin, hematocrit, platelet, mean corpuscular volume, mean platelet volume, platelet distribution width, and plateletcrit were recorded. Women who were 18–45 years of age and 6–14 weeks of gestational age were included. Exclusion criteria included conditions such as thyroid dysfunction, hematologic disease, history of thrombosis, SLE, multiple pregnancies, use of anticoagulants, smoking, and uterine anomalies. Blood samples were obtained from the antecubital vein. Ethylene diamine tetra acetic acid (K3EDTA) tubes were used and samples were examined within two hours at the latest. Missed abortion group blood samples were extracted immediately after diagnosis and complete blood count tests were performed with Cell-Dyn 3700 (Abbott, Abbott Park (USA)).

Statistical analysis

Continuous variables were expressed as either mean (standard deviation) or median values and categorical variables were expressed as n (%). Chi-square testing was used for comparing categorical variables between groups and independent T test was used for comparisons of continuous variables between groups. SPSS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0, Armonk, NY: IBM Corp.) was used for statistical analysis and a value of $P<0.05$ was considered statistically significant.

According to the power analysis based on platelet count, a sample size of 386 patients (193 per group) was required for 80% power and %5 conventional two-sided type 1 error.

A receiver operating characteristic curve was constructed to determine PLT, MPV and plateletcrit cut-off values for the diagnosis of the missed abortion.

Results

The mean age was higher in the missed abortion group ((29.44 (5.80) years vs. 27.20 (5.80) years)) ($P<0.001$). Mean gestational ages of the missed abortion and control groups were 60.79 (15.14) days and 62.94 (14.22) days, respectively. In terms of gestational age, gravida, parity and currently living child derivatives, the differences between the two groups were not statistically significant ($P=0.103$, $P=0.058$, $P=0.442$ and $P=0.089$, respectively). Previous abortion curettage was more frequent in the missed abortion group ($P<0.001$); the history of surgical operations was more frequent in the control group ($P=0.006$), and height and weight were similar between the two groups ($P=0.828$ and $P=0.684$, respectively) (Table 1).

In the missed abortion group, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), and platelet distribution width (PDW) were significantly higher ($P=0.005$, $P<0.001$, $P<0.001$ and $P=0.007$, respectively), whereas platelet count (PLT), mean platelet volume (MPV), plateletcrit (PCT) were significantly lower ($P=0.030$, $P<0.001$ and $P=0.008$, respectively) (Table 2).

Table 1: Comparison of groups regarding demographic data

	Missed abortion (n=228)	Control (n=272)	*P*-value
Age (year)	29.44 (5.80)	27.20 (5.80)	<0.001
GA (day)	60.79 (15.14)	62.94 (14.22)	0.103
Height (cm)	162.19 (6.05)	162.07 (6.18)	0.828
Weight (kg)	66.82 (11.82)	67.22 (10.10)	0.684

GA: Gestational age

Table 2: Comparison of groups regarding laboratory values

	Missed abortion (n=228)	Control (n=272)	Reference values	*P*-value
Hemoglobin (g/dL)	12.84 (0.97)	12.58 (1.06)	11-16	0.005
Hematocrite (%)	39.12 (2.50)	37.97 (2.81)	37-54	<0.001
Platelet (/mcL)	255956 (69735)	268875 (62548)	150000-400000	0.030
MCV (fl)	83.65 (6.55)	79.95 (6.16)	80-100	<0.001
MPV (fl)	9.01 (1.49)	9.46 (1.22)	6.5-12	<0.001
PCT (%)	0.237 (0.082)	0.255 (0061)	0.11-0.28	0.008
PDW (%)	17.77 (1.72)	17.36 (1.63)	9-17	0.007

MCV: Mean corpuscular volume, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width

Independent variables included in multiple logistic regression analysis are adjusted according to age. Hemoglobin values between the two groups remained different when the age factor was kept constant.

Receiver operating characteristic analysis was performed to determine the diagnostic PLT, MPV and plateletcrit values for missed abortion.

PLT <252.000 predicted miscarriage with 58% sensitivity and 54% specificity. The sensitivity and specificity of MPV <9.05 in predicting miscarriage was 61% and 48%. The same values for PCT <0.205 were 77.2% and 55.3% (Figure 1).

The platelet index (PCT, PDW, MPV) values remained different between the two groups when the age factor was corrected. When the platelet index data were compared with respect to abortion numbers in the missed abortion group, no significant difference was observed in MPV and PCT values. For every increasing number of abortions, PDW value decreased significantly by 0.693 units ([OR] -0,693, 95% CI -1,067- (-0,319)).

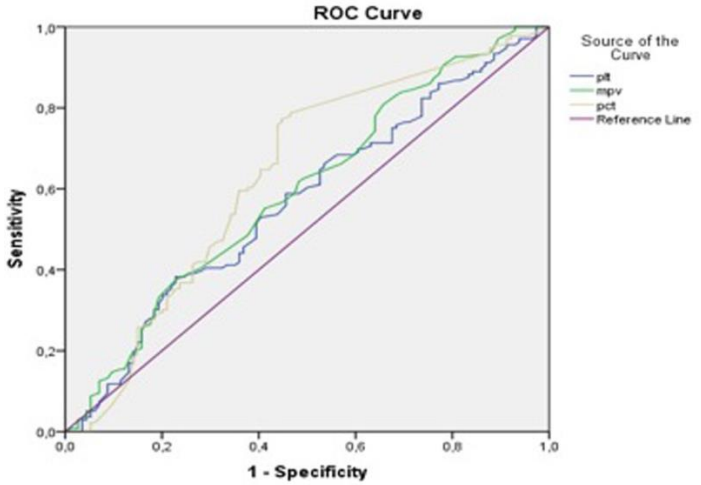

Figure 1: Receiver operating characteristic analysis performed to determine diagnostic mean platelet volume, platelet and plateletcrit values for missed abortion. PLT: platelet count, MPV: mean platelet volume, PCT: plateletcrit, ROC: receiver operating characteristic

Discussion

The etiology of missed abortion has been reported as maternal disease. Thrombophilia, which may be a maternal disease, increases susceptibility to clotting [10]. It is currently investigated whether a hypercoagulable state due to thrombophilia may predispose to immunological rejection or placental damage [11]. In a previous study, hysteroscopic biopsies obtained from the endometria of missed abortion patients were found to have increased thrombosis in the small endometrial vessels [12].

Platelets are primarily responsible for clotting, and their role has been of interest in thrombophiles and vascular pathologies. Platelet volume indices including MPV, PDW, PCT and platelet count are indicators of platelet activity, and these are routinely reported in automated full blood counts [13]. PDW represents the range of variability in platelet size, and it has been suggested that a large PDW may be an indicator of prothrombotic status. PCT, the product of MPV and platelet count, projects the number of platelets in a unit of blood volume and is a marker of total platelet mass [14].

The platelet parameters were investigated in various studies in cases of missed abortion. Kosus et al. [8] compared MPV and PLT values between 100 missed abortion cases and 100 normal pregnant women. MPV values were similar in missed abortion and control groups. Eroglu et al. [9] examined MPV and PDW values of 54 threatened, 46 missed abortion patients and 40 control subjects, both of which were found similar among all three groups.

In various studies on the loss of pregnancy, MPV was found to be higher than [15], lower than [16] or similar with the control group [17]. MPV, PCT, and PDW were significantly higher in studies that investigated platelet parameters in cases with recurrent pregnancy loss [18-21].

Past obstetrical history is an important predictor of subsequent pregnancy outcome. The risk of miscarriage in future pregnancies is approximately 20% after one miscarriage, 28% after two consecutive miscarriages, and 43% after three or more consecutive miscarriages [22]. In accordance with the literature, we found that the number of previous abortions in the missed abortion group was higher than the control group.

In our study, MPV value was lower in the missed abortion group. The results were different from studies which compared a control group with missed abortion patients. Unlike other studies, PDW value was higher in our missed abortion group. Although it has been suggested that microvascular pathology may be responsible for missed abortion, low MPV and high PDW drove us away from this hypothesis. We also found that Hb and Hct values were higher in the missed abortion group. An important part of the missed abortion patients consists of those with vaginal bleeding complaints, whose blood samples were taken upon hospital admission. It is our opinion that higher Hb and Hct values in the missed abortion group may be due to the relative hemoconcentration that occurs during the early stage of bleeding.

Limitations

Evaluation of the diagnostic accuracy of platelet indices in missed abortion would have been more accurate had we obtained the values before the incident and investigated changes in a sequential timeframe.

Conclusion

Our study is the largest series investigating platelet indices in patients with missed abortion. Although PDW value of the missed abortion group was higher than the control group, PLT, MPV and PCT were lower. The platelet indices parameters in missed abortion are inconsistent.

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Ultrasonographically marked catheterization of internal jugular vein in intensive care patients: Retrospective cohort study

Yoğun bakım hastalarında ultrasonografi kılavuzluğunda internal juguler venin kateterizasyonu: Retrospektif kohort çalışma

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Abstract

Aim: This study was designed to compare the method of internal jugular vein (IJV) catheterization with prior ultrasonographic (USG) skin marking with the conventional method regarding the performance of a less experienced practitioner in learning ultrasonographic manipulation and safely performing the cannulation.

Methods: The records of patients admitted to the Intensive Care Unit of Ataturk Chest Diseases and Chest Surgery Research and Training Hospital between April and September 2018 were retrospectively examined. 14 female and 26 male patients (n=40) whose IJV cannulations had been performed with the two above-mentioned methods were included in the study. The practitioner was theoretically trained by an experienced radiologist before the cannulation.

Results: The success rate was 65% in the conventional group and 95% in the USG skin-marked group; the difference was statistically significant (P=0.019). The mean time from the first entry of the needle to the skin to the placement of the catheter in successful cannulations in conventional and USG-marked methods were 110.6 (25.6) and 121.6 (28.3) seconds, respectively. There was no statistically significant difference (P=0.22).

Conclusion: This study shows that educating the inexperienced practitioner about the use of USG in IJV cannulation and successful application of skin marking method is important.

Keywords: Ultrasound, Internal jugular vein cannulation, Intensive care

Öz

Amaç: Bu çalışma, ultrason (USG) manipülasyonu öğrenen ve güvenli bir şekilde internal juguler ven (IJV) kanülasyonu yapan daha az deneyimli bir uygulayıcının performansı bakımından IJV'in işlem öncesi USG ile işaretlenmesi ile konvansiyonel yöntemin karşılaştırılması amacıyla düzenlendi.

Yöntemler: Çalışma, retrospektif olarak Atatürk Göğüs Hastalıkları ve Göğüs Cerrahisi Eğitim ve Araştırma Hastanesi Yoğun Bakım Ünitesinde Nisan ve Eylül 2018 tarihleri arasındaki kayıtların çalışılması ile yapıldı. Uygulayıcıya deneyimli bir radyolog tarafından teorik eğitim verildi. Toplamda 40 hastanın (14 kadın ve 26 erkek) IJV kanülasyonu iki farklı yöntemle gerçekleştirildi.

Bulgular: Konvansiyonel grupta başarı oranı %65 ve USG cilt-işaretli grupta %95 olup, fark istatistiksel olarak anlamlıydı (P=0.019). İğnenin cilde ilk giriş anından kateterin yerleştirilmesine kadar geçen ortalam süre sırasıyla 110.6 (25.6) ve 121.6 (28.3) saniye idi. İki grup arasında istatistiksel olarak anlamlı bir fark yoktu (P=0.22).

Sonuç: Bu çalışma, deneyimsiz bir uygulayıcıya IJV kanülasyonunda USG ve cilt işaretleme metodunun kullanımı konusunda eğitim vermenin önemli olduğunu göstermiştir.

Anahtar kelimeler: Ultrason, İnternal juguler ven kanülasyonu, Yoğun bakım

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Introduction

Internal Jugular Vein (IJV) cannulation, a central venous catheterization (CVC) method, is frequently preferred for hemodynamic monitoring, long-term fluid and antibiotic therapy, total parenteral nutrition and hemodialysis in intensive care unit (ICU) patients [1]. The puncture of IJV using anatomical landmarks has been described in many articles since 1966 [2-5]. Recently, IJV cannulation with ultrasonographic (USG) guidance has become a widely used method in ICUs and studies have reported that it is significantly superior to traditional anatomical marking techniques [1].

The steps of the conventional method in internal jugular vein catheterization are as follows: 1) Extend the patient's neck 2) Palpate the carotid artery and mark a triangle with clavicle and sternal leg of the sternocleoidomastoid muscle 3) Puncture the skin with the needle at a 30-40^o angle to the apex of this triangle while palpating the carotid artery with the free hand 4) Insert the needle in this direction. Nowadays, we use USG in ICUs for real time demonstration of CVC, but this method may cause a waste of time during emergencies. The risk of complications related to practitioner experience is an important concern.

In this study, we compared the method of internal jugular vein (IJV) catheterization with prior USG skin marking with the conventional method regarding the performance of a less experienced practitioner in learning USG manipulation and safely performing the cannulation.

Materials and methods

Ethics Committee and Study Protocol Approval (05/12/2018, App. No: 612) were obtained from Ankara Ataturk Chest Diseases and Chest Surgery Research and Training Hospital Ethics Committee and Medical Specialization Training Board. In this case-control study, the records of patients admitted to the Intensive Care Unit of Anesthesiology and Reanimation Clinic in Ataturk Chest Diseases and Chest Surgery Research and Training Hospital between April and September 2018 were retrospectively examined. The practitioner, a single physician lacking enough experience, who had previously performed IJV cannulation, was a pulmonology specialist within his first year in the ICU minor certification program as an intensive care resident with no previous experience of USG. The practitioner was given theoretical training on CVC and USG before the procedure. In addition, at least 8 hours of USG training practice of the vascular anatomy of the neck was held by an experienced radiologist. A total of 40 patients whose IJV cannulations had been performed with two different methods were randomly selected, divided into two groups of 20 patients and retrospectively studied. Only one method was used for each patient. Catheterization procedures were all carried out under the supervision of an experienced practitioner. In case of failure of IJV catheterization after three attempts or complication occurrence during catheterization, the supervising practitioner carried on with the procedure. Patients who were evaluated by the same practitioner were included in the study and randomized. Informed consent forms signed by the patients or their relatives if they were unable to give consent were obtained. Patients' necks were rotated 30^o to the contralateral side of the cannulation in Trendelenburg position before the procedure and this position was held throughout the catheterization process.

The conventional method involved IJV cannulation by using anatomical landmarks, without the help of USG marking. Sedation and analgesia were used while adhering to proper sterilization conditions. The common carotid artery pulse was palpated and skin above the common carotid artery was slightly retracted medially to make lateral puncturing possible.

In the USG-assisted method, the anatomical relationship between IJV and common carotid artery was evaluated; the distance to skin and variations were recorded with the USG device (SL1543 model 13-4 MHz linear probe Esaote® MyLab ™ Six). Using the edges of a linear probe, the puncture points and direction in the short (Figure 1) and long axes (Figure 2) of IJV were determined and marked with a wipe-resistant surgical marker pen (Figure 3). Then, IJV was cannulated in accordance with proper sterilization conditions considering this pen-mark only. Sedation and analgesic agents were used. Following both blind and USG-marked catheterizations, the cannula locations of patients were evaluated with USG (Figure 4).

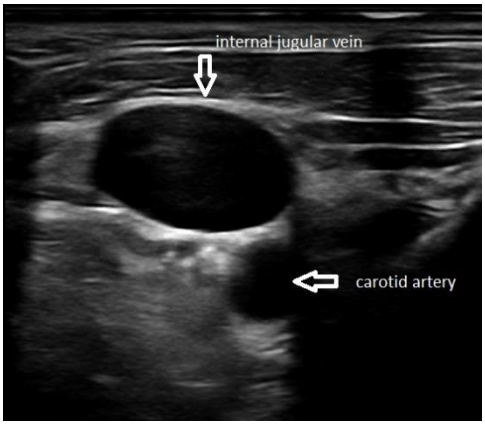

Figure 1: The puncture point in the short axis image of the IJV with USG

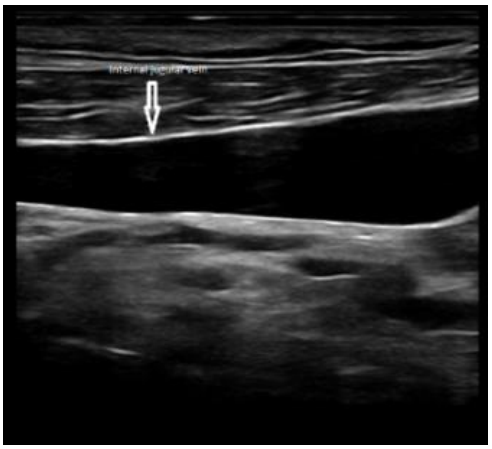

Figure 2: The long axis image of the IJV with USG

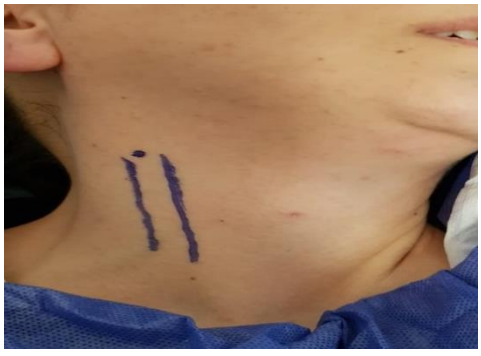

Figure 3: The puncture direction was marked with a surgical pen

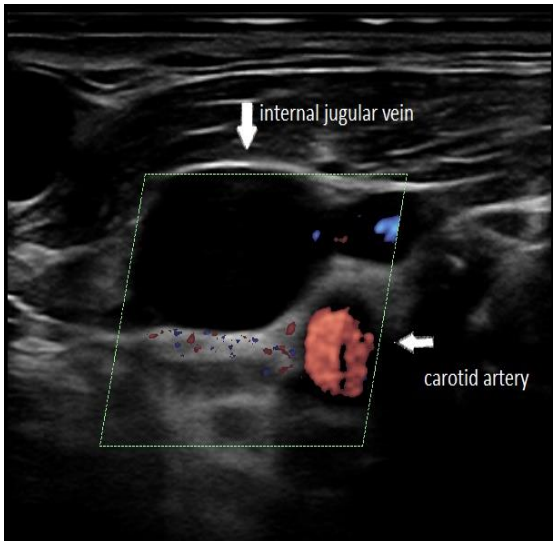

Figure 4: The cannula location of patient was evaluated with USG

TUORen® Central Venous Catheter Set and 18 G Y type introducer needle were used for puncturing. Also found within the set were a 0.035-inch in diameter and 60 cm long Nickel Titanium guide and a 7F 3-lumen catheter, which were used during catheterization. Age, gender, body mass index, international normalized ratio (INR) and platelet counts of the patients, the success and complications of the procedures, anatomical localization of IJV, the distance of the IJV to the skin, the time from insertion of the needle into the skin to the catheter placement and the number of punctures were recorded. Patients with INR >1.5 and/or platelet count <50.000/mm³, patients who did not accept the procedure or refused to sign the CVC consent form, those with skin diseases, anatomical defects, abscesses or active infections in the neck were excluded from the study.

Statistical analysis

Power analysis was based on the success rate differences of the groups in similar studies in the literature and a minimum sample size of 20 patients per group was calculated for 80% power and 0.05 type-I error. The confidence interval of this analysis was 34%. The data regarding the success rates between the two groups in this study were compared with Student T-test using SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) for Windows. Regression analysis was performed to determine whether body mass index and IJV depth were correlated. A *P*-value less than 0.05 was considered statistically significant.

Results

A total of 40 patients, 14 females and 26 males, were included in this study. Gender distribution was equal among groups. The mean ages of the group who underwent USG-assisted skin marking and the conventional group were 71.8 (9.4) and 71.3 (8.2) years, respectively. 39 of the patients' right IJVs were cannulated while 1 patient, who underwent left pneumonectomy had their left IJV catheterized.

IJVs of 80% of the patients in this study were located anterolateral to the common carotid artery, in accordance with the literature. 20% of the patients' IJVs lied anterior to the common carotid artery.

The average distance of IJV to skin in male and female patients in the USG-marked group were 7.3 (2.7) mm and 7 (3.2) mm, respectively. This difference was not statistically significant (P=0.48). The successful IJV catheterization rate of the USG-marked group was significantly higher (95%) than the conventional group (65%) (P=0.019).

The mean time from the first entry of the needle to the skin to the placement of the catheter in successful cannulations in conventional and USG-marked groups were 110.6 (25.6) and 121.6 (28.3) seconds, respectively. There was no statistically significant difference (P=0.22).

Simple linear regression analysis showed that increased BMI was significantly correlated with deeper-probed IJV (P=0.034). In both methods, minimal hematoma was seen with complication rates close to 15%. No further complications occurred.

Discussion

In this study, we compared the success rates of USG-assisted skin marked IJV catheterization method with the conventional technique as performed by an inexperienced practitioner. In a similar study involving newborns, USG-assisted skin-marking method had similar success and complication rates, which suggested that this method was applicable in the adult patient group [6]. IJVs of 80% of the patients in this study were located anterolateral to the common carotid artery, in accordance with an anatomic variance study. [7]. In addition, the distances from the IJV to the skin were similar in females and males.

Conventional IJV cannulation is known to be more difficult due to the narrowness of the area, more difficult palpation of carotid pulse and vagueness of anatomic landmarks in the neck in patients with increased BMI. Although a study has detected no significant difference between obese and non-obese patients in terms of IJV cannulation success, the puncture rates of common carotid artery were reported higher in obese patients and USG use for IJV cannulation was recommended [8]. In our study, we found that the distance of IJV to the skin increased with BMI. Therefore, when IJV cannulation is planned in obese patients, we recommend using prior or concurrent USG for the procedure.

In our study, the success of IJV cannulation was significantly higher in the USG-marked group as compared to the conventional one. There was no significant difference between the two groups in terms of procedure times. However, since the duration of the procedure includes the time between the needle contact with the skin and the placement of the cannula, we can foresee that the procedure will take longer in the USG-marked group if the pre-procedural USG imaging and marking time is added. Therefore, we believe that USG marking method is not suitable for patients requiring urgent central vascular access. In a study performed by Hideaki and Amano [9], IJV was localized prior to catheterization using the USG-skin marking method in one group and jugular venodilation method in the other. They reported that USG imaging had no contribution to cannulation success, but it was helpful when IJV could not be localized by venous jugular venodilation. Regardless of the level of experience, considering the anatomical variations of the IJV, USG use may become mandatory in IJV catheterization of some patients.

Limitations

This study was designed retrospectively, and all data of the patients could not be obtained. The cannulation was performed by a single practitioner; who eliminated factors depending on the practitioner. Comparing the success rate of one practitioner with different methods may prohibit comparison of different experiences. In our opinion, further research comparing cannulation methods among different practitioners with similar experiences would be beneficial.

Conclusion

In the literature, many studies can be found on IJV cannulation. However, we believe that this study regarding the use of USG in IJV cannulation and the successful application of the skin marking method by an inexperienced user is different and educational. Along with other studies, we believe that the comparison of concurrent USG cannulation of IJV with the conventional and USG-skin-marking methods by intensive care residents with limited experience will contribute to shaping central venous cannulation training.

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Evaluation of ischemia modified albumin levels in major depression patients

Major depresyon hastalarında iskemi modifiye albumin seviyelerinin değerlendirilmesi

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Abstract

Aim: Depression is an important public health problem, which has been associated with an antioxidant defense system. Ischemia-modified albumin (IMA) is a new biomarker that measures ischemia. The aim of this study was to evaluate IMA levels as a new parameter related to oxidative stress in patients with major depressive disorder (MDD).

Methods: This cross-sectional case-control study included 59 patients aged between 18-65 years who were admitted to our psychiatry outpatient clinic between June 2018 and December 2018, diagnosed with MDD and had not used psychotropic drugs for 3 months. In addition, 59 age and sex matched healthy controls were included in the study. Serum IMA and albumin levels were measured in blood samples taken from each patient and from control groups. Hamilton Depression Rating Scale (HDRS) was applied to the subjects to evaluate the depression level.

Results: Among the MDD group, 27 patients (45.8%) were male and 32 (54.2%) were female. The number of males and females in the control group were 29 (49%) and 30 (51%). Mean ages of the patients in MDD and control groups were 39.40 (12.20) and 38.67 (9.29) years, respectively. No statistically significant difference was found between the groups in terms of age and gender (P=0.942 and P=0.714, respectively). The mean IMA level of MDD and control group patients were 0.84 (0.39) and 0.82 (0.30), respectively; the difference was statistically significant (P<0.001). There was also a statistically significant difference between the albumin levels of the two groups (P=0.01). Correlation analysis showed a positive correlation between serum IMA levels and HDRS scores (r=0.235, P=0.008).

Conclusion: In our study, IMA levels of MDD patients were significantly higher than that of the control group. This result may be an indicator of increased oxidative stress in patients with depression. There is little data in the literature evaluating IMA levels in psychiatric disorders.

Keywords: Ischemia modified albumin, Major depressive disorder, Mood disorders, Oxidative stress, Biomarker

Öz

Amaç: Depresyon, önemli bir halk sağlığı sorunudur. Depresyonun antioksidan savunma sistemi ile ilişkisi olduğu bildirilmiştir. İskemi modifiye albümin (IMA), iskemi varlığını değerlendiren yeni bir biyobelirteçtir. Bu çalışmada Major depresif bozukluğu (MDB) olan hastalarda oksidatif stres ile ilgili yeni bir parametre olan IMA düzeylerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Bu kesitsel vaka-kontrol çalışmasına Haziran 2018 ve Aralık 2018 tarihleri arasında psikiyatri polikliniğimize başvuran 18-65 yaş arasında, MDB tanısı almış, psikotrop ilaç kullanmayan toplam 59 hasta ve 59 sağlıklı kontrol dahil edildi. Hasta ve kontrol grubundan alınan kan örneklerinde serum İMA ve albumin düzeyleri değerlendirildi. Depresyon seviyesini değerlendirmek için deneklere Hamilton Depresyon Derecelendirme Ölçeği (HDRS) uygulandı.

Bulgular: Depresyonlu hastaların 27'si (% 45,8) erkek, 32'si (% 54,2) kadın, kontrol grubunun 29'u (%49) erkek, 30'u (%51) kadındı. MDD grubunun yaş ortalaması 39,40 (12,20) yıl, kontrol grubununki 38,67 (9,29) yıldı. Hasta grubu ile kontrol grubu arasında yaş ve cinsiyet açısından istatistiksel olarak anlamlı fark bulunmadı (sırasıyla P=0,942 ve P=0,714). MDD ve control gruplarının ortalama İMA düzeyleri sırasıyla 0,84 (0,39) ve 0,82 (0,30) olup, aradaki fark istatistiksel olarak anlamlıydı (P<0,001). Ek olarak, iki grubun ortalama albümin seviyeleri arasındaki fark da istatistiksel olarak anlamlı bulundu (P=0,01). Korelasyon analizinde serum IMA düzeyleri ile HDRS skorları arasında pozitif korelasyon tespit edildi (r=0,235, P=0,008).

Sonuç: Çalışmamızda depresyon hastalarının İMA değerlerinin sağlıklı kontrollerden istatistiksel olarak anlamlı biçimde yüksek olduğu tespit edildi. Bu sonuç, depresyonu olan hastalarda artmış oksidatif stresin bir göstergesi olabilir. Literatürde psikiyatrik hastalıklarda İMA düzeylerini değerlendiren nadir veri bulunmaktadır.

Anahtar kelimeler: İskemi modifiye albümin, Major depresif bozukluk, Duygu durum bozuklukları, Oksidatif stres, Biyobelirteç

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Introduction

Major depressive disorder (MDD) is a pervasive and heterogeneous disorder described by anhedonia, depressed mood and altered intellectual capacity. The lifetime prevalence of MDD is 17% of the populace and results in gigantic auxiliary expenses to society [1]. Diagnosis and treatment of MDD depends on generally abstract evaluations of different manifestations speaking to numerous endophenotypes. To date, the natural bases for the heterogeneity of MDD remain ineffectively characterized. Toward this objective, distinguishing proof of natural markers could enhance the determination and arrangement of MDD subtypes in order to stratify patients into additional homogeneous, clinically unmistakable subpopulations. Despite years of research, a non-intrusive, quantitative clinical test to help in the determination and treatment of MDD remains elusive [2].

Considering late investigations of MDD, expectation toward enlightening diagnosis and treatment was increased. While no certain single biomarker was found, there is mounting proof of different dysregulated contributing elements, such as growth factors and additionally proinflammatory cytokines. In mood disorders, there is well studied evidence for altered endocrine factors (e.g., hypothalamic–pituitary–adrenal (HPA), thyroid, sex steroids) and metabolic dysregulation (e.g., insulin resistance). As an alternative to the single biomarker approach, developing biomarker panels to include various biological abnormalities, defining profile of different kind of serum growth factors, cytokines, hormones and metabolic markers may contribute to the heterogeneity of MDD, as well as treatment response. To define subgroups, severity and response, more patient samples are needed. Moreover, analytical devices for evaluating biomarkers are now available [3,4].

Systemic markers of oxidative stress include ischemia-modified albumin (IMA) and prolidase. Albumin is a protein of 585 amino acids. Bonding heavy transition metals (nickel, cobalt), the final amino acid terminal in the structure of albumin has the capacity to cause free radical damage and deterioration of the cell membrane integrity. It reduces the binding of metals to the N-terminal of albumin and this damaged new formed albumin is called IMA [5,6]. IMA has recently been proposed as a marker for oxidative stress. In addition, recent studies have emphasized that it increases the inflammation process [7-9]. On the other hand, it is also argued that oxidative damage caused by iron increases ischemia-modified albumin and in this context ischemia-modified albumin may appear as a new marker in determining oxidative damage caused by iron [10].

As far as we know, a study evaluating IMA levels in drug-free depression patients has not been found in the literature. The aim of this study was to evaluate IMA levels as a new parameter related to oxidative stress in patients with major depressive disorder.

Materials and methods

This case-control study included 59 patients aged between 18-65 years who were admitted to our psychiatry outpatient clinic between June 2018-December 2018, diagnosed with MDD and had not been using psychotropic drugs for 3 months. In addition, 59 age and sex matched healthy controls were included in the study. All participants were evaluated by 2 psychiatrists to confirm the appropriate diagnosis using the DSM-V (Diagnostic and Statistical Manual of Mental Disorders). Subjects with comorbid psychiatric or systemic disease, history of chronic drug use due to any disease, acute infection, iron deficiency anemia, bone marrow disease, smoking, morbid obesity, alcohol and substance use, pregnancy or breastfeeding were not included in the study. Serum IMA and albumin levels were measured in blood samples taken from the MDD and control groups. Biochemical tubes without preservatives were filled with 9 ml of blood and centrifuged at 2500 g for 10 minutes in half an hour. Serum IMA was measured spectrophotometrically in accordance with the method described by Bar-Or et al [11]. Yozgat Bozok University Clinic Research Ethics Committee approved the study (2017-KAEK - 189_2017.12.21_11) and it was performed under the ethical principles of the Declaration of Helsinki for medical research involving human subjects.

Assessment Tools

1. Data Collection Form

It is a form prepared by the researchers that includes the participants' age, gender, educational background, disease and remission period, medications, smoking, height and weight.

2. Hamilton Depression Rating Scale (HDRS)

The original version of the scale was conceived by Hamilton in 1960. Later, Williams advanced a recent version of the HDRS to improve the inter-rater reliability (Structured Interview for Hamilton Depression Rating Scale-21) [12]. It measures the level of depression and severity change in the patient. The scale is scored between 0-4 with 17 items and the highest score is 53. Depression severity is graded according to HDRS levels: low to 8-13, moderate to 14-18, severe to 19 and above. The validity and reliability study of the scale was conducted in our country [13].

Statistical analysis

Statistical analysis was performed using SPSS 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) software. The descriptive statistics of the data were calculated, and Kolmogorov Smirnov tests were applied for testing the normality distribution. Mann-Whitney U test was used for data comparison not showing a normal distribution. The Pearson's correlation test was used for the normally distributed data and the Spearman's correlation test was used for data not showing a normal distribution. A *P*-value of less than 0.05 was considered statistically significant.

Results

Among the MDD group, 27 patients (45.8%) were male and 32 (54.2%) were female. The number of males and females in the control group were 29 (49%) and 30 (51%). Mean ages of the patients in MDD and control groups were 39.40 (12.20) and 38.67 (9.29) years, respectively. No statistically significant difference was found between the groups in terms of age and gender (P=0.942 and P=0.714, respectively) (Table 1). The mean IMA level of MDD and control group patients were 0.84 (0.39) and 0.82 (0.30), respectively; the difference was statistically significant (P<0.001). Mean albumin levels in MDD

and control groups were 4.16 (0.36) and 4.03 (0.32), which was statistically significantly different (P=0.01) (Table 2). There was no statistically significant difference between male and female genders in terms of serum IMA levels in both patient and control groups (P=0.294 and P=0.117, respectively).

Correlation analysis showed a positive correlation between serum IMA levels and HDRS scores (r=0.235, P=0.008).

Table 1: Sociodemographic characteristics in patient and control groups

	Patient n=59	Control n=59	*P*-value Z value
Age Mean (SD)	39.40 (12.20) (min=18,max=65, median=45)	38.67 (9.29) (min=23,max=60, median=35)	0.942 -0.073
Gender n (%)	27 (45%) male 32 (55%) female	29 (49%) male 30 (51%) female	0.714 -0.367
BMI Mean (SD)	23.1 (1.84)	22.92 (1.57)	0.949 -0.064

BMI: Body Mass Index, Z: Mann-Whitney U test, SD: Standard deviation

Table 2: Distribution of HDRS, serum IMA and albumin levels in patient and control groups

	Patient n=59	Control n=59	*P*-value Z value
HDRS Mean (SD)	28.76 (8.29) (min=14, max=46, median=30)	2.58 (1.55) (min=0, max=6, median=2)	<0.001 -9.392
IMA Mean (SD)	0.84 (0.39) (min=0.66, max=0.92, median=0.84)	0.82 (0.30) (min=0.73, max=0.90, median=0.82)	<0.001 -3.33
Albumin Mean (SD)	4.16 (0.36) (Min=2.28, max=4.82, median=4.19)	4.03 (0.32) (Min=2.99, max=4.85, median=4.06)	0.01 -2.570

IMA: Ischemia Modified Albumin, HDRS: Hamilton Depression Rating Scale, Z:Mann- Whitney U test, SD: Standard deviation

Discussion

In our study, IMA levels of MDD patients were significantly higher than that of the control group. There was also a positive correlation between the severity of depression and IMA levels. Recent studies have shown that depression is associated with oxidative stress [14]. Although the mechanisms by which oxidative stress may be associated with depressive symptoms have not yet been fully elucidated, it has been noted that the brain is vulnerable to oxidative damage due to its relatively weak antioxidant defenses against the development of oxidative cellular injury and necrosis caused by free radicals resulting from the use of high oxygen [15]. Studies have shown that proinflammatory cytokine levels in the blood of depressed individuals are also increased [16]. In meta-analyzes, inflammation related markers such as Interleukin-6, tumor necrosis factor-alpha (TNF-α) and C-reactive protein (CRP) were reported to increase in depression patients [17,18].

For typical psychiatric diagnoses such as severe depression or schizophrenia, the probability of any biomarker achieving a sufficiently high degree of sensitivity and specificity is relatively low [2]. Utilization of different biomarkers may resolve this problem. Albeit singular biomarkers may give some more noteworthy dimension of genuine versus false positive and negatives, the prescient capacities may enhance when a few diverse biomarkers are collected into a gathering, or biopanel, of indicator attributes. Furthermore, the evaluation of a panel of markers could potentially contribute to the subdivision of a heterogeneous disease in a clinical interview with a similar phenotype. To define MDD phenotype, biomarkers can be gathered in subgroups which may be closely related to specific etiological pathways. This kind of grouping is going to show more certainly defined etiological reason of MDD subgroup. This could prompt progressively compelling, etiologically based treatments for subgroups of patients [19-21].

IMA has recently been proposed as a marker for oxidative stress and has been reported to increase the inflammation process. On the other hand, it is argued that oxidative damage caused by iron increase enhances IMA. In this context, IMA may be a new marker in determining iron induced oxidative injury. In our study, higher IMA levels were determined in depression patients than in healthy controls. There was also a positive correlation between the severity of depression and IMA levels. This result may be an indicator of increased oxidative stress in patients with depression.

In a study, no significant difference was found in serum IMA levels in bipolar disorder patients during the remission period when compared with the control group [22]. However, another study showed increased IMA levels in bipolar disorder patients during the remission period as compared to the control group, but no significant difference was found in unipolar depression patients [23]. Data from a limited number of studies evaluating IMA levels in psychiatric disorders differ. In our study, patients with moderate depression during the drug-free period were included in the study and patients who had conditions affecting oxidative parameters such as smoking and alcohol use, chronic disease and obesity were not included.

Limitations

Limitations of our study include being cross-sectional study and evaluation of a single oxidative parameter. Although attempts to reduce the factors that affect the oxidative system were made, some factors such as diet, exercise and sleep could not be standardized.

Conclusion

IMA levels, an important indicator of oxidative stress, were increased in patients with depression. This increase is correlated with the severity of depression. However more consistent data are needed to understand the role of IMA levels and oxidative stress in psychiatric disorders for evaluation as a biomarker. Therefore, a larger sample, treatment and follow-up studies in different patient groups will contribute to the literature.

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Mean platelet volume and platelet distribution width levels in discoid lupus erythematosus patients: A case-control study

Diskoid lupus eritematozus hastalarında ortalama trombosit hacmi ve trombosit dağılım genişliği seviyeleri: Bir olgu-kontrol çalışması

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Abstract

Aim: Platelets (PLT) play an important role in inflammatory reactions and immune responses. This study aims to evaluate PLT and PLT parameters in patients with discoid lupus erythematosus (DLE), which is characterized by inflammation.

Methods: In this case-control study, a total of 125 participants, consisting of 60 DLE patients and 65 healthy controls, were selected to participate. PLT, platelet distribution width (PDW), mean platelet volume (MPV), plateletcrit (PCT), the ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR) were studied retrospectively in both groups.

Results: The mean age of the patient group was 47.30 (15.14) years, and the mean age of the control group was 38.08 (13.33) years. There were no statistically significant differences between the PLT, PDW, MPV, PCT, NLR and PLR levels in DLE patients and healthy controls (P=0.365, P=0.988, P=0.160, P=0.851, P=0.898 and P=0.887, respectively).

Conclusion: To the best of our knowledge, there are no reports on PLT, PDW, PCT, NLR, PLR and MPV in patients with DLE. We did not find a significant difference in the DLE group. PLT parameters are low-cost tests that can be used to define inflammation levels in inflammatory diseases. Further prospective studies on this subject will contribute to this work.

Keywords: Platelets, Mean platelet volume, Platelet distribution width, Discoid lupus erythematosus, Inflammation

Öz

Amaç: Trombositler (PLT) inflamatuar reaksiyonlarda ve immün yanıtlarda önemli bir rol oynar. Bu çalışma, inflamasyonla karakterize diskoid lupus eritematozus (DLE) hastalarında PLT ve PLT parametrelerini değerlendirmeyi amaçlamaktadır.

Yöntemler: Bu vaka kontrol çalışmasında, 60 DLE hastası ve 65 sağlıklı kontrol grubu olmak üzere toplam 125 katılımcı seçilmiştir. PLT, trombosit dağılım genişliği (PDW), ortalama trombosit hacmi (MPV), trombosit (PCT), nötrofillerin lenfositlere (NLR) oranı ve trombositlerin lenfositlere (PLR) oranı retrospektif olarak her iki grupta da incelenmiştir.

Bulgular: Hasta grubunun yaş ortalaması 47,30 (15,14), kontrol grubunun yaş ortalaması 38,08 (13,33) idi. DLE hastalarında ve sağlıklı kontrollerde PLT, PDW, MPV, PCT, NLR ve PLR düzeyleri arasında istatistiksel olarak anlamlı bir fark yoktu (sırasıyla P=0,365, P=0,988, P=0,160, P=0,851, P=0,898 ve P=0,887).

Sonuç: Bildiğimiz kadarıyla DLE'li hastalarda hem PLT, PDW, PCT, NLR, PLR, hem de MPV hakkında çalışma yoktur. Çalışmamızda DLE grubunda anlamlı bir fark bulamadık. PLT parametreleri, inflamatuar hastalıklarda inflamasyon seviyelerini tanımlamak için kullanılabilecek düşük maliyetli testlerdir. Bu konuyla ilgili ileriye dönük çalışmalar bu çalışmaya katkıda bulunacaktır.

Anahtar kelimeler: Trombositler, Ortalama trombosit hacmi, Trombosit dağılım genişliği, Diskoid lupus eritematozus, İnflamasyon

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Introduction

Lupus erythematosus (LE) is an inflammatory and autoimmune connective-tissue disease that predominately affects the skin. Skin manifestations of LE are divided into LE-specific and LE-nonspecific skin lesions. LE-specific lesions include chronic, subacute and acute types. Discoid lupus erythematosus (DLE) is the most common form of chronic cutaneous lupus erythematosus (LE) [1]. DLE occurs more frequently in women aged in their 40s and 50s [2]. DLE may be present alone or occur in 20% of patients with systemic lupus erythematosus (SLE). DLE generally attacks the head and neck, particularly the scalp and ears. When DLE appears on the trunk, it is associated with an increased risk of progression to SLE [3]. LE is characterized by autoantibodies and immune complexes that are a consequence of loss of immune tolerance. However, the pathogenesis of DLE remains mostly unknown. T helper-1 (Th1) dominated inflammation is thought to play a role in the etiology of DLE [4].

Platelets (PLT) play a role in inflammatory reactions and immune response. Mean platelet volume (MPV) has been identified as a platelet activation marker that significantly affects inflammatory reactions [5]. Platelet distribution width (PDW), that shows the heterogeneity in PLT morphology, is clinically related to PLT activation [6]. Plateletcrit (PCT) is a novel biomarker in inflammatory and vascular diseases such as Crohn's disease, coronary artery disease, deep vein thrombosis and sepsis. The resulting PCT provides more comprehensive information about the total platelet mass than other platelet parameters and is more sensitive [7]. Among other parameters, the ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR) are simple markers of systemic inflammatory response. These parameters are commonly evaluated during routine blood tests [8]. Recently, they have been studied, individually or together, in relation to various dermatologic diseases such as psoriasis, rheumatologic diseases of dermatology, cutaneous vasculitis, atopic eczema, pityriasis rosea, Behçet's disease, recurrent aphthous stomatitis and pemphigus vulgaris [5,9-11]. There are no studies in the literature that investigate the relationship between DLE and these inflammatory markers, and to the best of our knowledge, this is the first study to examine the association between these markers and DLE.

This study aims to evaluate the relationship between MPV, PDW, PCT, NLR and PLR levels in patients with DLE compared to healthy controls and to ask: 'Can these markers be a specific indicator in disease?'.

Materials and methods

This study was approved by the Institutional Review Board on 17.04.2019 and numbered: 2019/74. This was a retrospective, case-control study conducted between January 2013 and March 2019. The study group consisted of patients with DLE of the face, scalp, neck and body and included healthy controls who had never experienced DLE. The demographic characteristics and laboratory information for both the sample and the controls were recovered from the health center's database. The data consisted of age, sex, laboratory markers as white blood cell count (WBC; K/uL), platelet count (PLT, K/uL), PCT, MPV (K/uL), neutrophil count (NE; K/uL), lymphocyte count (LY; K/uL), neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR).

The diagnosis of DLE in the patient group involved a combination of physical examination, histology and antibody serology. Patients with dermatological diseases other than DLE or who had an active infection, malnutrition, anemia, thrombocytopenia, immunodeficiency, chronic inflammatory skin disease, rheumatologic, hematologic, cardiac diseases, systemic lupus erythematosus or who used medication were excluded. The healthy control group comprised subjects chosen from the database who had no DLE or any other active infection, no systemic or dermatological-inflammatory disease and no history of medication use.

Statistical analysis

The data obtained for the study were analyzed using SPSS (Statistical Package for Social Sciences) for Windows 22.0. Number, percentage, mean and standard deviation were used as descriptive statistical methods for the evaluation of the data. The power of the test was calculated with G*Power 3.1 program. A sample size of 70 people, 35 in each group, was needed for 80% power and 0.05 type-1 error at 95% confidence interval (df=39; t=1.668). The t-test was used to compare the quantitative continuous data between the two independent groups. The relationship between variables was tested by chi-square analysis. The findings were evaluated at a 95% confidence interval and at a 5% significance level.

Results

Sixty patients with DLE and 65 healthy controls were evaluated in this study. The median age of the patient and control groups were 47.30 (15.14) years and 38.08 (13.33) years, respectively. The mean age of the patient group (47.3) was higher than the mean age of the control group (38.1) ($t_{(123)}$=3.620; P<0.001). Twenty (33.3%) patients were male and 40 (66.7%) were female; 33 (50.8%) control group participants were male and 32 (49.2%) were female. Women were significantly more common in the DLE group (x^2=3.884; P=0.036). The proportion of men in the control group was higher than in the patient group (Table 1). We did not find any significant differences between the groups according to the WBC, MPV, PLT, NLR, PLR, PDW, PCT values (P=0.481, P=0.160, P=0.365, P=0.898, P=0.887, P=0.988 and P=0.851, respectively). The laboratory findings are summarized in Table 2.

Table 1: The distribution of gender according to the groups

		Patients		Controls		X^2
		n	%	N	%	*P*-value
Gender	Male	20	%33.3	33	%50.8	3.884
	Female	40	%66.7	32	%49.2	0.036

Table 2: Average of laboratory parameters in groups

Groups	Patients (n=60)		Controls (n=65)		*P*-value
	Mean	SD	Mean	SD	
WBC	7.884	3.534	7.536	1.474	0.481
Neutrophil	4.536	2.783	4.480	1.295	0.884
Lymphocyte	2.570	1.519	2.330	0.562	0.253
NLR	2.071	1.446	2.044	0.838	0.898
Platelet	250.855	65.487	260.200	48.807	0.365
PLR	119.289	82.092	117.702	34.288	0.887
MPV	8.707	1.569	8.383	0.867	0.160
PDW	16.452	2.702	16.446	0.728	0.988
PCT	0.218	0.053	0.217	0.041	0.851

SD: Standard deviation

Discussion

DLE is the most common form of chronic cutaneous erythematosus. The lesions have a tendency to cause secondary atrophy or scarring. Most patients with DLE do not have significant systemic disease, yet DLE has relapsing‑remitting courses. [1]. PLT activation has been observed in patients with SLE; this PLT activation can make up the decrease in the PLT count consumed in SLE [12,13].

Complete blood count parameters can be calculated easily in routine and low-cost laboratory tests and provide very important markers of systemic inflammation [14]. In particular, PDW and MPV levels have been examined in recent studies. They have become popular and vital markers of PLT activation. In a study, Kim et al. [15] found higher PDW and MPV values in patients with psoriasis, a chronic inflammatory skin disease like DLE. In another study with lichen planus, Özlü et al. [16] found higher PDW levels and lower MPV levels in the patient group when compared to a control group. Studies with SLE showed lower MPV values and higher PDW values in patients and a positive relationship between PDW and disease activity [17,18]. In these studies, the decreased MPV values were explained by the consumption of large activated PLTs in extravascular sites of inflammation [19]. In our study, we did not find a significant difference between PDW and MPV levels in DLE patients and the healthy control group. This can be explained by the low rate of systemic association in patients with DLE and some differences in the pathogenesis, especially cutaneous inflammatory infiltrates that are dominated by Th1, but not Th17 in DLE cells in contrast to systemic lupus erythematosus.

Few dermatological studies have examined NLR and PLR in patients with psoriasis. Two of these studies reported a significant increase in NLR among patients relative to the control subjects [5,20]. Other studies have investigated the use of NLR and PLR with diabetes mellitus, acute coronary syndrome, ulcerative colitis, end-stage renal disease, tuberculosis, rheumatoid arthritis, cirrhosis, and familial Mediterranean fever [21,22]. There was no significance in PLR and NLR in our study.

In addition to the other studies mentioned, PCT has been recognized as a systemic inflammatory response marker. There has been no study that considers the relationship between PCT and dermatological diseases. In one study of an inflammatory disease, PCT was significantly elevated in patients with Crohn's disease compared with healthy controls [7].

There were some limitations to our study. First, this was a retrospective study and some of the patients' characteristics, such as their smoking history and dietary habits, were inadequate for evaluating their co-effects on the PLT indices and other factors. Second, as the study was retrospective, we could not investigate the relationship with disease severity. Third, the numbers of patients and controls were relatively small. Multi-center, prospective studies with larger sample sizes should be conducted in the future.

Conclusion

Our study provides the first report that the PLT and PLT parameters did not show a significant difference in insulating DLE patients. Further prospective works are needed to better understand the relevance of these findings.

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The relationship of serum galectin-3 levels with obesity and insulin resistance

Serum galektin-3 düzeylerinin obezite ve insulin direnci ile ilişkisi

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Abstract

Aim: Galectin-3 affects inflammation, cell adhesion, proliferation, differentiation and angiogenesis. Upon examining the pathogenesis of obesity and functions of galectin-3, we thought that galectin-3 may play a significant role in obese patients. This study aims to evaluate the relationship between obesity, insulin resistance and galectin-3 levels.

Methods: Eighty five patients aged between 18-50 years were included in this cross-sectional study. BMI>30 were considered obese, those between 25-30 and 18-25 were considered overweight and normal weight, respectively. Patients with HOMA-IR>2.5 were considered insulin-resistant, and those with <2.5 were evaluated as insulin non-resistant.Galectin-3 levels were measured by Enzyme-linked immunosorbent assay.

Results: Serum galectin-3 levels were significantly higher in obese patients, but not statistically significantly different between those with and without insulin resistance. Galectin-3 levels were also significantly correlated with BMI and total cholesterol levels, but not correlated with HOMA-IR.

Conclusion: In obesity, serum galectin-3 levels may increase to compensate for the inflammation. Our results make it difficult to establish a relationship between insulin resistance and galectin-3.

Keywords: Galectin-3, Obesity, Insulin Resistance, Diabetes Mellitus, Metabolic disease

Öz

Amaç: Galektin-3, inflamasyon, hücre yapışması, proliferasyonu, farklılaşması ve anjiyogenezi etkiler. Obezitenin patogenezi ve galektin-3'ün fonksiyonlarını incelediğimizde, galektin-3'ün obez hastalarda önemli bir rol oynuyor olabileceğini düşündük. Çalışmamızda obezite ve insülin direnci ile galektin-3 arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: 18-50 yaş aralığında erkek ve kadınlardan oluşan 85 olgu bu kesitsel çalışmaya dahil edildi. BMI >30 olan hastalar obez, 25-30 arasında olanlar fazla kilolu, 18-25 arasında olanlar normal kilolu olarak değerlendirildi. HOMA-IR değeri >2,5 olanlar insülin dirençli, <2,5 olanlar ise insülin direnci olmayan hastalar olarak gruplandırıldı. Serum galektin-3 düzeyleri Enzim-bağlı immunosorbent yöntemi ile ölçüldü.

Bulgular: Fazla kilolu ve normal kilolulara göre serum galektin-3 düzeyleri obezlerde daha yüksek düzeylerde idi. Fazla kilolu ve normal kilolular arasında serum galektin-3 düzeyleri anlamlı farklı değildi. İnsülin direnci olan ve olmayan grup arasında galektin-3 düzeyleri arasında herhangi bir fark görülmedi. Galektin-3 düzeyleri BMI ve total kolesterol ile korele iken, HOMA-IR ile arasında anlamlı bir korelasyon saptanmadı.

Sonuç: Obez hastaların serum galektin-3 seviyeleri, diğer gruplara oranla anlamlı olarak daha yüksek saptandı. Obezitedeki inflamatuvar süreçte kompensasyon amacı ile koruyucu etki göstermek üzere galektin-3 düzeylerinin arttığını düşünmekteyiz. Ancak, bulgularımız insülin direnci ve HOMA-IR ile serum galektin-3 düzeyleri arasında bir ilişki kurmayı güçleştirmektedir.

Anahtar kelimeler: Galektin-3, Obezite, İnsülin Direnci, Diabetes Mellitus, Metabolik hastalık

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Introduction

Galectin-3 is a member of the soluble beta-galactoside binding lectin family and affects cell adhesion, proliferation, differentiation, inflammation and angiogenesis [1]. Galectin-3 activity depends on its cellular localization. While extracellular galectin-3 stimulates apoptosis, intracellular galectin-3 in inhibits it [2]. Galectin-3 is expressed in a wide variety of cells, especially in macrophages and adipocytes. Recombinant galectin-3 induces pre-adipocyte proliferation in vitro [3].

Being overweight is associated with increased number of macrophages in dysfunctional adipocytes and the adipose tissue [4]. In addition to impaired lipid storage in excess weight, the release of adipokines and inflammatory cytokines is increased, which explains the low-grade systemic inflammation in overweight patients [2]. Although epidemiological studies have determined the relationship between visceral fat mass and metabolic disorders such as insulin resistance and obesity, the pathophysiological mechanisms are not clear [5]. Obesity is a chronic pro-inflammatory condition characterized by increased lipids and adipose tissue, which causes ectopic fat accumulation in different tissues, and increased pro-inflammatory cytokine levels [6]. It is also an important factor in the pathogenesis of type 2 diabetes mellitus [7].

When we examined the pathogenesis of obesity and the functions of galectin-3, we thought that galectin-3 may play an important role in these patients. This study aims to evaluate the relationship between obesity, insulin resistance and galectin-3 levels.

Materials and methods

This study was approved by the Local Ethics Committee and performed in accordance with the principles of Declaration of Helsinki. A total of 85 patients (18-50 years old, male and female) who were admitted to our internal medicine outpatient clinic between August 2018 and October 2018 were included in the study. Patients complying with the inclusion criteria were informed by the researchers. After obtaining informed consent form from the volunteers, detailed history of participants were taken. BMI was calculated by division of weight (kg) to the square of the height (m). Patients with BMI> 30 kg/m^2 were considered obese, those between 25 and 30 kg/m^2 were overweight, and those between 18 and 25 kg/m^2 were evaluated as normal weight. For the determining insulin resistance, HOMA-IR was calculated according to the formula: fasting insulin (uIU/mL) x fasting glucose (mg/dL) /405. Patients with HOMA-IR> 2.5 were considered insulin resistant.

Patients with a history of chronic disease, malignancy, diabetes mellitus, pregnant women, steroid users and immobilized patients were not included in the study. One more additional tube of blood was obtained from the volunteers during routine laboratory investigations. After resting for 20 minutes at room temperature, samples were centrifuged for 10 minutes on 4000 rpm and obtained sera were preserved at -80 °C. Galectin-3, glucose, urea, creatinine, cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol and insulin levels of patients were measured.

Measurements of galectin-3 and performance characteristics of the assay

On the day of analysis, the sera were left to thaw at room temperature. Enzyme-Linked Immuno Sorbent Assay (ELISA) kits (Human Galectin-3 ELISA, eBioscience, Lot No: 125631001) were usedfor the measurement of serum Galectin-3 levels. The analytical (linear) measurement range was 0.47 - 30 ng/mL for galectin-3. The minimal detection limit was 0.29 ng/mL. The reported intraassay and interassay CV's were <12 % and <10 %, respectively.

Statistical analysis

IBM SPSS version 20.0 (SPSS Inc, Chicago Illinois) was used for statistical analysis. The normal distribution of the parameters was analyzed with the Shapiro Wilk test. In addition to using descriptive statistics (mean, standard deviation, frequency) for the comparison of the quantitative data of parameters with a normal distribution, One Way Anova test was used in intergroup comparisons; Tukey's HSD test and Tamhane's T2 tests were used for determining the differing group. For non-normally distributed parameters, Kruskal Wallis test was used in intergroup comparisons and Mann Whitney U test in determining the differing group. Student-t test was utilized in comparing normally distributed parameters between two groups, and Mann Whitney U test was used for comparing the non-normally distributed parameters between two groups. The correlation between galectin-3 levels and other parameters was evaluated by non-parametric Spearman test. P<0.05 was considered statistically significant.

Results

The demographic and laboratory data of obese and non-obese groups are summarized in Table 1. Serum galectin-3 levels and BMI were found to be statistically significantly higher in obese patients compared to the non-obese group (P=0.003 and P<0.001, respectively). Other parameters were not statistically different between the two groups.

The demographic and laboratory data of study groups are summarized in Table 2. Serum galectin-3 levels were significantly higher in obese patients than the control and overweight groups (P=0.015 and P<0.001, respectively), but there was no significant difference between normal and overweight groups (P=0.977). Urea, creatinine, total cholesterol, HDL-cholesterol and LDL-cholesterol levels of the 3 groups were similar (P>0.05).

The results of correlation analysis between galectin-3 levels and other parameters are summarized in Table 3. A positive correlation was determined between galectin-3 levels, BMI and total cholesterol levels in all participants (P=0.002, r=0.337 and P=0.042, r=0.220, respectively).

The demographic and laboratory data of patients with or without insulin resistance are summarized in Table 4. Serum galectin-3 levels, age, HbA1c, creatinine, total cholesterol and LDL-cholesterol levels were not different between groups with and without insulin resistance (P>0.05).

Table 1: Demographic and laboratory data of obese and non-obese patients

	BMI<30 (n=39) Mean (SD)	BMI>30 (n=46) Mean (SD)	*P*-value
Galectin-3 (ng/mL)	23.4 (23.9)	38 (20.1)	0.003
Age (Years)	44.3 (9)	46 (10.4)	0.276
HOMA-IR	3.4 (3.7)	4.2 (2.5)	0.246
BMI (Kg/m^2)	26 (2.7)	35 (3.7)	<0.001
Fasting insulin (µIU/mL)	14.3 (13.9)	17.4 (10)	0.246
Fasting glucose (mg/dL)	92 (12)	96 (12)	0.125
HbA1c (%)	5.6 (0.4)	5.7 (0.3)	0.834
Urea (mg/dL)	24.2 (6.8)	24.6 (7.7)	0.839
Creatinine (mg/dL)	0.77 (0.13)	0.79 (0.47)	0.778
Total Cholesterol (mg/dL)	189 (37)	200 (47)	0.269
LDL-Cholesterol (mg/dL)	114 (35)	122 (44)	0.370
HDL-Cholesterol (mg/dL)	46.8 (12.6)	46.6 (10.1)	0.929
Triglyceride (mg/dL)	142 (104)	153 (92)	0.621

BMI: Body-Mass Index, HDL-cholesterol: High density lipoprotein- cholesterol, HOMA-IR: Homeostatic model of assessment- insulin resistance, LDL-cholesterol: Low density lipoprotein- cholesterol, SD: Standard deviation

Table 2: Demographic and laboratory data of study participants

	A BMI <25 (n:16)	B BMI:25-30 (n:23)	C BMI>30 (n:46)	Comparison of A-B *P*-value	Comparison of B-C *P*-value	Comparison of A-C *P*-value
Galectin-3 (ng/mL)	25.6 (28.4)	21.9 (20.7)	28 (20.1)	0.977	<0.001	0.015
HOMA-IR	1.5 (0.4)	4.7 (4.4)	4.2 (2.5)	0.001	0.869	<0.001
BMI (Kg/m^2)	23.2 (1.5)	28 (1.1)	35 (37)	<0.001	<0.001	<0.001
Age (Years)	40.6 (4.9)	46.8 (10.4)	46 (10.4)	0.069	0.848	0.026
Insulin(µIU/mL)	7.3 (2.5)	19.2 (16.4)	17.4 (10)	0.001	0.919	<0.001
Glucose(mg/dL)	85 (10)	97 (11)	96 (10)	0.001	0.584	0.0014
HbA1c (%)	5.6 (0.2)	5.8 (0.4)	5.7 (12)	0.001	0.107	0.015
Urea (mg/dL)	24.6 (7.3)	24 (6.5)	24.6 (7.7)	0.786	0.760	0.981
Creatinine (mg/dL)	0.78 (0.16)	0.78 (0.12)	0.8 (0.5)	0.597	0.512	0.358
TotaLcholesterol (mg/dL)	185.8 (32)	192 (41)	200 (47)	0.909	0.745	0.299
LDL-cholesterol (mg/dL)	114 (35.9)	114 (36.6)	122 (44)	0.940	0.606	0.645
HDL-cholesterol (mg/dL)	49.6 (10.9)	44.8 (13.5)	46.6 (10.1)	0.184	0.369	0.454
Triglyceride(mg/dL)	106 (48)	168 (124)	153 (92)	0.081	0.980	0.034

A: Normal weight group, B: Overweight group, C: Obese group. BMI: Body-Mass Index, HDL-cholesterol: High density lipoprotein- cholesterol, HOMA-IR: Homeostatic model of assessment- insulin resistance, LDL-cholesterol: Low density lipoprotein- cholesterol

Table 3: Correlation between galectin-3 levels and other parameters

		BMI	Fasting glucose	Fasting insulin	HbA1c	HOMA-IR	Total Cholesterol	LDL-Cholesterol
Galectin -3	r	0.337	0.066	0.039	0.018	0.037	0.220	0.209
	P-value	0.002	0.548	0.724	0.868	0.734	0.042	0.055
	n	85	85	85	85	85	85	85

Table 4: Demographic and laboratory data in subgroups with or without insulin resistance

	HOMA-IR<2.5 (n:36) Mean (SD)	HOMA-IR >2.5 (n:49) Mean (SD)	*P*-value
Galectin-3 (ng/mL)	33.6 (22.1)	28.4 (23.8)	0.294
HOMA-IR	1.6 (0.5)	5.4 (3.2)	<0.001
Age (Years)	28.8 (6.3)	33.6 (22.1)	0.005
BMI (Kg/m^2)	42.7 (8.9)	46.67 (10.6)	0.075
Insulin (µIU/mL)	7.5 (2.6)	22.3 (12.2)	<0.001
Glucose (mg/dL)	87 (9.8)	99 (12.6)	<0.001
HbA1c (%)	5.6 (0.4)	57 (0.4)	0.297
Urea (mg/dL)	22.4 (7.1)	25.7 (7.4)	0.039
Creatinine (mg/dL)	0.78 (0.51)	0.77 (0.17)	0.891
Total Cholesterol (mg/dL)	194 (44)	195 (43)	0.891
HDL-Cholesterol (mg/dL)	50 (10.7)	43.8 (10.7)	0.005
Triglyceride (mg/dL)	118 (64)	170 (112)	0.015
LDL-Cholesterol (mg/dL)	117 (44)	120 (38)	0.727

BMI: Body-Mass Index, HDL-cholesterol: High density lipoprotein- cholesterol, HOMA-IR: Homeostatic model of assessment- insulin resistance, LDL-cholesterol: Low density lipoprotein- cholesterol, SD: Standard deviation (17 patients with insulin resistance were overweight and 32 were obese. Of the patients without insulin resistance, 16 were normal weight, 6 were overweight, and 14 were obese.)

Discussion

In our study, serum galectin-3 levels of obese patients were higher compared to the overweight and normal weight groups. Increased levels of this molecule in obese patients werereported in previous studies as well [8-11]. Since most of the studies were experimental animal studies, being a clinical study that used international classifications in patient grouping, our study has brought a different perspective to the subject. In the first study regarding this topic, Weigert et al. [8] classified patients into normal weight (BMI <25), obese (BMI >25) and those with type 2 diabetes mellitus, and reported high serum galectin-3 levels in obese and type 2 diabetic patients. They also included overweight patients in the obese group and there were also non-obese patients with type 2 diabetes mellitus. According to internationally accepted criteria, we selected the obese group as BMI> 30 kg/m^{2}to for a more specific definition.

Galectin-3 levels were higher in the obese group. In our study, we did not find any significant difference between normal and overweight groups. In addition, we found a positive correlation between galectin-3, BMI and total cholesterol levels. There are various opinions about why the level of galectin-3 increases in obese patients. Krautbauer et al. [10] reported that adiponectin down regulates adipocyte and monocyte galectin-3 protein and impaired adiponectin activity in obesity causes elevations in galectin-3 levels. Reduced adiponectin levels have been reported in obese patients [12]. Therefore, galectin-3 levels may increase in obesity, since the inhibitory effect on galectin-3 is eliminated in adiponectin deficiency. Also, high IL-6 levels in obesity may increase levels of galectin-3 [11]. Jung-Hwan et al. [13] reported that high galectin-3 levels were associated with obesity, and that galectin-3 interacts directly with peroxisome proliferator-activated receptor (PPAR) -gamma and regulates the expression and transcriptional activation of PPAR-gamma. (PPAR) –gamma, a receptor located in nucleus, has a key role in lipid metabolism. It is activated by the PPAR-gamma ligands, binds to the PPAR-gamma response element, and increases the expression of target genes. Galectin-3 has been reported to be involved in adipogenesis by direct PPAR-gamma regulation.

There is no consensus about the roles galectin-3 in the body. Galectin-3 has been reported to play a protective role against inflammation in different models. Rhodes et al. [14] showed increased expression of galectin-3 in visceral adipose tissue and subcutaneous adipose tissue in mice with high fat diet-induced obesity. In dietary-associated atherosclerosis and diabetes-associated renal injury models, galectin-3 deficient mice were found to have increased inflammation [15]. These data suggest that galectin-3 plays a protective role in metabolic complications and inflammation associated with obesity [15-17].Galectin-3 binds to advanced glycation end products (AGE) and stimulates their degradation. Since AGE accumulate in long-lasting proteins and cause tissue damage associated with the severity of diabetic complications, we believe that high levels of galectin-3 may be protective [18].

Despite the apparent association of elevated galectin-3 levels with obesity, the relationship between insulin resistance and galectin-3 appears to be contradictory. Obesity-related insulin resistance is a characteristic precursor of type 2 diabetes mellitus. There are studies reporting that various molecules such as galectin-3 may be associated with insulin resistance and BMI. Li et al. [19] reported that galectin-3-knockout mice, in which circulating galectin-3 levels were reduced, needed more insulin when exposed to a high-fat diet or aging; galectin-3 was upregulated in obesity, and defined that it as a pro-inflammatory molecule which may cause insulin resistance. In the same study, a negative correlation between galectin-3 and HOMA-IR was reported. Baek et al. [20] also found that galectin-3 deficient mice were insulin-sensitive. In contrast, Pang et al. [16] reported that there was no difference in the insulin sensitivity of galectin-3 deficient mice. Darrow and Shohet [21] reported hyperglycemia with reduced plasma insulin levels in galectin-3 deficient mice indicating beta-cell dysfunction without a change in insulin sensitivity. Ohkura et al. [22] reported that galectin-3 was associated with decreased plasma insulin levels and insulin sensitivity in type 2 diabetics, but not with BMI. Galectin-3 was

also reported to inhibit insulin signals with a mechanism that directly binds the insulin-receptor [23]. Yılmaz et al. [24] reported high levels of galectin in patients with diabetes and pre-diabetes, possibly leading to diabetes and complications. Karlsen et al. [25] reported that overproduction of galectin-3 inhibited beta cell damage caused by the cytotoxic effects of interleukin-1 beta.

In our study, we found statistically insignificant differences in serum galectin-3 levels between groups with and without insulin resistance. We found insulin levels to be significantly higher in obese and overweight groups than control group. No correlation was found between galectin-3 levels, insulin and HOMA-IR in both the obese and non-obese groups. Therefore, we did not detect a relationship between insulin resistance and serum galectin-3 levels. Since there are contradictory results in the literature, more studies are warranted.

Limitations

There are some limitations of our study. First, the sample size could have been larger. Secondly, inflammatory cytokine levels were not studied in the sera.

Conclusion

We believe that galectin-3 levels are increased in obese patients for protective purposes, to compensate for the inflammatory process in obesity. Our results make it difficult to establish a relationship between insulin resistance and galectin-3. We believe that galectin-3 is an important molecule in monitoring treatment outcomes of metabolic diseases.

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Anti-osteoporotic effects of melatonin and misoprostol in glucocorticoid-induced osteoporosis: An experimental study

Glukokortikoid kaynaklı osteoporozda melatonin ve misoprostolün anti-osteoporotik etkileri: Deneysel çalışma

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Abstract

Aim: Although there are some treatment options for glucocorticoid induced osteoporosis (GIO), new drug alternatives are still needed. In this study, we aimed to determine the protective effects of misoprostol and melatonin in an experimental GIO model.

Methods: The rats were grouped into four, with 10 rats in each group. The 1st group was chosen as the control group, which were not intervened with. Group 2 was the steroid group, group 3 the misoprostol group and group 4, the melatonin group. To the rats in groups 2, 3 and 4, 10 mg/kg subcutaneous methylprednisolone was administered for 28 days. To the rats of the 3rd group, 200 mg/day misoprostol was given per day by a cannula to the stomach. The rats in the 4th group received 5mg/kg intraperitoneal melatonin during this 28-days period. Lumbar vertebrae and femur bone mineral density (BMD) of all rats were measured by Dual-energy X-ray absorptiometry (DEXA) and assessed in pre- and post-treatment periods.

Results: In the steroid group, when the pre- and post-treatment-BMD values of the rats were compared, statistically significant decreases were found in vertebrae, whole femur, femur proximal, femur diaphysis and distal femur bone regions (P=0.011, P=0.005, P=0.007, P=0.005 and P=0.013; respectively). In the misoprostol group, a statistically significant decrease was observed only in the whole femur region (P=0.012) when the pre- and post-treatment BMD values of the rats were compared, while no significant changes were observed in vertebrae, femur proximal, femur diaphysis and distal femur bone regions (P=0.093, P=0.401, P=0.161 and P=0.123; respectively). In the melatonin group, when the pre- and post-treatment BMD values of the rats were compared, a statistically significant decrease was observed only in the vertebrae region (P=0.009), no significant changes were observed in whole femur, femur proximal, femur diaphysis and distal femur bone regions (P=0.386, P=0.445, P=1.000 and P=0.483; respectively).

Conclusion: Positive effects of misoprostol and melatonin on bone metabolism were determined in this experimental study. Misoprostol and melatonin seem to be potential agents that can be used in the prevention of GIO.

Keywords: Glucocorticoids, Osteoporosis, Melatonin, Misoprostol

Öz

Amaç: Glukokortikoid kaynaklı osteoporoz için kullanılan bazı tedavi seçenekleri olsa da, yeni ilaç alternatiflerine hâlâ ihtiyaç duyulmaktadır. Çalışmamızda ratlarda glukokortikoid kaynaklı osteoporoz modelinde misoprostol ve melatoninin koruyucu etkilerini belirlemeyi amaçladık.

Yöntemler: Ratlar her grupta 10'ar adet olacak şekilde dört gruba ayrıldı: Grup1 kontrol, grup 2 steroid, grup 3 misoprostol, grup 4 melatonin grubu olarak belirlendi. Grup 2, 3, 4'teki ratlara 28 gün boyunca 10 mg/kg/gün subkutan metilprednizolon uygulandı. Grup 3'teki ratlara ilave olarak 200 mg/gün orogastrik misoprostol, grup 4'teki ratlara ilave olarak 5 mg/kg/intraperitoneal melatonin uygulandı. Tüm ratların lomber vertebra ve femur kemik mineral yoğunluğu DEXA yöntemi ile ölçülerek tedavi öncesi ve sonrası değerler karşılaştırıldı.

Bulgular: Steroid grubunda, çalışma sonrası vertebra, tüm femur, femur proximal, femur diaphysis ve distal femur kemik mineral yoğunluğu değerleri istatistiksel olarak anlamlı derecede düşük bulundu (sırasıyla; P=0,011, P=0,005, P=0,007, P=0,005 ve P=0,013). Misoprostol grubunda sadece tüm femur bölgesinde çalışma sonrası kemik mineral yoğunluğu düşük (P=0,012) olup vertebra, femur proximal, femur diaphysis ve distal femur bölgeleri osteoporozdan korunmuştu (sırasıyla; P=0,093, P=0,401, P=0,161 ve P=0,123). Melatonin grubunda sadece vertebra bölgesinde çalışma sonrası kemik mineral yoğunluğu düşük (P=0,009) olup tüm femur, femur proximal, femur diaphysis ve distal femur bölgelerinde osteoporozdan korunmuştu (sırasıyla; P=0,386, P=0,445, P=1,000 ve P=0,483).

Sonuç: Bu deneysel çalışmada misoprostol ve melatoninin kemik metabolizması üzerindeki olumlu etkileri belirlenmiştir. Misoprostol ve melatonin GIO'nun önlenmesinde kullanılabilecek potansiyel ajanlar gibi görünmektedir.

Anahtar kelimeler: Glukokortikoid, Osteoporoz, Melatonin, Misoprostol

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Introduction

Glucocorticoids are commonly prescribed treatment modalities in chronic inflammatory and autoimmune diseases in all age groups. Unfortunately, one of the main side effects associated with the long-term glucocorticoid treatment is alterations in bone mineral density (BMD) causing an increase in fracture risk [1]. Glucocorticoid treatment has been shown to cause a decrease in bone vasculature and induce apoptosis in both osteoblasts and osteocytes resulting in structural deterioration of bone tissue and osteoporosis [2,3].

Glucocorticoid induced osteoporosis (GIO) has two main mechanisms: Excessive bone resorption with osteoclasts and impaired bone formation due to a decrease in osteoblast count and action [4]. Although some medications such as bisphosphonates or anabolic agents have been suggested together with the maintenance of adequate calcium intake and normal vitamin D status in prevention and/or treatment of GIO, a general consensus is yet to be reached. In especially children, it is clear that the treatment of osteoporosis is more difficult than prevention [5].

Misoprostol (15–deoxi-16-hydroxy-methyl PGE1) is a methyl derivative of prostaglandin E1. In experimental studies, misoprostol treatment was associated with an increase in bone turnover, with a net anabolic effect [6]. Osteo-inductive effects of misoprostol in the early bone healing period were defined [7]. Misoprostol has also been determined as an alternative treatment for osteopenia and osteoporosis in women during the postmenopausal period [8].

Melatonin, N-acetyl-5-methoxytryptamine, is a tryptophan derived indolamine hormone that is released by the pineal gland and found in many tissues. The anabolic effects of melatonin on bone remodeling by increasing osteoblast proliferation and differentiation and suppressing osteoclastogenesis was priorly determined [9,10]. Bone remodeling, the equilibrium between formation and resorption of bone tissue, mainly depends on the work of osteoblasts and osteoclasts in harmony. Oxidative stress has been shown to interfere with multiple cellular events that induce mesenchymal stem cell differentiation, promote apoptosis of mature osteoblasts and accelerate osteoporosis by increasing bone resorption and decreasing bone formation [11]. Melatonin with its potent anti-oxidant properties and cyto-protective effects may also be considered a protective hormone for oxidative-stress-induced mechanisms in osteoporosis [12].

Thus, in this experimental study, we aimed to determine the effects of misoprostol and melatonin individually, in prevention of GIO when concurrently applied with glucocorticoids. To the best of our knowledge, this is the first study in literature, evaluating the protective effects of misoprostol and melatonin in GIO.

Materials and methods

Animal samples

Two months old 40 Wistar female rats with a mean body mass of 143.8(20.1) grams were included in this randomized, controlled and double-blinded experimental study. Rats were fed with standard laboratory food and water for 28 days. The room in which the rats were cared for was 24(3)^{o}C with light and dark cycles of 12 h; rats were scaled every 10 days. Two rats from the 3rd group were lost due to cannula damage.

Ethical approval was obtained from Inonu University Medical Faculty ethics committee (2003/23). Then the rats were divided into 4 groups with 10 rats per each:

1st group was determined as control group, without application of any drugs;

2nd group was determined as the GIO (steroid) group, with the administration of 10 mg/kg subcutaneous methylprednisolone as a single dosage per day for 28 days;

3rd group was determined as the misoprostol group, with the administration of 200 μg/day prostoglandine E1 (misoprostol) directly to the stomach with a metal cannula together with 10 mg/kg subcutaneous methylprednisolone administration as a single dosage per day for 28 days;

4th group was determined as the melatonin group, with the administration of 5 mg/kg intraperitoneal melatonin along with 10 mg/kg subcutaneous methylprednisolone administration as a single dosage per day for 28 days.

At the beginning and at the end of the study, all rats were anesthetized with 8 mg Xylazinhydroclorur and 75 mg/kg ketamine for bone mineral density measurements. After 28 days, under halothane anesthesia, euthanasia was performed by drawing intracardiac blood.

All animal procedures were conducted in accordance with the standards set forth in the guidelines for the care and use of experimental animals by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and the National Institutes of Health (NIH).

Bone mineral density measurement

The bone mineral density (BMD) measurements of lumbar vertebrae and femur of all rats were performed using DEXA (QDR 4500/W, Hologic Inc., Bedford, MA, USA) and data was analyzed by the same researcher.

Our DEXA machine uses 70 kV and 140 kV double energized X-ray. For the analysis of all interest sites “subregion analysis software” was used. BMD was measured as g/cm^2 from four sites of the right femur and lumbar vertebrae. The lumbar vertebrae region (R1), total femur region (R2), adjacent 3 femur interest sites (R3=1/3 proximal, R4=1/3 mid-site, R5=1/3 distal) were charted. Superior iliac margin levels on lumbar areas were drawn in rectangles of 17x5 mm height and width. Femur interest sites were drawn with 3 mm width (Figure 1).

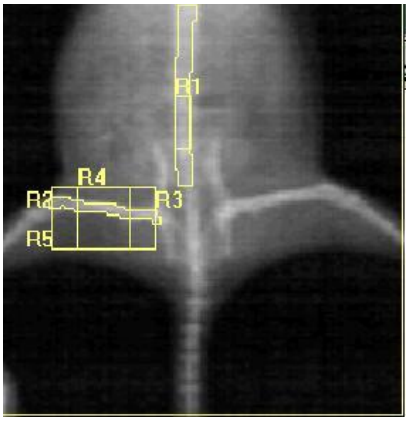

Figure 1: Interest sites specified and measured by DEXA

BMD rates showing BMD changes were calculated by using BMD data before and after the study. While a positive increase in BMD rates shows that post-study-BMD decreased, a negative increase in BMD rates shows that post study BMD increased.

$$\text{BMD rate} = \frac{\text{pre BMD} - \text{post BMD}}{\text{pre BMD}}$$

Statistical analysis

Statistical analysis was performed by using the statistical package for the social sciences version 17.0 (SPSS Inc., Chicago, IL, USA). Non-parametric tests were used for statistical analysis. Variables were shown as median and minimum-maximum values. Mann Whitney U test was used for comparisons between two independent groups and Kruskal-Wallis test was used for comparison of independent 3 or more groups. The post-hoc multiple comparisons with Mann-Whitney U test were statistically significant at $P<0.016$ for 4 groups. The significance of the differences between the two dependent samples was evaluated by Wilcoxon signed ranks test. $P<0.05$ was considered statistically significant.

Results

Groups were analyzed for BMD with DEXA measurements from R1, R2, R3, R4 and R5 interest sites and assessed as before treatment and after treatment. Data from all groups were assessed individually. Data before and after treatment in all groups are summarized in Table 1.

There were no statistically significant differences between the weight measurements of the rats before and after the study in control, steroid, misoprostol and melatonin groups (P=0.443, P=0.066, P=0.400 and P=0.445; respectively).

The pre-and post-study comparison of vertebrae, whole femur, proximal femur, femur diaphysis and distal femur BMD values of the rats in the control group revealed no changes, as expected (P=0.169, P=0.646, P=0.906, P=0.959 and P=0.241; respectively). In the steroid group, statistically significant decreases were found between pre- and post-treatment vertebrae, whole femur, proximal femur, femur diaphysis and distal femur bone mineral densities (P=0.011, P=0.005, P=0.007, P=0.005 and P=0.013; respectively). In the misoprostol group, upon comparison of pre- and post-treatment BMD values, a statistically significant decrease was observed only in the whole femur region (P=0.012) and no significant changes were observed in vertebrae, proximal femur, femur diaphysis and distal femur bone regions (P=0.093, P=0.401, P=0.161 and P=0.123; respectively). In the melatonin group, when the pre- and post-treatment BMD values of the rats were compared, a statistically significant decrease was observed only in the vertebrae region (P=0.009) and no significant changes were observed in whole femur, femur proximal, femur diaphysis and distal femur bone regions (P=0.386, P=0.445, P=1.000 and P=0.483; respectively). Pre- and post-treatment alterations of BMD values in vertebrae and femur regions are shown in Figure 2.

BMD rates and intergroup comparison of the study groups in related bone areas with BMD measurements are shown in Table 2.

When the BMD rates were compared between the groups, there were statistically significant differences in whole femur region, proximal femur and femur diaphysis regions (P=0.005, P=0.048 and P=0.005; respectively). There were no statistically significant differences in BMD values of the vertebrae and distal femur regions between the groups (P=0.104 and P=0.126; respectively).

Post-hoc multiple comparisons of BMD values for whole femur, proximal femur and femur diaphysis are summarized in Table 3.

In post hoc multiple comparisons in Table 3, BMD values of whole femur bone region were compared between the groups and the BMD value of the steroid group was found significantly higher than the control and melatonin groups (P=0.007 and P=0.002; respectively). There were no statistically significant differences between the control, misoprostol and melatonin groups (P=0.051 and P=0.880; respectively), between the steroid and misoprostol groups (P=0.131) and between the misoprostol and melatonin groups (P=0.110). The BMD values of the proximal femur region of the steroid group were found significantly higher than the control and melatonin groups (P=0.010 and P=0.013; respectively). There were no statistically significant differences between the control, misoprostol and melatonin groups (P=0.248 and P=0.821; respectively), between the steroid and misoprostol groups (P=0.594) or between the misoprostol and melatonin groups (P=0.374) in the multiple comparison of the BMD values of the proximal bone region. The femur diaphysis BMD values of the steroid group were found significantly higher compared to the control group and melatonin group (P=0.003 and P=0.002; respectively). There were no statistically significant differences between the control, misoprostol and melatonin groups (P=0.328 and P=0.940; respectively), between the steroid and misoprostol groups (P=0.026) and between the misoprostol and melatonin groups (P=0.286). BMD values of groups in femur regions that is showing significant differences in intergroup comparisons are shown in Figure 3.

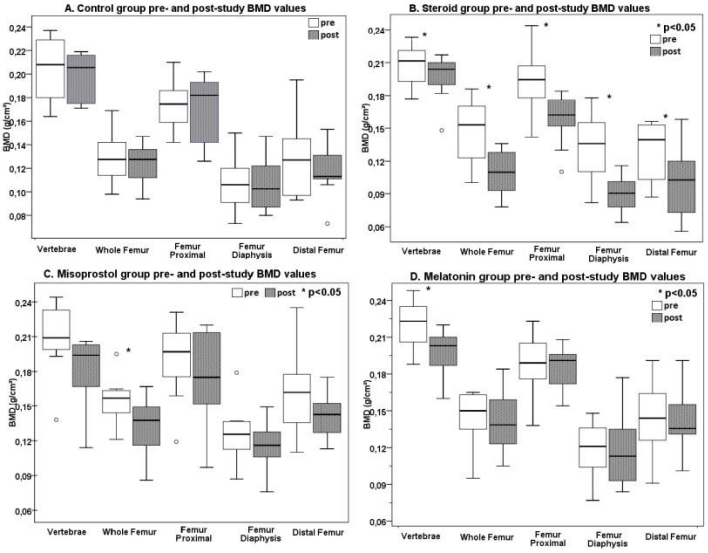

Figure 2: Pre- and post-study BMD alterations of vertebrae and femur regions. A: Control Group, B: Steroid Group, C: Misoprostol Group, D: Melatonin Group. * Significant difference between pre- and post-study BMD

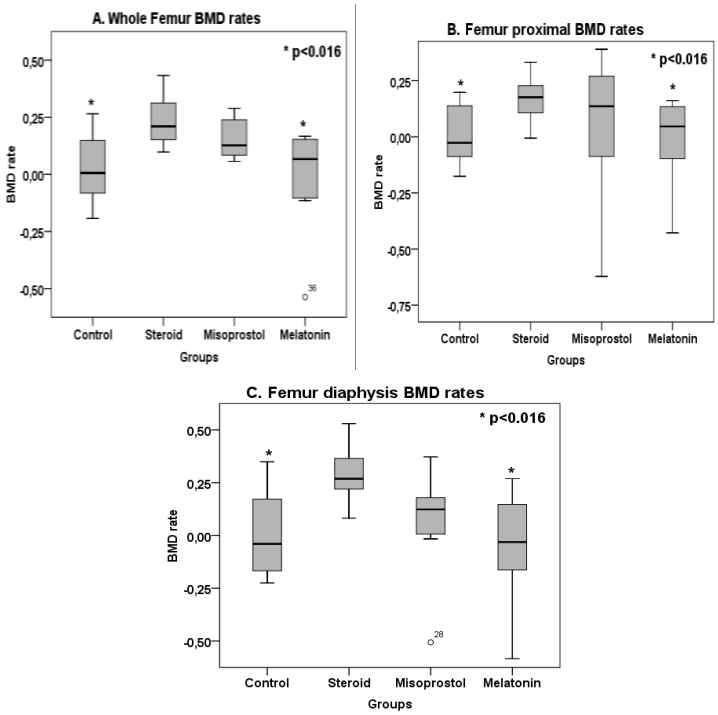

Figure 3: BMD rates of groups in femur regions that are showing significant differences in intergroup comparisons. A: Whole femur, B: Femur proximal, C: Femur diaphysis, * Significant differences compared to steroid group

Table 1: Weight and Bone Mineral Density variables in all groups before and after treatments

Groups	Variables	Before Median (Min-Max)	After Median (Min-Max)	*P*-value
Control (n=10)	Weight (gr)	150.0 (105-200)	149 (89-188)	0.443
	Vertebrae BMD (gr/cm²)	0.208 (0.164-0.237)	0.205 (0.171-0.219)	0.169
	Whole femur BMD (gr/cm²)	0.127 (0.098-0.169)	0.127 (0.094-0.147)	0.646
	Femur proximal BMD (gr/cm²)	0.174 (0.142-0.210)	0.182 (0.126-0.202)	0.906
	Femur diaphysis BMD (gr/cm²)	0.106 (0.073-0.150)	0.102 (0.080-0.147)	0.959
	Distal femur BMD (gr/cm²)	0.127 (0.093-0.195)	0.113 (0.073-0.153)	0.241
Steroid (n=10)	Weight (gr)	144 (83-165)	153 (99-181)	0.066
	Vertebrae BMD (gr/cm²)	0.211 (0.177-0.233)	0.204 (0.148-0.217)	0.011*
	Whole Femur BMD (gr/cm²)	0.153 (0.093-0.186)	0.109 (0.078-0.136)	0.005*
	Femur Proximal BMD (gr/cm²)	0.194 (0.142-0.244)	0.162 (0.110-0.184)	0.007*
	Femur Diaphysis BMD (gr/cm²)	0.136 (0.082-0.178)	0.090 (0.064-0.116)	0.005*
	Distal Femur BMD (gr/cm²)	0.139 (0.073-0.156)	0.102 (0.056-0.158)	0.013*
Misoprostol (n=8)	Weight (gr)	142.5 (121-163)	143.5 (115-164)	0.400
	Vertebrae BMD (gr/cm²)	0.209 (0.138-0.244)	0.194 (0.114-0.206)	0.093
	Whole Femur BMD (gr/cm²)	0.157 (0.121-0.195)	0.37 (0.086-0.167)	0.012*
	Femur Proximal BMD (gr/cm²)	0.197 (0.119-0.231)	0.175 (0.097-0.220)	0.401
	Femur Diaphysis BMD (gr/cm²)	0.125 (0.087-0.179)	0.116 (0.076-0.149)	0.161
	Distal Femur BMD (gr/cm²)	0.162 (0.101-0.235)	0.142 (0.113-0.175)	0.123
Melatonin (n=10)	Weight (gr)	143.5 (115-163)	140.5 (100-185)	0.445
	Vertebrae BMD (gr/cm²)	0.223 (0.188-0.248)	0.203 (0.160-0.220)	0.009*
	Whole Femur BMD (gr/cm²)	0.150 (0.095-0.165)	0.138 (0.105-0.184)	0.386
	Femur Proximal BMD (gr/cm²)	0.189 (0.138-0.223)	0.191 (0.154-0.208)	0.445
	Femur Diaphysis BMD (gr/cm²)	0.121 (0.077-0.148)	0.113 (0.084-0.177)	1.000
	Distal Femur BMD (gr/cm²)	0.144 (0.091-0.191)	0.135 (0.101-0.191)	0.483

P-values were determined by Wilcoxon Ranks test. * $P<0.05$

Table 2: BMD rates and intergroup comparison

Bone Regions	Groups	BMD rate Median (Min-Max)	*P*-value
Vertebrae	Control (n=10)	0.039 (-0.117- 0.101)	0.104
	Steroid (n=10)	0.051 (-0.005-0.164)	
	Misoprostol (n=8)	0.129 (-0.362-0.409)	
	Melatonin (n=10)	0.106 (-0.019-0.217)	
Whole Femur	Control (n=10)	0.006 (-0.193-0.265)	0.005*
	Steroid (n=10)	0.210 (0.098-0.432)	
	Misoprostol (n=8)	0.127 (0.057-0.289)	
	Melatonin (n=10)	0.067 (-0.537-0.167)	
Femur Proximal	Control (n=10)	-0.027 (-0.176-0.198)	0.048*
	Steroid (n=10)	0.176 (-0.006-0.332)	
	Misoprostol (n=8)	0.136 (-0.622-0.390)	
	Melatonin (n=10)	0.046 (-0.428-0.161)	
Femur Diaphysis	Control (n=10)	-0.040 (-0.225-0.349)	0.005*
	Steroid (n=10)	0.269 (0.082-0.530)	
	Misoprostol (n=8)	0.124 (-0.506-0.372)	
	Melatonin (n=10)	-0.032 (-0.584-0.269)	
Distal Femur	Control (n=10)	0.074 (-0.577-0.456)	0.126
	Steroid (n=10)	0.251 (-0.103-0.585)	
	Misoprostol (n=8)	0.132 (-0.591-0.404)	
	Melatonin (n=10)	0.036 (-0.560-0.195)	

P-values were determined by Kruskal-Wallis Test.* $P<0.05$

Table 3: BMD rates Post-hoc Multiple Comparison

Bone Regions	Groups		Difference	*P*-value
Whole Femur	Control	Steroid	-0.204	0.007*
		Misoprostol	-0.121	0.051
		Melatonin	-0.061	0.880
	Steroid	Misoprostol	0.083	0.131
		Melatonin	0.143	0.002*
	Misoprostol	Melatonin	0.060	0.110
Femur Proximal	Control	Steroid	-0.203	0.010*
		Misoprostol	-0.163	0.248
		Melatonin	-0.073	0.821
	Steroid	Misoprostol	0.040	0.594
		Melatonin	0.130	0.013*
	Misoprostol	Melatonin	0.090	0.374
Femur Diaphysis	Control	Steroid	-0.309	0.003*
		Misoprostol	-0.164	0.328
		Melatonin	-0.008	0.940
	Steroid	Misoprostol	0.145	0.026
		Melatonin	0.301	0.002*
	Misoprostol	Melatonin	0.156	0.286

P-values were determined by Man-Whitney U test; * $P<0.016$

Discussion

Glucocorticoids are the most common cause of drug induced osteoporosis. In this study, we compared the bone densitometry values of vertebrae and femur interest regions in rats that were treated with misoprostol or melatonin concurrently with 10 mg/kg/day methyl prednisolone for 28 days. At the end of the study, BMD values were determined to be significantly decreased in the GIO group, which was treated with methyl prednisolone only, indicating osteoporosis. In misoprostol administered group, the decrease in BMD was significant only in whole femur region. In the melatonin treated group, BMD was significantly decreased only in the vertebral regions, representing the protective effects of these agents. The lack of statistical significant differences in the misoprostol group in R1, R3, R4 and R5 regions and in melatonin group in R2, R3, R4 and R5 regions suggest that misoprostol and melatonin prevent osteoporosis induced by glucocorticoids.

With their well-known anti-inflammatory and immune modulating effects, glucocorticoids are commonly used in clinical practice. However, alterations in bone metabolism are one of the main adverse effects associated with glucocorticoid treatment in especially prolonged treatment modalities, leading to bone fragility and fractures. The main mechanism in GIO is the impaired osteogenesis. Glucocorticoids directly inhibit cellular proliferation and differentiation of osteoblasts and their maturation and activity [13,14]. Decreased bone formation is accompanied by an increase in bone resorption in prolonged usage of glucocorticoids. At a molecular level, glucocorticoids upregulate peroxisome proliferator-activated receptor gamma receptor 2 (PPARγ2) and alter the functions of Wnt/β-catenin signaling pathway which in turn favors the differentiation of pluripotent precursor cells to adipocytes instead of osteoblasts causing a decrease in osteoblast production. On the other hand, glucocorticoids also directly upregulate bone resorption by increasing the macrophage colony stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL) production and decreasing osteoprotegerin formation by osteocytes. Reduced physical activity, increased renal and intestinal losses of calcium and reduced production of growth hormone and insulin-like growth factor 1 (IGF1) are the other factors that also contribute to GIO [15,16].

In this study, osteoporosis was induced in rats with a previously reported method [17]. Briefly, all rats except controls

were injected subcutaneously (sc) with methylprednisolone 10 mg/kg/day for 4 weeks. In the steroid group, BMD values of lombar vertebrae and different femur sites were determined to be statistically significantly decreased compared with the control group, showing the development of osteoporosis. In addition, alterations in the BMD values of steroid group were statistically significantly higher than the control group, as expected.

Misoprostol is an analogue of PGE1 that is mainly used in gastrointestinal system diseases to inhibit gastric acid secretion or in gynecological diseases for induction of labor and cervical dilatation. Although the anabolic effects of misoprostol on bone turnover have been known for years, the data about the effects of misoprostol on osteoporosis is limited in the literature [18,19]. Misoprostol was shown to induce epidermal growth factor expression and production by annulus cells [18]. With long-term misoprostol treatment, an increase in bone turnover, possibly with a net anabolic effect, was reported by Raisz et al. [20] in an experimental model. In another experimental study, Sonmez et al reported that 60 days of misoprostol treatment (100 and 200 micrograms/kg/day) restored bone loss in the lumbar spine of rats who had bilateral oophorectomy in a dose-dependent manner [21]. Ahmet-Camcioglu et al. [22] investigated the effects of misoprostol on BMD in 60 oophorectomized rats and determined that misoprostol could prevent bone loss only in the vertebrae. Misoprostol is inexpensive, easy to access, stored at room temperature and is preferred due to its minimal side effects. During our study 2 rats from misoprostol group were lost because of gastrointestinal system hemorrhage due to damage done by oral feeding cannula. We applied 200 μg/day dosed misoprostol orally for 28 days. When the misoprostol treated group was compared with the steroid group, the decrease of the BMD on all interest sites were observed to be less. However, this decrease which is indicative of osteoporosis was significant only in the whole femur region in the misoprostol group. As a result misoprostol was found to protect the bones from GIO except whole femur region.

Anabolic effects of melatonin on bone remodeling have been stated before. Melatonin induces the differentiation of primary osteoblasts, increases procollagen type I c-peptide expression in normal bone cells, stimulates type 1 collagen synthesis and proliferation in bone cells and inhibits bone resorption and increases bone mass by decreasing RANKL-mediated osteoclast formation [23]. However, Sethi et al. [24] reported that, a continuous 21-day melatonin exposure was required to induce osteoblast differentiation from human mesenchymal stem cells to induce osteogenesis. Recently, Sharan et al. [25] determined that melatonin was a regulator of bone mass through MT2 receptors supporting the therapeutic role of melatonin in postmenopausal osteoporosis. Amstrup et al. [26] reported that a one-year melatonin treatment resulted in an increase in BMD at femur neck and in the spine in a dose-dependent manner. The dietary melatonin supplementation was defined to have beneficial effects against the age-related bone loss in old rats, improving the microstructure and biomechanical properties of bones in different studies [27]. Melatonin was also defined to improve estrogen deficiency-induced osteoporosis and impaired osteogenic differentiation through mediating the Wnt/β-catenin pathway [28]. Melatonin has anti-oxidant properties which may also be important in prevention of GIO [29]. In our study, when melatonin-treated group was compared with the steroid group, the decreases of BMD on all interest sites except vertebrae region were observed to be less. We determined that melatonin was effective in preventing BMD decreases in steroid treated rats. Consequently, melatonin protected bones from GIO except the vertebrae region.

Besides, there was a significant difference between the BMD values of groups showing the amount of BMD changes in the proximal femur, diaphyseal femur and whole femur regions. The BMD rates of the melatonin group were statistically significantly lower than the steroid group. However, there were no significant differences between BMD values of the misoprostol, steroid and control groups in related bone regions. In that aspect, we can suggest that concurrent melatonin administration may be more effective in preventing GIO than misoprostol.

The most effective method of diagnosis and treatment follow-up for osteoporosis is DEXA [30]. In our study we used DEXA to show BMD measurements as it is easy to apply, less costly, and it can give simultaneous measurements for peripheral and spinal bone structures with less radiation exposure in a shorter time. Some histological parameters were assessed in almost all of the above-mentioned studies, but when human applications are considered we believe they would not be practical.

Limitations

There are some limitations of this study. First, we did not analyze biochemical markers or histological evaluation of bone formation and destruction in rats. If these blood and urine tests or tissue analyses were available, we could have a more detailed data to understand the pathogenesis of GIO and protective effects of misoprostol and melatonin. The second point was that the lumbar region and femur were not sampled for histomorphometric investigations.

Conclusion

Positive effects of misoprostol and melatonin on bone metabolism in rats with GIO were determined in this study. Misoprostol and melatonin seem to be potential agents that can be used in the prevention of osteoporosis in the near future because they are inexpensive, cost-effective and patient-compliant with fewer side effects. Larger prospective, clinical studies are required to determine the exact role of these molecules on prevention of GIO.

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Prevalence of depression and anxiety disorders among bariatric surgery patients

Bariatrik cerrahi hastalarında depresyon ve anksiyete bozukluklarının sıklığı

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Abstract

Aim: Obesity carries with itself an increased risk of psychological distress, depression and anxiety. Several studies have proven that the best modality of treatment for morbid obesity is bariatric surgery. However, the outcome of bariatric surgery on psychological health varies between individuals. Comprehensive perioperative mental health evaluation for patients seeking bariatric surgery is important, as psychiatric comorbidities could result in poor outcomes, and based on our knowledge, studies on psychiatric outcomes post bariatric surgery are limited in Saudi Arabia. This study is aimed at assessing the impact of bariatric surgery on developing depression and anxiety symptoms.

Methods: Data for this cross-sectional study were collected from patients via an electronic self-administered questionnaire of both genders who underwent bariatric surgery during the period between July 2013 and July 2017 at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia.

Results: The total number of the participants was 214, wherein 66 (30.8%) were males and 150 (69.2%) were females. Participants who underwent bariatric surgery ranged between 17 and 64 years of age with a median age of 36.69 years. With regards to preoperative assessment, we found that 95.8% of our sample did not visit a psychiatry clinic. The postoperative percentage of depression and anxiety among patients was 67 (31.3%) and 40 (18.7%), respectively. Using multivariate regression analysis, patients' income was found to be significantly associated with anxiety, those who had higher income had less odds of being anxious compared to the group with low income (<3000 riyals) and this was statistically significant.

Conclusion: Compared to general population, the post bariatric surgery prevalence of anxiety and depression is high. We recommend pre- and postoperative psychiatric assessment for all bariatric surgery patients in centers where this has not yet been implemented in the pre- and postoperative protocols.

Keywords: Bariatric surgery, Obesity surgery, Preoperative assessment, Bariatric anxiety, Bariatric depression

Öz

Amaç: Obezite, artmış psikolojik stres, depresyon ve anksiyete riski taşır. Bazı çalışmalar morbid obezite için en iyi tedavi yönteminin bariatrik cerrahi olduğunu kanıtlamıştır. Ancak, bariatrik cerrahinin psikolojik sağlık konusundaki sonucu bireyler arasında değişmektedir. Bariatrik cerrahi arayan hastalar için kapsamlı perioperatif zihinsel sağlık değerlendirmesi önemlidir, çünkü psikiyatrik komorbiditeler kötü sonuçlara neden olabilir ve bilgilerimize dayanarak, Suudi Arabistan'da bariyatrik cerrahi sonrası psikiyatrik sonuçlarla ilgili çalışmalar sınırlıdır. Bu çalışma, bariatrik cerrahinin depresyon ve anksiyete semptomları geliştirmedeki etkisini değerlendirmeyi amaçlamaktadır.

Yöntemler: Bu kesitsel çalışmaya ilişkin veriler, Temmuz 2013 ile Temmuz 2017 arasında Kral Abdulaziz Üniversitesi Hastanesi (KAUH), Cidde, Suudi Arabistan'da bariatrik cerrahi uygulanan her iki cinsiyetten elektronik olarak uygulanan bir anket formu ile hastalardan toplandı.

Bulgular: Katılımcıların toplam sayısı 214 olup, 66'sı (%30,8) erkek, 150'si (%69,2) kadındır. Bariatrik cerrahi geçiren katılımcılar 17-64 yaşları arasındaydı ve ortanca yaşları 36,69 idi. Preoperatif değerlendirme açısından, örneklemimizin %95.8'inin bir psikiyatri kliniğini ziyaret etmediğini bulduk. Postoperatif depresyon ve anksiyete yüzdesi hastalar arasında sırasıyla 67 (%31,3) ve 40 (%18,7) idi. Çok değişkenli regresyon analizini kullanarak, hastaların gelirlerinin kaygı ile anlamlı bir şekilde ilişkili olduğu, daha yüksek geliri olanların düşük gelirli gruplara göre (<3000 riyal) daha az endişeli olma olasılıkları olduğu istatistiksel olarak anlamlı görülmüştür.

Sonuç: Bariatrik cerrahi sonrası genel popülasyona göre kaygı ve depresyon prevalansı yüksektir. Tüm bariatrik cerrahi hastaları için henüz uygulanmayan ve ameliyat öncesi protokollerde uygulanmayan merkezlerde psikiyatrik psikiyatrik değerlendirme yapılmasını öneriyoruz.

Anahtar kelimeler: Bariatrik cerrahi, Obezite cerrahisi, Preoperatif değerlendirme, Bariatrik kaygı, Bariatrik depresyon

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Introduction

Obesity is one of the major health problems that can lead to numerous comorbidities such as cardiovascular disease, metabolic syndrome and increased mortality [1-6]. Obese individuals have an increased risk of psychological distress, depression, anxiety and impaired health-related quality of life (HRQoL) [7]. Clinical significance of psychiatric disorders among obese patients is not fully understood; higher rate of depression has been observed among patients with obesity-related comorbidities like cardiovascular diseases and diabetes mellitus type 2 [8].

Several studies has shown that the best modality of treatment for morbid obesity is bariatric surgery [3, 4] which has been proven to be effective in controlling weight, thereby, increasing the survival rate and remarkably decreasing the overall mortality [9]. However, the outcome of bariatric surgery on psychological health, depression and anxiety varies between individuals. The most common psychiatric diseases among bariatric surgery candidates are anxiety disorders, mood disorders, binge eating disorder (BED), and personality disorders [10-12].

A study conducted in Norway reported a significant reduction in prevalence of psychiatric disorders from pre-operative assessment to follow-up for a one-year period after surgery [13], while a study in Germany revealed a gradual decrease in depression from 32.7% at baseline, to 16.5% at 6–12 months, and 14.3% at 2–3 years after surgery [14]. Other studies have also reported decreases in levels of depression up to two and even four years postoperatively [15]. However, some studies suggested the opposite including conditions wherein the improvements following surgery may not be maintained after the first post-operative year [16] and that the depressive symptoms may worsen in some patients [17]. Others suggested that patients who have undergone bariatric surgery may have a higher chance of depression, anxiety and other psychiatric illnesses compared to other obese individuals with similar preoperative characteristics [7]. Further studies have also reported that up to 65% of bariatric surgery patients endorsed a lifetime history of depression or mood disturbance [18,19]. As far as our knowledge on this subject is concerned, studies addressing the prevalence of psychiatric disorders among bariatric patients are limited in Saudi Arabia. This study is aimed at assessing the prevalence of depression and anxiety symptoms among patients who underwent bariatric surgery.

Materials and methods

Study design and data collection

This is a cross-sectional study targeting patients of both genders who underwent bariatric surgery at King Abdulaziz University Hospital (KAUH), Jeddah, Saudi Arabia. For a better representation of our data, we aimed at including all patients who underwent bariatric procedures in KAUH during July 2013 to July 2017. Patients with a history of major medical problems, such as psychiatric illness, drug or alcohol addiction were excluded from the study as were those with a case of pregnancy or malignant neoplasm. Informed consent was taken from all participants. The study protocol was reviewed and approved by Research Committee of the Unit of Biomedical Ethics at KAUH.

After reviewing the literature, we constructed an electronic self-administered questionnaire made of three parts. First is the demographic information – age, nationality, gender, marital status, education, household income, place of residence, and whether the patient has any chronic illness. Second is the preoperative data including body mass index (BMI), type of the bariatric surgery, and history of any psychiatric illness (based on record of visiting psychiatry clinic before and after the surgery). The third part consists of two questionnaires used to assess patient's anxiety and depression disorders, in which we adopted the Generalized Anxiety Disorder – 7 (GAD-7) assessment for anxiety evaluation, and Patient Health Questionnaire – 9 (PHQ-9) for depression evaluation.

The PHQ-9 and GAD-7 were developed by Robert L. Spitzer, MD, and colleagues, with an educational grant from Pfizer Inc. [20,21]. Different studies have confirmed the validity and reliability of the GAD-7 and PHQ-9 as suitable instruments to measure perceived anxiety and depression. The Arabic version of the PHQ-9 and GAD-7 were also approved to be valid and reliable among Arabic individuals [22]. The questionnaires were validated and piloted prior to the study.

Measures

Generalized Anxiety Assessment – 7 (GAD-7) Scale

The GAD-7 has been validated as a screening tool and a severity assessment scale for general anxiety disorder in clinical practice and research [20]. GAD-7 consists of seven items that reflected the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) [20], that asked the patients how often during the last 2 weeks they were complaining of each item. Response options were "not at all", "several days", "more than half the days", and "nearly every day," scored as 0, 1, 2, and 3, respectively. An eighth item was added to the questionnaire to assess the functional status of the participants and it was not used in the severity scale. Scores for the seven items range from 0 to 21. Severity scores were as follows: minimal (0-4), mild (5-9), moderate (10-14) and severe (15-21) [20]. A score of 10 or more was given for having good diagnostic sensitivity and specificity for identifying cases of GAD [20]. Participants within this category should be assessed by psychiatrist and may require further evaluation [23].

Patient Health Questionnaire – 9 (PHQ-9) Scale

The PHQ-9 contains nine items that corresponded to the nine symptoms of depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [21]. Here, each item is rated on a frequency scale of 0–3 with a maximum score for the 9 items being 27. Response options were "not at all," "several days," "more than half the days," and "nearly every day," scored as 0, 1, 2, and 3, respectively. A tenth item was added to the questionnaire to assess the functional status of the participants and it was not used in the severity scale. Categories of depressive symptom severity scale were – minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). Those who scored ≥10 (moderate - severe) were categorized as needing further evaluation and medical treatment [24].

Statistical analysis

Patient characteristics were presented across different categories by proportions. Continuous data was presented using mean and standard deviation, mean(SD). Unadjusted and adjusted logistic regression was carried out to analyze the association of anxiety and depression with baseline parameters and BMI after operation and reported in odds ratio (OR). Two-sided *P*-value of 0.05 or less were considered significant. Participants were categorized into two groups due to the small sample size for anxiety and depression: group 1 included minimal and mild; and group 2 included moderate and severe. Statistical analysis was performed using the Statistical Package for Social Sciences version 24.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

A total of 300 questionnaires were distributed, the response rate for which was 71.6%. Participants who reported psychiatric disorder preoperatively were excluded from the study. The analysis included 214 participants; 66 (30.8%) were males and 148 (69.2%), females. The median age of study participants was 36.69 years (17– 64 years). About half of our population (53.3%) had a bachelor's degree. Chronic medical diseases were present in (34.1%) of the patients; furthermore, 72.9% were morbidly obese. Demographic data of the participants has been documented in Table 1.

The mean preoperative and postoperative Body Mass Index (BMI) of the participants was 46.2 (8.8) kg/m^2 and 31.2 (7.6) kg/m^2, respectively (Figure 1). 182 (84.3%) of the participants underwent Sleeve Gastrectomy and 24 (11.1%) of the sample reported some sort of postoperative complications. With regards to preoperative assessment, we found that 95.8% of our sample population had not undergone any psychiatric assessment. Out of the 214 patients in our study, the percentage of patients who reported depression and anxiety post-bariatric surgery was 67 (31.3%) and 40 (18.7%), respectively (Figures 2 and 3). With regards to unadjusted univariate analysis of predictors of anxiety, we found that marital status, income and preoperative BMI were associated with anxiety. Using the multivariate regression analysis (Table 2), patients' income was found to be significantly associated with anxiety – those who had higher income had lower odds of being anxious compared to the group with low income (<5000 riyals) and this factor was statistically significant. Other factors such as marital status, preoperative BMI and post-operative BMI were not significant (Table 3). On the other hand, using unadjusted univariate analysis of predictors of depression, we found that income and post-operative BMI were associated with depression (Table 2). The multivariate regression analysis of predictors of depression in our study population did not show any significant predictors of depression in these patients' population (Table 3).

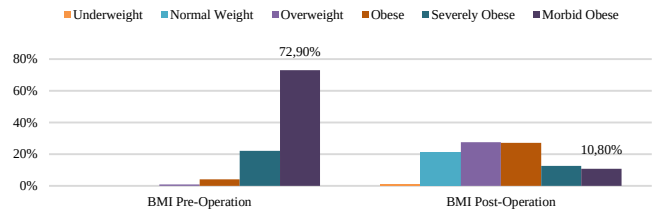

Figure 1: Differences in Body Mass Index (BMI) pre and post-operative

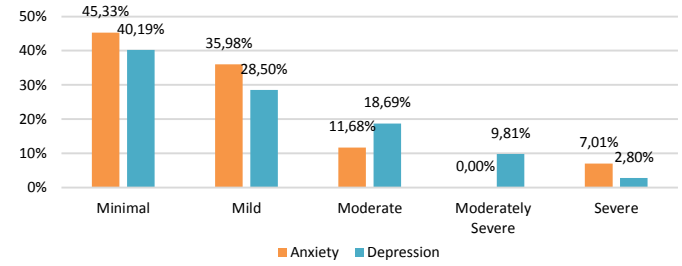

Figure 2: The distribution of anxiety and depression post-operative

Table 1: Demographic data for patients with anxiety and depression post-bariatric surgery

Variables		Total		Anxiety No		Anxiety Yes		Depression No		Depression Yes	
		n=214	100%	n=174	%	n=40	%	n=147	%	n=67	%
Age	Less than 30	57	26.6	46	21.5	11	5.1	42	19.6%	15	7.0
	30 - 39	75	35.0	62	29.0	13	6.1	50	23.4%	25	11.7
	40 - 49	56	26.2	45	21.0	11	5.1	39	18.2%	17	7.9
	50 and above	26	12.1	21	9.8	5	2.3	16	7.5%	10	4.7
Nationality	Saudi	178	83.2	146	68.2	32	15.0	124	57.9%	54	25.2
	Non Saudi	36	16.8	28	13.1	8	3.7	23	10.7%	13	6.1
Gender	Male	66	30.8	54	25.2	12	5.6	49	22.9%	17	7.9
	Female	148	69.2	120	56.1	28	13.1	98	45.8%	50	23.4
Marital Status	Single	58	27.1	42	19.6	16	7.5	39	18.2%	19	8.9
	Married	129	60.3	108	50.5	21	9.8	90	42.1%	39	18.2
	Divorced / Widowed	27	12.6	24	11.2	3	1.4	18	8.4	9	4.2
Education	High School or Less	58	27.1	47	22.0	11	5.1	39	18.2%	19	8.9
	Diploma	23	10.7	17	7.9	6	2.8	15	7.0	8	3.7
	Bachelor degree	114	53.3	94	43.9	20	9.3	81	37.9%	33	15.4
	Masters or PhD	19	8.9	16	7.5	3	1.4	12	5.6	7	3.3
Income	< 5000 SR	41	19.2	28	13.1	13	6.1	22	10.3%	19	8.9
	5000 - 10000 SR	86	40.2	73	34.1	13	6.1	64	29.9%	22	10.3
	> 10000 - 20000 SR	51	23.8	42	19.6	9	4.2	34	15.9%	17	7.9
	> 20000 SR	36	16.8	31	14.5	5	2.3	27	12.6%	9	4.2
Chronic Disease	No	141	65.9	117	54.7	24	11.2	99	46.3%	42	19.6
	Yes	73	34.1	57	26.6	16	7.5	48	22.4%	25	11.7
Pre-Operation BMI	Overweight / Obese	11	5.1	8	3.7	3	1.4	8	3.7	3	1.4
	Severely Obese	47	22.0	44	20.6	3	1.4	34	15.9%	13	6.1
	Morbid Obese	156	72.9	122	57.0	34	15.9	105	49.1%	51	23.8
Post-Operation BMI	Underweight / Normal	47	22.0	38	17.8	9	4.2	36	16.8%	11	5.1
	Overweight	59	27.6	53	24.8	6	2.8	42	19.6%	17	7.9
	Obese	58	27.1	45	21.0	13	6.1	41	19.2%	17	7.9
	Severely Obese	27	12.6	19	8.9	8	3.7	16	7.5	11	5.1
	Morbid Obese	23	10.7	19	8.9	4	1.9	12	5.6	11	5.1
Surgery Type	Sleeve	177	82.7	145	67.8	32	15.0	123	57.5%	54	25.2
	Bypass	32	15.0	25	11.7	7	3.3	22	10.3%	10	4.7
	Sleeve & Bypass	5	2.3	4	1.9	1	0.5	2	0.9	3	1.4
Date since operation	Less than 1 Year	71	33.2	59	27.6	12	5.6	47	22.0%	24	11.2
	1 - 2 Years	49	22.9	37	17.3	12	5.6	34	15.9%	15	7.0
	2 - 3 Years	49	22.9	40	18.7	9	4.2	32	15.0%	17	7.9
	More than 3 Years	45	21.0	38	17.8	7	3.3	34	15.9%	11	5.1
Post-surgical complications	No	190	88.8	157	73.4	33	15.4	132	61.7%	58	27.1
	Yes	24	11.2	17	7.9	7	3.3	15	7.0	9	4.2

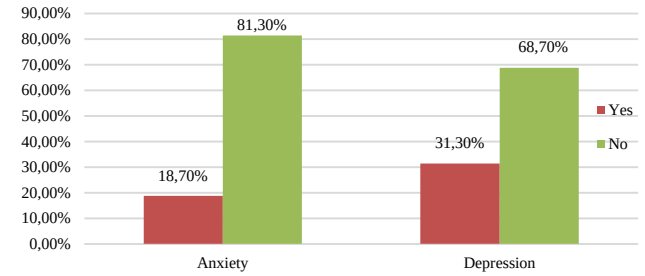

Figure 3: The percentage of anxiety and depression in the sample

Table 2: Unadjusted odds ratio (OR) estimates of factors for Anxiety and Depression (Logistic Regression). Comparisons were set as the reference category is the first

Variables	Anxiety				Depression			
	B	df	OR	*P*-value	B	df	OR	*P*-value
Age		3		0.986		3		0.695
Less than 30		3		0.986		3		0.697
30 – 39	-0.131	1	0.877	0.772	0.336	1	1.400	0.386
40 – 49	0.022	1	1.022	0.963	0.199	1	1.221	0.634
50 & Above	-0.004	1	0.996	0.994	0.560	1	1.750	0.266
Nationality		1		0.558		1		0.500
Saudi								
Non-Saudi	0.265	1	1.304	0.552	0.261	1	1.298	0.496
Gender		1		0.898		1		0.337
Male								
Female	0.049	1	1.050	0.898	0.386	1	1.471	0.244
Marital Status		2		0.111		2		0.915
Single		2		0.112		2		0.915
Married	-0.673	1	0.510	0.076	-0.117	1	0.889	0.730
Divorced or Widowed	-1.114	1	0.328	0.101	0.026	1	1.026	0.958
Education		3		0.808		3		0.862
High school or Less		3		0.797		3		0.862
Diploma	0.411	1	1.508	0.480	0.091	1	1.095	0.862
Bachelor	-0.095	1	0.909	0.819	-0.179	1	0.836	0.607
Masters or PhD	-0.222	1	0.801	0.756	0.180	1	1.197	0.744
Income		3		0.147		3		0.103
> 5000		3		0.131		3		0.102
5000 – 10000	-0.958	1	0.384	0.034	-0.921	1	0.398	0.021
10000 – 20000	-0.773	1	0.462	0.120	-0.547	1	0.579	0.205
> 20000	-1.057	1	0.347	0.072	-0.952	1	0.386	0.055
Chronic Disease		1		0.388		1		0.506
No								
Yes	0.314	1	1.368	0.385	0.205	1	1.228	0.505
Pre-Operation BMI		2		0.025		2		0.771
Overweight or Obese		2		0.067		2		0.774
Severely Obese	-1.705	1	0.182	.0059	0.019	1	1.020	0.979
Morbid Obese	-0.297	1	0.743	0.673	0.259	1	1.295	0.711
Post-Operation BMI		4		0.224		4		0.239
Underweight or Normal		4		0.265		4		0.238
Overweight	-0.738	1	0.478	0.194	0.281	1	1.325	0.531
Obese	0.199	1	1.220	0.683	0.305	1	1.357	0.497
Severely Obese	0.575	1	1.778	0.305	0.811	1	2.250	0.120
Morbid Obese	-0.118	1	0.889	0.859	1.099	1	3.000	0.042
Surgery Type		2		0.881		2		0.408
Sleeve		2		0.877		2		0.416
Bypass	0.238	1	1.269	0.613	0.035	1	1.035	0.933
Sleeve & Bypass	0.125	1	1.133	0.913	1.229	1	3.417	0.185
Date since Operation		3		0.689		3		0.682
Less than 1 Year		3		0.680		3		0.694
1 – 2 Years	0.467	1	1.595	0.309	-0.146	1	0.864	0.714
2 – 3 Years	0.101	1	1.106	0.835	0.040	1	1.040	0.919
More than 3 Years	-0.099	1	0.906	0.849	-0.456	1	0.634	0.286
Post-Operative Complications		1		0.184		1		0.494
No								
Yes	0.672	1	1.959	0.168	0.312	1	1.366	0.489

Table 3: Adjusted odds ratio (OR) of study factors. Comparisons were set as the reference category is the first.

Model and Factors Characteristics	Anxiety				Depression			
	B	df	OR	*P*-value	B	df	OR	*P*-value
Model								
Marital Status								
Single		2		0.091				
Married	-0.639	1	0.528	0.107				
Divorced or Widowed	-1.417	1	0.242	0.054				
Income								
< 5000		3		0.054		3		0.264
5000 – 10000	-1.273	1	0.280	0.009	-0.780	1	0.458	0.061
10000 – 20000	-1.090	1	0.336	0.042	-0.438	1	0.645	0.323
> 20000	-1.223	1	0.294	0.064	-0.762	1	0.467	0.139
BMI Pre-Operation								
Overweight or Obese		2		0.056				
Severely Obese	-1.868	1	0.154	0.046				
Morbidly Obese	-0.386	1	0.680	0.606				
BMI Post-Operation								
Underweight or Normal						4		0.507
Overweight					0.144	1	1.155	0.753
Obese					0.256	1	1.291	0.580
Severely Obese					0.640	1	1.897	0.233
Morbidly Obese					0.847	1	2.333	0.131

Discussion

Obesity is one of the main causes of multiple comorbidities and increasing mortality in the world today [1-6]. It is also considered as a main contributor for having depression, anxiety and psychological distress [7]. In this study, we aimed to find the percentages of depression and anxiety post bariatric surgery and the associated risk factors. According to our study, the prevalence of depression after bariatric surgery was 31.3%, and this is in excellent agreement with a study conducted in the United States, which showed that 32% of the candidates had depression in the second year post-operatively [25]. This prevalence is considered to be higher than the normal population; as a recent study in Saudi Arabia showed a much lower prevalence of depression (5.4%) among adults in the general population [26]. Another study showed that the lifetime prevalence of depression in Canada was 8.3% and the United States was 16.9% [27]. All of these percentages are still lower than the prevalence of depression observed in our study. On the other hand, a study that compared the preoperative and post-operative depression rates found that depression decreased postoperatively with no significant difference [28]. Another study in Germany, reported a significant decrease in depression post bariatric surgery from the baseline [14].

In a meta-analysis measuring the prevalence of anxiety across cultures, it was found that the estimated one-year and lifetime prevalence of anxiety disorders is 10.6% and 16.6%, respectively [29]. In our study, the prevalence of anxiety was 18.7%. Interestingly, a prospective study done in Brazil among 32 participants, found that the anxiety actually decreased significantly from 87.0% preoperatively to 56.5% postoperatively [30]. Furthermore, de Zwaan et al. [14] reported that the prevalence of anxiety disorders did not change after surgery in comparison with baseline. Thus, it seems that anxiety decreases post bariatric surgery, but still remains higher than the prevalence in the normal population.

In the current study, we found that marital status, income and preoperative BMI were associated with anxiety. A study published in 2014 among civilians aged more than 18 years showed that factors such as low self-esteem, family history of major depressive disorders (MDD), female gender, childhood sexual abuse, white race, lower educational attainment, number of traumatic experiences by age 21, and disturbed family environment were significantly associated with anxiety [31]. In the current study, we did not measure some of the above-mentioned risk factors. Among the factors that we did analyze, however, we were unable to find any association between years of education and female sex with anxiety; this could be attributed to the fact that our sample had a high proportion of female participants. A study conducted in Portugal concluded that the outcomes of bariatric surgery have a tendency to be related to the presence of depression [32]. Preoperative screening and treatment of anxiety and depression could add to the efficacy and amplify weight loss in patients after surgery, enhancing their quality of life in a more continuous manner. In our study, we were able to uncover the prevalence of postoperative anxiety and depression across the sample size which, compared to the to the prevalence in general population, is high. However, we could not have a measure of the preoperative prevalence of the same disorders in those patients as no routine preoperative screening had been performed prior to undergoing their surgical procedure.

Despite providing many interesting observations, our study has certain limitations. The first limitation is that it was a

cross-sectional study; it did not cover the whole population, and therefore the conclusions might differ across the sociodemographic variables. Consequently, it is imperative to conduct more longitudinal studies, including more assessment of patients in the follow-up aspect that would definitely provide further information to understand the association between psychiatric disorders and post bariatric surgery status. Secondly, the sample size of our study was small which may limit the generalizability of our findings, and therefore we suggest multiple center studies.

Conclusion

The results of our study have shown that the post bariatric surgery prevalence of anxiety and depression is high in comparison to the general population. Therefore, we strongly recommend pre- and postoperative psychiatric assessment for all bariatric surgery patients in centers where this has not yet been implemented in the pre- and postoperative protocols. The implementation of such screening might help control these disorders as well as improve the postoperative outcomes of bariatric surgery.

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Vitamin D status in infancy: What is the solution?

Bebeklikte D vitamini sorunu: Çözüm nedir?

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Abstract

Aim: Vitamin D deficiency and insufficiency are common public health problems throughout the world. Besides important multisystemic metabolic effects, vitamin D is necessary for a healthy skeletal system. Various reasons cause vitamin D deficiency in infancy, and supplementation is one of the treatment options. A nationwide supplementation program has been implemented in Turkey since 2005. In this study, we aimed to evaluate the efficacy of this program in our city.

Methods: All infants aged between one and twelve months who were referred to the pediatric outpatient clinics of the hospital and tested for serum 25-(OH)-D levels between January 1, 2015 and December 31, 2016 were enrolled in the study. Patients with chronic illnesses were excluded. Data was obtained retrospectively from the hospital registry. In accordance with the criteria of American Academy of Pediatrics, patients were divided into three groups based on serum 25-(OH)-D levels as follows: 25-(OH)-D<15 ng/ml were considered deficient, 15.1<25-(OH)-D<20 ng/ml were considered insufficient and sufficiency was defined as 25-(OH)-D>20 ng/ml.

Results: The study group consisted of 265 infants. The mean age of the group was 7.53 (2.75) months. Approximately 15% (n=39) of the study group had vitamin D deficiency, 10.5% (n=28) had insufficiency and Vitamin D levels of 74.4% (n=198) of the group were sufficient. Serum 25 (OH) D levels did not differ with gender, age or season (P=0.12, P=0.65 and P=0.09, respectively). Vitamin D levels were sufficient in 78.5% (n=150) of the urban area residents and 69.6% (n=32) of the rural area residents, between which there was no significant difference (P=0.32).

Conclusion: Our results established that supplementation is one of the ways to avoid limitations affecting serum vitamin D levels. Supplementation with 400 IU/day Cholecalciferol is provided during the first year of life by the Turkish Ministry of Health, which we believe rendered gender, age, time of measurement and residential area insignificant in terms of 25(OH) D levels. This supplementation program may solve the problem of vitamin D insufficiency or deficiency among disadvantaged groups.

Keywords: Vitamin D status, Cholecalciferol supplementation campaign, Infancy, Turkey

Öz

Amaç: D vitamini eksikliği tüm dünyada yaygın bir halk sağlığı sorunudur. Vitamin D pek çok sistemi ilgilendiren etkilerinin yanında iskelet sistemi sağlığı için gereklidir. Bebeklik döneminde çeşitli nedenlere bağı olarak D vitamini eksikliği gelişebilir. Yeterlilik sağlamanın yollarından biri destek tedavisidir. Türkiye'de 2005 yılından beri tüm bebekleri kapsayan ulusal bir kampanya ile vitamin desteği ücretsiz olarak sağlanmaktadır. Bu çalışmada amaç kampanyanın ilimizdeki etkinliğini saptamaktır.

Yöntemler: Çalışmaya hastanenin Çocuk Sağlığı ve Hastalıkları polikliniklerine 1 Ocak 2015- 31 Aralık 2016 tarihleri arasında başvuran, 1-12 aylıkken 25- hidroksi- D düzeyi çalışılan tüm sağlıklı bebekler dahil edilmiştir. Altta yatan kronik hastalığı olanlar çalışma dışı bırakılmıştır. Veriler kayıt sisteminden geriye dönük olarak elde edilmiştir. Katılımcılar Amerikan Pediatri Akademisi'nin belirlemiş olduğu kriterlere dayanarak serum 25 (OH) D düzeylerine göre gruplara ayrılmıştır. Bu gruplar sırası ile "eksiklik: <15 ng/ml", "yetmezlik: 15,1-20 ng/ml" ve "yeterlilik: >20 ng/ml" olarak belirlenmiştir.

Bulgular: Çalışmada 265 bebek değerlendirilmiştir. Yaş ortalaması 7,53 (2,75) aydır. Bebeklerin %14,7'sinde (n=39) D vitamini eksikliği, %10,5'inde (n=28) yetersizliği saptanmıştır. Grubun %74,4'ünde (n=198) yeterli düzey sağlanmıştır. Cinsiyete, yaşa veya ölçüm yapılan mevsime göre gruplar arasında 25 (OH) düzeyleri açısından anlamlı fark saptanmamıştır (sırasıyla P=0,12; P=0,65 ve P=0,09). Kentsel bölge sakinlerinin %78,5'inde (n=150), kırsal kesimde yaşayanların %69,9'unda (n=32) 25 (OH) D düzeyleri yeterli olup, aralarında anlamlı fark saptanmamıştır (P=0,32).

Sonuç: Vitamin desteği D vitamini eksikliğini kolaylaştıracak etmenlerin yok edilmesini sağlayan etkin bir yoldur. Türkiye Cumhuriyeti Sağlık Bakanlığı tarafından sağlanan günlük 400 IU dozundaki Kolekalsiferol desteği ile cinsiyet, yaş, ölçüm zamanı, yaşanılan yer gibi olumsuz etki oluşturabilecek değişkenler bertaraf edilebilmektedir. Aynı uygulamanın hassas gruplar için de uygulanabileceği düşünülmektedir.

Anahtar kelimeler: D vitamini düzeyi, Ulusal D vitamini desteği kampanyası, Bebeklik dönemi, Türkiye

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Introduction

Insufficient or deficient vitamin D is a common, important pediatric health problem throughout the world as well as in our country, despite our warm and sunny climate [1,2]. In the first year of life infants carry the risk of vitamin D deficiency (VDD) since breast milk cannot supply sufficient amounts [3,4]. Vitamin D is mainly synthesized in the skin under direct sunlight. VDD or vitamin D insufficiency (VDI) becomes inevitable unless adequate sunlight exposure and/ or vitamin D supplementation are provided. These problems result in poor bone health and multi-systemic problems related to cardiovascular, respiratory, and nervous systems as well as immunity [5]. A nationwide vitamin D supplementation campaign for providing free vitamin D drops for every infant in primary health care centers began in 2005. The recommended dose is 400 IU/day from the neonatal period to at least 1 year of age, preferably until 3 years old [5,6]. All infants were given free vitamin D (Cholecalciferol solutions that contain 133 IU vitamin D3 in one drop) drops and recommended to receive 400 IU (3 drops) daily to avoid vitamin D insufficiency (VDS). Following this campaign, the incidence of nutritional rickets, which used to be a crucial public health problem, decreased [7].

Serum 25- hydroxy vitamin D (25 (OH) D) is the primary metabolite of active vitamin D. Its half-life is longer than calcitriol (approximately three weeks vs 4-6 hours), which makes it a more reliable parameter to evaluate vitamin D status [8]. Serum 25 (OH) D concentration depends on direct sunlight exposure, seasons, latitude, skin pigmentation, clothing, maternal status, supplementation, or conditions that impair vitamin D metabolism and malabsorption. The cut-off value for 25 (OH) D is usually based on parathormone (PTH) levels to keep bone remodeling under control. Sufficient vitamin D level is the value that keeps PTH levels within normal ranges according to age [9]. Different authors or associations define vitamin D status with minor variations. The American Academy of Pediatrics (AAP) classified vitamin D status in the pediatric population using the following 25(OH) D levels: Severe deficiency : <5 ng/ml, deficiency: <15 ng/ml, insufficiency: 15 - 20 ng/ml, sufficiency: 20-100 ng/ml, excess: 101-150ng/ml, and intoxication: 150 ng/ml [10]. The Endocrine Society defined vitamin D status with a consensus statement: Deficiency: <30 nmol/ml (<12ng/ml), insufficiency: 30-50 nmol/l (12-20 ng/ml) and sufficiency: >50 nmol/ml (>20 ng/ml) as 1 ng/ml = 2.5 nmol/l. Here, the cut off value was <30 nmol/ml (<12ng/ml) to prevent nutritional rickets [11].

This study was designed to detect the efficacy of the supplementation programmed in our city based on AAP criteria ten years after the supplementation campaign began.

Materials and methods

This cross-sectional study with retrospective design was conducted in a small city located at 36^0 57’ 06’’- 36^0 31’ 53’’ longitude east and $41^0$04’ 54’’- 40^0 16’ 16’’ latitude north, in the middle Black Sea region. [12]. The climate is sunny between May and October with minimal air pollution [13]. All infants aged between one and twelve months who were referred to the pediatric outpatient clinics of the hospital and tested for serum 25-(OH)-D levels between January 1, 2015 and December 31, 2016 were enrolled in the study. Patients with chronic illnesses and those in need of regular drug therapy except iron supplementation were excluded. None had failure to thrive or developmental delay. Data was obtained retrospectively from the hospital registry. Serum levels of 25 (OH) D levels (normal range: 20-100 ng/ml) were measured by electrochemiluminescence with the Roche modular analytical E 170, through venous blood samples. The specificity and sensitivity of the method is 98% and 95% respectively with coefficient of variation (CV) value 6.8. Venous blood samples were obtained from all patients after physical examination between 8.30-12.00 AM, per hospital rules. For the evaluation of results the participants were divided into groups according to their serum 25(OH) D levels based on the American Academy of Pediatrics (AAP) criteria. 25-(OH)-D<15 ng/ml were considered deficient, 15.1<25-(OH)-D<20 ng/ml were considered insufficient and sufficiency was defined as 25-(OH)-D >20 ng/ml.

This study was approved by the Institutional Committee of Scientific Researches of Amasya University Sabuncuoğlu Şerefeddin Education and Research Hospital with (No. 62949364-000-6222/2017, 19/10/2017).

Statistical analysis

Statistical analyses were performed with SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL, USA). The data were presented as frequencies, medians and minimum–maximum, range or mean (SD) by descriptive statistics, as needed. The variables were evaluated using visual (histograms, probability plots) and analytical methods (Kolmogorov Simirnov test) to determine normal distribution. As the serum 25 (OH) D levels were not normally distributed, Kruskall Wallis test was conducted to compare its levels among different groups and Mann Whitney U test was performed to test the significance of pair-wise differences using Bonferroni corrections to adjust for multiple comparisons. The Chi-square test or Fisher’s exact test was used to compare variables among various groups. A *P*-value of less than 0.05 was considered statistically significant.

Results

The study group consisted 147 (55.3%) males and 118 (44.7%) females (n=265). The mean age of the group was 7.53 (2.75) months (1-12 months). 83 (31.3%) patients were younger than 6 months. 46 (19.4%) and 191(80.6%) patients lived in rural and urban areas, respectively.

The mean serum concentration of 25 (OH) D was 28.37 (12.49) ng/ml (3.30-94.5; median: 29.60 ng/ml) and none of the patients showed clinical signs of rickets. According to AAP classification, 14.7% (n=39) of the study group had VDD, 10.5% (n= 28) had VDI and 74.4% (n=198) had VDS. 9.8% (n=26) of the participants had VDD according to the Endocrine Society consensus statement (2015).

Vitamin D levels were 28.18 (12.23) ng/ml among the <6-month-old group and 28.45 (12.64) ng/ml among 6-12-month-old group. Deficiency was detected in 16.9% (n=14) of the younger group and 13.7% (n=25) of the older group. Age as a variable caused no significant difference between two groups (*P*=0.65).

The mean concentration of 25(OH) D levels were 28.40 (13.30) ng/ml in males and 30.10 (11.2) ng/ml in females; it did not differ with gender (P=0.12). 25(OH) D levels were sufficient in 80.5% (n=95) of the females and 70.1% (n=103) of the males. 10.2% (n=12) of the males and 18.4% (n=27) of the males had deficiency.

The serum levels of 25(OH) D were also compared among seasons. The mean concentration of 45 patients who were tested during winter was 24.32 (11.63) ng/ml. This value was 27.82 (12.66) ng/ml during spring, 30.73 (13.15; range: 4.2-73.0; median: 30.7) ng/ml during the summer and 28.81 (11.31) ng/ml during autumn. There was no significant difference in terms of serum 25(OH) D levels between seasons (P=0.09).

Mean concentration of serum vitamin D levels in those living in urban and rural areas were 28.88 (10.99) ng/ml and 28.40 (14.02) ng/ml, respectively. Vitamin D levels were sufficient in 78.5% (n=150) urban area residents and 69.6% (n=32) in rural area residents. There was no significant difference between two groups (P=0.32).

Vitamin D levels were also evaluated considering birth seasons. 50 of the participants were born in the winter, 47 in spring, 69 in the summer and 71 in autumn. The main concentration of 25 (OH) D levels were 31.88 (10.38); 25.60 (11.67); 27.22 (11.37); 30.24 (12.07), respectively. Approximately half of the vitamin D-deficient infants (48.4%; n=15) were born during summer, while 83.1% (n=59) of the autumn-born infants had sufficient serum vitamin D levels. Infants born in the summer and autumn had significantly better vitamin D levels (P<0.001). The vitamin D levels of all patients with respect to different variables are shown in Table 1.

Table 1: Distribution of vitamin D levels with regards to different parameters

Vitamin D Status	Deficiency n (%)	Insufficiency n (%)	Sufficiency n (%)	Total n	*P*-value
Gender					
Girls	12 (10.2)	11(9.3)	95 (80.5)	118	0.12
Boys	27 (18.4)	17 (11,6)	103 (70.1)	147	
Age (months)					
1-6 months	14 (16.9)	10 (12.0)	59 (71.1)	83	0.65
7-12 months	25 (13,7)	18 (9.9)	139 (76.4)	182	
Residence					
Rural area	9 (19.6)	5 (10.9)	32 (69.6)	46	0.32
Urban area	22 (11.5)	19 (9.9)	150 (78.5)	191	
Seasons of evaluation					
Winter	10.2 (22.2)	6 (13.3)	29 (64.4)	45	0.09
Spring	13(16.7)	7 (9)	58 (74.4)	78	
Summer	9 (10.7)	10 (11.9)	65 (77.4)	84	
Autumn	7 (12.1)	5 (8.6)	46 (79.3)	58	
Seasons of birth					
Winter	2 (4)	6 (12)	42 (84)	50	<0.001
Spring	9 (19.1)	7 (14.9)	31 (66)	47	
Summer	15 (21.7)	4 (5.8)	50 (72.5)	69	
Autumn	5 (7)	7 (9.9)	59 (83.1)	71	

Discussion

The main source of Vitamin D in the body is the photo conversion of 7- dehydrocholesterol to pre-vitamin D3 in the skin under direct sunlight [14]. The dietary intake is negligible in breastfed infants because the breast milk content of vitamin D is very low [3,4]. Formulas contain 400 U/ l vitamin D, and unless the infant consumes enough formula, deficiency becomes inevitable [3,5]. Insufficiency of maternal resources causes inadequate transplacental transition which contributes to poor vitamin D levels during infancy [15]. During the first year of life, direct sunlight exposure may be limited because of weather conditions or cultural habits. Supplementation seems to be the only way to avoid these limitations and the recommended dosage of 400 IU/ day is adequate if compliance is achieved. In this study group 74.4% of the participants had sufficient vitamin D levels. Comparison with respect to gender, age and seasons caused no difference, but mean concentration of 25 (OH) D changed significantly according to birth seasons.

The data of this study was classified according to AAP criteria and "deficiency" was defined as serum 25 (OH) D levels below 15 ng/ml. 14.7% of the participants were vitamin-D-deficient. A study from an industrialized city in north western Turkey reported that the mean 25 (OH) D level was 42.5 (25.8) ng/ml in infants aged between 84 and 365 days (263 (116)), and that 2.2% of all participants had vitamin D deficiency (<15ng/ml) [16]. Another study from Turkey defined deficiency as serum 25 (OH) D<20ng/ml, thus calculating deficiency rate as 57% [17]. In Hong Kong, the participants of a study did not receive vitamin D supplementation and the median serum 25(OH) D concentration at 3 months was 58 (IQR, 32-75) nmol/L. Among 155 infants, 52 (33.5%) had vitamin D deficiency, defined as serum 25(OH) D <50 nmol/L (<20 ng/ml) [18].

Deficiency starts prenatally because of poor vitamin D levels of pregnant women and 25 (OH) D levels of the cord blood are critically low even in sunny countries [15,19,20]. Turkish Ministry of Health recommends that vitamin D supplementation begin within the first days of life. Every infant is provided with 400 IU (3 drops) of Cholecalciferol solutions [6,16]. In this study group all participants were younger than one year and 74.4% of them had sufficient 25 (OH) D levels. Although supplementation is recommended throughout the whole life, after the first year, it is usually given up and a negative correlation emerges between 25 (OH) D levels and age [21]. Şahin et al. [1] reported sufficient vitamin D statuses in the first year of life but declared that the deficiency rate increased after the second year.

In this study 10.2% of the females and 18.4% of the males had deficiency, and the difference between genders was not significant. In the study of Sahin et al. [1], mean serum vitamin D levels were 30.5 (18.1) ng/ml in females and 34.7 (16.5) ng/ml in males in the first year of life. A study from İzmir had close results with a deficiency rate of 42.9% in males and 15.9% in females in a sample of 100 infants [17]. Many studies find that gender is key factor with increasing age, i.e. the increased deficiency rate among adolescent girls' [1,21].

As the main source of Vitamin D is skin synthesis under direct sunlight, seasons may cause significant changes in serum levels of 25 (OH) D [14]. Between February and May, the level is lower than other times of the year according to the data mining study of Şahin et al. [1]. In this study, the period of serum vitamin D level assessment had no significance, but season of birth proved important. In autumn-born-infants, sufficiency rate was higher than other seasons. Deficiency was frequent in infants born during winter. VDD in early infancy is related to maternal 25 (OH) D levels and studies showed that mothers who had given birth in summer and autumn had higher vitamin D levels [15]. Here, maternal 25 (OH) D levels of participants were not evaluated, which is one of the important limitations of this study. Unless patients lived at the same latitude, urban or rural areas of residence were not significant. This result was also compatible with a study from Ankara reflecting the data of a large cohort [22].

Limitations

This study has several limitations as it was retrospective and based on hospital registry. The type of vitamin D supplementation, dosage, sunlight exposure and nutritional habits of the participants were not taken in consideration. Vitamin D levels of the mothers and supplementation history during pregnancy are not known. Parathormone, calcium, phosphorus and alkaline phosphatase levels are not evaluated. The clinical statuses or bone mineral densities of the participants were not evaluated to directly predict bone health [23].

Conclusion

Our study established that supplementation is one of the ways to avoid limitations affecting serum vitamin D levels. Supplementation with 400 IU/day Cholecalciferol is provided during the first year of life by the Turkish Ministry of Health, which we believe rendered gender, age, time of measurement and residential area insignificant in terms of 25(OH) D levels. Studies show that these parameters become prominent when supplementation is given up with age or because of medical or financial reasons. Supplementation should be offered throughout the whole life to solve the public health problem of vitamin D deficiency or insufficiency.

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Can single-step dilatation technique in pediatric percutaneous nephrolithotomy be an effective alternative to stepwise dilatation?

Pediatrik perkütan nefrolitotomide tek aşamalı dilatasyon tekniği, aşamalı dilatasyona efektif bir alternatif olabilir mi?

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Abstract

Aim: The most important stage of percutaneous nephrolithotomy (PNL), which is an effective and reliable method in the treatment of large and complex kidney stones, is to create a suitable and effective tract after the accessory is provided. For this purpose, different techniques such as Amplatz, baloon and Alken dilators have been described. We aimed to compare the efficacy and safety of single-step Amplatz dilatation technique with stepwise Amplatz dilatation technique in pediatric PNL patients.

Methods: This is a retrospective cohort study. We evaluated the data from 75 PNL operations performed on 72 pediatric patients in our center within the last decade. The data from single-step dilation technique patient group (group 1, n: 41) and the stepwise dilatation technique patient group (group 2, n: 34) was compared in terms of durations of fluoroscopy and surgery, stone-free and complication rates, pre and postoperative hematocrit levels and blood transfusions rates.

Results: There was no significant difference between the groups in terms of demographic data, mean stone burden, duration of surgery, decrease in hematocrit, blood transfusion rates, stone-free rate and complication rates. The median fluoroscopy durations of group 1 and group 2 were 120 and 220 seconds, respectively. Duration of surgery and fluoroscopy were significantly shorter in the single-step dilatation group

Conclusion: PNL is a safe and effective procedure for pediatric stone diseases. Performing this procedure with a single-step dilatation technique ensures that children are less exposed to radiation.

Keywords: Single-step dilatation, Nephrolithiasis, Percutaneous nephrolithotomy, Fluoroscopy

Öz

Amaç: Büyük ve kompleks böbrek taşlarının tedavisinde etkili ve güvenilir bir yöntem olan perkütan nefrolitotomi (PNL) ameliyatının en önemli aşaması akses sağlandıktan sonra uygun ve efektif bir traktusun oluşturulmasıdır. Bu amaçla Amplatz, balon ve Alken dilatatörler gibi farklı teknikler tariflenmiştir. Biz pediatrik PNL ameliyatlarında single step Amplatz dilatasyon tekniğinin etkinlik ve güvenilirliğini aşamalı Amplatz dilatasyon tekniği yapılan hastalar ile karşılaştırmayı amaçladık.

Yöntemler: Bu çalışma retrospektif kohort çalışmasıdır. Son on yılda merkezimizde 72 pediatrik hastaya uygulanan 75 PNL ameliyatının verileri değerlendirildi. Single step dilatasyon tekniği (Grup 1, n:41) ile aşamalı dilatasyon tekniği (Grup 2. n:34) yapılan hastaların floroskopi ve cerrahi süreleri, taşsızlık ve komplikasyon oranları, ameliyat öncesi ve sonrası hematokrit seviyeleri ile kan transfüzyon oranları karşılaştırıldı.

Bulgular: Gruplar arasında hastaların demografik verileri, ortalama taş yükü, operasyon süresi, hematokritte azalma, kan transfüzyonu ihtiyacı, taşsızlık oranı ve komplikasyon oranları açısından anlamlı farklılık görülmedi. Grup 1 ve Grup 2 medyan floroskopi süreleri sırasıyla 120 ve 220 saniye olarak saptandı. Single step dilatasyon grubunda ameliyat ve floroskopi süreleri anlamlı olarak daha kısa olduğu saptandı.

Sonuç: PNL, çocuk taş hastalıklarında uygulanan güvenli ve etkili bir prosedürdür. Bu prosedürün tek adımlı dilatasyon tekniği ile yapılması çocuk hastaların daha az radyasyona maruz kalmasını sağlamaktadır.

Anahtar kelimeler: Tek aşamalı dilatasyon, Böbrek taşı, Perkutan nefrolitotomi, Floroskopi

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Introduction

The main goal of urinary stone treatment in children is to provide maximum stone-free rate with minimally invasive approach. Percutaneous nephrolithotomy (PCNL) was first used for the treatment of kidney stones in pediatric patients in 1985 and has since become the first treatment option with stone-free rates of 86.9-98.5%, especially in the treatment of large and complex kidney stones [1]. Although PCNL has advantages such as rapid postoperative recovery period, high stone-free rates, no reduction in renal function due to scarring, and no inhibition of renal growth, it may still cause serious complications such as high radiation exposure, organ injury, hemorrhage and sepsis [2]. Considering the 5-year recurrence rate of 55%, these children undergo a serious radiation exposure throughout the diagnosis and treatment processes [3].

Establishing an access tract is an important step in PCNL and may be accomplished using Amplatz dilators (semirigid polyurethane fascial dilators), Alken dilators (telescopic metal coaxial dilators), balloon dilators, and one-shot dilators [4]. In order to decrease radiation exposure and shorten the processing time in adult patients, single step dilatation technique was defined and studies about its effectiveness have been published [5]. To the best of our knowledge, there are no studies in the literature that have used this technique in pediatric patients.

In this study, we aimed to compare the data of pediatric patients who underwent PCNL by using single step dilatation technique or phased dilatation technique. We also evaluated the suitability of single step dilatation technique as a safe and effective method of dilatation in pediatric patients.

Materials and methods

Data source and patient selection

This is a retrospective cohort study. Following the approval of the İzmir Tepecik Research and Training Hospital ethics committee (File Number and Date: 2018 / 7-7, 28.06.2018) we retrospectively evaluated 72 pediatric patients (44 males, 28 females) that underwent 75 PCNL procedures in our clinic between May 2008 and March 2018. The PCNL surgery was performed for the treatment of staghorn stones, upper urinary tract stones larger than 2 cm, lower-pole stones larger than 1 cm, and stones resistant to extracorporeal shock waves. Patients were divided into 2 groups. The patients who underwent single-step dilatation technique were assigned into group 1 and the patients who underwent stepwise dilatation technique formed group 2. The groups were compared in terms of pre-, post-, and intra-operative variables. Prior to the procedure, all patients underwent general physical examination to evaluate any systemic diseases and a detailed medical history form including a body mass index (BMI) was filled.

Kidney, ureter and bladder X-ray, ultrasonography, and, when needed, a spiral non-contrast tomography were used to evaluate the renal anatomy and stone localization before PCNL. According to the radiological data, stones were classified as opaque and non-opaque. The terms “simple” or “complex” were used to easily identify the localization of stones [6]. Kidney stones localized only in the calyx or pelvis were defined as simple stones, while staghorn stones, pelvic stones, and stones that fill one or more calyxes were defined as complex stones. The stone burden was approximated by combining the measurements of width and length in mm^2, as measured on x-ray (KUB) or CT in cases with non-opaque stones. In cases with multiple stones, each stone was measured separately and the total value was considered as the total stone burden. In staghorn stones, the total stone burden was calculated by measuring the area of each stone piece in the pelvis and calyxes.

The operation time was accepted as the time from the first puncture to the insertion of the nephrostomy tube. Fluoroscopic imaging time during the operation, number of accesses, access sites, tract size, and the presence of perioperative complications were recorded. In this study, two days after the procedure x-rays of the urinary system or ultrasound (for non-opaque stones) were used to evaluate residual fragments. Operation success was defined as being stone-free or having residual stone fragments of 4 mm or less. Patients with stone fragments smaller than 4 mm were evaluated as having clinically insignificant residual fragments (CIRF), while patients with stones > 4 mm were considered as having residual fragments.

Other variables included in the analysis were age, gender, change in the serum creatinine level, stone size and feature. In this study, the blood loss estimation was measured by calculating changes in hematocrit and hemoglobin values (difference between last and first Htc/Hb values). The first Htc/Hb was considered as the values obtained preoperatively, while the last Htc/Hb value was considered as obtained 48 hours after the operation. Patients who underwent blood transfusion were evaluated separately. The indications for blood transfusion were the evidence of hemodynamic instability and the postoperative Htc values below 30%. Other variables pertaining to complication rates, nephrostomy removal time, and length of hospitalization were also evaluated. The postoperative complications were evaluated according to the modified Clavien classification.

Surgical technique

Under general anesthesia, an open-ended 5 or 6 F ureteral catheter was placed in the lithotomy position using a cystoscope and the bladder was drained with a Foley catheter. The patient was then brought to the prone position. The surgical field was wiped with povidone iodine and covered with sterile pediatric percutaneous cover. The radiation source C-arm fluoroscopy device was placed under the table. After the contrast agent was injected retrogradely from the ureter catheter, the collector system access was achieved with the guidance of biplanar fluoroscope with an 18-gauge Chiba (Boston Scientific, Natick, MA, USA) needle and triangulation or bull-eye technique. After access was established, a 0.038-inch hydrophilic guide wire (Sensor™ Guide Wire, Boston Scientific, Natick, MA, USA) was placed in the collector system. Under the guidance of the sensor, the tractus was formed by stepwise or single-step dilatation with Amplatz dilators. Amplatz sheath (Boston Scientific) was positioned in the renal collecting system, based on each patient’s body size and hydronephrosis status. In stepwise dilatation technique, tract dilatation was achieved with 6, 10, 14, 18 and 20/26/30 Fr Amplatz dilators up to the target

sheath size and planned appropriate Amplatz sheath (18, 20, 26 or 30 F) was placed. Meanwhile, in the single-step dilation technique, a planned Amplatz sheath (18, 20, 26 or 30 F) was placed by itself directly into the kidney via a sensor guide together with the Amplatz dilatators. The PCNL procedures were performed using 17 or 24 F rigid (Karl Storz) nephroscope. The stone crushing process was mostly carried out using ultrasonic lithotriptors. Pneumatic lithotriptor and holmium YAG laser were used when needed. At the end of the procedure, 14 Fr reentry Malecot catheter was placed in all patients. Four experienced surgeons who have completed at least 50 PCNL procedures on adults performed all pediatric PCNLs.

Statistical analysis

In the study, depending on the assumptions, descriptive statistics such as mean (standard deviation) or median (minimum-maximal) were used for numerical variable, while frequency (n) and percentage (%) were used for categorical data. If the parametric test assumptions were met, the Student t-test was used for analysis of the difference between the numerical values of single-step vs stepwise groups, while Mann-Whitney U Test was used if the parametric test assumptions were not met. A two proportion z-tests was used to determine whether there was a difference between the groups in terms of the incidence of categorical variables and the effect of those categorical variables on groups was evaluated either by Pearson chi-square test or Fisher-Freeman-Halton exact test, depending on the hypothesis. For all tests, Type I error probability was determined as $\alpha = 0.05$.

Results

The results of 72 pediatric patients (28 females and 44 males; mean age 9 years) who underwent 75 PCNL for kidney stones during the study period were included in this study. Three of the patients underwent bilateral PCNL procedures. The most common presenting symptom was abdominal or flank pain in 51 (71 %) patients. The other common symptoms were hematuria in 40 (55.5 %) patients and fever in 12 (16.6 %) patients. The results of the study were divided into two groups according to the dilatation technique. Group 1 consisted of 41 (54.7%) patients that were treated with single-step technique, while group 2 consisted of 34 patients (45.3%) that underwent stepwise dilatation technique. The body mass index of the groups was 18.7 (10.2-26.8) and 15.79 (11-32.6), respectively, and was significantly different between the groups (P=0.005). The mean stone burden was 420 (78-2475) and 382.5 (78-1760) mm^2 in groups 1 and 2, respectively (P=0.182). Detailed demographic data including previous treatments of the patients according to groups are shown in Table 1. Median operation time was 85 (24-155) min in group 1 and 90 (40-155) in group 2 (P=0.167). Fluoroscopy time was 120 (60-380) and 220 (60-600) seconds in groups 1 and 2, respectively (P<0.001). The stone-free rates were 73.2 and 67.6% in groups 1 and 2, respectively; which was not significantly different between the groups (P=0.226). When CIRF was included, stone-free rates were 80.5 and 85.2% in groups 1 and 2, respectively. Operation data are summarized in Table 2.

As shown in Table 3, no major complications or deaths were seen in our patient groups. There were no significant differences in complication rates between the groups. Some complications observed in the groups were pain, urinary leakage after removal of the nephrostomy tube, postoperative fever, bleeding, and pneumothorax. The mean hematocrit decline in group 1 (3.26) was not significantly different from that of the group 2 (2.65) (P=0.416). However, blood transfusions were needed for 1 patient in group 1 and 2 patients in group 2. In two patients (1 from each groups), urinary drainage persisted for more than 1 day after removal of the nephrostomy tubes, therefore Double J stents were consequently inserted in these patients. Two patients in group 2 underwent ureterorenoscopy because of renal colic attack following nephrostomy tube removal. The ureteral catheter was placed after removing stone pieces that fell into the ureter. The ureter catheters were removed at the 1st postoperative day. One patient from group 2 that had supracostal access developed pneumothorax following the removal of the nephrostomy tube and tube thoracostomy had to be performed for treatment.

There was no significant difference in creatinine levels between the groups (P=0.835). The mean duration of nephrostomy in groups 1 and 2 were 2 (1-3) and 2 (0-6) days, respectively, and there was no statistically significant difference between the groups (P=0.645).

Stone analysis was available for 32 procedures and revealed calcium oxalate in 19 (59.3%), uric acid in 7 (21.8%), struvite in 4 (12.5%), and cystine in 2 (6.3%).

Table 1: Demographic data of the patients

Characteristics	Group 1 Single-step n:41	Group 2 Stepwise n:34	*P*-value
Age, years Median (min-max)	9.1 (3-17)	8.3 (1-17)	0.182[a]
Female/male ratio, n	18 (43.9%)/ 23 (56.1%)	11 (32.4%)/ 23 (67.6%)	0.307[b]
BMI kg/m2 Median (min-max)	18.77 (10.2-26.8)	15.79 (11-32.6)	0.004[a]
Stone location, n/%			
Simple	22 (53.7%)	20 (58.8%)	0.654[b]
Complex	19 (46.3%)	14 (41.2%)	
Stone size, mm2 Median (min-max)	420 (78-2475)	382.5 (78-1760)	0.182[a]
Stone side R n/% L n/%	21 (51.2%)/ 20 (48.8%)	13 (38.2%)/ 21 (61.8%)	0.261[b]
Previous ipsilateral stone treatment, %			
None	34 (82.9%)	32 (94.1%)	0.164[c]
PCNL	4 (9.8%)	1 (2.9%)	
Open renal surgery	3 (7.3%)	1 (2.9%)	
History of ESWL	5 (12.2%)	8 (23.5%)	0.197[b]

BMI: Body Mass Index, ESWL: Extra shock wave lithotripsy a: Mann-Whitney U Test, b: Pearson Chi-square Test, c: Fisher-Freeman-Halton Exact Test

Table 2: Operative data of the patients

Characteristics	Group 1 Single-step	Group 2 Stepwise	*P*-value
Duration of the procedure, min; median (min-max)	85 (24-155)	90 (40-155)	0.167[a]
Fluoroscopy time, sec; Median (min-max)	120 (60-380)	220 (60-600)	<0.001[a]
Access n(%)			
Infracostal	33 (82.5%)	28 (82.4%)	0.987[b]
Supracostal	7 (17.5%)	6 (17.6%)	
Success, n/%			
SF	30 (73.2%)	23 (67.6%)	0.226[c]
CIRF (<4mm)	3 (7.3%)	6 (17.6%)	
RF	8 (19.5%)	5 (14.7%)	
Hemoglobin decrease Mean (SD)	1.06 (1.097)	0.88 (0.939)	0.470[d]
Hematocrit decrease Mean (SD)	3.26 (3.304)	2.65 (2.867)	0.416[d]
Difference in creatinine (pre vs postop) Median (min-max)	-0.1 (-1.20-0.30)	-0.1 (-0.50-0.10)	0.835[a]
Days of nephrostomy Median (min-max)	2 (1-3)	2 (0-6)	0.111[a]
Days of hospitalization Median (min-max)	1(1-10)	2(1-5)	0.222[a]

a: Mann-Whitney U Test, b: Pearson Chi-square Test, c: Fisher-Freeman-Halton Exact Test, d: Student's t Test, SD: Standard deviation

Table 3: Comparison of the rate of complications between the groups according to the modified Clavien classification

Clavien grade	Group 1 Single-step n:41	Group 2 Stepwise n:34	*P*-value
G1 total, n (%)	2 (4.8)	4 (11.7)	
Fever	1	2	
Pain	1	2	
G2 total, n (%)	3 (7.3)	2 (5.8)	
Blood transfusion	1	2	
UTI	2	0	
G3b Total, n (%)	1 (2.5)	4 (11.7)	
DJ for urinary leakage	1	1	
URS	0	2	
Pneumothorax	0	1	
Total, n (%)	6 (14.6)	10 (29.4)	0.122[a]

UTI: Urinary tract infection, DJ: Double J stent, URS; Ureteroscopy a: Two-Proportion z Test

Discussion

In recent years, a significant increase has been detected in the incidence of pediatric stone disease. The reason for this increase may be the ever-increasing sedentary lifestyle (TV, PC games and immobile life preferences, etc.) and the growing fast food consumption (salt consumption, excess weight, etc.) [7].

The main concerns in pediatric stone disease are the presence of underlying metabolic and anatomical disorders, the possible side effects of various treatment options on the developing kidney, and most importantly, high recurrence rates and exposure to radiation during a long-term follow up [8]. Since it was first introduced to pediatric cases by Woodside JR in 1985, PCNL has been a reliable and minimally invasive treatment option in the treatment of stones larger than 2 cm, large and complex stones, or kidney stones resistant to extracorporeal shock wave lithotripsy (ESWL) treatment [9]. Exposure to radiation during this procedure is a serious concern for both the surgical team and children, who are more susceptible to radiation poisoning. Frattini et al. [10] have defined a single-step dilatation technique that aims to reduce both the operative time and radiation exposure in adult patients.

After kidney access has been achieved, balloon dilatation, alkaline dilatators or Amplatz dilators can be used to create a suitable tract. Although some studies have shown that there is no significant difference between the use of balloon dilatators and Amplatz dilators for dilatation of the tract, there are studies that indicate that the stepwise use of Amplatz dilators can shorten both the duration of surgery and fluoroscopy time [11,12]. The use of balloon dilators for tract dilatation has been limited in Turkey due to high cost. Amirhassani et al. [4] showed that in adults, compared to the stepwise technique, a single-step dilatation technique shortened the operation time and fluoroscopy time. Suelozgen et al. [5] evaluated 932 adult patients who underwent PCNL and reported that single-step dilation technique was effective and safe. We could not find any studies comparing the stepwise Amplatz dilatation technique with single-step dilatation technique in pediatric patients. In our study, we found that both the operation time and the fluoroscopy time were significantly lower in the pediatric patient from single-step dilatation group compared to the stepwise dilatation group. We believe that this result is very important in showing that the single-step dilatation method can reduce pediatric patients' exposure to radiation. At the same time, it is known that performing PCNL under ultrasound guidance in pediatric patients reduces exposure to radiation during the access phase and also results in less injury to neighboring organs [13].

Frattini et al. [10] reported that stepwise dilatation technique was unsuccessful in two patients who had previously undergone open renal surgery, therefore suggested performing single-step dilation in those patients. However, both Sofikerim et al. [14] and Amjadi et al. [15] have reported that one-step dilatation technique provided easy access in the patients who underwent open renal surgery. They stated that this method is safe, associated with decreased radiation exposure in the patient and the surgical team, and can be applied as a standard treatment method of adult patients. In our study, the single-step dilation group included 2 patients who had previously undergone open renal surgery. An appropriate tract was established in these 2 patients with single-step technique and no further dilatation was required.

Hemorrhage has always been a major complication since the introduction of PCNL. While mild hemorrhages can be managed by conservative methods, moderate or severe hemorrhages may require transfusions. The rates of PCNL-related transfusions vary in pediatric patients. Fraser et al. [16] reported no hemorrhagic complications requiring transfusion, whereas Özden et al. [17] reported 24% transfusion rate in the first 25 patients and 10% in the next 28 patients. In the light of this data, they suggested that hemorrhage rates may decrease with the increase of clinical experience. In one study, stepwise and single-step dilatation patient groups were compared in terms of the effect of chosen technique on hemorrhage. Although the transfusion- requiring hemorrhage rates were lower in the single-step dilatation group, this difference was not statistically significant [18]. Desai et al. [19] reported that establishing more than one tract during PCNL and the diameter of those tracts being larger than 24 F were significant factors affecting the decrease in Hb values. It is suggested that a smaller tract diameter leads to less tissue displacement and less nephron damage. In addition to these factors, it is known that minor and careful manipulations during surgery may play an important role in the prevention of hemorrhages. In our study, a total of 3 patients had to undergo postoperative blood transfusions and the transfusion rate of the entire study population was 4%. Blood transfusion was performed in 1 patient in the single-step group and in 2 patients in stepwise dilatation group. The rates of transfusion requirement were lower in single-step dilation group compared to the stepwise dilation group, but as in aforementioned studies, the difference between groups was not statistically significant. In our study, the transfusion rates were lower than that in the literature. We believe that it was due to several factors, such as being able to establish a single tract in almost all patients, majority of the stones being simple in character, and having a highly experienced surgical team. We could not evaluate the effect of the tract diameter on hemorrhage because the tract numbers were equal in both groups and we did not do a sub-analysis of the groups in terms of tract diameters.

Postoperative fever and leakage around the nephrostomy tract are considered minor complications in pediatric PCNL patients [20]. In our study, 6 patients had postoperative fever and pain that responded to antibiotherapy and anti-inflammatory treatment. Although these minor complications were seen less frequently in the single-step group, this difference was not statistically significant.

In the literature, it is reported that the most frequently injured structures during PCNL, especially during entering near the 12th rib, are the pleura and the lungs [21]. In our study, 1 patient in the stepwise dilatation group (1.3%) developed hydropneumothorax requiring a chest tube insertion. This was probably due to the tract established between the 11th and 12th ribs. This patient recovered with the help of the chest tube drainage and was discharged without any further complications within 7 days.

PCNL operations have a very low mortality rate. No complications resulting in death have developed in our study.

Limitations

There are certain limitations in our study. The most basic of them are the retrospective design of the study and limited number of cases. The wide age range of patients, varying sheath sizes, the lack of a patient group that underwent balloon dilatation, the failure to perform sub-analysis of the factors affecting hemorrhage can be considered as other limitations.

Conclusion

PCNL surgery with single-step dilatation technique is safe, and can significantly reduce fluoroscopy time. The efficacy and reliability of this technique should be verified with further studies.

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Effect of cardiac rehabilitation on mortality related inflammatory markers

Egzersiz temelli kardiyak rehabilitasyonun mortalite ilişkili inflamatuar belirteçlere etkisi

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Abstract

Aim: Cardiac Rehabilitation (CR) is a rehabilitation method which decreases mortality in cardiac patients. The main goal of this study is to investigate the effect of CR on neutrophil-to-lymphocyte ratio (NLR) and thrombocyte-to-lymphocyte ratio (TLR), which are inflammatory markers directly related to mortality in cardiac patients. The secondary goal is to assess the effect of CR on functional capacity.

Methods: This retrospective cohort study consists of 211 CR patients who completed 30 sessions of tailored comprehensive CR programs. Their functional status and cardiovascular endurance were assessed with a 6- minute walk test and a cycle ergometer test. Inflammatory markers (TLR, NLR, sedimentation, CRP) were obtained from blood testing and demographic data were collected. After 30 sessions of CR all tests were repeated. No adverse events occurred during the exercise sessions.

Results: Among 211 patients enrolled in this the study, 114 (54%) were female and 97 (46%) were male. Mean age was 56.28 (10.25) years (min 21 - max 81 years). 94 (44.5%) patients were hypertensive, 24 (11.4%) had heart failure, 83 (39.3%) had coronary artery disease and 10 (4.7%) had arrhythmia. Mean range for the 6-minute walk test was 374.62 (61.75) meters before and 390.80 (62.87) meters after CR (P<0.001). Mean values of the maximum watts in cycle ergometer effort test were 50 watts before and 75 watts after CR (P<0.001). Before and after CR, NLR and TLR were 1.6, 1.4 and 107.59 (35.22), 101.46 (32.78), respectively (P<0.001). Sedimentation and CRP levels were 22.38 (11.55) mm/hour, 1.0 mg/dl before and 18.98 (10.06) mm/hour, 0.5 md/dl after rehabilitation, respectively (P<0.001).

Conclusion: CR can decrease the inflammatory markers TLR and NLR which are directly related to mortality in cardiac patients, while increasing the patients' functional capacity.

Keywords: Cardiac rehabilitation, Inflammation, Mortality

Öz

Amaç: Kardiyak rehabilitasyon kalp hastalarında mortaliteyi azaltan bir rehabilitasyon metodudur fakat bu etkisinin hangi parametreler üzerinden olduğuyla ilgili netlik yoktur. Nötrofil lenfosit ve trombosit lenfosit oranı kalp hastalarında mortaliteyle direk ilişkili inflamatuar belirteçlerdir. Bu çalışmanın amacı kardiyak rehabilitasyonun kalp hastalarında mortaliteyle direk ilişkili olan inflamatuar belirteçler (nötrofil lenfosit oranı, trombosit lenfosit oranı) üzerine olan etkilerini araştırmaktır. Çalışmanın ikincil hedefi ise kardiyak rehabilitasyonun aynı hasta grubunda fonksiyonel kapasite üzerine etkisini araştırmaktır.

Yöntemler: Bu çalışmaya 30 seans kardiyak rehabilitasyon programını tamamlayan 211 hasta dahil edilmiştir. Öncelikle hastaların fonksiyonel durumları 6 dakika yürüme testiyle, kardiyovasküler dayanıklılıkları bisiklet ergometer efor testi ile değerlendirilmiş, inflamatuar markerları (nötrofil lenfosit oranı, trombosit lenfosit oranı, sedimentasyon, CRP) kan testiyle bakılmış, demografik özellikleri kaydedilmiştir. 30 seans kardiyak rehabilitasyon sonrası bütün testler tekrar edilmiş ve istatistiksel analizleri yapılmıştır. Egzersiz seansları süresince herhangi bir yan etki gözlenmemiştir. Retrospektif bir kohort çalışmasıdır.

Bulgular: Bu çalışmaya 211 hasta alınmıştır. Hastaların 114'ü (%54) kadın ve 97'si (%46) erkektir. Ortalama yaş 56,28 (10,25) yaştır (minimum 21 - maksimum 81 yaş). 94 (%44,5) hastada hipertansiyon, 24 (%11,4) hastada kalp yetmezliği, 83 (%39,3) hastada koroner arter hastalığı ve 10 (%4,7) hastada aritmi mevcuttu. 6 dakika yürüme testinde kardiyak rehabilitasyon öncesi ortalama mesafe 374,62 (61,75) metre olup rehabilitasyon sonrası bu mesafe 390,80 (62,87) metreye çıkmıştır (P<0,001). Bisiklet ergometer efor testinin maksimum watt ortalama değeri tedavi öncesi 50 watt iken tedavi sonrası 75 watt olmuştur (P<0,001). Nötrofil lenfosit oranı tedavi öncesi 1,6 iken tedavi sonrası 1,4 olarak saptanmıştır; trombosit lenfosit oranı ise rehabilitasyon öncesi 107,59 (35,22) iken rehabilitasyon sonrası 101,46 (32,78) olarak saptanış olup her ikisindeki düşüşte istatistiksel olarak anlamlıdır (P<0,001). Sedimentasyon ve CRP düzeyleri rehabilitasyon öncesi sırasıyla; 22,38 (11,55) mm/saat, 1,0 mg/dl iken rehabilitasyon sonrası, 18,98 (10,06) mm/saat ve 0,5 md/dl olarak değişmiştir (P<0,001).

Sonuç: Kardiyak rehabilitasyon mortaliteyle direk ilişkili belirteçler olan nötrofil lenfosit oranını ve trombosit lenfosit oranını düşürür ve aynı zamanda hastaların fonksiyonel kapasitelerini artırır.

Anahtar kelimeler: Kardiyak rehabilitasyon, İnflamasyon, Mortalite

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Introduction

Atherosclerosis plays a key role in cardiovascular disease progression. Leucocyte recruitment and pro-inflammatory cytokines promote atherogenesis [1]. Inflammation worsens and triggers plaque complications, which are mortal [2]. It also causes thrombosis in addition to atherogenesis, and thrombocytes further worsen the atherogenic process by adding plaque complications of their own [3]. Neutrophil-to-lymphocyte ratio (NLR) is an easily calculated parameter to assess the inflammatory state of the patients [4]. It is also proved in a systematic review that NLR can be used to predict mortality in major cardiac events in acute coronary syndrome [5]. Thrombocyte-to-lymphocyte ratio (TLR) is another parameter which is also related to mortality in cardiac patients [6-10]

Cardiac rehabilitation (CR) is a multi-component rehabilitation program for cardiac patients designed to maximize secondary prevention from heart disease [11]. It has internationally accepted core components which are nutritional counseling (NC), risk factor modification (RFM), psychosocial management (PM), patient education (PE) and exercise training (ET) [12]. A Cochrane review showed that exercise-based CR reduces mortality and morbidity by 20% for coronary artery disease patients [13]. Another systematic review focused on the effects of the core components of CR on mortality and morbidity. In this study the authors showed that each of PM, ET and RFM clearly reduce the hazard ratio of mortality and concluded that comprehensive CR has substantial benefits in reducing mortality and morbidity [14]. A recent study showed that elderly patients who attended a cardiac rehabilitation program after trans-catheter aortic valve implantation had decreased mortality at 6 months [15].

There are various studies on the effects of CR on mortality in the literature. However, to the best of our knowledge, there are no studies about the effect of CR on mortality related inflammatory parameters, except for a very recent concurrent study on a relatively limited number of patients with only a specific type of cardiac disease [16]. In this study, we investigate the mechanisms that lower mortality in a large number of CR patients with a broad range of cardiac pathologies, and focus on inflammatory markers (NLR, TLR) which are directly related to atherosclerosis and mortality.

The primary aim of this study is to assess the effects of 10-week long CR (30 sessions) on mortality-related inflammatory markers in cardiac patients. Secondary aim is to assess the effect of CR on functional capacity. We hypothesize that CR would have a positive impact on mortality related inflammatory markers and functional capacity in CR patients.

Materials and methods

Study design

A single center, retrospective cohort study was performed by evaluating all CR participants between 01.01.2017-11.11.2018 in a Cardiovascular and Thoracic Surgery University Hospital. Adult patients older than 18 years of age who were directed to the CR unit and completed all 30 sessions and tests were included in the study. Exclusion criteria were hematological diseases, systemic inflammatory diseases, acute and chronic infection, cancer, autoimmune diseases and steroid treatment. The study was approved by a local ethics committee (Ethical approval: Haydarpaşa Numune Research Hospital Ethics Committee, 09.10.2017 HNEAH-KAEK 2017/KK/112) and was performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all the subjects. Patients' demographic data were collected.

Inflammatory markers

All patients were outpatient patients of the CR unit. Venous blood was drawn at the forearm after 8 hours fasting and was stored in plastic tubes containing EDTA. Absolute and relative white blood cell counts were generated automatically by Mindray BC6800. NLR was calculated as Neutrophil Absolute Count / Lymphocyte Count and TLR as Platelet Count / Lymphocyte Count. CRP was calculated with Architect C16000 with the turbidimetric method. The normal range of CRP was 0-0.5 mg/dl. Sedimentation was calculated with Alifax Test 1 THL automatically.

Functional capacity

Functional capacity was assessed with a 6-minute walk test. The patients were asked to walk as far as possible back and forth around the cones in 6 minutes in a 30 meters pathway. They were permitted to slow down or stop if needed. Conversation with patients during walking was avoided.

Submaximal cycle ergometer test was performed to evaluate endurance. Watts were increased by 25 in every two minutes. Borg scale was used to assess breath and muscle fatigue every two minutes. Arterial blood pressure (ABP) was measured at the beginning and every two minutes afterwards, automatically. Heart rate, SPO_2 and electrocardiogram were monitored continuously during test and recovery periods. In the case of angina, light headedness, confusion, cyanosis, dyspnea, hypoxia, significant muscle pain (Borg Scale $\geq$5) occurrence, ABP >180/100mmHg or reaching submaximal heart rate according to Karvonen formula, the test was stopped prematurely and the maximum watt was calculated.

Cardiac rehabilitation

Tailored CR program was planned for each individual patient according to their cycle ergometer test peak workload. For patients with a low initial test performance, low intensity interval training was prescribed. For those using beta blockers, the exercise program was prescribed independently from heart rate. All core components of CR were tailored to the patients' special needs. The CR program of each patient was evaluated after 10 sessions and updated according to their Borg scales assessed by a rehabilitation nurse during exercise sessions. Each exercise program began with warm-up and ended with recovery periods. Throughout the exercise, the patients' SPO_2, heart rate, ABP and electrocardiogram were continuously monitored. Before cycle ergometer program patients performed stretching exercises under supervision, and strengthening exercises were added to their programs after two weeks. These exercise sessions were designed to work large muscles of upper and lower extremity with 60-80% of maximum load at 10 repetitions for each muscle group.

All patients had NC from a dietitian, PM from a psychologist and patient education from a CR nurse, and

smokers were guided to tobacco cessation polyclinic. All tests were repeated in a week after completion of 30 sessions of CR.

Study endpoints

The Primary endpoint was observation of changes in inflammatory markers (NLR, TLR, Sedimentation, CRP). Secondary endpoint of the study was observation of improvement in functional capacity.

Statistical analysis

NCSS (Number Cruncher Statistical System 2007 Kaysville, Utah, USA) was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, first quarter, third quarter, frequency, percentage, minimum, maximum) were used to evaluate the study data. The normal distribution of quantitative data was evaluated with the Shapiro-Wilk test and graphical investigations. Dependent groups t-test was used for intra-group comparisons of quantitative variables showing normal distribution. Wilcoxon signed-ranks test was used for intragroup comparisons of quantitative variables that did not show normal distribution. The Mann-Whitney U test was used to compare two groups of data that were not normally distributed. Kruskal-Wallis test and double Bonferroni-Dunn test were used in the comparison of the groups with three or more normal distributions. Spearman Correlation Analysis was utilized to evaluate the relationships between variables. The threshold for statistical significance was $P<0.05$.

Results

Among 211 patients enrolled in this the study, 114 (54%) were female and 97 (46%) were male. Average age was 56.28 (10.25) years (min 21 - max 81 years). 94 (44.5%) patients were hypertensive, 24 (11.4%) had heart failure, 83 (39.3%) had coronary artery disease and 10 (4.7%) had arrhythmia. Demographic data of the patients is presented in Table 1. Mean range for the 6-minute walk test was 374.62 (61.75) meters before and 390.80 (62.87) meters after CR ($P<0.001$). Mean values of cycle ergometer effort test maximum watts were 50 watts before and 75 watts after CR ($P<0.001$). Before and after CR, NLR and TLR were 1.6, 1.4 and 107.59 (35.22) and 101.46 (32.78), respectively ($P<0.001$). Sedimentation and CRP levels were 22.38 (11.55) mm/hour, 1.0 mg/dl before and 18.98 (10.06) mm/hour, 0.5 md/dl after rehabilitation, respectively ($P<0.001$). The differences between inflammatory markers and functional capacity before and after CR are shown in Table 2. The changes in inflammatory markers NLR, TLR, Sedimentation and CRP are shown in detail in Figures 1, 2, 3 and 4, respectively. The changes in weight, BMI, functional capacity, sedimentation, and CRP did not significantly affect NLR and TLR (Table 3). NLR and TLR changes were independent from age and sex (Table 4).

Table 1: Demographic data

n=211		n	%
Sex	Female	97	46
	Male	114	56
Disease	Hypertension	94	44.5
	Heart Failure	24	11.4
	Coronary Artery Disease	83	39.3
	Arrhythmia	10	4.7
		Min-Max	Mean (SD)
Age (year)		21-81	56.28(10.15)
Weight(kg)	Before	50-130	80.64(13.32)
	After	50-133	79.44(13.15)

SD: Standard deviation

Table 2: Difference in inflammatory markers and functional capacity before and after CR

	Before Mean (SD)	After Mean (SD)	Difference Mean (SD)	*P*-value
‡NLR	1.6 (1.3, 2.2)	1.4 (1.2, 2)	-0.2 (-0.5, 0.1)	[b]<0.001**
TLR	107.59(35.22)	101.46(32.78)	-6.13(24.65)	[a]<0.001**
‡Sedimentation	20 (20, 20)	20 (14, 20)	0 (-9, 0)	[b]0.001**
‡CRP	1 (0.3, 1)	0.5 (0.2, 1)	0 (-0.5, 0)	[b]<0.001**
‡WBC	7.2 (6.3, 8.5)	6.8 (5.9, 8.1)	-0.5 (-1.2, 0.2)	[b]<0.001**
Platelet	255.33(55.43)	247.14(55.88)	-8.19(38.65)	[a]0.002**
Neutrophil	4.17(1.53)	3.84(1.20)	-0.33(1.15)	[a]<0.001**
Lymphocyte	2.53(0.80)	2.57(0.73)	0.04(0.56)	[a]0.344
MPV	8.14(1.45)	8.53(1.44)	0.39(1.27)	[a]<0.001**
6-minute walk test (meters)	374.62(61.75)	390.80(62.57)	16.18(43.77)	[a]<0.001**
‡Cycle Ergometer Test maximum watts	50 (50, 75)	75 (50, 100)	25 (0, 25)	[b]<0.001**

‡ Data are presented as median (first quarter, third quarter)
[a] Dependent groups t test, [b] Wilcoxon signed-ranks test, *$P<0.05$, **$P<0.01$

Table 3: The relation of NLR and TLR differences to other variables after cardiac rehabilitation

Before and after difference	Before and after difference			
	NLR		TLR	
	r	p	r	*P*-value
Weight (kg)	-0.109	0.115	0.034	0.628
BMI (kg/m^2)	-0.063	0.364	0.022	0.755
6-minute walk test (m)	0.066	0.342	-0.024	0.727
Cycle ergometer test maximum watt	-0.022	0.755	0.044	0.522
Sedimentation	0.019	0.785	0.031	0.650
CRP	0.036	0.601	0.007	0.923

r: Spearman's correlation coefficient, **$P<0.01$, *$P<0.05$

Table 4: Evaluation of NLR and TLR differences according to age and sex

		n	Before-After Difference NLR Median (Q1, Q3)	Before-After Difference TLR Median (Q1, Q3)
Age (year)	< 65 years	168	-0.14 (-0.5, 0.1)	-5.34 (-21.9, 9.4)
	≥ 65 years	43	-0.16 (-0.5, 0.1)	-3.08 (-30, 12.3)
	P-value		0,844	0,987
Sex	Male	97	-0.17 (-0.6, 0.1)	-3.30 (-20, 12.2)
	Female	114	-0.11 (-0.5, 0.1)	-5.34 (-23.5, 7.7)
	P-value		0,515	0,354

Mann Whitney U Test

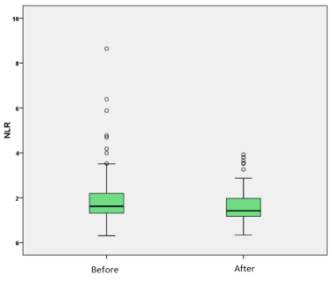

Figure 1: Changes in NLR before and after CR

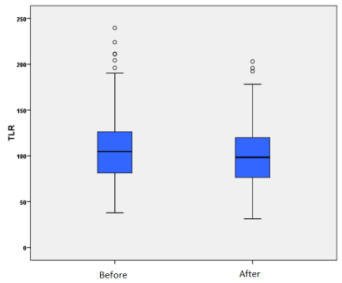

Figure 2: Changes in TLR before and after CR

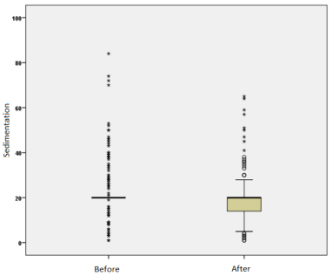

Figure 3: Changes in sedimentation before and after CR

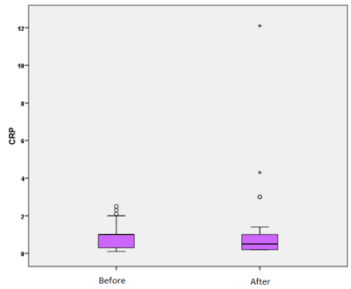

Figure 4: Changes in CRP before and after CR

Discussion

In our study, we investigated the underlying mechanism for the decrease of mortality rates in patients receiving CR. We focused on inflammatory markers which play a key role in atherosclerosis and thromboembolic events [1,2]. Our results show that NLR, TLR, which are mortality-related inflammatory markers, and CRP as well as sedimentation levels decrease and functional capacity increases with comprehensive CR.

CR is known to reduce mortality in cardiac patients with different diagnoses [13-15]. There are a list of core components of CR which are internationally agreed upon: NC, RFM, PM, PE and ET [12]. In a systematic review and network meta-analysis of 148 randomized controlled trials of 50,965 patients, researchers investigated which components are directly linked to decrease in mortality. They concluded that PM, ET, RFM each clearly reduced the hazard of mortality, while PE, ET and PM each reduced the hazard of morbidity. As a result, authors concluded that comprehensive CR has substantial benefits in reducing mortality and morbidity [14]. In our study, patients received all core components of cardiac rehabilitation.

While most studies in the literature focused on the decrease in mortality due to CR, the pathophysiological mechanisms that are at the heart of this reduction are not fully understood.

In cardiac diseases, atherosclerosis, inflammation, and leukocyte recruitment play a major role [1]. Inflammation leads the metabolism to a procoagulant state with help of thrombocytes, causing thrombosis [3]. In light of this knowledge, NLR and TLR are investigated as markers of inflammation and mortality in many cardiac diseases. They are also related to the non-dipper status of the hypertensive patients, resulting in more cardiovascular complications [4,6-9,17]. In a recent study, Fest et al. [18] followed up 8715 individuals for 12 years (2002-2014) to assess NLR association with mortality in the general population and concluded that NLR is a strong and independent risk factor for mortality in elderly population.

In our study we also focused on inflammatory markers (NLR, TLR) as they are directly related to mortality. We showed that after a 30-session comprehensively tailored CR program, the mean NLR value of the patients participating in the program showed a statistically significant decrease of 14.3% from its baseline value. Likewise, the mean TLR value showed a statistically significant decrease of 6% after CR. We further report a statistically significant decrease in other mortality related inflammatory markers, namely, CRP and sedimentation, for 211 patients who attended the comprehensive CR program.

A recent independent and concurrent study also investigated the effect of CR on inflammatory markers in 68 ST-elevated myocardial infarction patients and claimed that chronic inflammation may regress with CR. The limitations of the study, as stated by the authors, were the relatively low cohort number and evaluation of only ST-elevated patients [16]. In comparison, our study had a homogeneous group of cardiac patients and a significantly larger sample size (211 patients).

Another significant result of our study is that the changes in inflammatory markers are irrespective of age and sex. Hence, we claim that regardless of age and gender, everyone can take advantage of CR with the goal of decreasing mortality. Our results which evaluate the increase in functional capacity are also promising. The average range of the 6-minute walk test was extended by more than 15 meters after rehabilitation. The functional capacity, as measured by the cycle ergometer test, increased by 50% on average, as it was 50 watts before and 75 watts after CR. We conclude that functional capacity significantly increases with CR. This data is also compatible with current literature [19].

Inflammation has a significant role in atherosclerosis [1,2]. Elevated inflammatory markers such as thrombocyte-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio are linked to high mortality and morbidity in cardiac patients [4,6-9]. Cardiac rehabilitation has been proven to reduce mortality, morbidity and also increase functional capacity in cardiac patients [13-15,19].

The reason cardiac rehabilitation decreases mortality has not yet been shown via blood analysis. We aimed to investigate the effect of cardiac rehabilitation on mortality related inflammatory markers. According to our findings, a comprehensively tailored cardiac rehabilitation program can statistically significantly decrease neutrophil-to-lymphocyte and thrombocyte-to-lymphocyte ratios independent from age and gender, in a wide range of cardiac pathologies. This study shows the vital importance of referring patients diagnosed with cardiac pathologies to a cardiac rehabilitation clinic irrespective of age and gender.

Limitation

This study is a retrospective cohort study, which is its limitation. A prospective study on mortality and functional status with long-time follow up of patients is needed for further enlightenment on this subject.

Conclusion

We conclude that CR decreases the inflammatory markers (TLR, NLR) which are directly related to mortality in cardiac patients while increasing patients' functional capacity. The decrease in mortality-related inflammatory markers is independent from age and gender.

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Efficacy of prophylactic epidural saline for reducing postdural puncture headache in patients undergoing caesarean section

Sezaryen uygulanan hastalarda postdural ponksiyon baş ağrısının azaltılmasında profilaktik epidural salinin etkinliği

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Abstract

Aim: Post-Dural Puncture Headache (PDPH) is a common complication of spinal anesthesia during the postoperative period. The optimal means of prevention, management, and treatment of this disorder are uncertain. The objective of this current study was to investigate the effect of a 24 hours-continuous infusion of saline on the occurrence of PDPH in patients undergoing caesarean section and to provide a reference for the clinical prevention of PDPH.

Methods: This study included 126 patients aged between 18 and 45 years with an American Society of Anesthesiology physical status (ASA) score of 1-2, who underwent elective caesarean operation. Patients were randomized into control (n=63) and study groups (n=63). Spinal anesthesia was administered to both groups via a 27-gauche spinal needle. The study group was administered normal saline infusion for 24 hours with an easy-pump device through an epidural catheter.

Results: Seven control-group patients developed PDPH within the first 72 hours postoperatively while it was not observed in any of the study-group patients. Visual analogue scale and numerical rating scales were used for pain measurement. Five patients described mild pain while two described moderate pain. Severe headache was not observed in any patients at any time.

Conclusion: This study demonstrated that the administration of epidural saline during an elective caesarean under spinal anesthesia significantly reduced the incidence of PDPH and was not associated with any side-effects.

Keywords: Postdural Puncture Headache, Epidural saline, Spinal anesthesia, Cesarean section

Öz

Amaç: Postdural ponksiyon baş ağrısı (PDPH), ameliyat sonrası dönemde spinal anestezinin sık görülen bir komplikasyonudur. Bu bozukluğun önlenmesi, yönetimi ve tedavisi için en uygun yöntem belirsizdir. Bu çalışmanın amacı, 24 saat devam eden epidural salin infüzyonunun sezaryen geçiren hastalarda PDPH oluşumu üzerindeki etkisini araştırmak ve PDPH'nın önlenmesi için referans bilgi sağlamaktı.

Yöntemler: Çalışmaya Amerikan Anesteziyoloji Derneği fiziksel durumu (ASA) 1-2 olan, 18-45 yaş arası, elektif sezaryen ameliyatı yapılan 126 hasta dâhil edildi. Kontrol grubu (n=63) ve çalışma grubu (n=63) olarak belirlendi. Her iki gruba da 27 gauche spinal iğne ile spinal anestezi uygulandı. Çalışma grubuna epidural kateter yoluyla kolay pompa cihazı ile 24 saat boyunca normal salin infüzyonu yapıldı.

Bulgular: Kontrol grubunda 7 hastada ilk 72 saatte PDPH görülürken, çalışma grubunda PDPH görülmedi. Kontrol grubunda bulunan beş hasta, görsel analog skala ve sayısal derecelendirme skalasına göre PDPH'yi hafif ağrı ve iki hasta orta ağrı olarak tanımladı. Hastalarda şiddetli baş ağrısı görülmedi.

Sonuç: Bu çalışma, spinal anestezi altında elektif sezaryen sonrasında epidural salin uygulanmasının PDPH insidansını anlamlı derecede azalttığını ve herhangi bir yan etki ile ilişkili olmadığını göstermiştir.

Anahtar kelimeler: Postdural Ponksiyon Baş Ağrısı, Epidural salin, Spinal anestezi, Sezaryen

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Introduction

Cesarean section is preferably performed via regional anesthesia [1]. Minimizing complications by the introduction of new local anesthetic drugs and spinal needles rises its widespread use [2]. Post Dural Puncture Headache (PDPH) is a complication of regional anesthesia in the postoperative period. PDPH was defined as headache occurring in within 5 days of after lumbar puncture by the International Headache Society [3]. The pathophysiology of PDPH is not certain. Perforation of the dura causes cerebrospinal fluid (CSF) to leak through the subarachnoid space, decreasing CSF volume and pressure [4]. Typically, the headache is continuous, bilateral, frontal, retro-orbital, occipital, and extending to the neck, and may be accompanied by photophobia, nausea, tinnitus and hearing disorders. In more severe cases, diplopia and cranial nerve palsy may develop. These findings may be due to the traction of these cranial nerves [5]. Incidence is related to needle diameter, needle type and patient group. Young age, female gender and pregnancy are factors that increment the risk of PDPH [6]. The optimal means of prevention, management, and treatment of this disorder are indefinite. Conservative treatment consists of resting in the supine position, oral or intravenous fluid administration, analgesics, and caffeine. Despite conservative treatment, headaches may last for days. Epidural blood patch is a treatment method for this headache: Autologous blood is injected in the epidural space of the puncture level or one level below. This method is thought to stop CSF from further seepage by mass effect or coagulation [7].

When the literature is investigated, besides epidural blood patch, treatment options such as intrathecal catheter, epidural saline infusion and epidural morphine have been suggested. However, there is still a need for clinical evidence for their efficacy. Therefore, in our study, we aimed to determine the effect of a 24-hour continuous epidural prophylactic saline administration on PDPH in patients undergoing elective cesarean section.

Materials and methods

This case-control study was approved by the Institutional Review Board (Adiyaman University Ethics Committee, Approval no: 2014/10-7) and performed between January and December 2017 at Adiyaman University Educational and Research Hospital, Adiyaman, Turkey. A power analysis was done with G Power software to determine the appropriate sample size. The sample size calculation was based on an alpha error of 0.05 and a power of 80%. This gave a required total sample size of 63 for each group. Accordingly, a total of 126 ASA I-II patients who underwent elective caesarean operations between 18 and 45 years of age (pregnancy range, 38–42 weeks) were included in the study. Patients were divided into equal control and study groups using randomized numbers provided by an anesthesiologist. All included patients provided written informed consents prior to the study. Patients with coagulation disorders, migraine, vertigo or similar complaints, infection at the site of treatment, anticoagulant drug use, sepsis, spinal deformity, severe central nervous system disease, failure of the spinal canal puncture (epidural or spinal needle puncture failure) and those who did not accept the procedure were excluded from the study.

In both groups, vascular access was achieved with a 20 G cannula in the premedication room. 10 ml/kg 0.9% isotonic NaCl infusion was administered before the procedure for 30 minutes. After the patients were taken to the operating room, electrocardiography (ECG), heart rate (HR), noninvasive systolic blood pressure (SBP), diastolic blood pressure (DBP) and peripheral oxygen saturation (SpO2) were monitored in standard DII lead. Two experienced anesthesiologists performed all anesthesia procedures in a single operation. Aseptic and antiseptic conditions were achieved in all patients. Lumbar puncture was performed through the L3-4 intervertebral interspace with the patient in the sitting position. Patients in the control group received spinal anesthesia via 27 Gauge spinal needles (Pencan, B.Braun®, Melsunger, Germany). The flow of free CSF was observed and 12.5 mg hyperbaric bupivacaine was injected into the subarachnoid space. Patients in the study group received combined spinal and epidural anesthesia. Infiltration anesthesia was performed with lidocaine 3 ml (60 mg) by entering the L3-L4 interval space. Epidural interval was determined by resistance loss method with 18 G Tuohy needle. After detecting the epidural interval, dural puncture was performed through a 27 G spinal needle (Espocan; Set for combined spinal and epidural anesthesia, B.Braun®, Melsunger, Germany). The 12.5 mg hyperbaric bupivacaine was injected into the subarachnoid space after free CSF flow. After completion of the subarachnoid injection, the epidural catheter was fixed in the epidural space by moving 2-3 cm in the cranial direction, through the Tuohy needle. The tip of the catheter was connected to the easy pump and the preservative-free normal saline infusion at 2 ml/h was adjusted to last for 24 hours. The operation was allowed to start when spinal anesthesia was sufficient. Before regional block, measured heart rate, SBP, DBP, SPO2 values at 1, 5, 10, 15, 30, 45 minutes were recorded. Immediate complications such as hypotension were treated with appropriate doses of ephedrine (5-10 mg) in increments. The patients were at bed rest for first 6 postoperative hours, as part of the standard protocol of postoperative patient follow up. All patients received IV analgesics postoperatively. All participants were visited on the second day of the surgery. PDPH was defined as a frontal or occipital headache in the erect or sitting posture that was relieved with the supine position. PDPH was diagnosed based on visual analogue scale (VAS) and numerical rating scale (NRS). In the case of a headache, the pain of each patient was categorized into one of the three groups, according to VAS and NRS, as mild (VAS/NRS 1-3), moderate (VAS/NRS 4-7) and severe (VAS/NRS 8-10). All patients received a telephone call one week later by the anesthesiologist and were questioned about the possible delayed-onset symptoms.

Statistical analysis

The Statistical Package for the Social Sciences 15.0 program (SPSS Inc., Chicago, IL, USA) was used for the statistical study. One-sample Kolmogorov-Smirnov test was used to determine whether the data was distributed normally. Independent Two Samples t-test was used to compare the differences between spinal and epidural in terms of all the

variables. The results were reported as mean (standard deviation (SD)). Categorical variables were compared using the Chi-square test or Fisher's exact chi-square test, whichever was appropriate, and were expressed as counts and percentages. *P*-value <0.05 was considered statistically significant.

Results

One hundred and twenty-six patients were recruited in the study. Age, weight and height distribution were similar in both groups (Table 1). The total amount of IV fluids administered during the operation was 1728.57 (506.22) ml in control group and 1517.46 (429.75) ml in study group (*P*=0.001). There was no statistically significant difference between the two groups in terms of SBP, DBP and heart rate before operation (Table 2).

Table 1: Comparison between groups

	Control group	Study group	Total	*P*-value
Age (years)	31.30 (5.01)	30.83 (5.72)	31.06 (5.36)	0.62
Weight (kg)	80.13 (11.38)	77.97 (11.78)	79.05 (11.58)	0.29
Height (cm)	163.24 (5.68)	163.75 (6.51)	163.49 (6.09)	0.64
Total amount of administered intravenous fluid	1728.57 (506.22)	1517.46 (429.75)	1623.02 (479.52)	0.01

Values are presented as mean (Standard deviation).

Table 2: Preoperative parameters

Preoperative parameters	Control group	Study group	*P*-value
PRE-SBP	129 (16.20)	133.06 (18.89)	0.74
PRE-DBP	78.00 (16.50)	80.98 (21.94)	0.39
PRE-HR	97.79 (13.72)	98.16 (13.29)	0.88

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, HR: Heart rate. Values are present as mean (Standard deviation) .

Intraoperative vital parameters were measured at 1, 5, 10, 15, 20, 30 and 45 minutes. The results were similar in both groups (Table 3). Postoperative parameters were measured at 1, 5, 10, 15, 20, 30 minutes. The mean SBP value was measured at the 1st postoperative minute, which was higher in control group (*P*=0.005). The SBP values at the 30th postoperative minute (*P*=0.007) were lower in the control group (*P*=0.007). Other values were similar between the two groups (Table 4). The mean durations of operation (DO) were 45 minutes in both groups (Range of DO in the control group: 30-60 min, in the study group: 40-60 min). There was no significant difference in terms of operation time (*P*=0.158). The mean amount of ephedrine used in both groups was 10 mg (range, 0-40) (*P*=0.045) (Table 5). Nausea occurred in one patient from each group (*P*=0.75). Vomiting occurred in two patients in both groups (*P*=0.69). PDPH was observed in 7 patients in the control group within 72 hours and in no patients in the study group (*P*=0.007) (Table 6). Five patients described mild pain (VAS/NRS 1-3) and two patients described moderate (VAS/NRS 4-7) pain in control group. Severe headache (VAS/NRS 8-10) was not observed in any patients at any time. Mild PDPH was treated with bed rest and oral hydration at home. Moderate PDPH was treated with a combination of 250 mg oral paracetamol, 150 mg propyphenazone and 50 mg caffeine (Minoset Plus ®, Bayer), bed rest and oral hydration.

Table 3: Intraoperative parameters

Intraoperative parameters	Control group	Study group	*P*-value
SBP 1 min	116.11 (20.16)	117.37 (18.97)	0.72
SBP 5 min	102.94 (20.44)	104.76 (22.86)	0.63
SBP 10 min	109.03 (15.29)	109.21 (15.27)	0.94
SBP 15 min	108.30 (14.30)	111.43 (15.27)	0.23
SBP 20 min	112.33 (17.58)	108.79 (18.19)	0.26
SBP 30 min	125.86 (18.78)	112.17 (17.50)	0.98
SBP 45 min	113.24 (10.37)	147 (18.25)	0.15
DBP 1 min	65.78 (15.18)	68.48 (17.02)	0.35
DBP 5 min	54.60 (13.95)	59.02 (14.69)	0.08
DBP 10 min	57.33 (13.05)	58.75 (13.18)	0.54
DBP 15 min	57.79 (13.39)	58.08 (12.27)	0.90
DBP 20 min	60.46 (13.01)	58.14 (12.51)	0.31
DBP 30 min	60.41 (11.99)	60.79 (10.90)	0.85
DBP 45 min	61.60 (9.95)	62.92 (10.93)	0.48
HR 1 min	95.57 (16.68)	92.62 (18.87)	0.35
HR 5 min	94.57 (16.41)	94.06 (17.90)	0.86
HR 10 min	96.14 (14.69)	97.89 (14.58)	0.50
HR 15 min	96.73 (14.26)	96.97 (13.11)	0.92
HR 20 min	92.37 (16.41)	94.59 (12.11)	0.38
HR 30 min	95.92 (13.56)	94.52 (11.18)	0.52
HR 45 min	94.75 (12.01)	94.35 (11.53)	0.77

SAP: Systolic blood pressure, DAP: Diastolic blood pressure, HR: Heart rate, min: Minute. Values are presented as mean (Standard deviation) .

Table-4: Postoperative parameters

Postoperative parameters	Control group	Study group	*P*-value
SBP 1 min	132.89 (13.05)	121.65 (9.93)	0.005
SBP 5 min	117.21 (6.95)	119.70 (9.99)	0.04
SBP 10 min	120.79 (5.19)	122.16 (10.33)	0.35
SBP 15 min	122.79 (6.03)	122.90 (8.59)	0.62
SBP 20 min	120.60 (5.30)	121.60 (6.59)	0.53
SBP 30 min	116.62 (9.10)	121.16 (7.62)	0.007
DBP 1 min	65.57 (8.67)	66.81 (7.31)	0.38
DBP 5 min	67.41 (7.45)	67.37 (7.82)	0.97
DBP 10 min	68.75 (7.02)	69.38 (9.07)	0.35
DBP 15 min	71.05 (4.92)	70.19 (8.72)	0.66
DBP 20 min	71.05 (4.92)	70.19 (8.72)	0.91
DBP 30 min	64.63 (9.86)	67.54 (7.62)	0.06

SBP: Systolic blood Pressure, DAP: Diastolic blood pressure, min: Minute. Values are presented as mean (Standard deviation).

Table 5: Data

	Control group	Study group	*P*-value
Ephedrine (ml)	10 (0.40)	10 (0.40)	0.045
Duration of operation (minute)	45 (30.60)	45 (40.60)	0.158

Values are presented as median (min, max).

Table 6: Postoperative complications

Complications	Control group	Study group	*P*-value
Nausea	n : 1 (1.6 %) n : 62 (98.4 %)	n : 1 (1.6 %) n : 62 (98.4 %)	0.75
Vomiting	n : 2 (3.2 %) n : 61 (96.8 %)	n : 2 (3.2 %) n : 61 (96.8 %)	0.69
Post spinal headache (PDPH)	n : 7 (11.1 %) n : 56 (88.9 %)	n : 0 (0.0 %) n : 63 (100.0 %)	0.007

n: Number of patients. Values are presented as n (%).

Discussion

PDPH is more common in obstetric cases due to dehydration, rapid changes in blood volume and intraabdominal pressure changes during delivery [8]. We planned to study caesarean section patients due to the high risk of PDPH occurrence in obstetric spinal anesthesia. The consensus is that the incidence of PDPH is lower in the procedures performed with pencil point needles. The longitudinal extension of the fibers forming the dura membrane and the sharp-edged needles are referred to as the reason for the transverse cutting of these fibers. It is stated that pencil-point needles do not cut off the fibers forming the dura membrane and cause less CSF seepage [9]. There is moderate-quality proof that atraumatic needles derogate the risk of PDPH without increasing adverse events such as paresthesia or backache [10]. Needle tip design was important to avoid PDPH. For these reasons, we preferred to use atraumatic pencil point needles in our study. Overall epidural anesthesia procedure uses larger gauge needles compared with spinal anesthesia. However, it has been shown that pencil-point needles

used in epidural anesthesia, despite their larger gauge with spinal anesthesia, leads to lower PDPH incidence after an accidental dural puncture [9,10]. The 18-gauge tuohy epidural needle has an opening at the end of the needle and a curved tip intended to prevent dural puncture. It has been documented that 90% of PDPH occurs within approximately 72 hours of dural puncture [11]. Therefore, we evaluated patients who underwent cesarean section in terms of PDPH after 72 hours.

PDPH is an important complication occurring due to a decrease in CSF pressure after loss of CSF from the bore opened in the dura with the guide of the needle used in spinal anesthesia. To prevent PDPH, needle tips were designed conveniently, and needle diameters were reduced [10]. Therefore, we used a 27 G spinal needle in our study.

There were many studies in the literature showing that pencil point and small-diameter needles diminish the incidence of PDPH. Santanen et al. [12] studied the incidence of PDPH with a 27-gauge Quincke and Whitacre (a type of pencilpoint) needle in 676 patients. The incidence of PDPH was 2.7 % in the Quincke group and 0.37% in the Whitacre group. It appeared that PDPH decreased with a 27-gauge needle, but a pencil-point needle reduced the incidence even more. Jeanjean et al. [13] reported that the incidence of PDPH was 0.08 % in 1122 patients under 50 years of age with a 24-gauge needle. In their study conducted on 776 patients aged 20-45 years, Pjevic et al. [14] reported that the incidence of PDPH was 3.5% and higher in young patients, using a 25-gauge needle. In our study, PDPH was seen in 7/126 patients using the 27 G spinal needle. Based on the results of our study, we detected an obvious advantage of our current practice of using 27 G pencil point spinal needle in patients. Severe headache was not observed in any patients at any time.

Dural puncture involves passing a needle into the fluid-filled space around the spinal cord and nerve roots. However, leakage of fluid through the puncture created by the needle may cause a headache. Researchers have suggested various interventions to help prevent PDPH. One suggestion for preventing or treating this headache is to inject the patient's own blood around the puncture to stop the seepage. Recent studies show that the role of epidural blood patching in the prevention or treatment of the headache that may occur after dural puncture is inadequate [15]. Conservative treatment is convenient for most patients with PDPH because of its benign prognosis. Bed rest in the horizontal position and adequate hydration are often recommended [16]. In a recent study, there was no evidence suggesting that routine bed rest after dural puncture is beneficial for the prevention of PDPH. The role of fluid addition in the prevention of PDPH is still vague [17]. Numerous pharmaceutical agents have been offered to treat PDPH but there is no certainty about their clinical effectiveness. Caffeine was proven valid for treating PDPH, when compared with placebo. Gabapentin, hydrocortisone, and theophylline have been shown to diminish pain validity scores [18].

Bradbury et al. [19] reported that five techniques were associated with a reduction in the incidence of PDPH: performance of a prophylactic EBP, lateral positioning of the bevel of the epidural needle at the time of insertion, using a Special Sprotte needle, administration of epidural morphine, and administration of cosyntropin. The principal disadvantage of a prophylactic blood patch is the deposition of a matter that is a potential medium for bacterial growth. Infection is very scarce but carries grave possible consequences. Because of the unclearness of the benefit of prophylactic blood patches, without further proof, routinely offering this intervention cannot be verified [20]. Concerns have been expressed about the potential danger of an autologous epidural blood patch for the treatment of post-dural puncture headache. The immediate resolution of the headache with a blood patch is attributable to thecal compression raising CSF pressure. It is generally believed that the preliminary effect of the EBP is predicated on an increase in CSF pressure caused by the mass effect of the injected blood. This mass effect on the lumbar thecal sac has been demonstrated by magnetic resonance imaging [21]. An epidural injection of saline would, in theory, produce the same mass effect, and restore normal CSF dynamics. As saline is a sterile and relatively inert solution, epidural saline bolus or infusion appears to be an attractive alternative. Usubiaga et al. [22] demonstrated that rapid injection of 20 mL saline into the epidural space increased both lumbar subarachnoid and epidural pressures to as high as 85 mmH2O. Higuchi et al. [23] founded that injection of 5, 10, or 15 mL saline into the epidural space produced variable degrees and patterns of compression of the thecal sac between individuals, and large differences in the amount that flowed out of the intervertebral foramina. CSF density is also a variable, which could be associated with the incidence of headaches. Richardson and Wissler [24] have shown that pregnancy and the immediate postpartum period were associated with the lowest CSF densities. Progesterone may be a physiologic mediator of altered CSF densities during human pregnancy, because progesterone treatment of estrogen-primed nonpregnant rabbits significantly alters Sodium-Potassium-ATPase activity in isolated choroid plexi. This enzymatic activity is the primary driving force for CSF production [25]. Gill et al. [26] reported 12 cases of blindness after epidural fluid injection during epiduroscopy. The authors postulated that the rise in ICP associated with epidural injection likely led to retinal venous obstruction and subsequent venous hemorrhage. They recommended an epidural injection rate of no more than 1 mL per 1–2 seconds. We believe that 24-hour continuous infusion with an easy pumping device might have a clinical advantage by helping avoid the generation of excessively high pressures, and thus may prevent the consequent complications associated with rapid increases in CSF pressure. A survey of anesthesiologists in the USA showed that, to prevent PDPH, 19% placed an intrathecal catheter, 12–25% used epidural saline, and 10–31% applied an epidural blood patch as a prophylactic measure [27]. The use of epidural saline is 12-25%, demonstrating that clinical experience is beneficial. In addition, prophylactic single dose epidural saline has been reported to result in a decrease in the incidence of headaches following dural puncture [28].

In our study, the epidural continuous infusion of normal saline significantly reduced the incidence of PDPH. There are numerous variables in the pathophysiology of PDPH. One explanation for the beneficial effect of intrathecal saline is that

the increase in CSF pressure may result in approximation of the dura and arachnoid at the puncture site, thus sealing the defect. The most widely assumed theory concerning the cause of PDPH is based on the notion of loss of CSF through a dural tear. CSF volume alterations may be the closest explanation for the headache mechanism. The epidural space is a potential gap surrounding the dural sheath extensions and it is located between the dura and the periosteum, lying between the vertebral canal and the fibrous extensions to the ligaments. The slim dura in this area permits access to the cerebrospinal fluid of the local anesthetic and provides a basis for epidural anesthesia. The agents given in the epidural anesthesia practice are not injected directly into the neural tissues but require diffusion from the injection spot. The lumbar injection of saline raises epidural and intrathecal pressures. The reduced leakage allows the dura to repair. However, measurements of pressures generated in the subarachnoid and epidural spaces show that despite the significant increase in epidural pressure, the increase in subarachnoid pressure maintains the differential pressure on the dura. Also, saline may induce an inflammatory reaction within the epidural space, promoting closure of the dural perforation. PDPH was seen in 7 patients in the control group, but not observed in study group. We believe that epidural saline infusion is a safe and tolerable modality that effectively reduces the frequency and violence of PDPH with mild and limited adverse events.

We observed nausea and vomiting. Nausea and vomiting occurred in one and two patients from each group, respectively. These could be secondary to maternal hypotension, which in turn causes decreased cerebral blood flow.

Limitations

The limitations of this study included the fact that it was a single-center study. The study group patients were punctured twice, once with an 18-gauge Tuohy needle and once with the 27-gauge needle, whereas control group patients were only punctured once, using the 27-gauge needle. In addition, the pain threshold of the patients may have been different, and the classification of pain is not objective.

Conclusion

We investigated a low-risk technique for the prevention of PDPH. In our study, the preservative-free normal saline infusion via an epidural catheter was infused at a rate of 2 ml/h for 24 hours. The epidural continuous infusion significantly reduced the incidence of PDPH. This current study demonstrated that the administration of epidural saline during an elective caesarean section under spinal anesthesia significantly reduced the incidence of PDPH. Further studies on larger series are needed to evaluate its safety and efficacy.

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Extubation failure in operating room: Review of management in 50 patients at a single center

Ameliyat sonrası ekstübe edilemeyen hastalar: Tek merkezde 50 vakanın incelenmesi

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Abstract

Aim: Postoperative extubation failure is a serious complication of general anesthesia. Prolonged mechanical ventilation is associated with increased morbidity and late mortality. There are numerous factors affecting postoperative extubation failure. In our study, we aimed to evaluate these factors.

Methods: This retrospective cohort study was conducted on 50 patients who could not be extubated postoperatively between January 2016 and January 2019 in Medipol University Medical Faculty Hospital.

Results: The mean age was 61.2 (6.4) (50-77) years. 29 (58%) patients were male and 21 (42%) were female. The mean Body Mass Index was 29.3 (3.6) (12-36) kilogram/square meters (kg/m^2). Mean duration of surgery was 240 (27.6) minutes. 39 (78%) patients had chronic obstructive pulmonary disease and 13 (26%) had congestive heart failure. Perioperative oxygen saturation was ≤95% in 44 (88%) patients and >95% in 6 (12%) patients.

Conclusions: Chronic obstructive pulmonary diseases, congestive heart failure and low perioperative oxygen saturation are commonly seen in patients who could not be weaned from mechanical ventilation postoperatively. We advise watching out for patients with these risk factors.

Keywords: Extubation, Chronic obstructive pulmonary disease, Congestive heart failure, Perioperative oxygen saturation

Öz

Amaç: Ameliyat sonrası ekstübe edilemeyen hastalar genel anestezi için ciddi bir durumdur. Uzun süreli mekanik ventilasyon artmış morbidite ve geç mortalite ile ilişkilidir. Ameliyat sonrası ekstübe edilememeyi etkileyen birçok faktör vardır. Çalışmamızda, bu faktörleri araştırdık.

Yöntemler: Bu retrospektif kohort çalışma, Ocak 2016 - Ocak 2019 tarihleri arasında Medipol Üniversitesi Tıp Fakültesi Hastanesi'nde ameliyat sonrası ekstübe edilemeyen 50 hasta üzerinde yapıldı.

Bulgular: Yaş ortalaması 61,2 (6,4) (50-77) yıldı. 29 (%58) hasta erkek, 21 (%42) hasta kadındı. Ortalama Vücut Kitle İndeksi 29,3 (3,6) (12-36) kilogram / metrekare (kg/m^2), ortalama ameliyat süresi 240 (27,6) dakikaydı. Kronik obstrüktif akciğer hastalığı olan 39 (%78) hasta, konjestif kalp yetmezliği olan 13 (% 26) hasta vardı. Perioperatif oksijen satürasyonu 44 (%88) hastada ≤%95 ve 6 (%12) hastada >%95 idi.

Sonuçlar: Ameliyat sonrası ekstübe edilemeyen hastalarda kronik obstrüktif akciğer hastalıkları, konjestif kalp yetmezliği ve düşük perioperatif oksijen satürasyonu sıklıkla görülmektedir. Bu hastaların yönetiminde daha dikkatli olunması gerektiğini düşünüyoruz.

Anahtar kelimeler: Ekstübasyon, Kronik obstrüktif akciğer hastalığı, Konjestif kalp yetmezliği, Perioperatif oksijen satürasyonu

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Introduction

Patients are usually extubated postoperatively once ventilatory support or airway protection needs subside. However, some patients cannot be weaned from mechanical ventilation during this period [1]. The risk factors for failure of extubation include old age, male gender, smoking, high American Society of Anesthesiologists (ASA) score, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), and obesity [2]. Prolonged mechanical ventilation is associated with increased morbidity, long hospital stays and late mortality [3,4]. In this study, we aimed to evaluate patients who could not be extubated after surgery.

Materials and methods

This retrospective cohort study was conducted on 50 patients who could not be extubated postoperatively between January 2016 and January 2019 in Medipol University Medical Faculty Hospital. The age, gender, BMI, ASA score, presence of COPD or CHF and perioperative oxygen saturations of these patients were recorded.

Inclusion criteria

Patients older than 50 years with an ASA of I-III who underwent open elective abdominal surgery that lasted more than 200 minutes under general anesthesia were included in this study.

General anesthesia

Patients were premedicated with intravenous midazolam. General anesthesia was induced with propofol and fentanyl followed by vecuronium to facilitate endotracheal intubation. Anesthesia was maintained with sevoflurane and remifentanil titrated to maintain adequate anesthetic depth and hemodynamic stability by clinical monitoring.

Statistical analysis

Continuous variables with normal distribution are presented as mean (standard deviation). Categorical variables are presented as percentage and number.

Results

The mean age was 61.2 (6.4) (50-77) years. 29 (58%) patients were male and 21 (42%) were female. The mean Body Mass Index was 29.3 (3.6) (12-36) kilogram/square meters (kg/m^2). Mean duration of surgery was 240 (27.6) minutes. Mean ASA score was 1.6 (0.6) (2-3). 39 (78%) patients had chronic obstructive pulmonary disease and 13 (26%) had congestive heart failure. Perioperative oxygen saturation was ≤95% in 44(88%) patients and >95% in 6(12%) patients (Table 1).

Table 1: Demographic and clinical data of patients

Parameters	Value	
Age (Years, Mean (SD) (Min-Max))	61.2 (6.4) (50-77)	
Gender (Male/Female) (n/%)	29(58%)/21(42%)	
Body Mass Index (kg/m^2)	29.3 (12-36)	
ASA Physical Status	1.6 (2-3)	
COPD (n/%)	39(78%)	
CHF (n/%)	13(26%)	
Perioperative oxygen saturation (n/%)	≤95%	44(88%)
	>95%	6(12%)

SD: Standard deviation, kg: kilograms, m^2 :square meters, ASA: American Society of Anesthesiologists, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure

Discussion

The most widely accepted anesthetic method is general anesthesia, endotracheal intubation and controlled mechanical ventilation. Patients are usually extubated after the operation; however, some patients' need for ventilatory support continue during the postoperative period [5]. Its incidence being 1-5% [6,7], prolonged mechanical ventilation is associated with increased morbidity, long hospital stays and late mortality [3,4].

In our study, we evaluated 50 patients who received ventilatory support during the postoperative period. Risk factors for failure of extubation include old age (age>60), male gender, high ASA scores (ASA>2), COPD, CHF, and obesity [2,8]. The duration of surgery (>3 hours), having thoracic, upper abdominal, head and neck surgery, neurosurgery and emergency operations are also reportedly related to postoperative extubation failure [9,10]. The patients included in this study had undergone elective abdominal surgery under general anesthesia.

The postoperative intubation times are long in patients who cannot be weaned in the operation room. Consequently, complications such as atelectasis, pneumonia, pneumothorax, and pulmonary edema are more frequent [11,12]. In our study, 10% (n=5) of the patients developed atelectasis, all of whom improved with respiratory physiotherapy.

Limitations

The limitations of this study are its retrospective nature and small number of patients.

Conclusion

Despite the above-mentioned limitations, we found that COPD, CHF and low peri-operative oxygen saturation are commonly seen in patients who cannot be extubated in the operation room. We believe that necessary measures should be taken in these patients.

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Effect of loss of correction on functional outcomes in thoracolumbar burst fractures treated with short segment posterior instrumentation

Kısa segment posterior enstrümentasyon ile tedavi edilen torakolomber burst kırıklarında korreksiyon kaybının fonksiyonel sonuçlar üzerine etkisi

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Abstract

Aim: Burst fractures are defined as vertebra fractures involving the anterior and middle columns and are associated with kyphotic deformity and retropulsion of bone fragment into the spinal canal. Although their treatment is controversial in the literature, use of transpedicular screws and short segment posterior instrumentation are increasingly common practices. The aim of this study is to investigate the radiological and functional outcomes of thoracolumbar vertebra burst fractures treated with short segment posterior instrumentation and to examine the effects of postoperative correction loss on these results.

Methods: Patients who were surgically treated for thoracolumbar burst fractures and prospectively followed-up between 2000-2003 were scanned retrospectively for this cohort study. 48 patients were included in the study, of which 18 were females (37.5%) and 30 were males (62.5%). Denis Pain Scale (DPS) and Denis Work Scale (DWS) were used for functional analysis. Cobb angles that were measured preoperatively, on the first postoperative day, and at the last follow-up visit were used for evaluation of radiological outcomes. Spinal stenosis and remodelization rates were also calculated by computerized tomography obtained preoperatively and at the last follow-up. One-way ANOVA and Pearson correlation tests were used for statistical analysis.

Results: No patient had any chronic pain complaints, and none were unable to work. The mean Cobb angles in the preoperative, early post-operative and final controls were measured as 23.2, 4.9, and 12.3 degrees, respectively. While preoperative mean Cobb angle and mean correction were positively correlated (r=0.85, $P<0.001$), there was no correlation between preoperative mean Cobb angle and loss of correction (r=0.27, $P=0.43$). There was a correlation between correction and loss of correction (r=0.38, $P=0.008$). Spinal stenosis, which was 35.7% preoperatively, reduced to 17.1% in the last follow-up. The mean remodelization was 51.3%, which was significant ($P<0.001$). Loss of correction was found significant in patients with poor DWS ($P=0.003$), and no such relationship was found in DPS. No correlation was found between the Cobb angle at the last follow-up, DPS and DWS.

Conclusion: In conclusion, the loss of correction after short segment posterior instrumentation and fusion surgery is significantly higher in thoracolumbar burst fractures, especially when intraoperative correction exceeds 15 degrees. Denis Work Scale was significantly worse in patients with loss of correction above 10 degrees. The degree of loss of correction at the last follow-up is directly related to clinical and functional outcomes.

Keywords: Burst fractures, Kyphosis, Cobb angle, Remodelization, Loss of correction, Short segment posterior instrumentation

Öz

Amaç: Burst kırıkları, ön ve orta kolonu içeren, kifotik deformite ve kemik fragmanının spinal kanala retropülsiyonu ile ilişkili vertebra kırıkları olarak tanımlanır. Tedavileri literatürde tartışmalı olsa da transpediküler vida ve kısa segment posterior enstrümentasyon oldukça sık uygulanmaktadır. Bu çalışmanın amacı kısa segment posterior enstrümentasyon ile tedavi edilen torakolomber vertebra burst kırıklarının radyolojik ve fonksiyonel sonuçlarını ve postoperatif korreksiyon kaybının bu sonuçlar üzerine etkisini incelemektir.

Yöntemler: 2000-2003 yılları arasında torakolomber burst kırığı nedeniyle cerrahi olarak tedavi edilen ve prospektif olarak takip edilen hastalar, bu retrospektif kohort çalışması için retrospektif olarak tarandı. Çalışmaya 18'i kadın (%37,5), 30'u erkek (%62,5) olan 48 hasta alındı. Fonksiyonel analiz için Denis Ağrı Skoru (DPS) ve Denis İş Skoru (DWS) kullanıldı. Radyolojik analiz için preoperatif, postoperatif ilk gün ve son takipte ölçülen Cobb açıları kullanıldı. Ayrıca preoperatif ve son takipte çekilen bilgisayarlı tomografi aracılığı ile spinal stenoz ve remodelizasyon oranları hesaplandı. İstatistiksel analiz için tek yönlü ANOVA ve Pearson korelasyon testleri kullanıldı.

Bulgular: Hiçbir hastada kronik ağrı ya da işe geri dönememe şikâyeti görülmedi. Hastaların ameliyat öncesi, sonrası ve son kontrollerde ortalama Cobb açıları sırası ile 23,2, 4,9 ve 12,3 derece olarak ölçüldü. Ameliyat öncesi ortalama Cobb açısı ile ortalama korreksiyon arasında anlamlı bir korelasyon saptanırken (r=0,85, $P<0,001$); korreksiyon kaybı ile arasında anlamlı ilişki bulunmadı (r=0,27, $P=0,43$). Korreksiyon ve korreksiyon kaybı arasında bir korelasyon tespit edildi (r=0,38, $P=0,008$). Ameliyat öncesi %35,7 olarak hesaplanan spinal darlığın, son takipte %17,1'e gerilediği görüldü. Ortalama remodelizasyon %51,3 olarak hesaplandı. Spinal kanal remodelizasyonu anlamlı bulundu ($P<0,001$). 10 dereceden fazla korreksiyon kaybı olan hastalar ile DWS arasında anlamlı ilişki bulundu ($P=0,003$). DPS'de böyle bir ilişki bulunamadı. Son takipte ölçülen Cobb açısı ile DPS ve DWS arasında ilişki saptanmadı.

Sonuç: Sonuç olarak, kısa segment posterior enstrümentasyon ve füzyon cerrahisi sonrası korreksiyon kaybı, torakolomber burst kırıklarında, özellikle intraoperatif korreksiyon 15 dereceyi aştığında, belirgin olarak daha yüksektir. DWS, 10 derecenin üzerinde korreksiyon kaybı olan hastalarda anlamlı olarak daha kötüdür. Son takipteki korreksiyon kaybının derecesi doğrudan klinik ve fonksiyonel sonuçlarla ilgilidir.

Anahtar kelimeler: Burst kırıkları, Kifoz, Cobb açısı, Remodelizasyon, Korreksiyon kaybı, Kısa segment posterior enstrümentasyon

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Introduction

Burst fractures are defined as vertebra fractures involving the anterior and middle columns and associated with kyphotic deformity and retropulsion of bone fragment into the spinal canal. They are usually related to high-energy traumas [1-3]. The incidence of burst fractures in the thoracolumbar junction, where most of the vertebral fractures occur since it is the transition zone from a mobile thoracic segment to a less mobile lumbar segment, is between 10-20% [1-5]. In the literature, it is mentioned that late neurological deterioration is up to 17% after thoracolumbar vertebra burst fractures' conservative treatment, therefore these fractures are treated surgically [6]. Advantages of surgical treatment include providing early stabilization of the spine, thus reducing the possibility of neurological deterioration, improving kyphosis, and allowing early mobilization [6,7]. There are numerous surgical techniques, such as anterior surgery, long segment posterior instrumentation and transpedicular screws, and short segment posterior instrumentation. Although it is known that after the use of transpedicular screws and short segment posterior instrumentation, some of the correction is lost during follow-up, and correction losses between 3º and 12º [1,8,9] and failure rates of 9-56% have been reported in the literature [10-12], other surgical options with minimal loss of correction have relatively high morbidity [13,14]. To this extent, use of transpedicular screws and short segment posterior instrumentation became increasingly common.

The aim of this study is to investigate the radiological and functional results of thoracolumbar vertebra burst fractures treated with short segment posterior instrumentation and to examine the effects of postoperative correction loss on these results.

Materials and methods

Patients who were surgically treated for thoracolumbar burst fractures and prospectively followed-up between 2000-2003 were scanned retrospectively for this cohort study. After exclusion of polytrauma patients, patients who had neurological deficits, who were lost to follow-up and who had less than 1-year of follow-up, 48 patients [18 females (37.5%); 30 males (62.5%)] were included in the study. Mean age was 39.5 years (Range: 18-67 years). Fractures of all 48 patients were caused by high energy traumas. Among them, 23 (48%) had a car crash, 21(43.7%) fell from high, 3 (6.2%) had work accidents and 1 (2.1%) patient was assaulted. Denis Classification was used for preoperative radiological classification (Table 1) [15].

Surgical technique

Using posterior longitudinal incision, paravertebral muscles were scraped by using electrocautery. Care was taken to protect the posterior ligamentous complex. Fractured vertebra was detected using fluoroscopy. The cartilage faces of the facet joints were removed along the instrumentation site. Transpedicular polyaxial screws of appropriate length and diameter were placed at the upper and lower levels of the fractured vertebra. Properly inclined shaped rods were placed on transpedicular screws. The fracture line was distracted, and indirect reduction technique was performed using 3-point principle. Stability was improved by locking the system with transverse connectors. After indirect reduction and stabilization of the fractures were achieved by posterior instrumentation, the field was grafted by autograft which was taken from the posterior iliac wing and fusion was completed. After the insertion of one in hemovac drain in the operation lodge and one in the iliac wing, operation was completed. The same surgical team performed all operations. All complications were recorded.

Rehabilitation

Patients were mobilized on the second postoperative day with a Steindler type hyperextension full steel brace. Brace was used for 3-6 months (Mean: 4.5 months). Mean hospital stay was 7.4 days (Range: 5-14 days).

Sutures were removed in the second postoperative week. The patients were called for annual follow-ups after 45 days, 3 months, 6 months and 1 year. Mean follow-up time was 26.2 months (Range: 13- 38 months). Neurological examinations were repeated at all follow-ups. Anteroposterior and lateral radiographs were seen.

Functional analysis

Denis Pain Scale (DPS) and Denis Work Scale (DWS) were used to evaluate the postoperative clinical outcome [6,16]. According to the DPS, P1 has no pain; P2 has minimal pain but does not require treatment; P3 has moderate pain that does not interfere with work; P4 has moderate-to-severe pain and requires frequent treatment, and P5 has severe chronic pain [6]. According to DWS, W1 was specified as return to heavy work; W2 was specified as return to sedentary work or heavy work with restrictions; W3, a different full-time new job; W4, a different part time new job, and W5, unable to work [6].

Radiological analysis

In addition to the anteroposterior and lateral thoracic and lumbar radiographs at every follow-up, all patients underwent computed tomography preoperatively and at the first-year follow-up visit.

As an evaluation criterion, Cobb angle (calculated by using the upper endplate of the vertebra which is above the fracture level and the lower endplate of the vertebra which is below the fracture level) was measured on lateral radiographs of all patients, preoperatively, on the first postoperative day and last follow-up visit. In computed tomography, the narrowing of the spinal canal and remodelization were measured by the method described by Willen et al. [17,18]. The same surgeon performed all measurements (Figure 1).

Statistical analysis

Statistical analysis was performed using the SPSS 16.0 software version. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. One-way ANOVA analysis was performed for Cobb angle correction, loss of correction angle and remodelization. Pearson analysis was used to detect correlation between normally distributed variables such as follow-up time, loss of correction, Cobb angle, remodelization, DPS, DWS. A *P*-value of less than 0.05 was considered to show a statistically significant result.

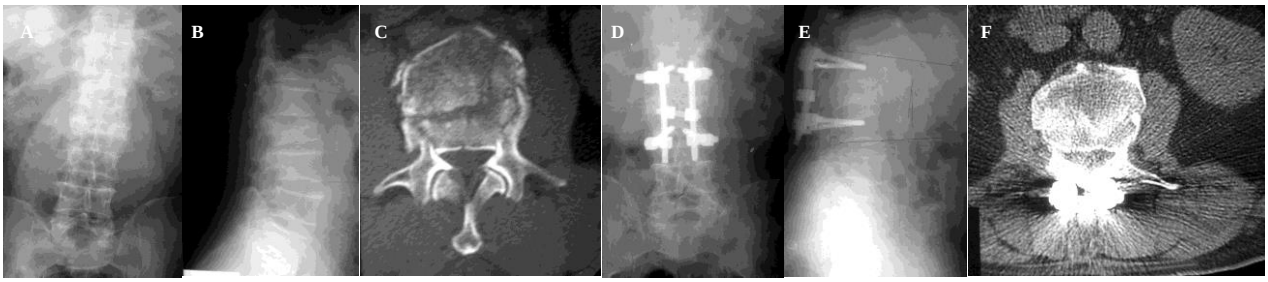

Figure 1: Case example of 59 years-old male patient with L2 vertebra burst fracture (A: Preoperative antero-posterior view, B: Preoperative lateral view, C: Preoperative computed tomography section, D: Postoperative 1-year antero-posterior view, E: Postoperative 1-year lateral view, F: Postoperative 1-year computed tomography section)

Results

No patients had chronic pain complaints, and none were unable to work. DWS and DPS were positively correlated (r=0.31, *P*=0.009). Detailed distribution of DPS and DWS of the patients are presented in Table 2.

The mean Cobb angles in the preoperative, early post-operative and final controls were measured as 23.2 (0.1), 4.9 (5.1), and 12.3 (8.9) degrees, respectively. The mean Cobb angle correction in early post-operative period was 18.1 (8.5) and the mean loss of correction at the last follow-up was 7.4 (7.7) degrees. While preoperative mean Cobb angle and mean correction were positively correlated (r=0.85, *P*<0.001), there was no correlation between preoperative mean Cobb angle and loss of correction (r=0.27, *P*=0.43). There was a positive correlation between correction angle and loss of correction (r=0.38, *P*=0.008). Finally, it was found that the loss of correction was significantly higher in patients with intraoperative correction rates above 15 degrees (*P*=0.006).

Spinal stenosis, which was calculated as 35.7% (SD:8.5) preoperatively, was reduced to 17.1% (SD:4.6) in the last follow-up (*P*<0.001). The mean remodelization was 51.3% (SD:9.3). The spinal canal remodelization was significant (*P*<0.001). There was a correlation between preoperative spinal stenosis and canal remodelization (r=0.30, *P*=0.04). No correlation was detected between canal remodelization and correction angle or loss of correction (r=0.22; *P*=0.07; r=-0.04, *P*=0.14, respectively).

The rate of loss of corrections greater than 10 degrees was statistically significant in patients with poor DWS (*P*=0.003). No such relationship was found in DPS. Correlation between correction angles and functional results are presented in Table 3 (Table 3)

Superficial wound infection occurred in 6 patients (12.5%) and were treated with antibiotherapy. Pedicle screw fractures were observed in 4 patients (8.3%) during the follow-ups, but no new surgical interventions were needed since there were no clinical complaints.

Table 1: Preoperative fracture classification

Denis classification	n	%
A	11	22.8
B	31	64.5
C	1	2.1
D	3	6.3
E	2	4.3

Table 2: Detailed distribution of DPS and DWS

		DWS					
		W1	W2	W3	W4	W5	Total
DPS	P1	16	0	0	0	0	16 (33.3.%)
	P2	3	20	0	0	0	23 (47.9%)
	P3	0	2	5	2	0	9 (18.8%)
	P4	0	0	0	0	0	0
	P5	0	0	0	0	0	0
	Total	19	22	5	2	0	r=0.31
		(39.6%)	(45.8%)	(10.4%)	(4.2%)		*P*=0.009

DPS: Denis Pain Score, DWS: Denis Work Score, P: Pain, W: Work, *P*: statistical significance value, r: correlation value

Table 3: Correlation between radiological and functional results

	DPS	DWS
Preoperative Cobb Angle	r=0.32	r=0.30
	P=0.002	*P*=0.004
Last Follow-up Cobb Angle	r=0.251	r=0.159
	P=0.54	*P*=0.77
Spinal Stenosis	r=0.26	r=0.17
	P=0.19	*P*=0.17
Correction	r=0.19	r=0.24
	P=0.36	*P*=0.48
Loss of Correction	r=0.27	r=0.39
	P=0.09	*P*=0.003

DPS: Denis Pain Score, DWS: Denis Work Score, *P*: statistical significance value, r: correlation value

Discussion

The use of transpedicular screws and short segment posterior instrumentation are still of preference in clinical practice, despite the rate of loss of correction and failure rates specified in the literature [8-12]. One of the most important reasons is that other surgical options known to have lower loss of correction during follow-ups are directly related to high morbidity [13,14]. Furthermore, it is still controversial in the literature whether loss of correction is associated with clinical functional outcomes. Therefore, this study investigating the relationship between loss of correction in short segment posterior instrumentation and radiological and functional outcomes is important because of its large cohort number.

In our study, correction of kyphotic deformity was achieved in all patients by short segment posterior instrumentation and fusion method, and the change in Cobb angle before and after the surgery was found significant. However, at the last follow-up, a significant loss of correction of 7.4 (7.7) degrees were found. These values were consistent with the literature. Esses et al. [19], in their study of short segment posterior instrumentation and fusion, reportedly encountered a mean loss of correction of 11.2 degrees. Sasso et al. [20] followed 23 patients with short segment posterior instrumentation for an average of 20 months and reported that they lost the correction they achieved in the 3rd postoperative month. The reason of this loss is not completely understood, but there are some explanations. Some writers believe that the large bone defect which is created in the fractured vertebra during the restoration of the height is the main reason of this loss. Also, the change of the intervertebral disc height is important. During surgery, the distraction affects the bone, not the discs. As time

goes by, the disc heights decrease in value, which is related with the post-traumatic degeneration [3,21,22]. Furthermore, overcorrection may affect the biomechanics of the posterior ligamentous complex and the whole vertebra. This may also explain the loss of correction.

Carl et al. [23], in their study of 38 patients who had short segment posterior instrumentation, a mean loss of 6 degrees of correction at the last follow-up and a final correction of 1 degree, reported that 32 of 33 patients were satisfied with the surgical results and 28 of them returned to work. On the other hand, Öner et al. [24] reported that loss of correction in kyphosis but not final kyphosis was associated with permanent pain. In our series, the preoperative Cobb angle and loss of correction were not correlated, but correction angle and loss of correction were found to correlate. Loss of correction was significantly higher in patients with intraoperative correction rate above 15 degrees. The rate of loss of correction greater than 10º was positively correlated with a poor DWS. On the other hand, no correlation was found between Cobb angle at the last follow-ups, DPS and DWS. In other words, a relationship between final kyphosis and functional and clinical outcomes could not be established whereas loss of correction was positively correlated with functional outcomes.

One of the parameters considered in the treatment of burst fractures of the thoracolumbar vertebra is the rate of spinal stenosis and decompression or remodeling of stenosis [19,25]. In their prospective study, Esses et al. [19,25] found that the rate of stenosis decreased from 58% to 4% in the anterior decompression group in the early postoperative period, and from 44.5% to 16.5% in the posterior surgery group. Authors believe that interventions with posterior distraction and instrumentation effectively decompress the spinal canal. Yazıcı et al. [26] compared patients treated with posterior surgery and conservatively in terms of canal remodeling and reported that the rate of canal remodelization in the surgically treated group was significantly higher than in the conservatively treated group, but that there was no significant difference between the two groups in terms of stenosis after treatment. Several studies report that stenosis following thoracolumbar vertebral burst fracture is remodelized by conservative treatment at a rate of approximately 50% [16]. In our cohort, we did not perform canal decompression to any of the patients; however, remodelization was seen in all. The mean remodelization was 51.3% (SD: 9.3), which was statistically significant (P<0.001). Remodeling was not affected by intraoperative correction or loss of correction. There was no relationship between stenosis and DPS and DWS in the last follow-ups. However, it is currently not possible to comment on how residual spinal stenosis can be affected by the degenerative process and how it will affect clinical and functional outcomes. Bohlman et al. [27] treated 45 patients due to late chronic pain and/or paralysis, using anterior decompression method at an average of 4.5 years after the first treatment, which were performed in numerous ways. The authors suggest that late-onset pain or paralysis occurs secondary to chronic neural compression, and this compression is due to the retropulsion of bone or disc fragments associated with traumatic kyphosis continue to narrow the neural canal. From this perspective, we think that patients should be followed up for a long time in terms of late spinal stenosis.

Limitations

There are some limitations in our study. The first is the short follow-up period. Although several studies have indicated that canal remodelization usually lasts up to 12 months after treatment and no significant remodelization occurs after 12 months, longer follow-up is required for neurological problems secondary to degeneration in the late period [28]. A second limitation is the absence of a control group. Controlled studies may support our results. Another limitation is that only subjective functional analysis was performed in our study. Objective analysis was not used.

Conclusion

The loss of correction after short segment posterior instrumentation and fusion surgery is significantly higher in thoracolumbar burst fractures, especially when intraoperative correction exceeds 15 degrees. Denis Work Scale was significantly worse in patients with loss of correction above 10 degrees. The degree of loss of correction at the last follow-up is directly related to clinical and functional outcomes.

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Review
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The management of clinically early ovarian cancer patients who have not undergone staging surgery

Evreleme ameliyatı geçirmemiş klinik olarak erken over kanseri hastalarının yönetimi

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Abstract

Four-thirds of patients with epithelial ovarian cancer are diagnosed at an advanced stage, and the main choice of treatment is primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy, or interval surgery after neoadjuvant chemotherapy in patients who are not eligible for optimal cytoreductive surgery. In patients with disease clinically confined to the ovary, The International Federation of Gynecology and Obstetrics (FIGO) recommends comprehensive staging to detect the real stage of the disease, but some these patients do not undergo staging during operation. Retrospective studies in the literature report that re-operation, adjuvant chemotherapy without re-operation or observation are some of the management options during the postoperative period for patients with clinically early stage disease. In this article, the management of these patients was reviewed in light of the current literature.

Keywords: Staging surgery, Chemotherapy, Ovarian carcinoma, Observation, Incomplete surgery

Öz

Epitelyal over kanseri olan hastaların dörtte üçüne ileri evrede iken tanı konur ve bu hastaların ana tedavisi primer sitoredüktif cerrahi, ardından adjuvan platin bazlı kemoterapi veya neoadjuvan kemoterapi sonrası sitoredüktif cerrahidir. Klinik olarak overde sınırlı hastalığı olan kadınlarda, Uluslararası Kadın Hastalıkları ve Doğum Federasyonu (FIGO) hastalığın gerçek evresinin tespiti için kapsamlı evreleme cerrahisi yapılmasını önermektedir, ancak bu hastalardan bazıları operasyon sırasında evreleme ameliyatı geçirmemiş olabilir. Literatürdeki retrospektif çalışmalara göre, klinik olarak erken evre hastalığı olan bu hastalar için tekrar ameliyat, tekrar ameliyat olmadan adjuvan kemoterapi veya gözlem tedavi seçenekleri olarak uygulanmaktadır. Bu yazıda, cerrahi evrelemesi yapılmamış bu hastaların yönetimi güncel literatür ışığında gözden geçirilmiştir.

Anahtar kelimeler: Cerrahi evreleme, Kemoterapi, Over kanseri, Gözlem, Tamamlanmamış cerrahi

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Introduction

Ovarian cancer is the most lethal gynecological cancer worldwide [1]. The life-time risk of getting ovarian cancer is 1/70 [2]. According to GLOBOCAN data, disease-related death rates are 50% in cervical cancer, 25% in endometrium cancer and 67% in ovarian cancer [1]. At the time of diagnosis, 60-75% of the patients have advanced disease (FIGO III-IV) [3,4]. Histologically, more than 90% of ovarian carcinomas are epithelial type (EOC) and 70% of them are high grade tumors [5–9].

The standard treatment of patients with EOC is primary cytoreductive surgery followed by adjuvant platinum-based chemotherapy. The goal of surgery is to achieve maximum (complete) cytoreduction. Many studies have shown that survival is directly associated with the rate of complete cytoreduction [10-13]. Neoadjuvant chemotherapy followed by interval surgery is considered an alternative option in patients who are not suitable for optimal surgery [13,14].

Patients with epithelial ovarian cancer who seem to have a clinically early stage disease, but who have not undergone comprehensive staging surgery, and therefore whose true stage of disease is unknown, can be defined as a separate group. There are no strong recommendations based on randomized controlled trials in the management of these patients in the period after surgery. In this article, we asked the question of whether these patients should undergo staging surgery, receive chemotherapy without surgery or whether mere observation is enough.

Standard approach in clinically early stage disease

Of patients with EOC, 25-30% are diagnosed in stage I-II (20-25% in stage I) (3). While serous type and high-grade histology predominate in advanced stage ovarian cancer, non-serous types and grade I-II histology are encountered slightly more frequently at the early stages [15].

The International Federation of Gynecology and Obstetrics (FIGO) proposed comprehensive staging surgery as the standard surgical approach for ovarian cancer in 1985. Staging surgery includes a vertical midline incision, peritoneal cytology, exploration, hysterectomy, salpingo-oophorectomy, omentectomy and pelvic-paraaortic lymphadenectomy. Appendectomy should also be added according to the studies of Ayhan et al. [16,17]. Laparoscopic surgical staging has become feasible in recent years [18-25].

Comprehensive staging surgery in ovarian cancer is recommended, but some patients with clinically early stage disease do not undergo staging [26]. For example, in a study by Skirnisdottir et al. [27], lymphadenectomy was included as part of the standard surgical procedure in 20 of 113 patients with early stage ovarian cancer. In another study, Trimbos et al. [28] reported that only 53% of patients with early stage ovarian cancer underwent comprehensive staging surgery. No apparent suspicion of malignancy during surgery, or technical deficiencies such as the absence of frozen section examination or the absence of a specialist surgeon for advanced surgery procedures may be common reasons for not performing comprehensive staging surgery. Staging surgery may be considered more likely if an expert surgeon performs the operation. It has also been shown that patients operated by a gynecological oncologist have longer survival [29].

In general, these patients are diagnosed with ovarian cancer after surgery without staging. The most frequently omitted steps of staging surgery are the removal of retroperitoneal lymph nodes and getting biopsies from the peritoneum [28]. These patients may be considered as having undergone incomplete surgery, therefore performing complementary surgery for staging is an option. On the other hand, surgery may be considered unnecessary because of the likelihood that the clinically early appearance of the disease is indeed correct. The risk of complications of comprehensive staging surgery and the additional stress of the second operation are some of the disadvantages. Some patients truly have limited disease in the ovary and surgery may be unnecessary [30-33], but it is undetectable without comprehensive staging surgery because there is no diagnostic method to detect occult metastases. The surgical option involves the possibility of an unnecessary surgery while the observation option involves an upstaging risk.

Risks of surgical staging

A comprehensive staging surgery carries various risks such as bleeding and transfusion, gastrointestinal or urinary tract trauma, nerve damage and anesthesia complications. Postoperative complications include infection, lymphedema, lymphocytes, deep venous thrombosis, and pulmonary embolism. In addition, repeated operations may cause stress in the patient. Tam et al. [34] reported 44% lymphocyst formation in patients undergoing pelvic lymphadenectomy. In a recent study evaluating 366 patients, Kuroda and colleagues reported that the cumulative incidence of lower limb lymphedema was 23.1% at 1 year, 32.8% at 3 years, and 47.7% at 10 years post-surgery [35]. Additionally, high body mass index ($\geq$25 kg/m^2), pelvic plus paraaortic lymphadenectomy, and lymphocyst formation were independently associated with lower limb lymphedema. The major morbidity rate associated with the staging surgery procedure was 7.4% according to Snider et al. [36].

Occult metastasis risk

Early stage disease has a latent risk of metastasis and the rate does not seem to be low according to several studies on this subject in literature [30-33]. Visual assessment is inadequate for the detection of micro metastases on the diaphragm, omentum, or lymph nodes. The detectability of occult metastases in positron emission tomography (PET) or magnetic resonance imaging is very poor. In the literature, PET sensitivity for lymph node metastasis is reported between 0 - 90% [37-42]. For metastases below 4 millimeters, sensitivity is too low (~12%) [41].

Staging of the patients with clinically early stage shows that up to 30% are in advanced stage. Garcia et al. [31] found that 29% of patients with clinically early stage who had complete surgical staging had a more advanced stage. Young et al. [30] stated that 31% of these patients were upstaged at the end of the surgical procedure. Ayhan et al. [32] reported an upstaging rate of 31%. In their study, the most common cause of upstaging was lymph node involvement (41%). After performing multivariate analysis, they found that grade 3 cancer, CA 125 >500, and positive ascites cytology were independent risk factors for

upstaging. In their review article, Kleppe et al. [43] reported that the mean incidence of lymph node metastases in clinical stages I-II EOC was 14.2% (range 6.1-29.6%), 7.1% of which were only in the para-aortic region, 2.9% only in the pelvic region, and 4.3% both in the para-aortic and pelvic regions. In a study of the occult metastasis ratio, Arlene et al reported that one-third of the patients with ovarian cancer without gross spread beyond the ovary were upstaged following comprehensive surgical staging [31]. According to literature data, 1 out of 3 patients with clinically early stage disease have widespread disease.

The National Comprehensive Cancer Network (NCCN) guide states that repeat surgery for staging or direct adjuvant chemotherapy are viable options in these patients [44]. There is no suggestion as to which patients are more suitable for which option. It is understood that a patient-based approach should be adopted, considering the benefits and disadvantages of the reoperation or adjuvant chemotherapy. The real stage of disease in the adjuvant chemotherapy approach is unknown. Some patients may have been administered unnecessary chemotherapy due to unknown stage of disease because chemotherapy is not necessary if the disease is FIGO stage 1A and low grade histology [44]. In fact, over-treatment and under-treatment are prevented by reoperation.

Role of chemotherapy in early stage ovarian cancer

In the ACTION (Adjuvant Chemotherapy in Ovarian Neoplasm) multicenter trial, 448 patients with early stage ovarian cancer (FIGO stage I–IIA) were randomly assigned after surgery to adjuvant chemotherapy or to observation [45]. Recurrence rates were lower in the adjuvant chemotherapy arm. Adjuvant chemotherapy improved recurrence-free survival but not overall survival. In this trial, chemotherapy provided better survival than observation in patients who could not undergo complete staging. This may be due to undetermined residual disease. The subgroup analysis performed in this study shows that chemotherapy is unnecessary in patients who have complete staging and the benefit of adjuvant chemotherapy appears to be limited to patients with non-optimal staging.

There is a limited number of studies evaluating the survival rates of these approaches. Le et al. [15] compared patients with early stage ovarian cancer who did not undergo surgical staging with those who underwent surgical staging. The recurrence rates in patients undergoing staging surgery were lower (10% vs 28%, P=0.036), although they had less adjuvant chemotherapy (36% vs 43%). Authors indicated that all clinically early-stage ovarian cancer patients should be considered for comprehensive staging surgery prior to further treatment. In the study of Le et al. [15], better survival was shown in the re-operation approach. In their study, unstaged patients had greater recurrence and lower overall survival rates, despite increased rates of chemotherapy.

Conclusion

There are no strong recommendations for the management of unstaged patients with apparent clinically early ovarian cancer. There is little conformity between the clinical evaluation and surgical stage in early stage ovarian cancer. Approximately one third of these patients are found to have a more advanced stage if they are operated on. Re-operation for staging seems to have a survival advantage according to several studies. Chemotherapy should be given to patients who cannot be re-operated. Our opinion is that observation is not an appropriate option in these patients.

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Review
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The relationship between zinc and hepatic steatosis

Çinko ve hepatik steatoz arasındaki ilişki

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is the most commonly diagnosed liver disease in the recent years, with a prevalence of 15-20% among normal population. Liver steatosis is also a complication of obesity and affects 22-52% of obese children. In this aspect, it is an important public health problem. Increases in the amount of fatty acids entering the liver, increase in fatty acid synthesis and disorders in its secretion are included in its pathogenesis. The relationship between zinc, which is the second most abundant trace element found in the body after iron and necessary for many enzymes to function properly, and fatty liver disease has been shown in previous studies. The aim of this review is to discuss the relationship between zinc and liver steatosis in the light of current studies and contribute to the literature.

Keywords: Zinc, Trace element, Hepatic steatosis

Öz

Non-alkolik yağlı karaciğer hastalığı (NAFLD), prevalansı normal popülasyonda %15-20'lere ulaşan, son yıllarda en sık görülen karaciğer hastalığıdır. Karaciğer yağlanması, obezitenin bir komplikasyonu olarak da karşımıza çıkmakta ve obez çocukların %22-52'ini etkilemektedir. Bu yönüyle önemli bir halk sağlığı sorunudur. Karaciğere gelen yağ asid miktarında artış, yağ asidi sentezinin artışı ve sekresyonundaki bozukluklar, karaciğer yağlanmasının patogenezindeki mekanizmalardan bazılarıdır. Ayrıca, vücutta demirden sonra en bol bulunan ikinci eser element olan ve pek çok enzimin fonksiyon göstermesi için gerekli olan çinko ile karaciğer yağlanması arasında bir ilişki olduğu yapılan çalışmalarda gösterilmiştir. Bu derlemeyi hazırlamaktaki amacımız, vücuttaki çinko miktarının karaciğer yağlanması ile ilişkisini açıklamak ve güncel araştırma sonuçlarını içeren bir veri hazırlamaktır. Bu yönüyle çalışmamızın literatüre katkı sağlayacağı kanaatindeyiz.

Anahtar kelimeler: Çinko, Eser element, Hepatik steatoz

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as the presence of fat, particularly triglycerides, in more than 5% of the liver by weight or the existence of fat vacuoles in more than 5% of the hepatocytes [1,2]. NAFLD is commonly seen as a complication of obesity and affects 22% to 52% of obese children [3]. Fatty liver disease is the most commonly diagnosed liver disease in recent years, especially in Western societies, and its prevalence reaches 15-20% in the normal population. Nonalcoholic fatty liver disease, together with macro-vesicular steatosis, represents a spectrum of liver diseases histopathologically characterized by alterations ranging from 'simple steatosis' to 'nonalcoholic steatohepatitis'. Histological findings suggest a transition from fat infiltration to an inflammatory / fibrotic disease that can progress to cirrhosis [4].

Increased amounts of fatty acids entering the liver in cases of obesity or starvation, excessive carbohydrate intake by diet or total parenteral nutrition and increased fatty acid synthesis in the liver, decreased beta-oxidation of fatty acids as a result of carnitine deficiency and mitochondrial dysfunction, and disturbances in the synthesis or release of very low density lipoprotein (VLDL-Cholesterol) due to disruption of apoprotein synthesis or protein malnutrition are the main causes of fatty infiltration in the liver (5). The relationship between liver steatosis and trace elements has been investigated in various studies.

Zinc (Zn) is an important trace element that plays a key role in biological functions such as cellular integrity and cell division, growth, and development [6,7]. Zn acts as a cofactor for many enzymes and proteins involved in regulatory, catalytic, antioxidant, anti-inflammatory and apoptotic processes [8]. Zn-binding proteins represent about 10% of human proteomes, including more than 300 enzymes with Zn ions in their catalytic domains. Zn plays a significant role in the regulation of gene expression through metal-binding transcription factors and metal response elements in the promoter regions of the regulated genes [9].

Zinc deficiency and metabolism

Zn deficiency is quite common in developing countries and may be caused by insufficient Zn intake, increased Zn loss or consumption in the body [10]. Some dietary fiber / phytates may reduce Zn absorption, which is concentration-dependent and occurs throughout the small intestine (mainly jejunum). In cirrhosis, Zn absorption may be defected, and its secretion typically increases. Zn deficiency has clinical manifestations such as skin lesions, depressed cognition, encephalopathy, impaired night vision due to changes in vitamin A metabolism, anorexia (possible changes in taste and odor acuity), hypogonadism, faulty wound healing, and altered immune functions [11]. Zn homeostasis is mainly regulated in the liver; its disruption has been associated with various diseases, such as cancer, diabetes, cardiovascular disease, and Alzheimer's disease [10].

Studies have shown that Zn deficiency is common in NAFLD [12]. The pathogenesis of NAFLD is not accurately known. Endotoxins / cytokines, oxidative stress and hyperinsulinemia are associated with NAFLD development [13]. Zn is associated with hepatosteatosis because it is an important trace element for many enzymes in the synthesis, storage, release, and effects of insulin [12]. The relationship between Zn intake and chronic fatty liver disease is complex, for Zn affects the normal homeostasis of the liver, and the liver plays a central role in Zn hemostasis. Accordingly, deficiencies of this mineral impair liver functions and endanger the recovery and restoration of liver tissues [14].

The effects of Zn co-supplementation on NAFLD before and/or after disease progression are not clear enough [12]. In a previous study, it was shown that the combination of Zn and selenium supplementation had better effects on serum glucose, lipid profile and hepatic fat accumulation after the progression of fatty liver disease as compared to before. These results may be due to depletion of Zn and selenium in fatty liver disease [12]. Increasing evidence suggests that Zn plays a critical role in regulating hepatic lipid metabolism [15].

Stress hormones and pro-inflammatory markers such as tumor necrosis factor-α cause changes in Zn metabolism [16]. NAFLD causes a low degree of inflammation [17]. In this respect, it is highly possible that Zn levels are changed in NAFLD patients due to inflammation.

Zn deficiency, glucose intolerance and insulin resistance may be predisposing to diabetes mellitus and coronary artery disease [18,19]. Several studies have shown that Zn has beneficial effects on insulin resistance, glucose and lipid profiles in patients with diabetes or metabolic syndrome [15,20,21].

Many studies have reported low plasma Zn levels in obese subjects [22,23]. Liver steatosis is considered a complication of obesity [2]. It has been reported that approximately 50% of obese adolescents are also obese in their adulthood [24]. Childhood obesity affects approximately 25-30% of children [25]. For this reason, the relationship between Zn, liver steatosis and obesity is extremely important starting from childhood.

In an experimental study, Zn levels were reported lower in the fatty liver group compared to the rats in the control group in a NAFLD model, which was formed with an excess fatty diet [26]. This data is scientific proof that NAFLD causes Zn deficiency.

Pathogenesis of nonalcoholic fatty liver disease

The mechanism underlying the formation and progression of NAFLD is not fully understood. NAFLD patients are more prone to cardiovascular diseases. NAFLD and cardiovascular diseases are two commonly distinguished diseases in the general population. It has been reported that Zn supplementation reduces the risk factors of cardiovascular disease by causing changes in relevant laboratory tests in patients with NAFLD after disease progression [26].

Oxidative stress plays a key role in the development of NAFLD, particularly in its progression from steatosis to steatohepatitis [27]. The hypothesis emerging in the pathogenesis of non-alcoholic steatohepatitis is a "two-hit theory' including fat accumulation as the first hit and oxidative stress as the second hit [28]. Zn has also been shown to have potential effects on the attenuation of lipid peroxidation in an experimental animal model [29,30]. Since Zn is important for many oxidative and antioxidant molecules in the body [8], it should be kept in mind

that Zn deficiency may be related to liver fattening through the oxidative and antioxidant system.

In a study conducted on patients with HCV-related chronic liver disease, Zn deficiency was reported to increase hepatic iron overload in the liver, increase insulin resistance and trigger hepatic steatosis by facilitating lipid peroxidation [31].

Mikhail et al. [32] demonstrated a close association between Zn deficiency and hepatic steatosis in an experimental fatty liver animal model induced by tetracycline. In this study, the authors concluded that Zn deficiency and a decrease in high-density lipoprotein cholesterol (HDL-Cholesterol) synthesis lead to an exacerbation of hepatic steatosis in experimental animals.

Zn deficiency usually results in impaired liver function or regeneration in patients with chronic liver disease [33]. Indeed, Zn supplementation has been shown to protect against liver damage in an experimental animal model of hepatic fibrosis [34]. An increase in hepatic Zn content with Zn supplementation has been shown to defend the liver from damage [35].

Conclusion

NAFLD is an inflammatory disease with abnormal lipid deposition in the liver. Studies have shown that Zn deficiency is present in these patients and that Zn supplementation is effective against this disease. However, the available data suggest that Zn may be more effective in restraining the progression of the disease rather than preventing its formation in the first place. Given the small number of studies on the subject, further research will clarify the relationship between the formation, progression and treatment of hepatic steatosis and body Zn levels.

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Review
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Breast cancer and ovulation induction

Meme kanseri ve ovulasyon indüksiyonu

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Abstract

Breast cancer is the most common malignancy of women at reproductive age. Nowadays, with increasing early diagnosis, survival rate is higher, which is why the number of patients wanting to get pregnant are on the rise. Fertility preservation, ovulation induction, the safety of these interventions and pregnancy results are discussed in this review.

Keywords: Breast cancer, Ovulation induction, Infertility

Öz

Meme kanseri, üreme çağındaki kadınların en sık görülen malignitesidir. Günümüzde meme kanseri erken teşhis edilir ve hastaların sağkalım oranı yüksektir. Bu nedenle hamile kalmak isteyen hastalar çok yaygındır. Bu derlemede doğurganlığın korunması, ovulasyon indüksiyonu ve indikiyonun güvenliği ve gebelik sonuçları tartışılmıştır.

Anahtar kelimeler: Meme kanseri, Ovulasyon indüksiyonu, İnfertilite

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Introduction

Breast cancer is the most common malignancy of women at reproductive age. According to data published by WHO, it constitutes 25% of all cancers [1]. In Europe, the incidence of breast cancer is 30/100,000 for women in the premenopausal period. Regarding the estimations, invasive breast cancer will emerge in one of each 202 women before the age of 39 in the USA [2].One-fifth of these women are diagnosed before the age of 45 and the 5-year survival rate increased up to 91.0% in 2007, while it was 74.6% between 1975 and 1979 [3]. The majority of women with breast cancer have to undergo chemotherapy, which is life-saving, but has negative effects on ovarian reserve. The American Society of Clinical Oncology recommended the early introduction of certain alternatives at the beginning of chemotherapy to preserve fertility in young women [4]. Regarding women who want to get pregnant in the future, referral to a specialist gynecologist just after the diagnosis will minimize the time between diagnosis and the initiation of chemotherapy and increase the potential of fertility preservation. The duration of these interventions is 2-3 weeks. The fertility preservation procedures may be implemented between surgery and chemotherapy.

Fertility preservation methods in women with breast cancer

Breast cancer patients usually undergo an adjuvant hormone therapy for 5 years. Pregnancy is contraindicated during neoadjuvant therapy. At the time appropriate for pregnancy, the ovarian reserve may be insufficient for a natural conception. Therefore, clinicians should refer to some techniques to preserve the fertility in women who plan to have a child in the future, before anti-cancer treatment impairs fertility.

There are several alternatives for fertility preservation: Vitrification of oocytes, embryo freezing, ovarian tissue freezing, and in vitro maturation of oocytes. The latter two, which are less common in daily practice, are still considered as experimental methods. The cryopreservation of embryos is the most common. In recent years, vitrification of oocytes became gradually popular. The cryopreservation of oocytes and embryos is usually implemented after the controlled ovarian hyperstimulation (KOH). The cryopreserved embryos and oocytes may be stored for years without any negative effect on their viability. A higher rate of the frozen embryos survives during the freeze-thaw process compared to the unfertilized oocytes (50%-70% vs >90%). In an experienced center, the live birth rate in patients, who received frozen oocyte for IVF, is 21%, while the same rate is approx. 60% for IVF cycles containing fresh oocytes [5].

KOH is not recommended after the initiation of chemotherapy. The response to the stimulation and the quality of the harvested oocytes decline with each chemotherapy session. It may cause double helix breaks in the DNA in human oocytes. Therefore, a waiting period of 6 months is recommended before pregnancy for women who undergo chemotherapy. During this 6-month waiting period, the follicles with DNA damage are eliminated from the primordial follicles [6].

Oocyte freezing - Matured Oocytes

Cryopreservation of matured oocytes is an alternative for women, who do not have a partner for IVF and do not prefer the donor sperms. Unlike the embryos and sperms, oocyte cryopreservation is a rather difficult technique, as the oocytes contain less water and consequently, they are more sensitive to injury related to the development of ice crystals. Meiotic fibers, cellular skeleton, cortical granules, and zona pellucida are particularly sensitive to freezing [5].

Cryopreservation of ovarian tissue

Women with BRCA positivity and hereditary breast-ovarian cancer syndrome are not suitable for cryopreservation of the ovarian tissue for later transplantation of it because of the risk of the development of ovarian cancer. However, in the future, storage of frozen-thawed ovarian tissue band will may be possible to obtain the oocyte maturation and IVF implementation [6].

Treatment with GnRH agonists

In women who are not suitable for cryopreservation procedures (because of timing, specific reasons related to cancer or other patient problems), some clinicians prefer GnRH (Gonadotropin-Releasing Hormone) agonist therapy to preserve the ovarian function. GnRH agonists are not recommended as the first-line therapy in fertility preservation, as it was demonstrated that they are not superior to the embryo or oocyte freezing [7]. The protective mechanism of GnRH agonists on fertility is not fully elucidated yet. Nevertheless, patients should be informed that this treatment method may provide a limited benefit to fertility preservation. The GnRH agonists suppress the ovarian function and therefore ovaries may be relatively less affected by the toxic effects of chemotherapy. However, follicles are exposed to the toxic agents, which damage DNA, even though the ovarian hormone production is inhibited. As the primordial follicles do not express gonadotropin receptors, it is not known how the treatment with GnRH agonists will increase the survival of the cells [8].

The GnRH agonists are mainly used for the relief of the metrorrhagia. The evaluation of the efficacy of the GnRH treatment on fertility preservation is rather difficult, as most of the studies focused on this topic are not based on reliable criteria. The levels of the anti-Müllerian hormone (AMH) and antral follicle counts (AFC) are established markers of the ovarian reserve. In studies focused on AMH and AFC, it was reported that GnRH agonists were not effective in the preservation of the ovarian reserve. Long-term analyses showed that GnRH did not preserve the ovarian reserve or fertility [9].

Data related to the effects of the suppression of the ovarian function by GnRH agonists on fertility in women undergoing chemotherapy are conflicting and methodological errors limit the interpretation as mentioned above.

The primordial follicles, which constitute the ovarian reserve, do not have receptors for FSH or GnRH agonists. Therefore, they are not able to respond to any hormonal manipulation [7].

Alternatives for women who cannot undergo KOH

In breast cancer patients with large mass lesion and rapid progress, neoadjuvant chemotherapy is initiated before the surgery just after the diagnosis. If KOH is not applicable due to the timing and safety reasons, the harvest of the immature oocytes may be an alternative. Under emergency conditions, after the harvest of the oocyte in the luteal phase (instead of in

vivo conventional maturation), in vitro maturation (IVM) and preservation with embryo freezing (IVF) may be an alternative.

In fact, fertility preservation is a complex process, as breast cancer is often sensitive to estrogen and supra-physiological estradiol, which is produced during KOH, may induce the proliferation of the cancer cells. Standard KOH protocols significantly increase estrogen concentrations. The mean estradiol level, which has a peak of 300pg/ml during a natural cycle, may increase up to 456-6957pg/ml during KOH [10]. This is a concern in women with breast cancer, as many breast cancers contain estrogen receptor positive (ER+) cells, which may be affected negatively from the supra-physiological estradiol levels related to ovarian stimulation. Even breast cancer, which is diagnosed as estrogen receptor negative (ER-), may be sensitive to estrogen particularly if exposed to high estrogen levels. Therefore, the exposure to estrogen should be minimized during KOH in this patient group.

Studies showed that endogenous and exogenous estrogen might play a key role in the pathogenesis of breast cancer. However, none of these studies supported the hypothesis, which suggested that short-term exposure to exogenous estrogen may impair the prognosis in breast cancer [11].

Standard KOH protocols may be changed to decrease the potential damage related to the increased estradiol levels.

Neither cancer cells, nor healthy cells in the breast respond to the gonadotropins (FSH, LH). On the other hand, exposure to estrogen induces the proliferation in cancer cells in ER (+) patients depending on the dosage. Besides, as estradiol stimulates angiogenesis, which is critical for the tumor neovascularization, may induce the proliferation of the breast cancer cells. Its long-term usage stimulates the production of insulin-like growth factor 1, which is mitogenic on breast cancer cells [12].

A more conservative approach to women with breast cancer to decrease the temporarily elevated estrogen concentrations during KOH will minimize the potential risks. The complications related to KOH in women with breast cancer is not limited to women with ER (+) malignancy. The tumor cells may be classified as “estrogen receptor negative” if less than 10% of the cells stained positive for the estrogen receptor and these cells may be clinically important. The receptor heterogeneity leads to the overlooking ER (+) cells and approximately 15%-20% of the reports may contain false-negative results. Breast cancer is a heterogeneous and complex disease with different responses to the hormonal stimuli and clinical applications depending on the gene mutation in the cell receptors and the diverse methylation pattern.

In women with ER (+) breast cancer, there is strong evidence that minimizing the estrogen exposure may decrease the recurrence and the cancer-related mortality. Two agents, which are widely used for this purpose, are receptor modulators such as aromatase inhibitors and selective estrogen-binding tamoxifen (TMX), which inhibit the catalytic conversion of androstenedione to estrone and of estradiol to testosterone [13].

Aromatase inhibitors

The aromatase inhibitors (e.g. letrozole) are used in breast cancer patients for the in vitro fertilization (IVF) and the ovarian stimulation in combination with gonadotropins. The maximum estradiol levels close to the levels observed in natural cycles are the advantage of the ovarian stimulation with the aromatase inhibitors. A protocol consisting of letrozole and follicle stimulation hormone (FSH) combination is used for the ovarian stimulation in most of the women with breast cancer undergoing IVF for the embryo or oocyte cryopreservation. This combination causes low estradiol levels and enables high oocyte harvesting. Theoretically, these agents have a good safety profile. It was observed that letrozole cycles cause a more significant decline in estradiol levels compared to anastrozole [14].

Studies showed that letrozole administration together with the FSH stimulation provided comparable cycle periods, number of harvested embryos and rates of conception and decreased the need for gonadotropins by 44% (a retrospective, controlled study focused on women in similar age group, who underwent IVF due to the tubal reasons). Although letrozole may be used in doses of 0.1-10mg/day, the usual daily dose is between 2.5mg and 5mg. It was recommended that estrogen levels should be checked in every examination and letrozole dose be increased to 10mg if estrogen levels follow a high course [15].

Safety - The safety of the letrozole

FSH protocol is investigated with a prospective clinical study. In this study, 79 of 215 women with breast cancer received letrozole and FSH during KOH and the remaining 136 patients were in the control group.

Although the time between breast surgery and chemotherapy was longer (mean: 34 or 45 days) among women who underwent IVF compared to those who did not, the risk of recurrence was 0.56 in those who have received IVF treatment (95% CI: 0.17-1.9). There was no significant difference between the groups with respect to survival rate. The same investigators conducted another study to evaluate the safety and applicability of two sequential stimulation cycles in patients with breast cancer. In two cycles compared to one cycle, more oocytes (16 vs 9) and more embryos (6.4 vs 3.7) were harvested without a significant prolongation of the time between surgery and chemotherapy (64 days vs 58 days). The recurrence rates in the groups were comparable after a 59-month follow-up period [16].

Pregnancy Rates In a study which was conducted on 131 breast cancer patients (≤stage 3), who underwent ovarian stimulation with letrozole for fertility preservation and 33 infertility cases, the comparison of the data did not show any difference between the groups considering the live birth rates. Reddy et al found similar results in their study [17,18].

Tamoxifen (TMX)

TMX which is a selective estrogen receptor modulator and has an anti-estrogenic effect on the breast tissue is as effective as the clomiphene citrate in the anovulatory infertility treatment. Therefore, it seems to be useful in breast cancer patients. The safety and efficacy of TMX were demonstrated in prospective studies, in which the breast cancer patients treated with TMX were compared with control groups consisting of breast cancer patients with a natural IVF cycle [19].

In patients stimulated with TMX, less cycle cancellation occurred (1/15 vs 4/9) and more mature oocytes (1.6±0.3 vs 0.7±0.2) and embryos (1.6±0.3 vs 0.6±0.2) were harvested. While embryo was harvested in all 12 patients who underwent

KOH with TMX, embryo harvesting was successful only in 3 ut oof 5 patients who underwent natural cycle IVF [20].

As TMX acts on estrogen receptors instead of inhibiting estrogen production, TMX treatment does not decrease estrogen levels during KOH. Therefore, peak estradiol levels were higher in the TMX group compared to the control group. However, it was observed that the rates of the cancer recurrence did not increase after a 2-year follow-up. Studies are reporting that the rate of cancer recurrence did not increase for 10 years after TMX administration for KOH in the conventional IVF cycle [19].

The efficacy of the letrozole-FSH protocol for KOH was demonstrated with a prospective study, in which letrozole/low-dose FSH (LetFSH-IVF), TMX/low-dose FSH (TMX FSH-IVF) and only TMX (TMX-IVF) were compared [19]. LetFSH-IVF provided the highest embryo yield (LetFSH-IVF: 5.3±0.8; TMX FSH-IVF: 3.8±0.8 and TMX-IVF: 1.3±0.2) and the lowest estradiol levels (LetFSH-IVF: 380±57; TMX-IVF: 419±39 and TMX FSH-IVF: 1182±271pg/mL) [21].

The KOH process in patients with gene 1 (BRCA) mutation among infertile cases with breast cancer exhibits different features. The low response to KOH (3% vs 33%) and low oocyte development (7 vs 12) are additional concerns in carriers of BRCA 1 compared to BRCA-negative patients [22].

A wide range of studies showed that carriers of BRCA mutation go through menopause earlier than BRCA-negative patients. It was demonstrated that the serum levels of anti-Müllerian hormone (AMH) were decreased and BRCA 1-mutant mice had less primordial follicles at birth [23].

In the carriers of BRCA mutation, the mechanism of the decreased ovarian reserve was explained with the deficiency of DNA repair in the BRCA-mutant oocytes, which makes them more sensitive to the genotoxic stress such as oxygen radicals and chemotherapy. In a cross-sectional study that was conducted on approx. 700 women, serum levels of AMH were found 25% lower in the carriers of BRCA mutation compared to BRCA-negative subjects. Taking these accumulating data into consideration, it may be suggested that the carriers of BRCA mutation are more defenseless against the gonadotoxic effects of the cancer treatments [24].

Typically, there is a gap of 4-6 weeks between breast cancer surgery and the initiation of chemotherapy. Although the oocytes can be harvested during a natural cycle, the yield is very low. The interval of 4-6 weeks is sufficient for the completion of one KOH and oocyte harvesting cycle. An early application to the endocrinologist may even give time for two cycles and more oocytes may be harvested for cryopreservation [25].

Although several different protocols were already introduced, protocols containing gonadotropin antagonists are usually preferred. As the treatment with a gonadotropin antagonist started on the 21st day of the previous cycle causes prolonged downregulation, timing problems emerge and therefore, is not much preferred. The antagonist agents may be started in the luteal phase of the previous cycle and thus the resorption of the corpus luteum is accelerated and synchronized follicle development can be achieved during the menstruation period [26]. This method is one of the treatment options preferred for the estrogen receptor-positive breast cancer patients [27]. If 3mg cetrorelix is administered in the mid-luteal phase, the menstruation occurs in a couple of days and KOS might be implemented without wasting time in cancer patients [28].

In the conventional ovarian stimulation protocols, starting induction in the early stage of the follicular phase is the rule. A standard approach was developed based on the opinion that better clinical results could be achieved with this principle. However, as the first day of the next cycle should be waited for this approach, the treatment may be delayed. Some ovarian stimulation protocols with random start were developed for cases, in which the onset of the next menstruation cannot be waited [29].

Studies showed that mostly 2 follicle development waves occurred between two ovulation cycles (3 waves in 30% of patients) and it was reported that oocyte harvesting could be performed twice or thrice during this interval [30].

If a suitable follicular development wave is achieved thanks to this process, random ovulation induction forms can be implemented as a late follicular and luteal ovulation induction in the same cycle except for the classical ovulation induction. Depending on the same principle, more than one ovulation induction in both follicular and luteal phases can be carried out in the same cycle [31,32].

Accordingly, the suggestion that the majority of the oocytes, which are harvested during the luteal phase are atretic, is disputable.

The late follicular phase is defined as the 7th day of the menstrual cycle when the 13-mm dominant follicle appears and the progesterone level is under 2ng/ml. In patients in this phase, who have a timing problem, KOH is started without antagonist agents if the follicle is smaller than 12mm and continued until the spontaneous LH peak, while the follicle size is <12mm. After the LH peak, the gonadotropin stimulation is started and GnRH antagonist is administered after the secondary cohort becomes >13 mm to inhibit the premature LH peak, or hCG is administered. GnRH administration is also an option for ovulation. After 2-3 days, the ovarian stimulation is started in the luteal phase.

If the ovulation already occurred or induced or the patient is in the luteal phase, a conventional protocol with a gonadotropin antagonist can be started. In this process, induction must be continued with FSH without including LH to support corpus luteum, which is luteolyzed due to the effects of the antagonist agent. The inductions implemented in the late follicular phase and luteal phase last approx. 2 days longer than the conventional approaches and lead to the usage of more gonadotropin [33]. Contrary to general belief, the presence of corpus luteum in the luteal phase or increased progesterone do not have any negative effect on follicular development. Harvesting oocytes at independent times in the same cycle supports the physiological changes defined in the ovarian physiology.

The most common protocol, which is used to stimulate patients with breast cancer, consists of 5mg oral letrozole administered after the 2nd or 3rd day. The ideal doses of the follicle stimulation hormone (FSH) are <13 IU/l with an estradiol level <60pg/ml. After a 2-day treatment, recombinant FSH (rFSH) (150-300IU/day) is added to the letrozole treatment. If the serum estradiol concentration exceeds 250pg/ml or the size

of the follicle exceeds 13mm, a GnRH antagonist is started to prevent a premature peak of LH. The follicular growth is monitored until the diameters of at least two follicles reach 20mg and ovulation is triggered with a GnRH antagonist. The comparison of the GnRH antagonists with hCG for triggering capacity showed that the GnRH antagonists cause a greater and faster decrease of the estradiol level without decreasing the number of the oocytes.

The induction protocol started with letrozole is implemented along with the addition of rFSH and triggering of the ovulation with the GnRH antagonists (e.g. triptorelin) independent from the molecular phenotype of breast cancer. In letrozole cycles, ovarian stimulation can be initiated randomly within the cycle without making concession on the fertilization rates. Similar IVF success rates were reported for the stimulations started in the 2nd day and 15th day of the cycle [34].

Ovulation induction protocols in patients with estrogen receptor positive breast cancer

Time constraints

The chemotherapeutic agents used in the treatment of breast cancer are gonadotoxic. As these agents are administered just after the diagnosis, there will be usually no time for the ovarian stimulation and harvesting oocytes, which requires generally 2-3 weeks.

The oncologists do not recommend the delay of KOH. Therefore, it is normal to start with the stimulation in the 2nd-3rd days of the menstrual cycle. The strategy may change according to the timing of the cycle. If the cycle is in the early proliferative phase and the dominant follicles are not dominant yet, stimulation can be initiated even though the patient is not on the 2nd or 3rd day of the cycle. If the cycle is in the late phase and the diameter of the dominant follicle exceeds 18mm, direct oocyte harvesting and vitrification can be carried out. Afterwards, a GnRH antagonist is administered for 5 days. If the diameter of the dominant follicle is smaller than 18mm, it can be stimulated with minimum FSH doses until the diameter reaches 18mm. Then a GnRH antagonist is given for 5 days [35].

If the ultrasonographic examination and blood progesterone levels indicate that the patient is in the secretory phase, a GnRH antagonist is administered for 4-5 days and then stimulation be started. The goals of the GnRH antagonist administration are to keep estradiol levels under 60pg/ml and not to delay the treatment until a new physiological cycle starts. Single or double trigger protocols with hCG and GnRH analogs are used for the harvesting of mature oocytes from the small antral follicles in patients with an insufficient response. In breast cancer patients, the use of a GnRH agonist trigger during KOH enables a rapid decline in the estradiol concentrations after the oocyte harvesting. Likewise, the risk of hyperstimulation is decreased with this method. Besides, more oocytes are harvested without decreasing pregnancy or live birth rates. The decreased pregnancy and live birth rates which are reported in the fresh cycles during the administration of a GnRH agonist trigger are not encountered in the “cryo cycles” or donor cycles, and this is believed to have occurred secondary to the endometrial receptor defects. As cryopreservation is usually used for fertility preservation, the decrease in the pregnancy rates seen during the cycles triggered by the GnRH agonist is not relevant [36].

Approximately 70%-80% of breast cancers are androgen receptor positive (AR+). As the aromatase inhibitors prevent the conversion of androgens to estrogens, the androgen levels may increase during the letrozole treatment. It is not elucidated yet whether the androgenic effects have proliferative or anti-proliferative effects on the breast cancer cells [37].

The androgen receptor may inhibit the ER activity in breast cancer cell proliferation induced by estradiol and the increased androgen concentrations during KOH depending on the letrozole treatment does not seem to have harmful effects [38].

Response to KOH cycles in breast cancer

Cancer is related to catabolism and insufficient nutrition. Several patients lose so much weight, that the fertilization capacity is impaired depending on the negative effects of the weight loss on the hypothalamus-hypophysis axis. Furthermore, the emergence of psychological stress increases the levels of prolactin and endogenous opioids. Therefore, the disease may affect the ovarian response even before chemotherapy and radiotherapy. Anderson et al. showed in their study that AMH levels, which were measured before chemotherapy in cancer patients, were lower than the healthy women in the same age group. Moreover, the number of antral follicles was fewer in women with cancer compared to the healthy control group in the same age group [39]. A recently published meta-analysis showed that women with cancer, who underwent KOH, produced fewer oocytes compared to healthy women in the same age. In this analysis, gonadotropins were higher and the stimulation duration was longer in the cancer group [40].

The recurrence rate of breast cancer reaches its peak level in the 18th month and 5th year after surgery. This rate declines within the next 15 years. Considering these data, KOH was related always to some concern in breast cancer patients. These concerns were aggravated with the addition of the teratogenicity risk [41].

Taking the limited data in the studies into consideration, we are still not able to come to a definitive conclusion about the safety of KOH with TMX. TMX has a similar chemical structure to diethylstilbestrol and it may have teratogenic effects if administered during pregnancy. However, if it is used for the ovulation induction before pregnancy, there is no place for concerns related to the teratogenicity [42]. TMX is approved for ovulation induction in some countries. The exposure of the embryo to drugs is different from the exposure of the oocytes to drugs during the ovulation induction. The increase of the risks of malformation and cardiac anomalies in 150 infants after the ovulation induction with letrozole raised some concerns about the safety of this method and the manufacturer of this drug included certain warnings related to the usage of letrozole before menopause in the leaflet. All these findings were not published in a peer-reviewed journal because of the methodological limitations and inappropriate demographic reports.

The medical differences between the treatment and control groups and lack of information about pregnancy termination in the control groups are the main limitations of

these studies. The results of a more comprehensive study (n=2707 females) did not support an increased risk for the fetus during the letrozole treatment [43].

Even Novartis, which is the responsible manufacturer of letrozole (Femara), does not recommend the usage of letrozole as an inducer. In a brand new retrospective study, natural cycles (n=3136) were compared with IVF cycles (KOH with letrozole; n=7921) (1.5% natural cycle, 1.9% letrozole cycle; *P*=0.52). It was found out that there was no significant increase in the rate of major congenital anomalies in women treated with letrozole [44].

In a study conducted with 911 neonates, the rates of major and minor congenital malformation were comparable between the women who became pregnant after letrozole or clomiphene citrate treatment [45].

Regarding the concerns related to recurrence, the aromatase inhibitors are superior to TMX in the prevention of the breast cancer recurrence [46]. Studies showed that letrozole administration during KOH decreased estrogen levels without any significant effect on oocytes. Letrozole suppresses the estrogen levels during KOH cycles better than anastrozole, which is another aromatase inhibitor [47].

However, the following findings should also be kept in mind: In the largest study focused on the KOH with letrozole (n=120 breast cancer patients), patients were followed for 5 years [48].

In another study focused on the recurrence, the participants followed for 272-600 days after KOH and no difference was found between the KOH patients and non-KOH patients for breast cancer recurrence [49].

Conclusion

Studies related to KOH, which is used for fertility preservation in breast cancer patients, still exhibit an observational value. The study sample sizes are limited and the follow-up periods are relatively short. It is easy to imagine the difficulties of a randomized controlled design in this patient population. The available data show that KOH implemented with letrozole does not significantly impair the prognosis in breast cancer patients. Besides, this treatment decreases the estradiol concentration without decreasing the number of oocytes and impairing the quality of oocytes. Likewise, it cannot be suggested that KOH cycles either with letrozole or with TMX may cause teratogenic effects.

Further studies with a long-term design and larger sample sizes are needed for more definitive conclusions on the safety of KOH in patients diagnosed with breast cancer.

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Review
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The two new surgical techniques for vaginal cuff prolapse and uterine prolapse

Vajinal kaf prolapsusu ve uterus prolapsusu için iki yeni cerrahi teknik

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Abstract

Pelvic organ prolapse and vaginal cuff prolapse are clinical conditions that affect women's quality of life and require surgical treatment. In this study, we aimed to present apical vaginal prolapse and uterine descensus treatment with two new techniques. The classical sacrospinous ligament fixation technique fixes only one or two corners of the vaginal apex to the sacrospinous ligament, but it does not support the upper anterior and posterior vaginal fascia. Since it expands the upper part of the vagina with a suture put on the sides of the vaginal apex, it may not only expose the anterior and posterior vaginal walls to greater intraabdominal pressure and cause cystocele and enterocele development, but lead to sexual problems, as well. Apart from this, if sacrospinous colpopexy is performed to one side only, the vaginal apex is deviated towards the fixation, thus spoiling the vaginal anatomy. With our following methods, we imitate the physiological anatomy: Transapical circular Sacrospinous colpopexy (TACSAC) and Transcervical apical circular Sacrospinous uteropexy (TACSU). TACSAC: Bilateral side walls of the vaginal apex are marked with a color pencil 2 cm medially to the right and left ischial spine and 2 cm in length. Vaginal apex walls are bilaterally and vertically incised until the submucosa layer. Two submucosal tunnels are opened by using a right-angle clamp between the tips of two vertical incisions on the vaginal apex. The vaginal apex is fixed with a TOT mesh through these channels. In TACSU, the same procedure is followed for the cervix. These methods are more likely to mimic normal anatomy, easier to perform, and lower risk of complications.

Keywords: Pelvic organ prolapse, Vaginal cuff prolapse, Sacrospinous colpopexy

Öz

Pelvik organ prolapsusu ve vajinal kaf prolapsusu kadınların yaşam kalitesini etkileyen ve cerrahi tedavi gerektiren bir klinik durumdur. Bu çalışma ile biz apikal vajinal prolapsus ve uterin desensusun tedavisini sunmayı hedefledik. Klasik sakrospinöz ligament fiksasyon tekniği, vajinal kaf'ın sadece bir veya iki köşesini sakrospinöz ligamana sabitler, ancak üst ön ve arka vajinal fasyaya herhangi bir destek vermez. Vajina apeksinin yanlarına konan bir sütür ile vajinanın üst kısmını genişlettiğinden, bu durum sadece ön ve arka vajinal duvarların daha büyük karın içi basıncına maruz kalmasına neden olmaz aynı zamanda sistosel ve enterosel gelişimine neden olur, ancak genişlemiş vajinal apeks cinsel sorunlara neden olabilir. Bunun dışında sakrospinöz kolpopeksi sadece bir tarafa yapılırsa, vajinal apeks fiksasyona doğru saparak vajinal anatomiyi bozar. Geliştirdiğimiz yöntemlerle fizyolojik anatomi taklit edilmiş olacaktır. Bu teknikler transapikal sirkuler sakrospinoz ve transservikal apikal sakrospinoz uteropeksi dir. TACSAC; Renkli kalemle bilateral olarak vajinal apeksin yan duvarları medial olarak sağ ve sol iskiyal spinden 2 cm uzunluğunda 2 cm olarak işaretlenir. Vajinal apeks duvarları, sublukoza kadar iki taraflı ve dikey olarak kesilir. Vajinal kaf üzerinde iki dikey insizyonun uçları arasında dik açılı bir klemp kullanılarak iki submukozal tünel açılır. Vajinal apeks bu kanallardan TOT meshi ile sabitlenir. TACSU serviksi olan hastalarda da benzer şekilde uygulanır. Bu yöntemler normal anatomiyi daha çok taklit eden, uygulanabilirliği daha kolay ve komplikasyon riski daha düşük yöntemlerdir.

Anahtar kelimeler: Pelvik organ prolapsusu, Vajinal kaf prolapsusu, Sakrospinöz kolpopeksi

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Introduction

As women live longer and healthier lives, pelvic floor disorders continue to become even more prevalent and are an important health and social issue. The cardinal-uterosacral complex suspends the upper third of the vagina as well as the uterus from the bony sacrum. Collagen fibers arising from the uterosacral ligaments fuse distally with the visceral fascia over the cervix, lower uterine segment, and upper vagina to form the pericervical ring. Disruption of the cardinal-uterosacral complex may result in uterine descensus or vaginal vault (apical) prolapse. The goal of pelvic reconstructive surgery is to restore anatomy, maintain or restore visceral function, and maintain or restore normal sexual function. Sacrospinous ligament is a strong ligament that runs within the coccygeus muscle from the ischial spine to the sacrum [1,2]. The fixation of the vaginal apex to the sacrospinous ligament, the tendinous component of the coccygeus muscle, was first described in mid-20th century. Traditionally, access is extraperitoneal via the rectovaginal space with penetration of the pararectal fascia (Denonvillier's fascia) at the level of the ischial spine to expose the muscle and ligament [3]. Bilateral sacrospinous ligament suspensions have also been advocated; however, these techniques may impose a greater degree of tension on the sutures and, at times, create a band of apical vagina across the rectum at the level of the suspension. Whether this can cause defecatory dysfunction is debatable [4].

Abdominal sacral colpopexy and vaginal sacrospinous colpopexy have been demonstrated to be equally effective in the treatment of vaginal vault prolapse. Subjective and objective assessment, patient satisfaction, and the impact on quality of life were similar in both groups. Sacral colpopexy was associated with a longer operating time, slower return to daily life, and greater cost than the sacrospinous colpopexy [5]. The disadvantages of the classical sacrospinous colpopexy procedure include (a) an unnatural lateral vaginal deflection toward the fixation site, (b) an inability to perform without excessive tension when the vaginal length is compromised, (c) high rates of anterior vaginal prolapse following the procedure, (d) occasional need to shorten or narrow the upper vagina when a fibromuscular defect involves much of the apical area [3].

The classical sacrospinous ligament fixation technique fixes only one or two corners of the vaginal apex to the sacrospinous ligament, but it does not support the upper anterior and posterior vaginal fascia. Since it expands the upper part of the vagina with a suture put on the sides of the vaginal apex, it may not only expose the anterior and posterior vaginal walls to greater intraabdominal pressure and cause cystocele and enterocele development, but lead to sexual problems, as well. Apart from this, if sacrospinous colpopexy is performed to one side only, the vaginal apex is deviated towards the fixation, thus spoiling the vaginal anatomy. We present a new and simple surgical technique for the treatment of apical vaginal cuff prolapse, developed by us, which may eliminate these complications of the classical sacrospinous fixation technique.

Sacrospinous suspension, in which one or both of the sacrospinous ligaments are sutured to the vaginal apex, is one of the few vault prolapse repairs. Although sacrospinous suspension is the vaginal procedure most familiar to general gynecologists, it is not ideal. It relies on only 1 or 2 sutures to hold the vagina in place until scarring occurs; it creates a small amount of dead space at the attached end of the vagina; and when performed unilaterally, it causes deviation of the apex toward the ligament of attachment [2].

Transapical circular Sacrospinous colpopexy (TACSAC) and Transcervical apical circular Sacrospinous uteropexy (TACSU) by mini incisions are the two new and simple techniques suggested by us for the treatment of the apical vaginal prolapse and uterine descensus.

The new surgical technique-1

Transapical circular sacrospinous colpopexy (TACSAC)

This procedure may be performed under epidural, spinal or general anesthesia. Patients are placed in the lithotomy position with thighs flexed at approximately 90°. After cleaning the entire surgical area with antiseptic, an in-dwelling catheter is placed. All patients are administered an intravenous perioperative antibiotic prophylaxis [6]. The vaginal apex is grasped with two Allis clamps and pulled out so that the extent of the prolapse can be assessed. The vagina is then reduced to the level of the ischial spines. Bilateral side walls of the vaginal apex are marked with a color pencil, 2 cm in length and 2 cm medially to the right and left ischial spine (Figure 1). Then, vaginal apex is pulled out again and the marked vaginal apex walls are incised until the submucosa layer bilaterally and vertically. Two submucosal tunnels are opened by using a right-angle clamp between the tips of two vertical incisions on the vaginal apex (Figure 2). The vaginal apex is again reduced to the level of the ischial spines. The next step is entry into the perirectal space. A window can be created with the tips of a tonsil clamp or a hemostat. The sacrospinous ligament can be palpated by palpating the spine and moving the fingers dorsally and medially. The excess tissue on the cervical sacrospinous ligament can be removed by blunt dissection. The rectum and surrounding connective tissue are typically swept medially with blunt dissection and pararectal space is entered. The sacrospinous ligament complex is visualized, and ischial spine is palpated. The coccygeus muscle-sacrospinous ligament complex running posteriomedially from the ischial spine to the sacrococcygeal area is exposed and grasped with a long-handled Allis or Babcock clamp. The ligament can be grasped with an Allis clamp or Babcock to isolate the tissue away from vessels and nerves. Then, under direct vision, the tip of the long-handled Deschamps is penetrated into the right sacrospinous ligament 2 cm medial to the ischial spine and a TOT mesh implant is passed. A tip of TOT mesh implant passed through the sacrospinous ligament is passed to the left side through one of the submucosal tunnels connecting two vertical incisions. The same procedure is applied on the right side. The tip of TOT mesh implant passed through the right sacrospinous ligament is passed to the left side within the other submucosal tunnel connecting two vertical incisions. While the two tips of the prosthetic implant in the left side is pulled down, the vaginal apex is pushed upward with the left hand. The two tips of the prosthetic implant are then connected with a single vicryl suture under the vaginal mucosa and excess parts of its tips are excised (Figure 3). Each one of the vertical mucosal incisions on the vaginal apex is then

closed with interrupted 3-0 absorbable sutures (Figure 4). The ideal material should be inert, mechanically and infection resistant. At the surgery of pelvic organ prolapse, the trend is towards the use of polypropylene mesh with low fiber density [3,7]. According to the current evidence of the great tolerance of the TVT or TOT polypropylene mesh, in this procedure, TVT or TOT polypropylene mesh can be used to reduce the risk of infection and erosion.

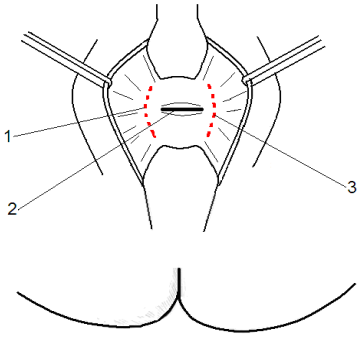

Figure 1: Vaginal apex pushed as far as level of ischial spines upwards with two Allis clamps (1-Marked right lateral edge of vaginal apex, 2-Vaginal cuff scar, 3-Marked left lateral edge of vaginal apex)

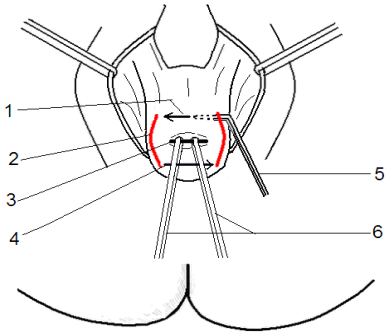

Figure 2: Traction of vaginal apex outwards with Allis clamps (1-Anterior vaginal tunnel, 2-Marked right lateral edge of vaginal apex, 3-Vaginal cuff scar, 4-Posterior vaginal tunnel, 5-Right-angled clamp, 6-Allis clamps)

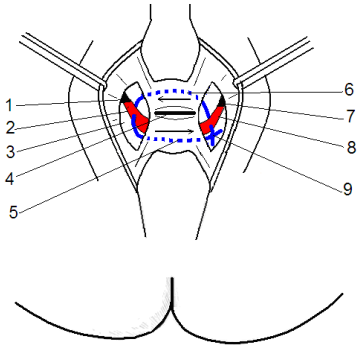

Figure 3: View of mesh tape attached circularly and submucosally to the vaginal apex (1-Right ischial spine, 2-Right sacrospinous ligament, 3-Right lateral incision to vaginal apex, 4-Vaginal cuff scar, 5-TOT mesh in posterior vaginal tunnel, 6-TOT mesh in anterior vaginal tunnel, 7-Left ischial spine, 8-Left sacrospinous ligament, 9-Sutured ends of mesh)

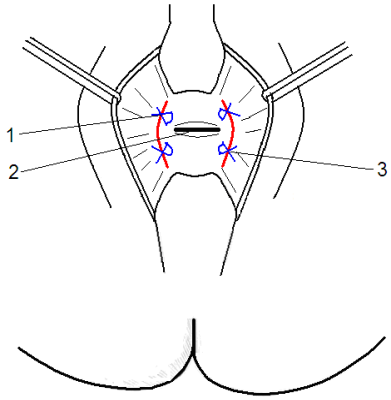

Figure 4: Sutured vaginal apex incisions (1, 2 and 3 sutured vaginal apex incisions)

To avoid vascular and neural complications is particularly important during penetration of the sacrospinous ligament. Penetration of the muscle-sacrospinous ligament complex must be performed through its midline and 2 cm medially to the ischial spine, not posteriorly.

If an enterocele sac is present, it is mobilized off the posterior vaginal wall up to its neck; the sac is opened and the peritoneum excised, and the defect is closed with purse-string sutures. If the patient requires a cystocele repair or a stress urinary incontinence procedure, these should be performed following the sacrospinous colpopexy. After the colpopexy sutures are tied, a posterior colpoperineorrhaphy is performed. The vagina is then packed with moist gauze for 24 hours. Patients can be discharged within 24-48 hours.

The disadvantages of the classical sacrospinous fixation procedure include (a) an unnatural lateral vaginal deflection toward the fixation site, (b) an inability to perform without excessive tension when the vaginal length is compromised, (c) high rates of anterior vaginal prolapse following the procedure, (d) occasional need to shorten or narrow the upper vagina when a fibromuscular defect involves much of the apical area [3]. Distortion of the vaginal vault, whether anteriorly, posteriorly, or laterally, can lead to a recurrent prolapse opposite the vaginal vault in a significant number of patients. The presented technique, however, reapproximates the upper vagina in the midline over the levator plate [1].

This new procedure may prevent the recurrence of a vaginal prolapse, but it does not disturb vaginal anatomy. It rather constitutes a strong fascial support for the vaginal apex and the upper part of the anterior and posterior vaginal walls and shortening or narrowing the upper vagina is not required. It is a simple procedure to perform, and blood loss is less compared to bilateral or unilateral classical sacrospinous colpopexy procedure. This technique forms a circumferential fibrous ring surrounding the apex of vaginal cuff. Because this fibrous ring will cause to unite sacrospinous ligaments with both upper vesicovaginal and rectovaginal fascia, it constitutes a strong fascial support to vaginal apex.

The new surgical technique-2

Cervical sacrospinous uteropexy (CSU)

A similar procedure with TACSAC, with a few technical differences, can be performed to young patients with uterine descensus. Uterine cervix is grasped with a tenaculum and it is pushed into the vagina as far as ischial spinous level. The next step is to palpate the ischial spines, and then bilateral mucosal incisions of 2-3 cm in length are performed vertically on the side fornices 2 cm medially from the ischial spines. The upper and lower tips of bilateral vertical incisions are connected by a submucosal tunnel using a right-angled clamp from the front and back of the cervix. Contrary to that of the cuff prolapse, anterior and posterior cervical submucosal tunnels are formed when the cervix is on the level of the ischial spins. Following the cervical submucosal tunnels, as in cuff prolapse, TOT mesh is passed through the left sacrospinous ligament, and its tip is passed to the right side through anterior cervical tunnel. Then, this tip, passing through the right sacrospinous ligament, is passed to the left side through the posterior cervical tunnel. The tips of the mesh are sutured to make the cervix level with ischial

spines, and excess mesh tips are removed. Lateral fornix incisions are closed with two or three sutures. With this procedure the pericervical fascial ring are connected the the sacrospinous ligaments bilaterally, forming a strong fascial support for uterus.

This technique might be the gold standard treatment for apical vaginal prolapse and uterine prolapse. However, a longer follow-up to support its widespread use and to confirm the effectiveness of this procedure is necessary.

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Acute prosthetic vascular graft distortion in the subclavian region: A case report and a review of the literature

Subklavian bölgede akut prostetik vasküler greft distorsiyonu: Literatürün gözden geçirilmesi ve bir olgu sunumu

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Abstract

A 68-year-old male patient was admitted to the emergency department with complaints of sudden swelling under his right clavicle. He had undergone right axillo-femoral and femoro-femoral crossover bypasses 1.5 months ago due to peripheral artery disease. The subclavicular swelling had started one day ago. Physical examination revealed a pulsatile mass expanding from under the right clavicle towards the right breast. In auscultation, a murmur was heard on the mass and the patient was hospitalized with a diagnosis of pseudoaneurysm. Doppler ultrasonography revealed a 10x10 cm pseudoaneurysm sac in the right subclavian area. Hemoglobin level had decreased to 5.9 mg/dL. 2 units of erythrocyte suspension was transfused, after which the patient was operated emergently. During the operation, hemorrhage from the proximal and distal subclavian arteries was controlled with a fogarty catheter advanced to the subclavian artery via the brachial artery and axillo femoral graft. When the pseudo-aneurysm sac was incised, the synthetic vascular graft between the right axillary and right femoral arteries was observed to have dislocated distal to the axillary anastomosis area by approximately 1 cm. A new graft interposition was performed after resecting the torn synthetic graft section. The patient was discharged after an uneventful postoperative period.

Keywords: Vascular graft, Pseudoaneurysm, Emergency operation, Complications

Öz

68 yaşında erkek hasta sağ klavikula altında ani başlayan şişlik ile acil servise başvurdu. Anamnezinde hastaya periferik arter hastalığı nedeniyle 1,5 ay önce sağ aksillo-femoral ve femoro-femoral crossover bypass yapıldığı öğrenildi. Subkavikular bölgede kolun aşırı yukarı ve geriye doğru gerilme hareketi sonrası aniden başlayan ve giderek artış gösteren şişliği vardı. Fizik muayenede sağ klavikula altından başlayan koltuk altına ve sağ memeye doğru yayılım gösteren pulsatile kitle tespit edildi. Oskültasyonda kitle üzerinde üfürüm duyuldu ve pseudoanevrizma ön tanısıyla yatırıldı. Acil şartlarda damar cerrahı tarafından yatak başı yapılan Doppler Ultrasonografide subklavian bölgedeki şişliğin pseudoanevrizma kesesi olduğu ve yaklaşık boyutunun 10x10 cm olduğu tespit edildi. Acil rutin kan tetkiklerinde Hemoglobin seviyesi 5,9'e kadar düşmüştü. Bunun üzerine acil kan hazırlığının ardından 2 ünite eritrosit süspansiyonu verildikten sonra acil operasyona alındı. Hastanın proximal ve distal subklavian arterdeki kanama kontrolü brakial arter ve aksillo-femoral greft yoluyla subklavian artere gönderilen fogarty kateteri ile sağlandı. Pseudoanevrizma kesesi açıldığı zaman sağ aksiller arter ile sağ femoral arter arasındaki sentetik vasküler greftin aksiller anastomoz alanına yaklaşık 1 cm mesafeden ayrılmış olduğu görüldü. Yırtılmış olan sentetik greft bölümü rezeke edilerek yeni bir greft interpozisyonu yapıldı. Postoperatif dönemde problemi olmayan hasta şifa ile taburcu edildi.

Anahtar kelimeler: Vasküler greft, Pseudoanevrizma, Acil operasyon, Komplikasyonlar

Introduction

The use of grafts in vascular surgery began in 1913 with Pringle, who used vein grafts in two patients. The rapid development of prosthetic grafts in the last 40-50 years led to their use in vascular surgery [1]. Polytetrafluoroethylene (PTFE) and Dacron are the most commonly used prosthetic grafts. Various complications may occur due to errors in their manufacture or use. We herein present a case of PTFE graft rupture and associated pseudoaneurysm.

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Case presentation

A 68-year-old male patient was admitted to the emergency department with complaints of sudden swelling under his right clavicle. He had undergone right axillo-femoral and femoro-femoral crossover bypasses 1.5 months ago due to peripheral artery disease. The subclavian swelling began suddenly one day ago when the patient fully extended and raised his right arm. Physical examination revealed a pulsatile mass expanding from under the right clavicle towards the right breast. All peripheral pulses of the patient were palpated. In auscultation, a murmur was heard on the mass and the patient was hospitalized with a diagnosis of pseudoaneurysm. Doppler ultrasonography revealed a 10x10 cm pseudoaneurysm sac with turbulent blood flow in the right subclavian area (Figure 1).

His hemoglobin level had decreased to 5.9 mg/dL. Two units of erythrocyte suspension was transfused, after which the patient was operated emergently. Under general anesthesia, a skin incision was made at the level of the 6th intercostal space; the previous right axillo-femoral graft was found and slung. 5000 units of heparin was administered. Graftotomy was performed to the axillo- femoral PTFE (Brand unknown) graft. There was bleeding from both the proximal and distal ends of the graft, and a 6F Fogarty catheter could not be advanced more than 30 cm toward the proximal end. Thinking it was in the pseudo-aneurysm sac, the catheter was withdrawn to be advanced through the brachial artery in order to control the hemorrhage within the sac. An incision was made in the right antecubital region and the brachial artery was slung. The distance from the skin to the proximal end of the previous subclavian anastomosis was measured. Following brachial arteriotomy, a 4F Fogarty catheter was advanced to the proximal end of the subclavian pseudo-aneurysm, its balloon inflated until vessel occlusion occurred and left in position. The pulsation in the sac disappeared and pressure dropped. Having reduced blood loss by achieving hemostasis in the proximal subclavian artery, the old infraclavicular incision scar was re-incised and hematoma was evacuated. Pseudo-aneurysm sac was visualized and incised to explore the area of the previous anastomosis. The Fogarty catheter just advanced from the brachial artery was seen in place. The PTFE graft with a 7 mm ring was observed to have dislocated approximately 1 cm distal to the axillar anastomosis (Figure 2). After the resection of the torn parts of the previous graft, 7 mm ring PTFE (Bards®) graft interposition was performed with 6/0 prolene suture for vessel continuity (Figure 3). After the hemorrhage control, one Hemovac drain was placed in the incision site. The subcutaneous and skin layers were closed anatomically.

On postoperative examination, the patient's peripheral pulses were palpated normally. After a week-long uneventful postoperative period, the patient was discharged.

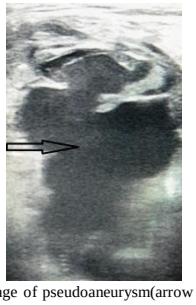

Figure 1: Doppler ultrasonography image of pseudoaneurysm(arrow sign according to pseudoaneurysm in right subclavian area)

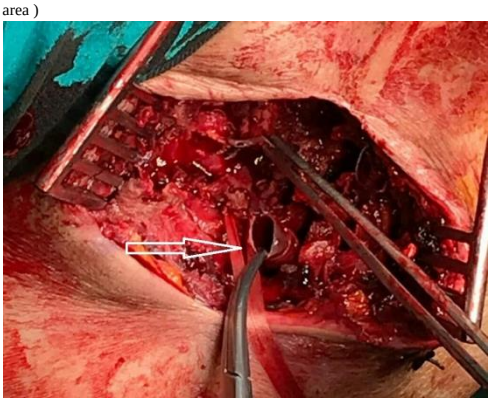

Figure 2: Intraoperative view (Arrow sign showing torn graft in right subclavian area)

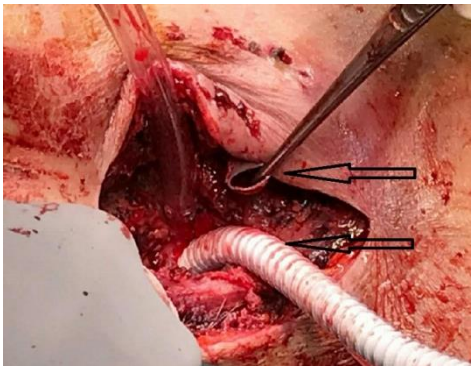

Figure 3: Intraoperative view (Arrow signs indicate graft interposition in right subclavian area)

Discussion

Graft production technologies have become highly advanced. Easy to suture, flexible, non-aneurysm-forming, low-risk grafts with low thrombogenic potential are being produced. Although the development of this technology reduces complications, the ideal prosthetic graft has not yet been produced. Graft selection according to the anatomical position is an important part of the bypass procedure. Dacron grafts are preferred in aortic surgeries and PTFE grafts are preferred in mid-sized arterial surgeries (inguinal and infra-inguinal regions) [2].

PTFE grafts have been used safely for many years in lower and upper extremity peripheral revascularization procedures. Reasons for preference include low thrombogenicity, easy suturability, flexible structure, low infection risk, high resistance to vascular wall stress, durability, long-term stress protection, no need for pre-intervention before use, no aneurysm development, no bleeding from pores and re-operation possibility due to thrombosis even after a long time [3].

Achieving hemostasis with balloon catheters, a life-saving method in both vascular and cardiac injuries, has been used for many years [4-6]. Bleeding in difficult-to-reach, narrow regions such as the subclavian area, makes it challenging to perform anastomosis and reduces its quality. Hemorrhage control in a proximal anastomotic region, especially in re-do cases, is

quite difficult. In this case, we advanced the Fogarty catheter through the axillo-femoral synthetic graft for hemostasis but failed to access the subclavian artery due to the complete rupture of the synthetic graft. We then advanced a Fogarty catheter intra-arterially through the brachial artery and were able to achieve proximal hemostasis in the pseudo-aneurysm.

Several rings of the PTFE graft should be removed to increase the quality of the anastomosis and reduce the risk of hemorrhage; however, one should be careful not to damage the graft's supportive layer in the process. In our patient, PTFE graft distortion occurred after trauma; however, it may also have occurred secondary to an error in the graft manufacturing phase or damage to the graft structure during the removal of the rings.

Massive blood transfusion is known to cause serious complications and should be avoided if possible [7,8]. Lack of preoperative planning and premature exploration of the pseudoaneurysm sac could have caused life-threatening blood loss until the bleeding source was visualized. In this case, proximal flow and distal back flow at the site of the previous anastomosis were obstructed with the inflated balloons of the Fogarty catheters. Blood recovery systems, i.e. Cell Saver®, may be used for cases which preventive procedures are not performable.

Sullivan et al. reported complications occurring in axillo-femoral bypass patients after fully extending and raising the affected arm [9]. In our patient, complete graft rupture and distortion were observed after the exact same movement. Barht et al. [10] reported successfully operating a traumatic graft rupture after axillo profundal bypass in a 76-year-old patient. The incidence of graft ruptures is around 5% [11]. There are limited number of studies reporting axillo-femoral graft ruptures and distortions [9-15]. PTFE graft rupture and development of pseudoaneurysm are rare complications in vascular surgery. Arterial bleeding, i.e. brachial, radial or femoral arteries, are often controlled by applying pressure. The subclavian region, however, is difficult to reach surgically, which makes its hemostasis almost impossible- particularly during re-do surgeries.

Complications such as graft rupture are rare but life-threatening in vascular surgery. We believe that pre-operative planning is highly important and lifesaving in such cases.

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Case report
Olgu sunumu

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Use of video-laryngoscopy in pediatric patients with Ehlers-Danlos syndrome: Two case reports

Ehlers-Danlos sendromu tanılı iki pediatrik hastada videolaringoskop kullanımı: İki olgu sunumu

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Abstract

Difficult airway management is one of the most challenging situations for an anesthesiologist. If not handled properly, it can lead to severe complications, even death. Video-laryngoscopy (VL) is one of the many techniques developed for this purpose. Ehlers-Danlos Syndrome (EDS) is a rare disease requiring possible difficult airway management due to temporo-mandibular dysfunction or occipito-atlanto-axial instability. We herein present two pediatric EDS cases who required surgery. The first case was a 9-year-old, male, ASA II EDS patient scheduled for strabismus surgery, and the second case was a 12-year-old, male, ASA III EDS patient who was also diagnosed with a brain cyst and lymphoma, due for emergency surgery for acute abdomen. With their heads in a neutral position, both patients were intubated without tissue trauma at first attempt using video-laryngoscopy. No complications were encountered in both cases. We believe that using video-laryngoscopy for managing difficult pediatric airways may be beneficial in avoiding complications.

Keywords: Ehlers-Danlos, Anesthesia, Difficult airway, Video-laryngoscopy

Öz

Zor hava yolu yönetimi, anestezist için en problemli durumlardan biridir ve komplikasyonlara, hatta ölüme neden olabilir. Videolaringoskop, bu sebeple geliştirilen tekniklerden birisidir. Ehlers-Danlos Sendromu, temporomandibular disfonksiyon veya oksipito-atlanto-aksiyel instabilite nedeniyle zor hava yolu yönetimine ihtiyaç duyulabilen nadir bir hastalıktır. Burada Ehlers-Danlos Sendromu (EDS) tanılı iki olgu sunulmuştur. İlk olgu, 12 yaşında, ASA II, EDS tanılı, strabismus nedeniyle cerrahi planlanan erkek hasta, ikinci olgu ise 9 yaşında, ASA III, EDS, beyin kisti ve lenfoma tanılı, akut batın sebebiyle acil cerrahiye ihtiyacı doğan erkek hastadır. Her iki hasta, başları nötral pozisyondayken, dokuyu travmatize etmeden, video-laringoskop ile ilk denemede entübe edilmiştir ve herhangi bir komplikasyonla karşılaşılmamıştır. Olası komplikasyonlardan kaçınmak için pediatrik zor hava yolu yönetiminde video-laringoskop kullanımının faydalı olacağını düşünüyoruz.

Anahtar kelimeler: Ehlers-Danlos, Anestezi, Zor hava yolu, Videolaringoskop

Introduction

Ehlers-Danlos Syndrome (EDS) is an inherited connective tissue disorder characterized by defects in collagen synthesis and structure with an incidence of approximately 1:15000 [1]. Temporomandibular dysfunction, risk of joint luxation, premature spondylosis or subclinical occipito-atlanto-axial instability may lead to difficult airway management and intubation [2]. We herein present two cases in which video-laryngoscopy (C-MAC® Karl STORZ) was used to avoid hyperextension and complications during airway management.

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Case presentation

Our first case was a 12-year-old, 155-cm-tall male EDS patient weighing 35kg, scheduled for strabismus surgery. Preoperative echocardiography revealed mitral valve prolapse with 1st degree mitral and tricuspid regurgitations. The second case was a 9-year-old, 138-cm-tall male EDS patient weighing 28 kg, due for emergency surgery for acute abdomen. He was also diagnosed with lymphoma and a brain cyst. In both patients, physical examination revealed hypotonicity, decreased muscle mass, thinning of skin and increased elasticity, increased bruises (cigarette burns) (Figure 1A-1B), fragile skin, arachnodactyly, pes planus, marfanoid body structure, disproportionate extremity length, hypermobile joints (Figure 2) and pectus excavatum. Written informed consent forms with signatures from the patients' first-degree relatives were obtained. Endotracheal tubes and laryngeal airway masks of different sizes were prepared in the operating room before anesthesia induction. Both patients' vital signs and electrocardiographic changes were monitored. Caution was taken not to increase patients' peak airway pressures during mask ventilation. Anesthesia was induced with 1 mcg/kg remifentanil, 3 mg/kg propofol and 0.6mg/kg rocuronium following preoxygenation. With the head in a neutral position, both patients were intubated with 5F cuffed endotracheal tubes at first attempt using video-laryngoscopy (C-MAC® Karl STORZ) (Figure 3A-3B). Anesthesia was maintained with a 50% oxygen/air combination and 2% sevoflurane. During the operation, all vital signs were stable. Postoperative decurarization was achieved with 2 mg/kg sugammadex. After gentle aspiration of the oral cavity and observation of adequate spontaneous breathing, both patients were extubated uneventfully and taken to the recovery room following their response to verbal stimuli. They were sent to their corresponding clinics after Aldrete scores of both patients were 10.

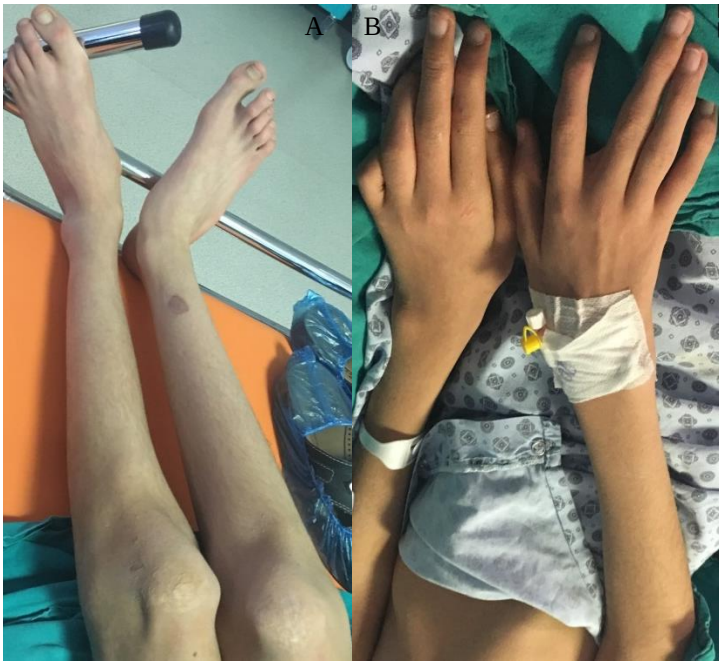

Figure 1A -1B: Patient one: Bruises, cigarette burns and arachnodactyly are observed.

Figure 2: Patient two: Hypermobile joint

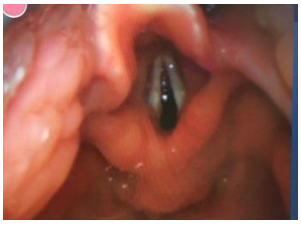

Figure 3A: Videolaryngoscopic image of patient one

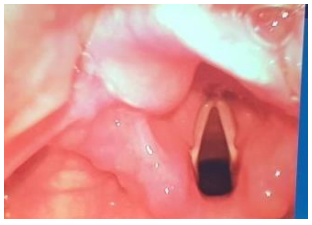

Figure 3B: Videolaryngoscopic image of patient two

Discussion

EDS has first been defined by Russian dermatologist Dr. Tschernogobow, Drs Ehlers and Danlos in 1982. The genetic heterogeneity of EDS was described in the 1960s and molecular defects in the pathway of collagen biosynthesis were identified in 1972 [5]. Six major types of EDS have been defined: Classic (Types I and II), hypermobile (Type III), vascular (Type IV), kyphoscoliotic (Type VIA), arthrochalasia (Types VIIA and VIIB) and dermopraxis types (Type VIIC) [6]. Type IV (autosomal dominant form) is the most common, while X-linked recessive and autosomal recessive (Type VI) forms are the rarest [3]. De-novo mutations have been reported in 50% of all patients with no family history of the disease [4]. There are major and minor diagnostic features in each subtype, but each patient should be evaluated individually. Our patients were both diagnosed with hypermobile EDS. There are no clear guidelines regarding general or regional anesthesia in EDS patients [7]. Our patients had general anesthesia.

Laboratory tests of EDS patients are usually within normal limits and do not provide accurate information regarding the risk of bleeding [8]. Thorough physical examination is needed to detect skeletal anomalies, i.e. scoliosis, especially in patients scheduled for regional anesthesia. Bleeding history should be taken carefully. Our patients had no history of bleeding. The tissues of EDS patients are extremely sensitive and require gentle care. In order to prevent post-operative complications, compression-induced neurological injuries, care should be taken during positioning, endotracheal intubation, oropharyngeal aspiration, venous access procedures and surgical intervention [8-9].

In their studies, Sood et al. [10] and Yen et al. [10] both reported that cervical joint and temporomandibular joint dysfunction due to excessive mobility made airway manipulation difficult and caused intubation difficulties by affecting mouth opening under general anesthesia. In their study, Naohiro Ohshita et al. [12] warned that subclinical temporo-mandibular joint and neck joint problems may cause joint dislocation and intubation difficulties, and suggested avoiding neck

hyperextension. Jiang et al. [13] showed that the use of VL increased intubation success and shortened time in difficult endotracheal intubations. Watt et al. [14] reported that the use of VL protected the airway, causing less trauma. Madziala et al. [15] advocated that using video-laryngoscopy at first attempt of intubation may be beneficial in pediatric emergencies requiring difficult airway management and patients with an immobile cervical spine.

In our cases, we used video-laryngoscopy to keep the head in a neutral position and were able to intubate the patients on the first attempt without damaging tissues. EDS patients should be thoroughly evaluated perioperatively and sufficient equipment must be prepared to prevent complications. We believe that the use of video-laryngoscopy would be beneficial in avoiding intubation difficulties and possible head and neck joint complications and thus, neurological damage in EDS patients.

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DOI: 10.28982/josam.602855

Journal of Surgery and Medicine
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Re: “Increased signal intensity in the unenhanced T1-weighted magnetic resonance in the brain after repeated administrations of a macrocyclic-ionic gadolinium-based contrast agent”

Re: “Makrosiklik-iyonik gadolinyum-bazlı kontrast ajan ile tekrarlanan uygulamalar ile T1 ağırlıklı kontrastsız manyetik rezonans görüntülemedeki sinyal intensite artışı”

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Keywords: Gadolinium retention, Brain MRI, T1 hypersignal

Anahtar kelimeler: Gadolinyum tutma, Beyin MRI, T1 hipersinyal

Dear Editor,

We have read with a great interest the paper by Kavak and Özdemir [1], recently published online in the Journal of Surgery and Medicine. In a total of 61 patients with lung cancer, with no brain metastasis, no history of radiation, no history of renal failure they reported an increase in signal intensity (SI) in unenhanced T1-weighted MRI in the brain following repeated administrations of gadoterate meglumine at the standard dose of 0.1 mmol/kg of body weight. The increase in SI was reported in several brain areas: dentate nucleus (DN), pons (P), globus pallidus (GP) and thalamus (T). As stated by the authors, the mean SI in DN, P, GP and T were divided by the mean values obtained from the cerebrospinal fluid (CSF) to standardize the SI measurements and an increase in the four respective ratios was reported as well. These results are conflicting with all the published data from well controlled studies showing no increase in signal intensity with macrocyclic agents [2]. Furthermore, several methodological aspects of that study do not match with the recently published recommendations [2].

First, although it is stated that a minimum of 3 injections and a maximum of 5 injections were given, the cumulative dose (mean and range) of gadoterate meglumine is not specified.

Second, the DN-to-pons ratio has not been assessed although this ratio has been used in most of the reported studies. The author did not justify why they did not choose pons as the reference region. Considering the pharmacokinetic profile of macrocyclic agents in the CSF compartment [3, 4, 5], CSF is not an appropriate reference region to standardize SI values from other cerebral regions. The reported ratio increases (DN/CSF, P/CSF, GP/CSF, T/CSF) could be due to specific variations from CSF signal intensity. In addition, since the ratio of the means is different from the mean of the individual ratios, the ratios should have been calculated for each individual instead of dividing, for each specific brain area, the mean SI by the mean SI in CSF. Last, but not least, the increase in SI value in pons, which is commonly recognized as reference region, strongly suggests an experimental bias favorizing a global increase in SI values in multiple brain regions beyond the DN and GP known as the specific brain regions for gadolinium deposition.

Third, there was no control group without gadolinium-based agents injection. In absence of control group, the impact of CSF SI on SI ratio values cannot be evaluated and increases in SI values cannot be confirmed.

Fourth, DN, P, GP, and T SI changes were reported between first and last unenhanced MRI. Additional time points, which were available in this study, since correlation between ratio values and number of MRI was tested, should have been shown for a robust conclusion.

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Ethics Committee Approval: The letter is not a study with human participants. There are no experiments on animals. This letter does not contain any studies on human participants or animals performed by the author. There is no identifying information of participants.
Etik Kurul Onayı: Bu mektup, insan katılımcılarla yapılan bir çalışma değildir. Hayvanlar üzerinde deney yoktur. Bu mektupta, insan katılımcıları veya yazar tarafından gerçekleştirilen hayvanlar üzerinde yapılan hiçbir çalışma yoktur. Katılımcıların tanımlayıcı bilgisi yoktur.

Conflict of Interest: No conflict of interest was declared by the authors. The authors of this letter are employees of Guerbet.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir. Bu mektubun yazarları Guerbet'in çalışanlarıdır.

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Fifth, it is stated that “The number of examinations had a moderately positive correlation with DN/CSF ratio and a strongly positive correlation with the P/CSF ratio” which is not consistent with the correlation coefficient values reported in the Table 3, e.g. 0.490 and 0.577, respectively. Both values represent only moderate correlation. In the absence of individual data (which could have been reported in a graph) the conclusion is misleading.

Finally, the Stojanov [6] and Rossi-Espagnet [7] studies were reported without mentioning the respective associated controversies on these publications [8,9].

Taking into consideration these significant limitations, the authors might mitigate their conclusion emphasizing that further studies – with more robust approach - should be investigated to confirm these unexpected results.

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