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Safety and accuracy of cannulated versus non-cannulated iliac screws: Cohort study

Kanüllü ile kanülsüz iliak vidaların güvenilirliği ve doğru yerleşimi: Kohort çalışma

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Abstract

Aim: Fixation with iliac screw is often used in long-segment instrumentation with lumbosacral fusion. Polyaxial screws are sent with fluoroscopy, computerized tomography, and navigation, or by freehand. In our study, we compared the accuracy of the cannulated iliac screw (CAS) and classic iliac screw (CLS) sent under fluoroscopy.

Methods: This study was planned as a cohort study. Patients who underwent long segment fusion and sacroiliac fixation in our clinic between 2015 and 2018 were included in our study. The follow-up period of the patients was at least one year. All radiological and clinical data of patients were followed. Computerized tomographies obtained in the postoperative period were used to investigate the accuracy of the screws. Malposition of the screws was classified as medial, lateral and anterior perforation.

Results: Sixty-six iliac screws of 29 patients who met the study criteria were evaluated. There were 15 patients (34 screws) in the classical screw group and 14 patients (32 screws) in the cannulated screw group. The classic screw group had two screws (one medial, one lateral) malpositioned, while the cannulated screw group had no screw malpositions. There was no statistically significant difference between the two groups. No complications were encountered in both groups during the intraoperative and postoperative periods. While two screws loosening was observed in the CLS group, one screw loosening was observed in the CAS group. No statistically significant difference was found. There was no screw breakage in either group.

Conclusion: The use of cannulated iliac screws for sacroiliac fixation is an effective and reliable treatment option.

Keywords: Bone screw, Joint, Lumbosacral, Sacroiliac

Öz

Amaç: İliak vida ile fiksasyon lumbosakral füzyon yapılan uzun segment enstrumanlarda sıklıkla kullanılırlar. Bu işlem için çoğunlukla floroskopi, CT, Navigasyon eşliğinde veya serbest gönderilen poliaksiyel vidalar kullanılır. Biz çalışmamızda floroskopi kontrolü ile gönderilen kanüllü vida (CAV) ve klasik iliak vidanın(CLV) doğruluğunu karşılaştırdık.

Yöntemler: Çalışma, kohort çalışması olarak planlandı. Çalışmamızda 2015-2018 yılları arasında kliniğimizde uzun segment füzyon ve sakroiliak fiksason yapılan hastalar kullanıldı. Hastaların takip süresi en az bir yıl idi. Hastaları takiplerindeki tüm radyolojik ve klinik verileri toplandı. Vidaların doğruluğunu araştırmak için postoperatif dönemde çekilen CT'ler kullanıldı. Vidaların malpozisyonları medial, lateral ve anterior perforasyon olarak sınıflandırıldı.

Bulgular: Çalışma kriterlerine uyan 29 hastanın 66 iliak vidası değerlendirildi. Klasik vida grubunda 15 hasta (34 vida), kanüllü vida grubunda 14 hasta (32 vida) mevcuttu. Klasik vida grubunda iki vida malpozisyonu mevcutken (bir medial, bir lateral), kanüllü vida grubunda hiç vida malpozisyonu yoktu. İki grup arasında istatistiksel olarak anlamlı fark yoktu. Her iki grupta da cerrahi esnasında ve sonrasında herhangi bir komplikasyonla karşılaşılmadı. CLV grubunda iki vida gevşemesi görülürken CAV grubunda bir vida gevşemesi görüldü. İstatistiksel olarak anlamlı fark bulunamadı. İki grupta da vida kırılması görülmedi.

Sonuç: Sakroiliak fiksasyon için kanüllü iliak vida kullanımı etkili ve güvenilir bir tedavi seçeneğidir.

Anahtar kelimeler: Kemik vida, Eklem, Lumbosacral, Sakroiliak

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Introduction

In spinal deformities, the fusion of the lumbosacral region is still very difficult, although the strength of the instruments is increased and the load on the instruments is reduced by osteotomy techniques. In long-segment fused spinal deformities, the bone quality of the sacrum is insufficient to maintain the global alignment of the spine [1-3]. For this reason, in long segment fusions, S2 pedicle screws, alar screws, S2 alar screws, Galveston rods, S2 alar iliac screws and iliac screws are frequently used to support this fusion [2,4,5].

Although it is a safe option, it is vital to place the iliac screws in the right place due to the close relationship of the iliac wings with the visceral organs and neurovascular structures. Several techniques have been developed to improve the accuracy of the screws. These include palpation of the sciatic notch with wide soft tissue dissection, placing screws with fluoroscopy [6,7], use of intraoperative computerized tomography (CT) or navigation [8-11] and lastly, inserting iliac screws through the cannula, as we do [10,12].

In different studies, the accuracy of iliac screws has been investigated and it has been reported that there are around 15% incorrectly sent screws. We hypothesized that when we insert cannulated screws into the iliac wings, the screws will move in a more accurate direction. For this reason, we used cannulated screws in patients who underwent long spinal fusion in our clinic and compared the accuracy of these screws with the classic iliac screws we used before. In different studies, the authors used the cannulated pedicle screws as S2 alar screws and mentioned good results [10,12]. However, we did not find any study showing that it was used and compared for the classic iliac screw. For this reason, to the best of our knowledge, our study is the first study comparing the classic iliac screw and cannulated iliac screw.

Materials and methods

This study was planned as a cohort study. Patients who underwent sacroiliac fixation due to spinal deformity, lumbosacral nonunion and long-segment fusion between 2015-2018 were included in the study. Those with less than one year-follow-up periods and those without postoperative computerized tomography (CT) were excluded from the study. The classic iliac screw (Group 1) was used in patients operated between 2015-2016, and the cannulated iliac screw was used in patients operated between 2017-2018 (Group 2) (Figure 1). The surgeries of all patients were performed by Y.S., an experienced surgeon in spinal surgery.

Surgical procedure

All patients were operated using a posterior midline incision at the radiolucent table. The incisions starting from the spinous processes were extended to the level of the sacroiliac joint. All tissues from spinous processes to transverse processes were dissected laterally. The posterior iliac crest was palpated and the erector spinae muscle was dissected laterally. Posterosuperior iliac spines (PSISs) were detected. The most protruding part of the PSIS was excised with an osteotomy. It was advanced by 30 mm by aiming the anteroinferior spinous process with Straight Path Opener, laterally by 20-30 degrees and caudally by 30-40 degrees. Then the path opener was retracted and the path opened with the tip of the blunt probe was advanced until it touched the cortical bone. The probes placed in both iliac wings were checked with C-arm scope. During the control, care was taken to ensure that the probes and screws were inside the iliac teardrop (Figure 2A, 2B), because it is possible to control the medial and lateral walls of the iliac wing and the upper end of the sciatic notch (the zenith of the sciatic notch) with the iliac teardrop.

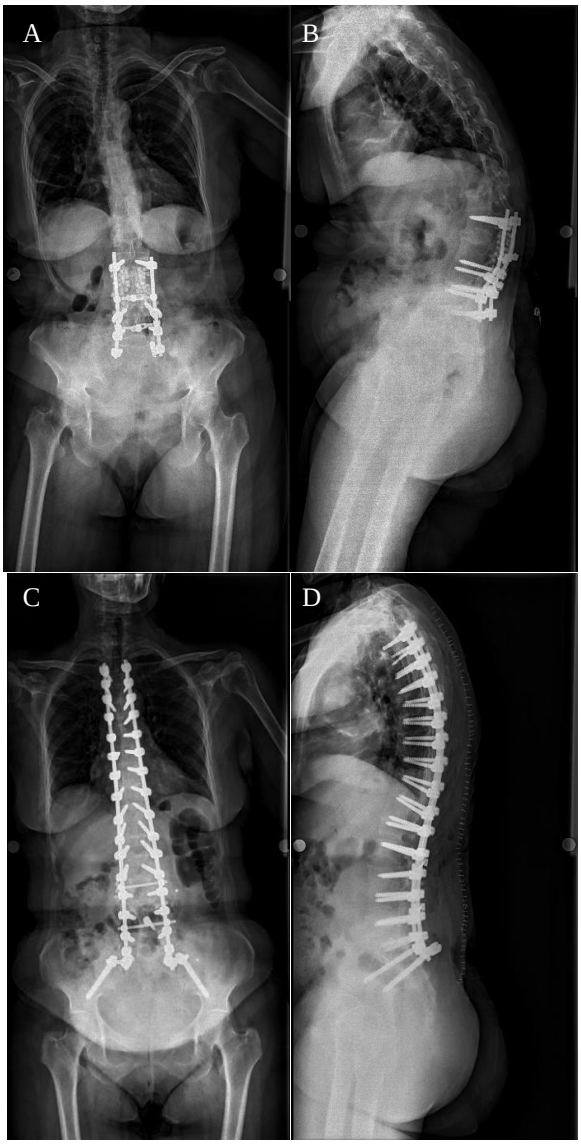

Figure 1: Anteroposterior and lateral X-ray view of kyphosis deformity developing after the operation due to spinal stenosis (A, B). To correct the deformity, the patient underwent instrumentation and 3 levels of Ponte osteotomy between the thoracic 3rd vertebra and the iliac wing. A cannulated iliac screw was used for the iliac wing detection (C, D).

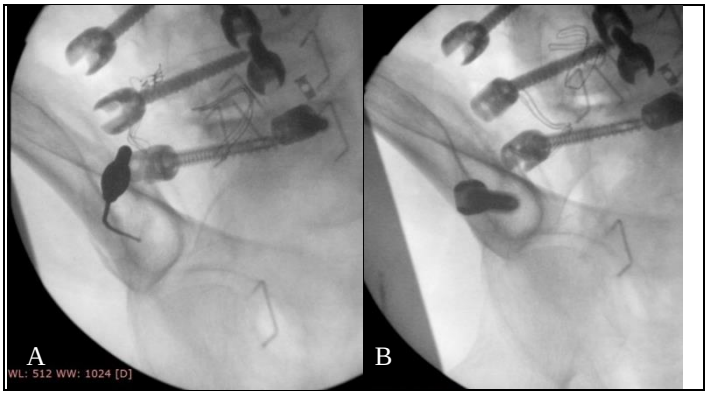

Figure 2: Care was taken to ensure that the blunt-tipped probe and screws were in the iliac tear drop during fluoroscopy control (A, B)

In the classic screw group, the path was widened with the classic tapper after the probe was removed, and then the screws sent following the cortices were checked by the probe. In the cannulated screw group, after removing the thick probe, a guidewire of the same thickness was placed. The guide was controlled with a C-arm scope. After the path was widened with a cannulated tapper, a screw was sent through the guide. While the screw was being sent, we checked the progress of the guidewire. If the guidewire was moving along with the screw, we pulled back the screw and opened another path. Also, after the screw was sent in the bone about 50 mm, the guidewire was withdrawn so that it did not cause a possible organ injury. After the screw placement process was completed, the accuracy of the screw was checked again with the guidewire. The width of the iliac screws was 7.5-9 mm and 70-95 mm long.

Evaluation of the screw malposition

CTs taken in the postoperative period or during follow-ups were used to evaluate screw malposition. The images in the axial, coronal and sagittal plan were examined by Toy S., and metallic densities extending beyond the cortical bone in any of these images were evaluated as screw malposition. Medial and lateral perforations of both groups were recorded. Superior and inferior perforations were evaluated as lateral perforations.

Also, X-rays taken in the last follow-up of patients were interpreted to evaluate the screws for breakage and loosening.

Statistical analysis

Data were analyzed using SPSS version 20.0 (IBM Corp; Armonk, NY, USA. Independent samples t-test and Mann–Whitney U tests were used for the comparisons of normally and non-normally distributed independent groups, respectively. Fisher's exact test was used for categorical variables. A *P*-value <0.05 was accepted as statistically significant.

Results

After the operation, 66 iliac screws (34 classical screws, 32 cannulated screws) were evaluated in 29 patients (15 classical screws, 14 cannulated screws) with computed tomography. In the preoperative period, ten patients were diagnosed with degenerative scoliosis, nine patients with neuromuscular scoliosis, four patients with flat back, and six patients with iatrogenic kyphosis.

There was no significant difference between the ages (*P*=0.253) of the groups, or in terms of postoperative fusion levels (12.87-12.36) (*P*=0.413). The follow-up period of group 1 was longer than group 2 (30.87 months – 20.00 months) (*P*=0.009) (Table 1).

Table 1: Patient demographics

	Total	Classical screws	Cannulated screws	*P*-value
Number of patients	29	15	14	0.096
Mean of age	51.48 (18.96)	47.53 (18.98)	55.71 (18.67)	0.253
Level of fusion	12.62 (3.73)	12.87 (3.72)	12.36 (3.87)	0.413
Follow-up periods	25.62 (9.92)	30.87 (8.40)	20.00 (8.37)	0.009
Number of screws	66	34	32	0.942
Number of wrong screws	2	2	0	0.483
Loosening of screws	3	2	1	1.00

Group 1 had two screw malpositions (1 medial, 1 lateral) (Figure 3), while group 2 had none. There was no statistically significant difference between the two groups (*P*=0.483). No symptomatic visceral organ or vascular injuries were observed in either group.

In groups 1 and 2, two and one screw loosenings were observed, respectively. No statistically significant difference was found (*P*=1.00). There was no screw breakage in either group.

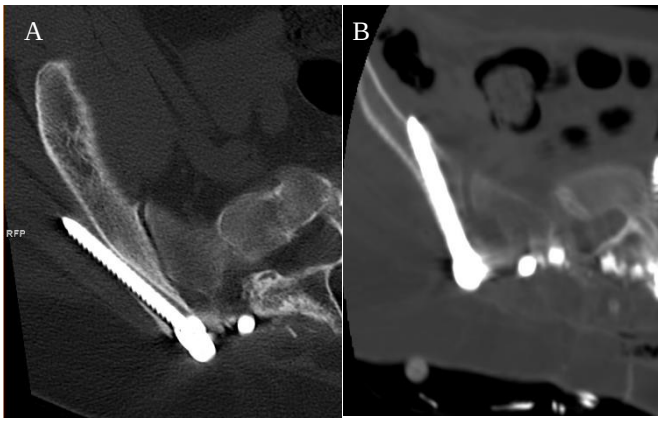

Figure 3: Iliac screw causing lateral wall injury (A), An iliac screw that was seen causing medial iliac wall injury (B)

Discussion

In spinal deformities with long-segment fusion reaching the sacrum, iliac fixation is mostly included in the fusion, since the bone density of the sacrum cannot withstand the force of stress. S2 alar screws, classic iliac screws, Galveston rods, and S2 alar iliac screws, which are iliac fixation techniques, have been shown to be effective for rigid lumbosacral fixation [1-3]. Although conventional iliac screws require additional connection and require wide tissue dissection and are obvious from the skin, these methods are still commonly used sacroiliac fixation methods [5,13,14].

Although the effectiveness and reliability of the iliac screws have been proven, the screws cannot always be sent as intended. Misplaced screws can also cause cortical injuries and neurovascular injuries [5,12]. The accuracy of iliac screws has been shown to vary between 80% and 100% in different studies [3,10,15-17]. In these studies, different methods are tried to decrease screw accuracy and complication rate. The most important of these methods are intraoperative tomography and navigation. Although some of the studies on these methods show that it increases screw accuracy [10], there are also studies showing that it does not affect it at all [16]. With these methods, there is less tissue dissection and less wound site problems and shorter operation times. It also causes less radiation exposure. However, they come with some disadvantages. The first one is the high cost, which makes them unavailable in most centers. They also increase the likelihood of infection, as different devices constantly enter the site of operation [18]. In addition, the use of intraoperative CT increases the radiation exposure of both the patient and the surgical team. In fact, almost all of the screws sent with navigation are sent with the guidewire after navigation, and screws are sent over the guidewire [13,19-21]. The guide prevents the screw from changing the direction of the wire. We were inspired by this, and sent the cannulated iliac screws through the guidewire.

Different studies have proven that the use of cannulated screws in spinal surgery is an effective and reliable method [10,12,22,23]. In our study, we tried to increase our screw accuracy using cannulated iliac screws and compared them with the group in which we used classic iliac screws. Although there was no significant difference between the two groups, we did not

observe screw malpositioning in any patient we used cannulated screws on. The most important reason for this is that the cannulated screw guide prevents the direction of the screw from changing and the accuracy of the screw can be controlled with the cannula.

Although almost all of the iliac screws sent by navigation are cannulated screws, there were only two studies in the literature using cannulated iliac screws without navigation. In a non-controlled study, Choi et al. [12] placed cannulated iliac screws in 16 patients using the S2 AI technique. In this study where 93.8% of the screws were placed in the right place, no complications were encountered. Also, since there was no patient follow-up in this study, no information was provided regarding screw strength. Hlubek et al. [10] examined 111 patients with iliac screws, after they sent cannulated iliac screws with the freehand technique from the traditional and anatomic entry points to a group and compared the accuracy of the screws in this group with the group to which they sent iliac screws with navigation from three different entry points (traditional, anatomic and S2AI). They did not find any significant differences between the two groups (89% - 96%).

One of the most important criticisms of the cannulated screws is the concerns about screw strength and its effect on relaxation. We have not found any biomechanical studies on the stability of the iliac screws. Although the cannulated screws have been shown to be more fragile than conventional screws in a biomechanical study with pedicle screws [24], no weakness has been found in clinical studies [22,23]. To avoid any breakage problem while inserting a cannulated iliac screw, we sent the cannulated taper to the end and tried to bury it in the bone tissue with only the polyaxial part of the screw outside. We did not find any screw breakage after an average of two years of follow-up. In terms of screw loosening, we did not find a significant difference between the two groups.

Limitations

Since the most important limitation of our study was its retrospective nature, we could not investigate the effect of using cannulated screws on radiation exposure, bleeding amount and operation time. Although we are the only study investigating cannulated iliac screw strength, we think that our follow-up time is short to evaluate screw breakage and screw loosening.

This case series that we have done is the first clinical study for cannulated and classical iliac screws using for iliac fixation. This manuscript will be to lead the prospective studies with more patients and longer follow-up in the future. We think that with these studies, concerns about the use of cannulated iliac screws will disappear.

Conclusions

In this case series, we discovered that the usage of classical iliac screws, which are mostly preferred for sacroiliac fixation, do not have a statistically significant difference when compared with cannulated iliac screws. We can easily say that using cannulated screws for sacroiliac fixation is an effective and reliable treatment option. Also, based on our results, we can emphasize that the strength of cannulated screws should not be a matter of concern.

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Association of hypertension with generalized obesity in rural south-western Nigeria

Nijerya'nın kırsal güneyindeki genel obezite ile hipertansiyon ilişkisi

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Ethics Committee Approval: Approval was obtained from the Ethics and Research Committee of Olabisi Onabanjo University Teaching Hospital (REF: OOUTH/DA.326/508). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: There is a rising prevalence of hypertension worldwide with Africa reported to have the greatest disease burden. Obesity is the major risk factor for hypertension. This study aims to determine the prevalence of hypertension and its relationship with general obesity in rural south-western Nigeria.

Methods: Cross-sectional descriptive survey was conducted in two rural communities in Remo North Local Government area of Ogun State, Nigeria. Four hundred and twelve (412) participants comprising 216 (50%) males, aged 20-70 years, were studied. Participants were screened for generalized obesity and hypertension according to standard protocols. Hypertension was defined according to the seventh report of Joint National Committee on Prevention, Detection, Evaluation and Treatment of high blood pressure (JNC VII). Associations between obesity and hypertension were determined by analysis of variance (ANOVA), Pearson's correlation and Chi-Square tests.

Results: The mean of all the blood pressure indices (systolic, diastolic and mean arterial blood pressure) increased from first to fourth quartile of body mass index (BMI) (For trend, P<0.001). The prevalence of hypertension was 32.5% (28.6% in males and 36.4% in females). Compared to males, more females had systolic hypertension (45.1% vs 33.5%, P=0.02). The prevalence of hypertension increased with age (P<0.001 for systolic blood pressure (SBP) and diastolic blood pressure (DBP); P=0.019 for isolated systolic hypertension (ISH), and BMI (X^2=8.508, P=0.019 [95% CI, 0.001-0.038]). BMI correlated with both systolic and diastolic blood pressures (P<0.001).

Conclusions: The prevalence of hypertension is high and it is positively associated with obesity in the population. Aggressive lifestyle intervention to curb obesity is necessary to prevent hypertension and future cardiovascular disease.

Keywords: Hypertension, Obesity, Cardiovascular diseases, Prevalence

Öz

Amaç: Dünya çapında hipertansiyon prevelansında bir artış bildirilmekle birlikte, Afrika'nın en yüksek hastalık yüküne sahip olduğu bilinmektedir. Obezite, hipertansiyon için major risk faktörüdür. Bu çalışmada Güneybatı Nijerya'nın kırsal kesiminde hipertansiyon prevalansı ve genel obezite ile ilişkisinin araştırılması amaçlanmıştır.

Yöntemler: Nijerya'nın Ogun Eyaleti, Remo Kuzey Yerel Yönetim bölgesinde iki kırsal toplulukta bir kesitsel tanımlayıcı anket yapılmıştır. Yaşları 20-70 arasında değişen, 216'sını erkeklerin oluşturduğu (%50) toplam 412 hasta incelenmiştir. Katılımcılar, standard protokollere göre genel obezite ve hipertansiyon açısından taranmıştır. Hipertansiyon, Ortak Ulusal Yüksek Tansiyonun Önlenmesi, Saptanması, Değerlendirilmesi ve Tedavisi Komitesi'nin yedinci raporuna göre tanımlanmıştır (JNC VII). Obezite ve hipertansiyon arasındaki ilişki Pearson'un korelasyon testi ve ki-kare testi ile belirlendi.

Bulgular: Tüm kan basıncı endekslerinin ortalaması (sistolik, diyastolik ve ortalama arteriyel kan basıncı) vücut kitle indeksinin (BMI) ilk dördüncü çeyreğinden arttı (Eğilim için P<0,001). Hipertansiyon prevalansı %32,5'tu (erkeklerde %28,6 ve kadınlarda %36,4). Erkek olgulara kıyasla kadınlarda sistolik hipertansiyon daha sık gözlemlenmekteydi (%45,1'e karşı %33,5, P=0,02). Hipertansiyon prevalansı yaşla birlikte artmaktaydı (sistolik kan basıncı (SBP) ve diyastolik kan basıncı (DBP) için P<0,001); izole sistolik hipertansiyon (ISH) ve BMI için P=0,019 (X^2=8,508, P=0,019 [% 95 CI, 0,001-0,038]) BMI, hem sistolik hem de diyastolik kan basınçları ile korelasyon gösterdi (P<0,001).

Sonuç: Hipertansiyon prevalansı yüksektir ve popülasyondaki obezite ile pozitif olarak ilişkilidir. Hipertansiyonu ve gelecekteki kardiyovasküler hastalıkları önlemek amacıyla obeziteyi azaltmak için agresif yaşam tarzı müdahalesi gerektirmektedir.

Anahtar kelimeler: Hipertansiyon, Obezite, Kardiyovasküler hastalıklar, Prevalans

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Introduction

Arterial hypertension is a major cardiovascular risk factor, resulting in stroke, ischemic heart disease, heart failure, and contributes to the burden of kidney disease [1]. There is a rising prevalence of hypertension worldwide [2], and Africa, including Nigeria, is reported to have the greatest burden of the disease [3]. The estimated prevalence of hypertension in Nigeria ranges between 2.1% to 47.2% depending on the population [4,5]. In 2016, reports from semi-urban cities revealed prevalence rates of 27% and 44.9% in south-east and south-west Nigeria, respectively [6,7]. Egbi et al. [8] determined a prevalence of 50% in a rural community in south-south Nigeria in 2018. Globally, death resulting from hypertension and its complications are also increasing [2].

Obesity has been recognized as a disease and a major risk for global deaths [9]. It constitutes a major public health challenge because of its co-morbidities. General obesity is strongly associated with arterial hypertension [10], which is increasing in some populations [11]. Several authors [12-16] have documented the association of obesity and hypertension, and the link is attributed to increased leptin, low adiponectin, activation of rennin-angiotensin-aldosterone system, increased sympathetic drive, sodium retention, and endothelial dysfunction [17]. The frequent occurrence of obesity and hypertension have led to the term "obesity-related hypertension". Fortunately, obesity is preventable.

There are challenges in the management of hypertension in rural communities in Nigeria [18]. Therefore, emphasis should be laid on prevention of its major risk factors such as obesity. This study sought to determine prevalence of arterial hypertension and its association with generalized obesity in two rural communities in south-western Nigeria.

Materials and methods

This is a cross-sectional descriptive survey of Isara and Ode-Remo communities, in Remo North local government area of Ogun State, Nigeria. The local government was chosen because of convenience. Approval was obtained from the Ethics and Research Committee of Olabisi Onabanjo University Teaching Hospital (REF: OOUTH/DA.326/508). The consent of the king and community leaders was sought after initial sensitization visits to the communities. People who met the inclusion criteria were told to meet at a designated point for the screening. The participants included market men and women, artisans, farmers, drivers, and few civil servants.

With the aid of a pre-tested structured questionnaire, demographic and clinical parameters such as age, gender, marital status, occupation, history of hypertension were obtained. The blood pressure, height, and weight were measured.

Anthropometric measurements

The height was measured (in meters) to the nearest 0.1 meter with a calibrated meter rule placed horizontally against the wall. The subjects were asked to be barefooted and wore light clothing. Subjects were asked to stand on a flat surface, with weight distributed evenly on both feet, heels together and the head positioned so that the line of vision is perpendicular to the body. The arms hung freely by the sides, and the head, back, buttocks and the heels were in contact with the vertical board. The movable headboard was brought onto the topmost point on the head with sufficient pressure to compress the hair [19]. The weight was measured (in kilograms) with a weighing scale without shoes and with the patient wearing light clothing, to the nearest 0.1kg [19].

The Body Mass Index (BMI) was measured as the ratio of weight (kg) to the square of the height (m^2), and classified as follows: ≤18.5 kg/m2, underweight; 18.5-24.9kg/m^2, normal; 25.0-29.9 kg/m^2, overweight; 30.0-34.9 kg/m^2, class 1 obesity; 35.0-39.9 kg/m^2, class 2 obesity; ≥40.0 kg/m^2, class 3 obesity [19].

Blood pressure measurement

Blood pressure was measured with a standard mercury sphygmomanometer with the subjects in the sitting position and the arm resting on a table at the same level of the heart. Systolic and diastolic blood pressures were obtained with the appearance and disappearance of the Korotkoff sounds (Phases I and V) respectively. Hypertension was defined as systolic blood pressure of (SBP) >140mmHg and /or diastolic blood pressure (DBP) >90mmHg. Blood pressure was further classified as follows: SBP <120mmHg and DBP <80 mmHg, normal, SBP 120-139mmHg or DBP 80-89 mmHg, prehypertension, SBP 140-159mmHg or DBP 90-99mmHg, stage 1 hypertension, SBP >160 mmHg or DBP >100 mmHg, stage 2 hypertension [20]. Isolated systolic hypertension (ISH) was defined as SBP ≥140mmHg and DBP <90mmHg.

Statistical analysis

Using the statistical package for social sciences (SPSS) version 16 (Chicago, IL, USA), Chi-square (χ^2) test was used to find the association between categorical variables (expressed as percentages) and t-test to compare continuous variables (expressed as mean). Body mass index was further categorized into quartiles, and the means of blood pressure indices (SBP, DBP, and mean arterial pressure [MAP]) were compared with one-way analysis of variance (ANOVA). Pearson correlation was used to find the association between blood pressure and body mass index. Level of significance was inferred at $P<0.05$.

Results

Four hundred and twelve (412) individuals comprising 206(50%) males were included in the study. Table 1 shows the mean values of Age, SBP, DBP, and MAP according to the quartiles of BMI for all participants. The means of all blood pressure indices increase from first to fourth quartiles of BMI (For trend, $p<0.001$). The overall prevalence of hypertension (BP≥140/90mmHg), systolic hypertension, diastolic hypertension and isolated systolic hypertension were 32.5%, 39.3%, 35.4%, 10.7% respectively (Table 2). Compared to males, more females had systolic hypertension (45.1% vs 33.5%, $P=0.02$).

Table 3 shows the prevalence of hypertension stages. More females had stage 2 systolic hypertension than males (24.8% vs 12.6%).

The prevalence of systolic hypertension increased with age in both men and women, ($P<0.001$), whereas the prevalence of diastolic hypertension increased with age in women only ($P<0.001$, Table 4). The prevalence of ISH also increased with

age in all participants (P=0.019). Overall, prevalence of systolic and diastolic hypertension was highest among those who were 70 years old and above.

Table 1: Mean values of age and blood pressure indices according to quartiles of body mass index

	Quartile 1 mean(SD) n=103	Quartile 2 mean(SD) n=103	Quartile 3 mean(SD) n=103	Quartile 4 mean(SD) n=103	F	*P*-value
Age(years)	47.2(16.8)	39.0(16.1)	43.4(15.6)	48.6(11.9)	8.3	<0.001
SBP (mmHg)	126.8(26.6)	132.0(22.9)	130.9(22.6)	145.1(27.4)	10.3	<0.001
DBP (mmHg)	78.7(13.5)	81.4(14.1)	79.5(13.8)	90.1(17.4)	13.0	<0.001
MAP (mmHg)	94.7(16.8)	98.3(16.0)	96.6(15.7)	108.4(19.6)	13.2	<0.001

SD: Standard deviation, BMI: Body mass index, DBP: Diastolic blood pressure, SBP: Systolic blood pressure

Table 2: Prevalence of hypertension among participants

Characteristics	All n=412 n (%)	Males n=206 n (%)	Females n=206 n(%)	*P*-value
BP≥140/90mmHg	134(32.5)	59(28.6)	75(36.4)	0.115
SBP ≥140mmHg	162(39.3)	69 (33.5)	93(45.1)	0.020
DBP ≥90mmHg	146 (35.4)	70(34.0)	76(36.9)	0.607
ISH	44(10.7)	20(9.7)	24(11.7)	0.633

BMI: Body mass index, DBP: Diastolic blood pressure, ISH: Isolated systolic hypertension, SBP: Systolic blood pressure (ISH is defined as SBP ≥140mmHg and DBP <90mmHg)

Table 3: Prevalence of hypertension according to the stages of hypertension

Characteristics	All n=412 n (%)	Males n=206 n (%)	Females n=206 n (%)	X^2 (df)	*P*-value	95% CI
SBP				37.3(3)	<0.001	0.000-0.007
Normal	112 (27.2)	41 (19.9)	71 (34.5)			
Pre-hypertension	138 (33.5)	96 (46.6)	42 (20.4)			
Stage 1	85 (20.6)	43 (20.9)	42(20.4)			
Stage 2	77(18.7)	26 (12.6)	51(24.8)			
DBP				2.7(3)	0.471	0.423-0.519
Normal	142 (34.5)	69 (33.5)	73 (35.4)			
Pre-hypertension	124 (30.1)	67(32.5)	57 (27.7)			
Stage 1	84 (20.4)	44 (21.4)	40 (19.4)			
Stage 2	62 (15.0)	26 (12.6)	36 (17.5)			

DBP: Diastolic blood pressure, SBP: Systolic blood pressure

Table 4: Prevalence of hypertension in relation to age and gender

Characteristics	Age (years) 18-29 n (%)	30-39 n (%)	40-49 n (%)	50-59 n (%)	60-69 n (%)	>=70 n (%)	*P*-value
SBP							
All	13(14.9)	28(31.1)	24(35.3)	32(52.5)	40(52.5)	25(64.1)	<0.001
Males	13(20.0)	21(36.2)	8(22.2)	13(52.0)	10(62.5)	4(66.7)	<0.001
Females	0(0.0)	7(21.9)	16(50.0)	19(52.8)	30(58.8)	21(63.6)	<0.001
DBP							
All	15(17.2	24(26.7)	29(42.6)	27(44.3)	28(41.8)	23(59.0)	<0.001
Males	15(23.1)	20(34.5)	15(41.7)	9(36.0)	7(43.8)	4(66.7)	0.180
Females	0(0.0)	4(12.5)	14(43.8)	18(50.0)	21(41.2)	19(57.6)	<0.001
ISH							
All	5(5.7)	11(12.2)	3(4.4)	8(13.1)	3(7.7)	3(7.7)	0.019
Males	5(7.7)	8(13.8)	0(0.0)	4(16.0)	3(18.8)	0(0.0)	0.121
Females	0(0.0)	3(9.4)	3(9.4)	11(21.6)	11(21.6)	3(9.1)	0.126

DBP: Diastolic hypertension, ISH: Isolated systolic hypertension, SBP: Systolic blood pressure

As the degree of obesity increases, so does the prevalence of hypertension. More than 50% of those with overweight and class 1 obesity had hypertension (Figure 1). There is significant correlation between SBP (r=0.258, P<0.001) and DBP (r=0.276, P<0.001) with body mass index (Figures 2 and 3).

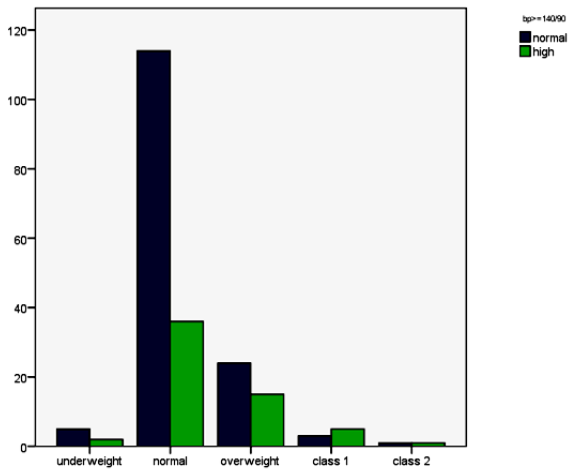

Figure 1: Relationship between obesity and hypertension in all the participants (X^2=8.508, df=5, P=0.019 (95% CI, 0.001-0.038))

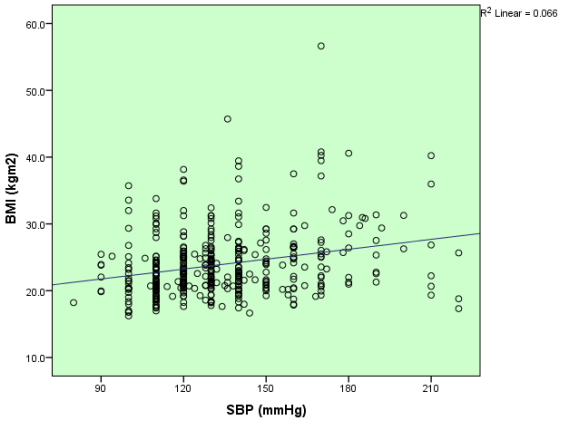

Figure 2: Scatterplot showing relationship between body mass index and systolic blood pressure (Correlation between BMI and SBP, r=0.258 (P<0.001))

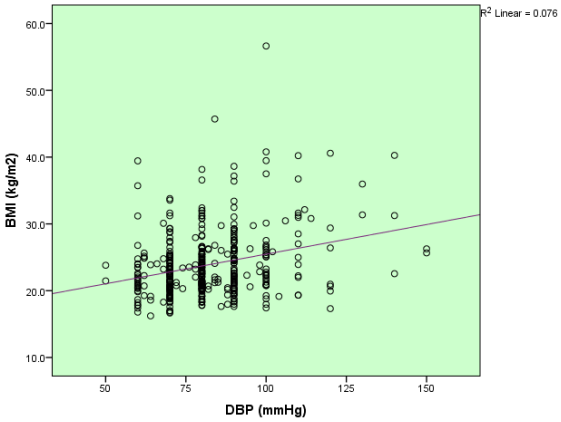

Figure 3: Scatterplot showing relationship between body mass index and diastolic blood pressure (Correlation between BMI and DBP, r=0.276 (P<0.001))

Discussion

Obesity is one of the most important causes of hypertension worldwide. We sought to determine the prevalence of hypertension in two rural communities of south-western Nigeria, and its association with general obesity.

Prevalence of hypertension

The overall prevalence of hypertension (BP ≥140/90mmHg) in the rural communities studied is 32.4%, higher than findings from studies from some rural communities in Nigeria, [21,22], 19.3% in rural northern Ghana [23], and 14.5- 23.5% in rural India [24,25], but lower than the prevalence of 45.8% from a rural community in Enugu, south-eastern Nigeria [26], and 44.9% from south-west Nigeria [7]. The prevalence of hypertension was higher in our study than the Ghanaian study probably because our subjects were older, had higher mean BMI and waist circumference values. Conversely, the lower prevalence of hypertension in our study than the Enugu study may be ascribed to our subjects being younger than theirs. Similar to our findings, a more recent study from Ghana revealed a prevalence of 32.5% [13].

In contrast to what most authors reported, hypertension was equally present in both genders, but systolic and stage 2 hypertension was more prevalent among the female participants [21,26-30]. This may be due to the older age, and higher prevalence of obesity among the females. Hypertension is known to be strongly associated with age and obesity [10,28]. The World Health Organization also reported a higher prevalence of hypertension in Nigerian females [27].

Systolic and diastolic hypertension was present in 39.3% and 35.4% of the people studied, higher than a prevalence of 31% and 22.5% respectively for SBP and DBP in Abia state, south-eastern Nigeria [29]. In addition, both the female and male subjects in our study had higher prevalence of DBP hypertension than in the Abia study. Furthermore, SBP was more prevalent in our female population than those in Abia (45.1% vs 30.5%) [29]. Nevertheless, the prevalence of systolic hypertension in males (33.5%) in our study is similar to the findings in male population in Abia, south-eastern Nigeria, (33.5%) [29].

Few studies reported isolated systolic hypertension (ISH) in Nigeria, even though it has been shown to correlate with cardiovascular diseases in Systolic Hypertension in the Elderly Program (SHEP) study [31]. Isolated systolic hypertension was present in 10.7% of the people studied, akin to a prevalence of 13.3% in north central Nigeria [32], but higher than 6.6% prevalence in an earlier study in rural south-western Nigeria [33]. It is however lower than a prevalence of 22.1% in another study in south-western Nigeria [34] and 39.4% in a study from rural south-eastern Nigeria [35]. This may be due to the fact that the study from the south-western Nigeria was conducted in a semi urban community unlike ours which was from a rural setting, and the participants from the study from rural south-eastern Nigeria were older than those in our study. Our study further showed that the prevalence of ISH increases with age, as reported by previous authors [31,36]. Adediran et al. [37] also showed that hypertension and related disorders were more prevalent in urban setting. The impact of urbanization on hypertension can further be deduced from a study by Ulasi et al. [38], in which those from urban community had higher prevalence of hypertension despite their younger age compared to participants from rural community [38]. Generally, hypertension prevalence increases with age [39].

Pre-hypertension defined as SBP ≥120 but <140mmHg and/or DBP ≥80 but <90 mmHg was found in 31.8% of the participants in our study. It was reported to occur in 44.5% [25] and 45.5% [6] of Indians and Nigerians, respectively. These rates are high and worrisome because it is not a benign condition. Okwuonu et al. [6], reported its association with proteinuria. It has also been shown that SBP ≥110-115mmHg is associated with increased cerebrovascular diseases (ischemic and hemorrhagic strokes), ischemic heart disease, chronic kidney disease, and death [2].

Relationship between hypertension and obesity

In this study we found a positive and linear relationship between hypertension and general obesity. The percentage of participants with hypertension increases with the class of obesity. The means of SBP, DBP and MAP significantly increases with higher quartiles of index. Furthermore, obesity significantly correlates with both SBP and DBP. Previous workers also found that obesity was a major predictor of hypertension [29,35,40,41]. It was reported by Amole et al. [40] that 72.9% of people with obesity had hypertension. Gao et al. [41] reported that general obesity increased the prevalence of obesity by 23% and 37% in males and females, respectively. They also found that the hypertensive effect of general obesity was greater than that of isolated upper body obesity. Dua et al. [42] reported a positive correlation between obesity with both SBP and DBP.

Obesity-induced hypertension is attributed to increased leptin, low adiponectin, activation of rennin-angiotensin-aldosterone system, increased sympathetic activity, increased sodium retention, and endothelial dysfunction [17]. Obesity is associated with insulin and leptin resistance resulting in hyperinsulinemia and hyperleptinemia, respectively. The two abnormalities result in elevated sympathetic activity, which is associated with increased vascular resistance and sodium reabsorption [17]. The adipose tissue increases angiotensinogen, aldosterone, endothelin, resistin and other substances which all act in concert and contribute to high blood pressure [17,43-44]. In view of this, successful prevention and management of obesity is expected to lower the incidence and prevalence of systemic hypertension.

Limitations

The cross-sectional design of this study cannot establish causality between obesity and hypertension. Furthermore, the precise contribution of obesity to hypertension was not determined in this population.

Recommendation

Aggressive health education on healthy lifestyle to prevent obesity should be incorporated into the primary health care system. This will in turn curb hypertension in communities.

Conclusion

The prevalence of hypertension is high and it is positively associated with obesity in rural communities of south-western Nigeria.

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Effect of anti-TNFα treatment on Tp-e interval and Tp-e/QT ratio in patients with ankylosing spondylitis: A case-control study

Ankilozan spondilit hastalarında anti-TNFα tedavinin Tp-e mesafesi ve Tp-e/QT oranı üzerine etkisi: Bir vaka-kontrol çalışması

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Abstract

Aim: Ankylosing spondylitis (AS) is an axial spondyloarthropathy with multisystemic involvement. Anti-TNFα agents play a significant role in treatment options of this disease. In the literature, there is contradictory data about the effects of AS disease and anti-TNFα therapy on ventricular repolarization parameters. In this present study, we examined whether electrocardiographic parameters which reflect ventricular repolarization like QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc are different in AS patients than the control group and the effect of anti-TNFα agents on these parameters.

Methods: Sixty patients diagnosed with AS (33 patients treated with anti-TNFα, 27 patients treated with non-anti-TNFα) and 60 healthy subjects were included in the study. Demographic, biochemical, electrocardiographic, and echocardiographic parameters of the study and control groups were compared. Tp-e interval was measured as the time interval between the T wave's peak point and down slope tangent intersecting with the isoelectric line.

Results: Heart rate, QT, QTc, and QRS were similar in both groups (*P*=0.232, *P*=0.660, *P*=0.220, and *P*=0.846, respectively); Tp-e (*P*=0.013), Tp-e/QT (*P*=0.006), and Tp-e/QTc (*P*=0.041) values were higher in the study group. Comparison analysis performed between groups treated with anti-TNFα and non-anti-TNFα showed no statistically significant difference in terms of heart rate, QT, QTc, QRS, Tp-e, Tpe/QT, and Tp-e/QTc values (*P*=0.916, *P*=0.655, *P*=0.335, *P*=0.999, *P*=0.731, *P*=0.848, and *P*=0.901, respectively).

Conclusion: Although QT and QTc values were similar between AS patients and the control group, Tp-e, Tp-e/QT, and Tp-e/QTc values were higher in AS patients. Additionally, anti-TNFα treatment had a neutral effect on these parameters.

Keywords: Ankylosing spondylitis, T peak-to-end, Tp-e/QT, Anti-TNFα treatment

Öz

Amaç: Ankilozan spondilit (AS) multisistemik tutulumla seyredebilen bir aksiyal spondiloartropatidir. Anti-TNFα ajanlar bu hastalığın tedavisinde önemli bir rol oynarlar. Literatürde AS hastalığı ve anti-TNFα tedavinin ventriküler repolarizasyon parametreleri üzerine etkileri hakkında çelişkili veriler mevcuttur. Sunulan bu çalışmada, QT, QTc, Tp-e, Tp-e/QT ve Tp-e/QTc gibi ventriküler repolarizasyonu gösteren elektrokardiyografik parametrelerin AS hastalarında, kontrol grubuna göre farklı olup olmadığını ve anti-TNFα ajanların bu parametreler üzerinde etkili olup olmadığını araştırdık.

Yöntemler: AS tanılı 60 hasta (anti-TNFα ile tedavi edilen 33 hasta, non-anti-TNFα ile tedai edilen 27 hasta) ve 60 sağlıklı gönüllü çalışmaya dahil edildi. Çalışma ve kontrol grubunun demografik, biyokimyasal, elektrokardiyografik ve ekokardiyografik parametreleri karşılaştırıldı. Tp-e aralığı, T dalgasının tepe noktası ile izoelektrik çizgiyle kesişen aşağı eğim teğeti arasındaki zaman aralığı olarak ölçüldü.

Bulgular: Kalp hızı, QT, QTc ve QRS her iki grupta benzer iken (*P*=0,232, *P*=0,660, *P*=0,220 ve *P*=0,846, sırasıyla); Tp-e (*P*=0,013), Tp-e/QT (*P*=0,006) ve Tp-e/QTc (*P*=0,041) değerleri çalışma grubunda istatistiksel anlamlı olarak daha yüksekti. Anti-TNFα ajanlar ile tedavi edilen ve non-anti-TNFα ajanlar ile tedavi edilen gruplar arasında karşılaştırma analizi yapıldığında ise, kalp hızı, QT, QTc, QRS, Tp-e, Tp-e/QT ve Tp-e/QTc değerlerinde istatistiksel anlamlı farklılık izlenmedi (*P*=0,916, *P*=0,655, *P*=0,335, *P*=0,999, *P*=0,731, *P*=0,848 ve *P*=0,901, sırasıyla).

Sonuç: QT ve QTc değerleri AS hastaları ile kontrol grubu arasında benzer iken; Tp-e, Tp-e/QT ve Tp-e/QTc değerleri çalışma grubunda daha yüksek idi. Ek olarak, anti-TNFα ajanlar bu parametreler üzerine nötral etkiliydi.

Anahtar kelimeler: Ankylosing spondylitis, T peak-to-end, Tp-e/QT, Anti-TNFα treatment

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Introduction

Ankylosing spondylitis (AS) is a chronic and progressive spondyloarthropathy that is more common in young adults. The pathological process of the disease is characterized by bone erosion in sacroiliac joint and vertebral process, new bone formation, and syndesmophyte and ankylosis development in the later stages [1,2]. AS primarily affects the spine, however, it can also be a cause of morbidity and mortality due to multisystemic involvement. These include acute uveitis, peripheral arthritis, enthesitis, psoriasis, aortic root, and gut inflammation [1].

Cardiac involvement is seen in 2-10% of AS patients, being more common in long-term patients [3,4]. The most frequent presentations in cardiac involvement include aortic regurgitation, aortitis at ascending aorta level, rarely mitral insufficiency and conduction system disorders such as atrioventricular block and bundle branch blocks. Additionally, ventricular repolarization abnormalities have also been shown in studies with AS patients. However, no consistent results were obtained on the effects of AS on electrocardiographic parameters that show ventricular repolarization like QT, QTc, QT dispersion, Tp-e and Tp-e/QT [5-7].

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine that is contributory in the pathogenesis of AS. Anti-TNFα agents like etanercept, adalimumab and infliximab are options in AS treatment [8]. Previous studies investigated the effects of these agents on ventricular repolarization parameters like QT and QTc and contradictory results were obtained [5,9]. Longo et al. [5] showed that anti-TNFα drugs have neutral effect on QT and QTc intervals; Senel et al. [9] reported shortened QTc interval after infliximab treatment.

In this study, we investigated if ventricular repolarization parameters such as QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc were higher in AS patients in comparison to the control group and the effect of anti-TNFα drugs on these parameters.

Materials and methods

Study population

In the outpatient clinic of department of physical therapy and rehabilitation of our hospital, patients followed-up with AS diagnosis were reached through hospital database and 60 patients were included in the study. 'ASAS/EULAR recommendations for the management of axial spondyloarthritis' guideline was used for AS diagnosis [10]. Patients were assigned into anti-TNFα treated (n=33) and non-anti-TNFα treated groups (n=27). Sixty age- and gender-matching healthy subjects were included in the study as the control group.

Exclusion criteria included patients with coronary artery disease (CAD), diabetes mellitus (DM), hypertension (HT), moderate-severe valvular heart disease, morbid obesity, liver and kidney dysfunction, active infection, antiarrhytmic medication and the presence of bundle branch block or atrioventricular block.

Disease activity was evaluated by using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [This index is calculated with parameters like fatigue, spinal pain, peripheral arthritis, enthesitis and morning stiffness severity and duration and 4 or higher scores can indicate active disease.] [11].

Blood samples were obtained on admission from each patient for the measurement of complete blood count, liver and kidney function tests and bleeding profile. 12-hour fasting serum lipid profiles were measured by standard enzymatic methods. Transthoracic echocardiographic (Vivid 7 Dimension, GE Medical Systems, Horten, Norway) examination was performed for each participant.

The study was approved by local ethics committee (Ahi Evran University, number: 2019-14/151 and date: 06/08/2019) and informed consents were obtained from all the participants.

ECG examination

Twelve-lead ECGs were obtained for all participants with a paper speed of 25 mm/s and voltage of 10 mm/mV using a MAC 2000 (GE Medical Systems Information Technologies, Inc., 8200 W, Milwaukee, WI, USA) electrocardiograph while the participant was resting in the supine position. All ECGs were scanned and transferred into digital media and manually evaluated with x400 magnification on a personal computer. ECG measurement values were transferred to the database as the mean value of 3 consecutive beats over precordial lead V5 [12,13].

The QT interval was measured from the beginning of the QRS complex to the end of the T wave and QT interval was corrected using the Bazett's ($QTc=QT/RR^{-2}$) formula [14]. The Tp-e interval was measured by using the tangent method which is calculated as the time interval between the T wave's peak point and down slope tangent intersecting with the isoelectric line [15]. If a U wave followed the T wave, the T wave offset was measured as the nadir between the T and U waves [16]. When the T wave was negative or biphasic, the end point of the T wave was regarded as when the trace returned to the baseline. Then, Tp-e/QT and Tp-e/QTc ratios were calculated.

ECG readings were measured manually by two cardiologists blinded to the participant data. The interobserver and intraobserver coefficients of variation were 3.1% and 2.8%, respectively.

Sample size calculation

Sample size calculation was performed with G-Power 3 calculator at the power of 0.80, alpha error of 0.05 and an estimated effect size of 0.50, which yielded the optimal group size of 60 participants each.

Statistical analysis

SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics of the variables are represented as mean (standard deviation [SD]) and frequency (n (%)). Independent t test was used for the comparison of two groups. *P*-value of 0.05 was considered statistically significant for all statistical analyses.

Results

Basal demographic, biochemical, electrocardiographic, and echocardiographic characteristics of the study group (n=60) and control group (n=60) are presented in Table 1. In both groups, mean ages (38.91 [9.83] vs 39.80 [12.90], *P*=0.719) and

male gender ratios (75% vs 57%, *P*=0.078) were similar. Thirty-three patients in the study group received anti-TNFα treatments (infliximab: 11, adalimumab: 9, golimumab: 10, and etanercept: 3), while 27 patients were administered NSAIDs.

Table 1: Comparative analysis of demographic, biochemical, and electrocardiographic data of the study and control groups

Variables	Study group (n=60)	Control group (n=60)	*P*-value
Age (years)	38.91 (9.83)	39.80 (12.90)	0.719
Sex (males, %)	45 (75%)	34 (57%)	0.078
BMI (kg/m^2)	25.53 (3.87)	24.37 (2.63)	0.516
Smoking rate (n, %)	34 (57%)	32 (53%)	0.895
Glucose (mg/dL)	90.78 (15.07)	98.76 (12.11)	0.022
eGFR (mL/min)	105.07 (16.73)	99.84 (15.08)	0.179
Total protein (g/dL)	7.26 (0.43)	7.06 (0.40)	0.454
Albumin (g/dL)	4.40 (0.34)	4.90 (0.27)	0.003
Triglyceride (mg/dL)	142.20 (47-391)	137.91 (34-286)	0.828
Total cholesterol (mg/dL)	174.77 (41.06)	175.95 (38.79)	0.912
LDL cholesterol (mg/dL)	101.58 (37.47)	101.58 (36.02)	1.000
HDL cholesterol (mg/dL)	44.00 (12.07)	44.95 (11.72)	0.763
WBC (K/uL)	8.55 (2.06)	7.78 (1.71)	0.094
Platelet (K/uL)	288.55 (62.84)	273.75 (56.17)	0.295
MPV (fL)	10.20 (0.82)	9.98 (0.96)	0.286
hs-CRP (mg/dL)	0.92 (0.02-6.48)	0.24 (0.03-0.78)	0.087
ESR (mm/h)	13.76 (3-67)	-	-
RF (IU/mL)	6.28 (0-25)	-	-
LVEF (%)	63.13 (3.96)	62.75 (2.87)	0.655
BASDAI score	4.22 (0-9.75)	-	-
Electrocardiographic parameters			
Heart rate (beats/min)	77.98 (11.83)	74.86 (10.21)	0.232
QT (ms)	342.57 (23.86)	345.07 (26.03)	0.660
QTc (ms)	389.21 (20.61)	383.13 (22.88)	0.220
QRS (ms)	90.73 (10.86)	91.22 (10.80)	0.846
Tp-e (ms)	68.83 (9.24)	63.80 (7.59)	0.013
Tp-e/QT	0.201 (0.027)	0.185 (0.020)	0.006
Tp-e/QTc	0.177 (0.025)	0.166 (0.016)	0.041
Drug usage for AS			
NSAID (n, %)	27 (45%)	-	-
Infliximab (n, %)	11 (18%)	-	-
Adalimumab (n, %)	9 (15%)	-	-
Golimumab (n, %)	10 (16%)	-	-
Etanercept (n, %)	3 (5%)	-	-

BMI: body mass index, eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, HDL: high density lipoprotein, hs-CRP: high sensitive C-reactive protein, LDL: low density lipoprotein, LVEF: left ventricular ejection fraction, MPV: mean platelet volume, NSAID: nonsteroidal anti-inflammatory drug, RF: rheumatoid factor, WBC: white blood cell

In both groups eGFR, total protein, triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol, WBC, platelet, MPV, and hs-CRP values were similar (*P*=0.179, *P*=0.454, *P*=0.828, *P*=0.912, *P*=1.000, *P*=0.763, *P*=0.094, *P*=0.295, *P*=0.286, and *P*=0.087, respectively). Glucose (90.78 [15.07] vs 98.76 [12.11], *P*=0.022) and albumin values (4.40 [0.34] vs 4.90 [0.27], *P*=0.003) were lower in the study group. Mean values of erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF), which were not evaluated for the control group, were 13.76 and 6.28, respectively, in the study group. Mean BASDAI score in study group was 4.22.

Heart rate, QT, QTc, and QRS were similar in both groups (*P*=0.232, *P*=0.660, *P*=0.220, and *P*=0.846, respectively). Tp-e (68.83 [9.24] vs 63.80 [7.59], *P*=0.013), Tp-e/QT (0.201 [0.027] vs 0.185 [0.020], *P*=0.006) and Tp-e/QTc (0.177 [0.025] vs 0.166 [0.016], *P*=0.041) values were higher in the study group.

When the patients in the study group were divided into two subgroups based on whether anti-TNFα treatment was received, no statistically significant difference was found between the anti-TNFα treatment group (n=33) and the non-anti-TNFα group (n=27) in terms of heart rate, QT, QTc, QRS, Tp-e, Tp-e/QT and Tp-e/QTc parameters (*P*=0.916, *P*=0.655, *P*=0.335, *P*=0.999, *P*=0.731, *P*=0.848, and *P*=0.901, respectively) (Table 2).

Table 2: Comparative analysis of electrocardiographic data from patients with AS treated with anti-TNF-α and non-anti-TNF-α agents

Variables	Treated with anti-TNF-α (n=33)	Treated with non-anti-TNF-α (n=27)	*P*-value
Heart rate (beats/min)	78.13 (11.29)	77.78 (12.74)	0.916
QT (ms)	343.90 (24.51)	340.89 (23.45)	0.655
QTc (ms)	391.68 (18.75)	386.08 (22.77)	0.335
QRS (ms)	90.73 (8.87)	90.73 (13.17)	0.999
Tp-e (ms)	69.23 (7.42)	68.33 (11.28)	0.731
Tp-e/QT	0.202 (0.024)	0.200 (0.031)	0.848
Tp-e/QTc	0.177 (0.019)	0.177 (0.032)	0.901

Discussion

In this study, comparison of AS patients and the control group showed similar heart rate, QRS, QT and QTc values in both groups, whereas, Tp-e, Tp-e/QT and Tp-e/QTc parameters were higher in the study group. In addition, there was no difference in any of the mentioned parameters between the anti-TNFα treatment group and the non-anti-TNFα group among the study group.

Cardiac conduction system disorders and arrhythmias are more common in AS patients compared to the normal population. Atherosclerotic process triggered by the increased amount of inflammatory cells, chemokines, and cytokines, cardiomyocyte damage, and myocardial fibrosis are being suggested as the cause [17,18]. Increased TNFα levels in these patients lead to arrhythmias by causing hypertrophy, apoptosis, fibrosis and consequent dilation in the left ventricle [19]. Conduction system disorders, ranging from bradycardia [5,20] to first [20] and third-degree atrioventricular block [21] are especially caused by interventricular septal fibrosis and atrioventricular nodal anomalies. Also, in patients with AS, supraventricular [22] and ventricular arrhythmias (ventricular extrasystole, couplet, and salvo beats) [23,24] were observed more frequently than in the control group. And recent studies have been focusing on parameters that indicate ventricular repolarization such as QT, QTc, QTd, Tp-e and Tp-e/QT in AS patients. In a study conducted by Yildirir et al. [7] with 88 AS patients, QTd and corrected QTd values were found to be higher in the study group than the control group. And the elevation of these parameters was determined to be associated with the duration of the disease. Longo et al. [5] evaluated 100 patients with spondyloarthropathy, majority of them having AS, and found longer QT interval values in the patient group than the control group and found similar QTc values in both groups. Contradictory to these studies, Kazmierczak et al. [24] found similar QT, QTc and QTd values with the control group in their study where 31 AS patients were evaluated with ECG and 24-hour holter monitoring. In addition to QTd, Acar et al. [6] examined ECG parameters like Tp-e and Tp-e/QT that indicate transmural dispersion of ventricular repolarization [25,26] in AS patients, and found that QTd, corrected QTd, Tp-e and Tp-e/QT parameters were higher in the AS patients in comparison to the control group. In our study, we found similar QT and QTc values in both groups, and higher Tp-e, Tp-e/QT and Tp-e/QTc values in the study group compared against the control group.

Pathophysiology of spondyloarthropathies is still not fully explained. However, inflammatory component of the process is relatively understood with the identification of key immune cell groups and key cytokines like TNFα and interleukin-17 (IL-17). Treatment strategies that target these cytokines are being utilized in a highly effective manner for

disease control. While nonsteroidal anti-inflammatory drug treatment (NSAIDs) can clinically significantly and continuously decrease disease activity [27], by combining anti-TNFα agents with NSAID treatment, additional benefits have been observed in many patients in terms of disease remission [28]. In a recent study, anti-TNFα drugs have been shown to improve cardiovascular functions by decreasing subclinical myocardial inflammation evaluated with cardiac magnetic resonance imaging (CMR) in patients with rheumatoid arthritis, AS and psoriatic arthritis [29]. In addition, the effect of these drugs on ventricular repolarization parameters was also examined in these patients and highly inconsistent results were obtained. In a study by Di Franco et al. [30], anti-TNFa drugs like infliximib and etanercept were shown to increase QT and QTd in comparison to basal value at the end of year 1 in patients with RA and spondyloarthropathy. In another study conducted on spondyloarthropathy patients, no difference was found between QT and QTc values between the groups using and not using anti-TNFa [5]. In a study by Senel et al. [9], intravenous infliximab treatment was administered to 21 AS patients in active period and decrease was observed in QTc compared to basal values at the end of month 6, while there was no difference in terms of QTd values. In our study, previously not studied effects of anti-TNFa drugs on Tp-e, Tp-e/QT and Tp-e/QTc parameters were examined in addition to their effects on QT and QTc intervals and as a result, neutral effects were observed on all of these parameters.

Limitation

The results of the study should be considered and interpreted with several limitations in mind. Firstly, this was a single-center study that had small sample size for the study and control groups. Secondly, the data on the duration of anti-TNFa treatment of the patients was absent. Therefore, regression analysis between the duration of anti-TNFa treatment and electrocardiographic parameters showing ventricular repolarization could not be performed. Due to the small size of the study group, regression analysis was not performed between each anti-TNFa regimen and electrocardiogaphic parameters. Thirdly, measurements were performed manually as the computer software of the ECG device is not available in our facility.

Conclusion

To our knowledge, this study is the first that investigates the effect of anti-TNFα drugs on parameters such as Tp-e, Tp-e/QT and Tp-e/QT that indicate ventricular repolarization in AS patients. Our study revealed higher Tp-e, Tp-e/QT and Tp-e/QT values in the study group than the control group and that anti-TNFα drugs had neutral effect on these parameters. In light of these deductions, evaluation of patients with AS in terms of arrhythmic risk and detection of high-risk patients may help to prevent arrhythmic events. Further, wider-scale studies are needed to validate our results.

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Review of fetal choroid plexus cysts: A cross-sectional study on 9244 pregnant women

Koroid pleksus kistlerinin değerlendirilmesi: 9244 gebe kadın üzerine kesitsel bir çalışma

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Abstract

Aim: It was revealed in many studies conducted on unselected populations that the size, bilaterality and number of choroid plexus cysts (CPCs) are correlated with various degrees of aneuploidy risk. This article deals with the natural history and significance of numbers, sizes and bilaterality of CPCs in a selected population.

Methods: This cross-sectional study was conducted on 9244 pregnant women attending to our department between March 2014 and March 2018. After exclusion criteria was applied, 87 patients with isolated CPCs remained. All records of the patients were screened and needed data were recorded.

Results: A total of 9244 prenatal sonographies had been performed during this period. Isolated CPC was detected in 87 fetuses. CPCs were visualized unilaterally in 83 cases (95.4%) and bilaterally in 4 cases (4.6%). Among 83 unilateral cases, 45 had left sided (51.7%) and 38 had right sided CPCs (43.7%). The size of the cysts ranged between 3 mm to 5.1 mm with an average of 3.51 (0.06) mm. Double tests (n=24) and quadruple tests (n=63) had 2 and 5 abnormal results, respectively. All had normal karyotypes. Four samples were dropped out due to premature rupture of membranes (n=2) and intrauterine fetal death (n=2). It was found that the outcomes of all remaining fetuses (n=83) were normal and no anomalies were seen until birth.

Conclusion: Multiple CPCs in a single choroid plexus or bilaterality were not associated with abnormal fetal karyotype and therefore we think that isolated CPCs has a good prognosis.

Keywords: Choroid plexus cyst, Ultrasonography, Fetus

Öz

Amaç: Rastgele popülasyonlar üzerinde yapılmış bir çok çalışmada koroid pleksus kistlerinin (KPK) boyut, bilateralite ve sayısının çeşitli derecelerde anöploidi riski ile ilişkili olduğu ortaya konulmuştur. Bu makale seçilmiş bir popülasyonda, KPK'ların sayı, boyut ve bilateralitesinin doğal seyri ve önemini ele almaktadır.

Yöntemler: Bu kesitsel çalışma Mart 2014 ve Mart 2018 arasında departmanımıza başvuran 9244 gebe kadın üzerinde yürütüldü. Dışlama kriterleri uyguladıktan sonra geriye izole KPK'li 87 hasta kaldı. Hastaların tüm kayıtları tarandı ve ihtiyaç duyulan veriler alındı.

Bulgular: Bu dönemde 9244 prenatal sonografi uygulanmıştı. 87 fetüste izole KPK tespit edildi. KPK'lar 83 (%95,4) vakada tek taraflı ve diğer 4 (%4,6) vakada çift taraflı olarak izlendi. Tek taraflı olan 83 vakanın 45'inin (%51,7) sol taraflı ve 38'inin (%43,7) sağ taraflı KPK'sı vardı. Kistlerin boyutu, 3,51 (0,06) mm lik bir ortalamayla, 3mm den 5,1mm ye uzanıyordu. İkili test (n=24) ve dörtlü testlerin (n=63) sırasıyla 2 ve 5 anormal sonucu vardı. Hepsi normal karyotipe sahipti. Dört vaka membranların prematür rüptürü (n=2) ve intrauterin fetal ölüm (n=2) nedeni ile çalışmadan çıkarıldı. Kalan tüm fetüslerin (n=83) akıbetinin normal olduğu bulundu ve doğuma kadar hiçbir anomali izlenmedi.

Sonuç: Tek bir koroid pleksusta çoğul KPK ve bilateralite anormal fetal karyotiple ilişkili değildi, bu yüzden izole KPK' lerinin iyi bir prognoza sahip olduğunu düşünüyoruz.

Anahtar kelimeler: Koroid pleksus kisti, Ultrasonografi, Fetüs

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Introduction

Fetal choroid plexus cysts (CPC) are often detected during the second trimester ultrasound screening as fluid-filled structures within the lateral ventricles of the fetal brain and requires a need to formulate a protocol for management and counseling [1-3]. These cysts may be single/multiple, unilateral/bilateral [4]. They are detected in 1-3,6% of all fetuses, and 90% are resolved by 26-28th week of gestation [5]. Although it is mostly a benign condition occurring after accumulation of CSF within rapid growing ventricles, it may be as a result of a chromosomal abnormality, mainly, Trisomy 18 (T18) [3,4].

The relationship between CPC and Trisomy 18 was first discussed in 1984 by Chudleigh et al. [1], and CPC was observed in 30-50% of Trisomy 18 cases [5,6]. The probability of aneuploidy rises if other structural anomalies are detected in ultrasonographic examination, or if maternal serum screening indicates higher risk of abnormality [7,8]. Most of the studies have assessed the correlation of T18 and CPC in these situations. These published trials have failed to address the potential bias in the patient population being studied. In many ultrasound referral centers, advanced maternal age, abnormal alpha-fetoprotein (AFP), and previous anomaly comprise the majority of patients undergoing second-trimester sonography. In such a high-risk population, it would not be surprising to see an occasional Trisomy 18 or 21 fetus that coincidentally has a choroid plexus cyst. Concordantly, few have discussed isolated CPCs (with no other abnormal sonographic findings). Therefore, this relatively common finding seems to cause some degree of anxiety and worry among parents getting confused and uncertain regarding the health condition of their fetuses. Thus, this study was designed to evaluate the outcome of isolated CPCs detected in screening sonography and to specify its clinical significance.

Materials and methods

This descriptive study was conducted on 9244 pregnant women undergoing prenatal screening in our department at Special Koru Hospital, between March 2014 and March 2018. All sonography reports had been documented by a computerized database, along with medical records of laboratory and genetic tests.

The ultrasound reports of all 9244 pregnancies were evaluated to find out fetuses with CPC. We carefully noted whether there was any document of major anomalies in the cerebellum, lateral cerebral ventricles, spine, facial profile, four-chamber view of the heart, extremities, abdomen, umbilical cord, kidneys, bladder and/or any sonographic soft markers. If there was any abnormality, the patient was excluded from the study. Then, results of double test, quadruple test, fetal echocardiography, and amniocentesis (which were performed as ordered by a perinatologist) were reviewed. Demographic parameters (to detect possible risk factors), ultrasound examinations and results of para-clinical tests were obtained from the database. Then we checked delivery records and first postnatal visit records of babies for any anomalies. Consequently, we had 87 patients that had isolated CPCs.

This study was approved by a research ethics committee and institutional review board at Special Koru Hospital ethics committee (9/29/2018-10).

Statistical analysis

All information obtained was entered into statistical package for the social sciences, version 15.0, SPSS Inc, Chicago, Illinois, USA (SPSS). Descriptive statistics were used to calculate the frequency (n), percentage (%), central tendency (mean, median & mode) and dispersion (range, variance, SD, maximum & minimum) for each variable when appropriate.

Results

In a period between March 2012 and March 2018, we found that prenatal screening sonography had been performed on 9244 pregnant women in our department. Totally, 87 fetuses with isolated CPCs were found during this period.

The mean age of the mothers was 28.21 (0.6) years. There were 87 fetuses with CPCs. CPCs were visualized unilaterally in 83 cases (95.4%) and bilaterally in other 4 cases (4.6%). Among 83 unilateral cases, 45 had left sided (51.7%) and 38 had right sided CPCs (43.7%). Among the left sided group, 6 patients (7%) had multiple (two) CPCs whereas in right sided group there were 8 (9%) patients having multiple (two) CPCs. As a result, there were a total of 98 CPCs in 87 patients (Table 1). The size of the cysts ranged between 3 mm to 5,1 mm with a mean of 3.51 (0.06) mm. Mean gestational weeks at detection and resolution of the cysts were 16.20 (0.05) and 30.71 (0.39), respectively (Table 2). Locations of the cysts within the ventricle were anterior (15 cysts-15.3%), posterior (13 cysts-13.3%) and middle (48 cysts-48.9%) portions for single cysts. For multiple cysts, locations were anterior-posterior (8 cysts-8.2%), anterior-middle (10 cysts-10.2%) and posterior-middle (4 cysts-4.1%) (Table 3). Of the 87 patients, 9 cases (10%) were above 36 years old. Age distribution of the cases is presented in Table 4.

Table 1: Laterality of cysts

	Patient n (%)	Cyst n (%)
Left sided	45 (51.7)	48 (48.9)
Right sided	38 (43.7)	42 (43)
Bilateral	4 (4.6)	8 (8.1)
Total	87 (100)	98 (100)

Table 2: Maternal age, gestational age when detected and resolved, and cyst diameter

Maternal age (y) mean (SD)	Gestational age when detected (w) mean (SD)	Gestational age when resolved(w) mean (SD)	Cyst diameter (mm) mean (SD)
28.21 (0.6)	16.20 (0.5)	30.71 (0.39)	3.51 (0.06)

y: year, w: week; mm: millimeter

Table 3: Locations of the cysts within the ventricle and maternal age

Location	Number of cases n (%)	Maternal age (y) Mean (SD)
Anterior	15 (15.3)	29.4 (2.14)
Posterior	13 (13.3)	28.30 (1.53)
Middle	48 (48.9)	27.43 (0.72)
Anterior + posterior	8 (8.2)	30.25 (1.93)
Anterior + middle	10 (10.2)	29.4 (1.6)
Posterior + middle	4 (4.1)	30.5 (1.5)

y: year

Table 4: Maternal ages in pregnancies complicated by choroid plexus cysts

Maternal age (y)	Number of cases n (%)
15-19	9 (10.3)
20-24	13 (15.1)
25-29	30 (34.4)
30-35	26 (29.9)
≥36	9 (10.3)
Total	87 (100)

y: Year

Twenty-four women had been assessed by double test, of which 22 were normal. In addition, quadruple tests were performed for 63 fetuses, which demonstrated normal results in 58 cases. Among fetuses with abnormal quadruple test results,

the risk factors of Down syndrome were 1/33, 1/58, 1/76, 1/82, 1/88, 1/88, 1/90 and 1/92. However, amniocentesis did not reveal any abnormality (Figure 1). Fetal echocardiography was performed for 58 cases (66.6%), which were all normal.

During the study, four patients were excluded due to premature rupture of membranes (PROM) (n=2) and intrauterine fetal death (IUFD) (n=2). CPCs gradually disappeared by 30th week in all other 83 fetuses and no anomaly was seen in follow-up sonographic examinations (Figure 2).

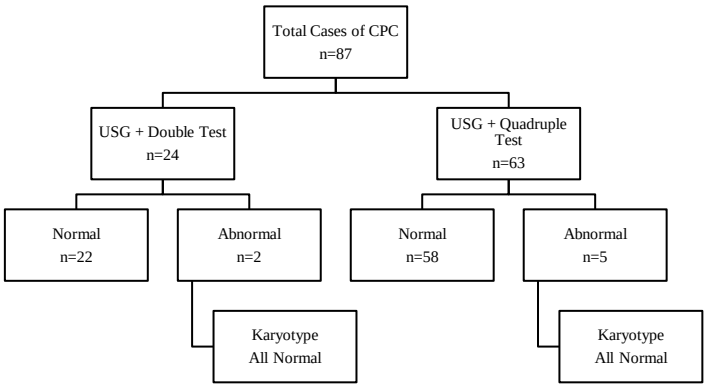

Figure 1: Mother Serum Screening correlated with ultrasound evaluation of isolated choroid plexus cyst cases

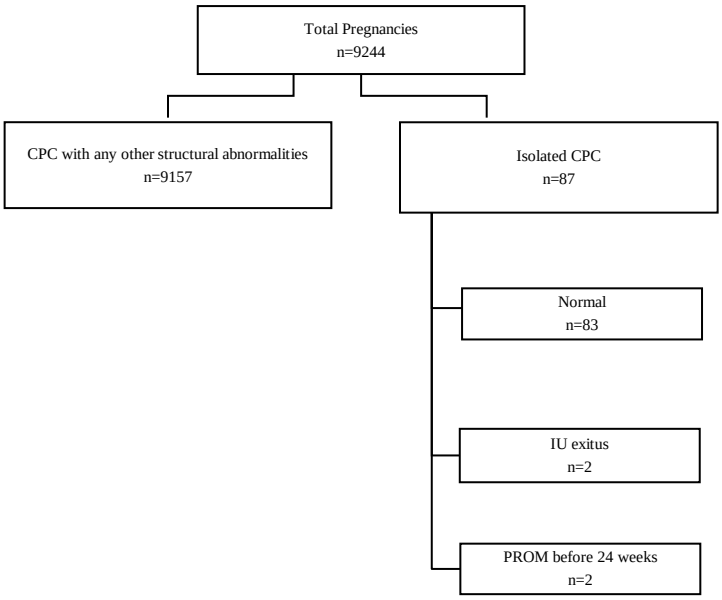

Figure 2: Outcome of isolated fetal choroid plexus cyst cases

Discussion

The mean prevalence of isolated choroid plexus cysts in our population was 2%, which is similar to those reported by Gabrielli et al. [3] and Chan et al. [9] (2.5%, and 2.3%, respectively). Similarly, the prevalence of isolated CPC in the study of Perpignano et al. [10] is 2.5%, while it is 0.18% in the study conducted by Clarke et al. [11] and 0.33% in the study of Camurri et al. [2]. However, the last two studies were conducted on unselected populations. The initial time of sonographic detection of CPC in our study was the 16th week of gestation according to last menstrual period (LMP), whereas it was first diagnosed in 15th week by Bronsteen and colleagues. Mean gestational age of diagnosis in this study was 16th week in comparison with the 19th week in the study of Bronsteen et al. [12]. All CPCs were resolved by the 30th week in our patients while Dipietro and colleagues reported that CPCs regressed by the 28th week in their study [13].

Landy et al. [4] stated that no parameters studied, including maternal demographics (age, race, median gravidity, and median parity), gestational weeks at the time of first and last sonograms, and choroid plexus cyst characteristics (location, number, dimensions, and resolution) are important on predicting aneuploidy. In their 116-patient study there were no aneuploidies. In our trial we also did not encounter any aneuploidy, which is why we could not evaluate the correlation between aneuploidy and choroid plexus cyst characteristics (location, number, dimensions, and resolution).

Bronsteen and colleagues [12] assessed 49435 fetuses aged 16-25 weeks and discovered 1209 CPC cases in 11 years, of which, 1060 CPCs were isolated and without anomalies, similar to our findings. Cheng et al. [14] conducted a follow-up evaluation of CPC, nuchal translucency (NT) and other sonographic markers of aneuploidy (particularly T18) in 7795 pregnancies until birth. CPC was present in 98 fetuses, among which 82 cases were isolated CPCs and 16 cases were NT or other soft markers. All isolated CPCs had good prognosis and no abnormality was seen among them. Their study demonstrated that isolated CPC shows good outcomes, which confirms our current findings.

Lopez et al. [15] believe that "when CPC is detected by sonography, amniocentesis or chorionic villus sampling (CVS) will be required if mother serum screening is abnormal". In this study, there were only 2 abnormal double test results and 5 abnormal quadruple test results, all with normal karyotypes. In a study conducted by Sullivan et al. [16] on 128 fetuses with CPC, mother serum screening (triple test and/or αFP level) was compared to amniocentesis results and physical examination after birth. Their findings demonstrated that among 112 fetuses with isolated CPCs, mother serum screening was positive in 22 cases (19.6%), of which just two fetuses had T18. Although one fetus with T18 was detected among other 90 cases with normal serum screening results, this patient had been evaluated by means of single αFP screening (not triple test). They concluded that triple test adjunct to ultrasound screening is a reliable method to find out high risk fetuses with isolated CPC, whereas amniocentesis needs to be done only in cases with abnormal serum screening.

Contrary to our results Nicolaides et al. [17] stated that Chromosomal abnormalities, specifically trisomy 18, should be ruled out if the CPCs are larger than 1 cm, bilateral, or irregular in shape. In cases of a single CPC, abnormal karyotypes were detected in 3.59%, and in cases of multiple CPCs in both choroid plexuses, they were detected in 3.93%. The risk of trisomy was 2.05% (trisomy 18 in 1.54% and trisomy 21 in 0.26%). Each trisomy 18 occurred in cases where CPCs measured more than 7 mm, and most cases of trisomy 18 (83.3%) were detected when a CPC was larger than 1 cm.

Limitations

This study is limited by its retrospective nature and referred patient population. The referred patient base, which may not be truly representative of the population in general, also may reflect incomplete data. Prospective randomized trials with a larger sample size are needed to solve the controversies over the patients with isolated CPCs.

Conclusion

As a result, with respect to the mentioned findings, it can be concluded that isolated CPC is a benign condition resolving spontaneously, with no clinical significance, especially when mother serum screening is in normal range. Multiple CPCs filling a single choroid plexus and bilaterality were not associated with abnormal fetal karyotype and therefore carry favorable prognosis. These data may be helpful when counseling patients with this unusual appearance of CPCs. Regarding counselling the parents, one should choose the optimistic sentences not to cause unnecessary anxiety.

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Acute effect of cigarette smoking on frontal planar QRS-T angle in apparently healthy subjects with habitual smoking

Sigara içen sağlıklı bireylerde anlık sigara içiminin frontal planar QRS-T açısı üzerine etkileri

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Abstract

Aim: It has been well recognized that smoking exerts various detrimental cardiovascular effects. Although the effect of chronic smoking on cardiac electrophysiology is well known, little is known about the effect of acute smoking on surface ECG. Previous reports suggested that frontal planar QRS-T angle (fpQRS-Ta), measured by surface ECG, may be associated with ventricular arrhythmias and cardiac death. Hence, we primarily aimed to assess the effect of acute smoking on fpQRS-Ta.

Methods: A total of 92 apparently healthy subjects [44 female, 48 male, mean age 38.7(8.02) years] with smoking habit were enrolled in this prospective cohort study between May-July 2019. Demographic and clinical characteristics were recorded, and fpQRS-Ta together with some ECG parameters were noted before and 10 minutes after smoking for comparison. Spearman's analysis was implemented to seek the probable correlation of the difference between pre- and post-smoking ECG parameters.

Results: Ten minutes after smoking, median heart rate, QRS duration and fpQRS-Ta increased significantly (72.6 beats/min vs 81.5 beats/min, $P<0.001$; 84 ms vs 86 ms, $P=0.012$; 14.5° vs 25°, $P<0.001$; respectively), while PR and QTc duration did not significantly change (150.0 ms vs 150.0 ms, $P=0.774$; and, 423.5 ms vs 429.5 ms, $P=0.372$). In Spearman's correlation analysis, the difference between pre- and post-smoking fpQRS-Ta significantly and negatively correlated with C-reactive protein (CRP) levels (r: -0.272, $P=0.027$).

Conclusion: Acute smoking may widen fpQRS-Ta in healthy habitual smokers, and serum CRP negatively correlates with the degree of fpQRS-Ta widening. Our observation may further enlighten the pathophysiological mechanism of smoking in cardiac arrhythmias and sudden death.

Keywords: Cigarette smoking, Frontal planar QRS-T angle, Electrocardiography, Nicotine

Öz

Amaç: Sigara içiminin çeşitli kardiyovasküler etkilere sahip olduğu iyi bilinmektedir. Kronik sigara içiminin kardiyak elektrofizyoloji üzerine etkileri daha net tanımlanmış olduğu halde, akut sigara içiminin yüzey EKG'si üzerindeki etkileri hakkında çok az bilgi mevcuttur. Daha önceki çalışmalarda yüzeysel EKG ile hesaplanan frontal planar QRS-T açısının (fpQRS-Ta) ventriküler aritmiler ve kardiyak ölüm ile ilişkili olabileceği ifade edilmiştir. Bu nedenle bu çalışmada temel olarak akut sigara içiminin fpQRS-Ta üzerindeki etkilerini incelemeyi amaçladık.

Yöntemler: Bu çalışma prospektif kohort çalışmasıdır. Mayıs ve Temmuz 2019 tarihleri arasında sigara içme alışkanlığı olan sağlıklı 92 birey [44 kadın, 48 erkek, ortalama yaş 38(8.02) yıl] çalışmaya prospektif olarak dâhil edilmiştir. Demografik ve klinik özelliklerin kaydedildi; yanı sıra sigara içiminden önceki ve akut sigara içiminden 10 dakika sonraki bazı EKG parametreleri ile birlikte fpQRS-Ta not edilerek karşılaştırma yapıldı. Sigara içimi öncesi ve sonrası EKG parametrelerinin arasındaki olası ilişkilerin incelenmesi amacıyla Spearman korelasyon analizi yapıldı

Bulgular: Medyan kalp atım hızı, QRS süresi ve fpQRS-Ta sigara içiminden 10 dakika sonra anlamlı şekilde arttı (sırasıyla 72,6 atım/dak vs 81,5 atım/dak, $P<0,001$; 84 ms vs 86 ms, $P=0,012$; 14,5° vs 25°, $P<0,001$). PR ve QTc sürelerinde sigara içimi sonrasında anlamlı değişim izlenmedi (sırasıyla 150,0 ms vs 150,0 ms, $P=0,774$; 423,5 ms vs 429,5 ms, $P=0,372$). Spearman korelasyon analizinde ise sigara içimi öncesi ve sonrası fpQRS-Ta değişiminin C-reaktif protein (CRP) ile anlamlı ve negatif bir korelasyona sahip olduğu belirlendi (r: -0,272, $P=0,027$).

Sonuç: Sigara alışkanlığı olan bireylerde akut sigara içimi fpQRS-Ta'de genişlemeye neden olabilir ve bu genişlemenin derecesi CRP ile negatif korelasyon göstermektedir. Çalışmamızda elde ettiğimiz sonuçlar, sigara içiminin kardiyak aritmi gelişimi ve ani ölüm üzerindeki patofizyolojik etki mekanizmasının açıklanmasına ışık tutabilir.

Anahtar kelimeler: Sigara içiciliği, Frontal planar QRS-T açısı, Elektrokardiyografi, Nikotin

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Introduction

It has long been recognized that chronic cigarette smoking associates with various cardiovascular disorders, such as coronary artery disease, acute coronary syndrome, stroke, arrhythmias and sudden death [1-4]. Apart from its chronic detrimental effects, acute exposure to cigarette smoke also appears to cause hemodynamic and cardiac electrophysiologic modifications through complex mechanisms [5,6].

Nicotine was reported to delay ventricular repolarization, thereby increasing susceptibility to cardiac arrhythmias by catecholamine release, boost sympathetic nervous system activation and delay membrane repolarization via directly blocking inward K+ channels in ventricular myocardial cells [4,7]. Carbon monoxide, another important constituent of cigarette smoke, is likely to induce cardiac arrhythmias by hindering oxygen transportation to cardiac tissues. Research on animal models as well as human studies reported an increased likelihood of complex ventricular arrhythmias in the setting of coronary ischemia [8,9]. Among other known acute hemodynamic effects of smoking are an increase in blood pressure, heart rate, vascular resistance and hence cardiac workload, possibly due to acute escalation in sympathetic tone and transient hypoxia [10].

Frontal planar QRS-T (fpQRS-T) angle is a surface electrocardiographic (ECG) parameter indicating the angle between QRS and T-wave axes [11]. Moreover, it provides an electrophysiological insight regarding the crude orientation of ventricular depolarization and repolarization vectors. Recently, fpQRS-T angle has appealed much to the researchers and become a topic of interest due to accumulating evidence that suggests fpQRS-T might be of utility in prognostic as well as diagnostic scopes [12-16]. Previous studies suggested that increased fpQRS-T angle would translate into increased cardiovascular and all-cause deaths in diabetes mellitus, acute myocardial infarction, ischemic heart diseases and heart, and even in general population [14-18].

Predicated on these premises, we hypothesize that acute exposure to cigarette smoke would widen fpQRS-T angle in otherwise healthy subjects with a smoking habit.

Materials and methods

A total of 92 apparently healthy subjects [hospital staff, 44 females, 48 males, mean age 38.7(8.02) years] with smoking habit were enrolled in this prospective cohort study between May 2019 and July 2019. The participants had no previous history of any major clinical problems. Smoking habit was defined as at least 3 cigarette smoking per day for at least 1 year. All participants were subjected to a comprehensive physical examination, and echocardiographic and ECG evaluation to inquire probable cardiac disorders. The exclusion criteria were set as following: History of cardiovascular disease, diabetes mellitus, hypertension, endocrine disorder, cerebrovascular disease, chronic renal failure and chronic inflammatory disease, acute infections, and being on chronic medication. The body-mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Obesity was defined as BMI >30 kg/m2.

Written informed consent was obtained from every participant and the institutional ethics committee approved the protocol of the study (Kirsehir Ahi Evran University Ethics Committee, No: 2019-08/95, Date: 04/30/2019). This study complies with the standards of the Declaration of Helsinki.

Smoking, laboratory analysis and electrocardiographic evaluation

All participants were asked to refrain from cigarette smoking, alcohol, caffeinated beverages, and food intake at least 8 hours prior to study. On the day of the study, a standard 12-lead ECG (MAC 2000, GE Medical Systems, Milwaukee, WI, USA) with 50 mm/sec paper speed and 10 mm/mV amplitude was recorded as baseline strip while the patient was resting in supine position and quietly respirating for at least 10 minutes between 7:30-09:00 AM in the morning. Afterward, they were asked to smoke a single cigarette as in their daily routine. Ten minutes later, another ECG strip was recorded again with the patient in supine position to compare with the prior ECG strip.

R-R, QT, PR and QRS intervals were measured manually from Lead 2 [19]. Then, QT interval was corrected (QTc) for heart rate using Bazett's formula [20]. The definitions were as follows: R-R interval: The time between two consecutive R waves. PR interval: The time from the beginning of P wave to the beginning of QRS complex. QT interval: The time from the beginning of Q or R wave to the end of T wave where it intersects with the isoelectric line. The mean of the three consecutive beats was calculated to end up with the ultimate values. These intervals were measured by an experienced cardiologist blinded to the study data to prevent interobserver variability.

As for the QRS and T-wave axes, they were obtained from the intrinsic reports provided by the ECG device [13,14,21]. To compute the fpQRS-T angle, the absolute difference between the QRS and T-wave axes were measured to obtain values between 0 and 180°. The value was subtracted from 360° if it exceeded 180°.

Venous blood samples were drawn through venipuncture between 7:30-9:00 am before the baseline ECG recording. Routine serum biochemical parameters were measured using standard laboratory methods via Roch Cobas 8000 Autoanalyser, and hematological parameters were defined by using Sysmex XN-1000 automated blood cell counter (Sysmex Corporation, Kobe, Japan).

Statistical analysis

The statistical analysis was implemented using SPSS (Version 21.0 for Windows, SPSS Inc, Chicago, USA). Quantitative data were assessed for normality with the Kolmogorov- Smirnov test. Categorical variables of the subjects were presented in numbers and percentages, whereas continuous variables were expressed as mean (SD) and median (25-75 interquartile range). Since ECG parameters intended to be compared showed non-normal distribution, comparison of these parameters before and after smoking were performed using Wilcoxon signed-rank test. Spearman's correlation analysis was done to determine the linear correlation between the changes in fpQRS-T angles and demographic and laboratory parameters of the patients. *P*-value was regarded as statistically significant when <0.05.

Results

Our study population's demographic and clinical characteristics were presented in Table 1. Among 92 subjects enrolled, 44 (47.8%) were female and 48 (52.2%) were male. Mean BMI was 26.69 (4.16) kg/m^2. There was no clinically crucial disorder detected during history taking and physical examination. Moreover, echocardiography and ECG revealed no important cardiac problems. Normal sinus rhythm was evident in ECG strips of all subjects.

Table 2 represents the ECG parameters before and after 10 minutes of cigarette smoking in a comparative manner. No statistically significant difference was observed before and after smoking in respective median QTc (423.5 ms vs 429.5 ms, *P*=0.372) and PR durations (150.0 ms vs 150.0 ms, *P*=0.774). However, median heart rate and QRS duration were significantly increased 10 minutes after smoking compared with baseline (72.6 beats/min vs 81.5 beats/min, *P*<0.001: and 84 ms vs 86 ms, *P*=0.012). Moreover, the median fpQRS-T angle which was 14.5 (IQR:8-21) degree at baseline widened significantly to 25 (IQR:18-39) degree 10 minutes after smoking (*P*<0.001).

Spearman's correlation analysis depicted a significant and positive correlation between fpQRS-T angles before and after smoking (r=0.576, *P*<0.001) (Figure 1). Furthermore, upon interrogating probable correlations of fpQRS-T angle differences before and after smoking with the other ECG parameters and the subjects' baseline demographics, only C-reactive protein (CRP) level was revealed to correlate significantly but negatively with the difference between pre- and post-smoking fpQRS-T angles (r:-0.272, *P*=0.027) (Figure 2, Table 3).

Table 1: Demographic and clinical characteristics of the study participants (n=92).

Variable	Value
Age, years	38.7(8.0)
Gender, female, n (%)	44 (47.8%)
Body-mass index, kg/m^2	26.69(4.16)
LVEF, %	62.1(3.12)
Total cholesterol, mg/dL	170.1(32.4)
LDL cholesterol, mg/dL	97.1(29.3)
Triglyceride, mg/dL	141.2(107.7)
HDL cholesterol, mg/dL	44.0(10.3)
CRP, mg/dL	0.27(0.44)
WBC, 10^3/uL	8.46(2.68)
Hb, g/dL	14.02(3.0)
MCV, fL	86.5(5.3)
RDW, %	13.0(1.15)
Platelets, 10^3/uL	258.5(53.7)
Neutrophil, 10^3/uL	4.95(2.57)

LVEF: left ventricular ejection fraction, LDL: low-density lipoprotein, HDL: high-density lipoprotein, CRP: C-reactive protein, WBC: white blood cell count, Hb: hemoglobin, MCV: mean corpuscle volume, RDW: red cell distribution width. Values were given in mean(SD)

Table 2: Electrocardiographic parameters of the study subjects before and 10-min after acute smoking

Variable	Before smoking	After smoking	*P*-value
Heart rate, beats/min	72.6 (69-79)	81.5 (78-86)	<0.001
fpQRS-T angle, degree	14.5 (8-21)	25 (18-39)	<0.001
PR interval, ms	150 (131.5-160)	150 (135.5-160.5)	0.774
QRS duration, ms	84 (78-94)	86 (80-94)	0.012
QTc interval, ms	423.5 (404-438)	429.5 (407-443)	0.372

fpQRS-T: frontal planar QRS-T. Values were given as median (25-75 interquartile range)

Table 3: Correlation of the deference between pre- and post-smoking frontal planar QRS-T angle with demographic and clinical characteristics.

Variable	r	*P*-value
Age	0.056	0.599
Body-mass index	0.048	0.699
Total Cholesterol	0.165	0.178
Triglyceride	-0.054	0.664
HDL cholesterol	-0.125	0.318
LDL cholesterol	0.205	0.099
CRP	-0.272	0.027*
WBC	-0.011	0.917
Hb	0.062	0.563
Platelets	0.159	0.134
RDW	-0.149	0.160

***** Correlation is significant at the 0.05 level, HDL: high density lipoprotein, LDL: low density lipoprotein, CRP: C-reactive protein, WBC: white blood cell count, RDW: red cell distribution width, r: Rho

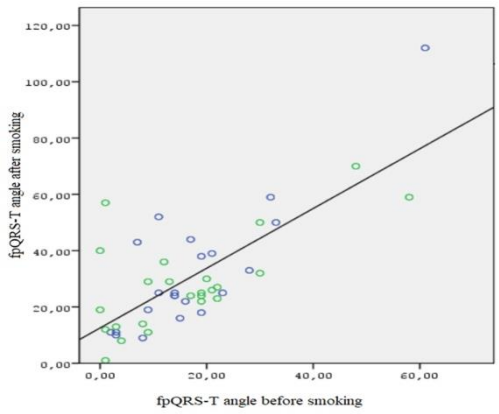

Figure 1: Correlation between pre- and post-smoking fpQRS-T angles (r=0.576, *P*<0.001; correlation is significant at 0.01 level)

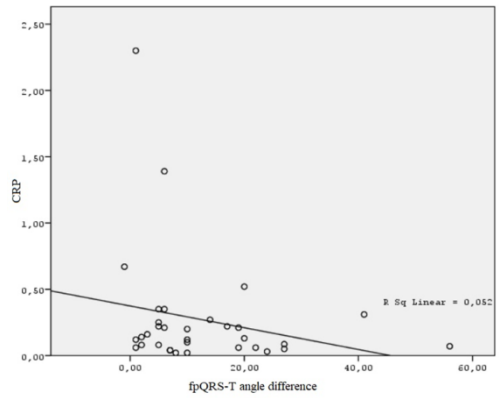

Figure 2: Correlation of the difference between pre- and post-smoking fpQRS-T angle and C-reactive protein (r= -0.272, *P*=0.027, correlation is significant at 0.05 level).

Discussion

Chronic smoking has been a robust risk factor for chronic and acute cardiovascular events. Moreover, habitual smoking brings about a chronic inclination to decreased vagal tone, blunted baroreflexes, and increased sympathetic autonomic tone. This unopposed escalation in sympathetic autonomic tone is implicated to a certain extent in all cardiovascular and hemodynamic complications of smoking in addition to its detrimental effects on vascular endothelium and its induction of systemic inflammation [22].

Other than its chronic effects, acute exposure to cigarette smoking causes a rapid catecholamine discharge from nerve endings and also stimulation of sympathetic nervous system through neural nicotinic acetylcholine receptors, which in turn is responsible for the acute increase in heart rate and blood pressure especially within 10 minutes of smoke exposure [23].

In their study, Akbarzadeh et al. [5] showed a significant increase in the heart rates of healthy non-smoker subjects as well as otherwise healthy professional-smokers 10 minutes after smoking compared with the baseline ECG. Karakaya et al. [6] reported a significant decrease in mean RR interval within 10 minutes after cigarette smoking compared with the same interval at baseline in a cohort of non-smokers. However, this statistically significant decrease vanished after 10 minutes in their study. In another study conducted on chronic heavy smokers by Karakaya et al. [24], heart rate significantly increased 15 minutes after smoking compared to baseline. In agreement with the previous studies, we also documented a heart rate increase 10 minutes after smoking in a cohort of otherwise healthy habitual smokers.

Although there are relatively more studies reporting significant increase in various parameters of ventricular repolarization such as QT interval, QTc interval, Tp-e interval, Tp-e/QT and Tp-e/QTc ratios, QT-dispersion (QTd) and corrected QT-dispersion (QTcd) between long-term smokers and non-smokers [25-27], studies on acute effect of cigarette smoking on different ECG parameters are very scanty and focus only on such parameters of ventricular repolarization as QT-dispersion (QTd) and corrected QT-dispersion (QTcd) with conflicting results. Akbarzadeh et al. [5] and Khosropanah et al. [28] reported an escalation in QTd and QTcd following acute exposure to cigarette smoke, whereas another study by Karakaya et al. [24] did not reveal a significant difference either in QTd and QTcd or in QT interval. İlgenli et al. [26] also did not find a significant difference in PR, QT and QTc intervals between baseline and following acute cigarette smoking. In agreement with the findings of Karakaya et al. [24] and İlgenli et al. [26], we also did not find a significant change in QTc and PR intervals after acute smoking. The discrepancy between the results of these different studies may have stemmed from the male-only inclusion methodology of the former two studies, as it may be speculated that autonomic nervous system discharge and opposing baroreflexes would have influenced the pooled data of these studies by modulating the cardiac electrophysiology to varying degrees. On the other hand, the latter two studies and ours enrolled female subjects as well.

fpQRS-T angle is a relatively novel ECG index utilized in the risk assessment of cardiac and overall deaths. It proves much more useful in risk stratification either QRS axis or T-wave axis alone [16]; however, there is no certain reference range for a normal fpQRS-T angle owing to its variability by age and gender. On the other hand, the spatial QRS-T angle is actually more revealing with regard to risk of ventricular arrhythmias, sudden arrhythmic death, cardiovascular death and overall death compared with fpQRS-T angle [29]. However, since most of the physicians are not acquainted with the spatial QRS-T angle due to its lack of wide availability, fpQRS-T angle appeals more to them owing to the fact that it is readily available from a surface ECG and has a significantly well correlation with the spatial QRS-T angle [12].

In healthy persons possessing normal cardiac structure, fpQRS-T angle is expected to be narrow. On the other hand, wider fpQRS-T angles point out to a more heterogeneity and distortion in the delicate balance between ventricular depolarization and repolarization, which translates into the presence of such cardiac fabric that is relatively more susceptible to ventricular arrhythmias and hence cardiovascular and all-cause deaths [30-32].

The main strength of our study is that contrary to the previous reports we mainly sought to assess the status of fpQRS-T angle after acute cigarette smoking, together with its probable correlations with demographic and clinical characteristics in healthy habitual smokers. We found that fpQRS-T angle dramatically widened 10 minutes after acute smoking. To our knowledge, this is the first study that compares this novel electrocardiographic parameter in the setting of acute smoking.

Of note, serum CRP level interestingly showed a significantly negative correlation with the degree of difference between pre- and post-smoking fpQRS-T angles in our study. This may seem paradoxical at first glance. Previous reports suggested that chronic exposure to cigarette smoke led to an elevation in serum levels of inflammatory markers such as interleukin-6, tumor necrosis factor-alpha and CRP in smokers [2,33-35]. Furthermore, chronic tobacco use may lead to gradually more nicotine tolerance, desensitization of autonomic nervous system, and blunting in baroreflexes compared with non-smokers and those smoking cigarette for a relatively shorter periods [22,36]. In this respect, it would be prudent to conjecture that lower serum CRP level may reflect relatively shorter periods of total tobacco exposure and hence a relatively more dramatic sympathetic nervous system response, catecholamine release and more direct effect membrane K+ channels on cardiac myocytes compared with those smokers with longer periods of total tobacco exposure, which in turn translate into a more dramatic widening in fpQRS-T angle soon after acute smoking.

Although there is no certain reference range for a normal fpQRS-T angle, some studies opt to regard a fpQRS-T angle <45 degrees as normal, between 45-90 degrees as borderline and >90 degrees as abnormal [11,16,37]. In their study, Chua et al. [16] pointed out to a cut-off value >90 degrees for a fpQRS-T angle to predict sudden cardiac death independently of the left ventricular ejection fraction in a large cohort of patients possessing cardiovascular disease risk factors. One may be eager to speculate that both pre- and post-smoking values of fpQRS-T angles seem within the expected range for healthy subjects. However, since we detected a significant and positive correlation between fpQRS-T angles before and 10 minutes after acute smoking in Spearman's analysis, this finding is very likely to be used as a future perspective in other studies such that a wider fpQRS-T angle at baseline expected in patients with heart failure, prior myocardial infarction and high blood pressure could be subject to a much greater widening compared with a narrower fpQRS-T angle healthy subjects.

Limitations

This study should be evaluated together with some limitations. Firstly, our study is a single-center study and includes a relatively small number of subjects. Secondly, the amount of the nicotine and tar that each participant consumed during a single cigarette smoking was not recorded, as different cigarette brands may have quite variable ingredients and amounts. This may have affected our study results. Thirdly, the participants were not stratified according to their total years of tobacco use to make a further comparison based on such stratification. In addition, we did not follow up the subjects for potential future cardiovascular endpoints.

Conclusion

Our study shows that even single smoking may widen fpQRS-T angle, a novel parameter with cardiac prognostic significance, 10 minutes after cigarette smoking in healthy subjects with habitual smoking. In addition, serum CRP level correlates negatively and significantly with the degree of fpQRS-T angle widening. Our observation may shed further light on the pathophysiological mechanism of smoking in cardiac arrhythmias and cardiac death. However, future studies, especially on patients with cardiovascular risk factors, are warranted to confirm and further enhance our findings.

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Local or general anesthesia for carotid endarterectomy: Which anesthesia technique should be preferred?

Karotid endarterektomi için lokal veya genel anestezi: Hangi anestezi tekniği tercih edilmelidir?

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Abstract

Aim: Carotid endarterectomy is performed in order to prevent disability or fatal stroke in patients with carotid stenosis. The objective of this study was to analyze and compare patients undergoing carotid endarterectomy under general or local anesthesia, and to determine whether the local anesthesia method is superior to general anesthesia in terms of postoperative morbidity and mortality.

Methods: A total of 80 patients who underwent carotid endarterectomy due to significant carotid arterial stenosis under general or local anesthesia in the cardiovascular surgery clinic of our hospital between November 2016 and January 2019 were included in this prospective cohort study. Forty carotid endarterectomy operations were performed under general anesthesia and 40 under local anesthesia. The study groups were divided as the general anesthesia group and local anesthesia group. Both groups were compared in terms of sociodemographic characteristics, preoperative risk factors, postoperative complications, operation time and length of hospital stay.

Results: No statistically significant difference was found between the two groups in terms of age and gender (P=0.665, P=0.636; respectively). The groups were similar in terms of the rate of asymptomatic patients, stroke or myocardial infarction, postoperative complications including minor stroke, cranial nerve damage, hematoma and internal carotid artery occlusion (P=0.264, P=0.780,P=1.000, P=0.870, P=0.870, P=1.000, P=0.723, respectively). The mean operation time and length of hospital stay were statistically significantly shorter in the local anesthesia group compared to general anesthesia group (P<0.001, P=0.655; respectively).

Conclusion: Local anesthesia provided shorter operation time and length of hospital stay for carotid endarterectomy procedure. Further comprehensive prospective studies are needed to clarify benefits of the use of local anesthesia for carotid endarterectomy.

Keywords: Carotid endarterectomy, Local anesthesia, General anesthesia, Complications, Mortality

Öz

Amaç: Karotid endarterektomi, karotid stenoz bulunan hastalarda sakatlığı veya ölümcül inmeyi engellemek için uygulanan bir prosedürdür. Bu çalışmanın amacı genel veya lokal anestezi teknikleri altında karotid endarterektomi uygulanan hastaları analiz ederek karşılaştırmak ve lokal anestezi yönteminin postoperatif morbidite ve mortalite açısından genel anesteziden daha üstün olup olmadığını belirlemektir.

Yöntemler: Kasım 2016 ve Ocak 2019 tarihleri arasında hastanemizin kardiyovasküler cerrahi kliniğinde ciddi karotid stenoz nedeniyle genel veya lokal anestezi altında karotid endarterektomi prosedürü uygulanan toplam 80 hasta bu prospektif kohort çalışmaya dahil edilmiştir. Prosedür 40 hastada genel ve 40 hastada lokal anestezi altında uygulanmıştır, ve çalışma grupları genel anestezi grubu ve lokal anestezi grubu olarak ikiye ayrıldı. İki grup sosyodemografik özellikler, preoperatif risk faktörleri, postoperatif komplikasyonlar, operasyon süresi ve hastanede kalış süresi açısından değerlendirilmiştir.

Bulgular: İki grup arasında yaş ve cinsiyet açısından anlamlı bir fark saptanmamıştır (sırasıyla P=0,665, P=0,636). Benzer şekilde genel anestezi ve lokal anestezi grupları arasında asemptomatik hastaların oranı, inme veya miyokard enfarktüsü insidansı açısından anlamlı fark saptanmamıştır (sırasıyla P=0,264, P=0,780, P=1,000). Postoperatif komplikasyonlardan minor strok (P=0,870), kraniyal sinir hasarı (P=0,870), hematom (P=1,000) ve internal karotis arter oklüzyonu (P=0,723) açısından iki group arasında anlamlı fark saptanmamıştır. Ortalama operasyon süresi ve hastanede kalış süresinin lokal anestezi grubunda genel anestezi grubuna kıyasla istatistiksel olarak anlamlı şekilde daha kısa olduğu saptanmıştır (sırasıyla P<0,001, P=0,655).

Sonuç: Lokal anestezi ile karotid endarterektomi prosedürü için daha kısa operasyon süresi ve hastanede kalış süresi saptanmıştır. Karotid endarterektomi prosedürü için lokal anestezi kullanımının yararlarını aydınlatmak amacıyla daha fazla kapsamlı prospektif çalışma gereklidir.

Anahtar kelimeler: Karotid endarterektomi, Lokal anestezi, Genel anestezi, Komplikasyonlar, Mortalite

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Introduction

Stroke is the most common cause of neurologic disability in the developed and developing countries. Carotid endarterectomy (CEA) is performed in order to prevent disability or fatal stroke in patients with carotid stenosis. The main goal of CEA is to successfully remove atherosclerotic plaque and to reconstruct the carotid artery without perioperative complications [1-4]. Patients with carotid stenosis may be asymptomatic, have transient ischemic attacks or minor stroke. Safety and effectiveness of CEA have been commonly demonstrated in the literature [5,6]. The primary aims of anesthesia during CEA is to maintain airway control and oxygenation, provide good operative conditions for the surgeon, and enable cerebral monitoring. This method can be performed under both general anesthesia (GA) and local anesthesia (LA). The choice of the anesthetic technique depends on familiarity of the surgeon with the procedure, general status and preference of the patient. On the other hand, performing CEA under LA has increased especially within the last 30 years. Studies are continuing to investigate the use of LA during CEA to reduce the risk of postoperative complications [7,8]. LA can be achieved with local filtration, superficial and/or deep cervical plexus blockage with and without ultrasound guidance [9]. The most important advantage of performing CEA procedure under LA is the ability to evaluate the patient clinically without a need for monitoring devices. LA allows communication with the patient, enabling the surgeon to take necessary actions when needed. In addition, adverse outcomes seen with GA such as sore throat, weakness, nausea, and vomiting can be eliminated with LA. On the other hand, the advantages of GA over LA include more easily provided oxygenation and ability to adjust arterial CO_2 tensions [10]. However, evidence about the benefits of agents used during GA is not enough [8]. Anesthetists and surgeons have been in debate on superiority of both techniques for years [11].

The objective of this study was to analyze and compare patients undergoing CEA under GA and LA, and to determine whether LA technique is superior over GA in terms of postoperative morbidity and mortality.

Materials and methods

This prospective cohort study included a total of 98 patients who underwent CEA due to carotid stenosis under GA or LA in the cardiovascular surgery clinic of our hospital between November 2016 and January 2019. Asymptomatic patients with carotid artery stenoses of >70% and >80% were confirmed with radiologic imaging. Definitive diagnosis was established through Doppler ultrasonography and/or angiographic assessment. Patients aged under 18 or over 80 years old, those in the terminal period with low life expectancy, patients with advanced congestive heart disease or cancer, those who preferred any of the anesthesia methods, those lost to follow-up, patients who underwent additional surgical interventions and those in whom LA was converted to GA due to intolerability or anxiety were excluded from the study (n=18). Remaining 80 patients were included in the analysis. CEA priority was determined according to the degree and/or side of the symptoms in patients with bilateral carotid artery stenosis.

Patients were randomly assigned to GA or LA groups with the closed envelope method. Accordingly, 40 CEA operations were performed under GA and 40 under LA. Patients in LA and GA groups were compared in terms of sociodemographic characteristics, preoperative risk factors, postoperative complications, operation time and length of hospital stay.

LA was performed using 0.75% ropivacaine. Sixteen mililitres was used to infiltrate the skin and underlying tissue. Intravenous sedatives and anxiolytic agents were used as recommended by the anesthesiologist.

In GA group, patients were intubated. Remifentanil infusion was used together with etomidate and propofol for anesthesia. During the procedure, patients were monitored with ECG, blood pressure and oxygen saturation. GA was conventionally performed using patches in all patients. All patients were admitted to the intensive care unit for 24 hours.

Sample size calculation

Sample size estimation was based on the method described by Faul et al. [12]. Using the G*Power 3.1 program, based on the existing findings and by taking alpha = 0.05 and d = 0.8, the effect size of the sample was determined to be large and the power of the study was calculated as 94.2%.

Ethics statements

Approval of Uludag University Clinical Researches Ethics Committee (decision no: 2016-18/10, approval date: 11/01/2016) was obtained prior to the study. All patients were informed about the study objectives in details and gave verbal and written consent. The study was conducted in accordance with the Declaration of Helsinki.

Statistical analysis

Data obtained in the study were statistically analyzed using SPSS v 21.0 (SPSS Inc, Chicago, IL, USA) package software. Continuous variables were expressed as mean (standard deviation), while categorical variables were given as frequency and percentage. Continuous variables were compared between the two groups with Mann-Whitney U and independent t test, and categorical variables with Chi-square test. $P<0.05$ values were considered as statistically significant.

Results

CEA operations were performed under GA in 40 (50%) and under LA in 40 (50%) patients. Among them, 70% (n=28) were male in GA group, while this rate was 62.5% (n=25) in LA group. The mean age was found as 64.83 years in GA group and 66.87 years in LA group. No statistically significant difference was found between GA and LA groups in terms of age and gender ($P=0.665$, $P=0.636$; respectively). Of the patients, 42.5% (n=17) were asymptomatic in GA group, while this rate was 57.5% (n=23) in LA group. There was no statistically significant difference between GA and LA groups in terms of the rate of asymptomatic patients ($P=0.264$). Comorbidities of the patients in both groups are given in Table 1.

Investigation of the smoking statuses of the patients revealed that 60% (n=24) of the patients in GA group and 47.5% (n=19) of the patients in LA group were smokers. No statistically significant difference was observed between both groups in terms of smoking ($P=0.380$). Looking at the preoperative risk

factors, stroke was found in 7 (17.5%) patients in GA group and 9 (22.5%) patients in LA group. A history of myocardial infarction (MI) was found in 6 (15%) patients in GA group and 6 (15%) patients in LA group. No statistically significant difference was found between GA and LA groups in terms of the incidence of stroke and MI (P=0.780, 1.000; respectively). Contralateral occlusion was found in 55% in both groups.

Right-sided CEA was performed in 52.5% (n=21) of the patients in GA group and 55% (n=22) of the patients in LA group. Intraoperative maximum and minimum blood pressure values were 123 (21) and 110 (25) mmHg in GA group, and 165 (21) and 140 (22) mmHg in LA group. Accordingly, intraoperative blood pressure values were significantly higher in LA group. Mortality did not occur in any patient following the procedures. Postoperative complications of the patients in GA and LA groups are presented in Table 2.

Themean operation times in the GA and LA groups were 89.9 (10.1) minutes and 60.2(5.5) minutes, respectively. Accordingly, the mean operation time was statistically significantly shorter in LA group (P<0.001).The mean lengths of intensive care unit and hospital stay were found as 1.4 (0.3) and 5.5 (1.3) days in GA group and 1.1 (0.2) and 3.6 (0.5) days in LA group. The mean length of hospital stay was also statistically significantly shorter in LA group (P=0.655). Perioperative outcomes of the patients in GA and LA groups are shown in Table 3.

Table 1: Comorbidities of the patients in GA and LA groups

	GA Group (n=40)		LA Group (n=40)		*P*-value
	n	%	n	%	
Diabetes mellitus	7	17.5	11	27.5	0.228
Peripheral arterial disease	14	35.0	12	30.0	0.473
Hypertension	32	80.0	28	70.0	0.560
Renal dysfunction	4	10.0	2	5.0	0.177

Table 2: Postoperative complications of the patients in GA and LA groups

	GA Group (n=40)		LA Group (n=40)		*P*-value
	n	%	n	%	
Minor stroke	1	2.5	0	0.0	0.870
Cranial nerve damage	1	2.5	0	0.0	0.870
Hematoma	1	2.5	1	2.5	1.000
Internal carotid artery occlusion	2	5.0	1	2.5	0.723

Table 3: Perioperative outcomes of the patients in GA and LA groups

	GA Group (n=40)	LA Group (n=40)	*P*-value
Mean operation time (min)	89.9 (10.1)	60.2 (5.5)	<0.001
Mean length of intensive care unit stay (day)	1.4 (0.3)	1.1 (0.2)	0.655
Mean length of hospital stay (day)	5.5 (1.3)	3.6 (0.5)	<0.001

Discussion

Numerous prospective and retrospective studies have reported that CEA is the most efficient treatment method in both asymptomatic and symptomatic patients with carotid artery stenosis [13]. European Vascular Surgery guidelines recommend CEA for patients with carotid artery stenosis >70% [14]. Advancements both in surgical experience and anesthesiology have reduced the incidence of surgical complications in CEA procedures performed under both GA and LA [5]. However, there is still debate of which anesthesia technique is superior over the other, and the choice of anesthesia technique largely depends on the preference of the surgeon and tolerability of the patient. While LA provides a better perioperative hemodynamic stability during CEA, this technique also enables direct evaluation of neurologic status of the patient. On the other hand, GA is indicated for non-cooperating patients, it is more comfortable for the surgeon and allows cerebral flow and perfusion. Depending on the developments in modern anesthesia techniques, some surgeons prefer to use GA, because of decreased patient anxiety and lower cerebral oxygen requirement with the GA method [15].

There are many comorbid risk factors increasing surgical morbidity-mortality rates in patients with carotid atherosclerosis. In a comprehensive study conducted in 22 countries worldwide, 90% of all strokes were associated with the most common 10 risk factors: These factors include previous tension, smoking, diabetes mellitus (DM), insufficient physical activity, high waist-to-hip ratio, high diet risk score, alcohol abuse, stress/depression, cardiovascular disease and high apolipoprotein B/apolipoprotein A1 ratio [16]. In our study, the most common comorbidities were found as hypertension in 75%, occlusive arterial disease in 32.5%, diabetes mellitus in 22.5% and renal dysfunction in 7.5% of the patients. However, no statistically significant difference was found between GA and LA groups in terms of accompanying diseases. In our study, 42.5% of the patients in GA group and 57.5% of the patients in LA group were asymptomatic. No statistically significant difference was found between the groups in terms of the rate of asymptomatic patients. Similarly, in a retrospective study by Lobo et al. [17], no significant difference was found between GA and LA groups in terms of the rate of asymptomatic patients. In this, study a history of MI was found in 15% of the patients in both groups. Watts et al. [18] reported the incidence of MI history as 18% in GA and 15% in LA groups, which is consistent with our study. We found a history of previous stroke in 17.5% of the patients in GA group, and 22.5% of the patients in LA group. These rates were reported as 23.7% and 29.7% respectively in a study by Lutz et al [19].

One of the important advantages of LA is reduced variability in intraoperative blood pressure values. In our study, fluctuations in intraoperative blood pressures were significantly lower in LA group. Also, Allen et al. [20] examined 679 CEA procedures performed under GA or LA and found that blood pressure instability was higher in GA group compared to LA group.

It has been reported that performing CEA in awake patients has the advantage of a shorter operation time compared to the operations carried out under GA [21]. In their study, Kalko et al. [22] reported shorter operation times with LA technique. In our study, the mean operation time was measured as 89.9 minutes in GA group and 60.2 minutes in LA group. Similarly operation times for both techniques reported by Watts et al. [18] were very close to our results. The authors reported the mean operation time as 88 minutes in GA group and 63 minutes in LA group. On the other hand, there have been studies reporting longer operation times. In a study by Lutz et al. [19], the mean operation times were reported as 111.38 minutes in GA group and 103.98 minutes in LA group, which were both longer. We attributed this difference between the studies to different operation techniques used during CEA procedures.

Mortality rates used by the American Heart Association (AHA) to formulate recommendations for CEA are based on studies older than 10 years. In a more recent study by Ederle et al. [23] conducted in 2010, 120-day mortality from CEA was

reported as 0.8%. In another study performed by Brott et al. [24] in the same year, 30-day mortality was reported as 0.3%. In our study, no mortality was seen in any patient. In a study by Toktas et al. [25] comparing GA and LA methods, 2 patients died in GA group. Some studies reported no significant difference between the two methods in terms of mortality [26-28].

Postoperative complications related to CEA procedure include MI, perioperative stroke, bleeding, cervical hematoma, nerve injury, infection, and carotid restenosis. In our study, postoperative complications included internal carotid artery occlusion in two, hematoma in one, cranial nerve injury in one, and minor stroke in one patient in the GA group, while internal carotid occlusion was seen in one and hematoma in one patient in the LA group. No statistically significant difference was observed between the two groups in terms of postoperative complications. Similarly, Kalko et al. [22] reported no significant difference between GA and LA techniques in terms of postoperative complications. In the study by Watts et al. [18], hemodynamic instability and cardiopulmonary complications were significantly lower in the LA group, while no statistically significant difference was found between both groups in terms of the other postoperative complications. In another study by Ferrero et al. [29] evaluating 428 patients who underwent CEA procedures under GA or LA, no significant difference was found between both groups, and no mortality was observed in any patient. Additionally, in a recent study by Saraç et al [30], the authors shared an institutional experience on 215 patients undergoing CEA procedures under local anesthesia, and suggested that low rates of complication and great rates of patency might be obtained using local anesthesia at CEA procedures.

In our study, the mean length of hospital stay was found as 5.5 days in GA group and 3.6 days in LA group. Accordingly, the mean length of hospital stay was statistically significantly shorter in LA group. Kalko et al. [22] also reported shorter duration of hospitalization in LA group compared to GA group.

According to our results, no statistically significant difference was found between both methods in terms of postoperative complications, while operation time and length of hospital stay were significantly lower with LA method. The reason for not preferring CEA under LA is that this method decreases the degree meticulousness. However, increasing surgical experience with LA prevents this difficulty.

Limitations

This study was conducted in a single center and included a relatively small number of patients. This limited our statistical analysis especially for the comparison of postoperative complications. However, prospective design of the study and randomization of the patients to the two groups are strengths of our study.

Conclusion

The results of our study demonstrated that LA performed for CEA enabled the surgeons to assess neurologic status of the patient and provided shorter operation times. However, further prospective studies with a larger series of patients and longer follow-up durations are needed to clarify benefits of the use of LA for CEA procedure.

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Comparison of salter osteotomy results in two different age groups in the treatment of developmental hip dislocation

Gelişimsel kalça çıkığı tedavisinde salter osteotomisinin iki farklı yaş grubundaki sonuçlarının karşılaştırılması

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Abstract

Aim: Surgical treatment of developmental hip dislocation is highly challenging in children of walking age. The most common complications following surgery include avascular necrosis and redislocation. In this study, we aimed to compare the preoperative and postoperative acetabular index, avascular necrosis (AVN) and redislocation rates between two age groups of open reduction and Salter osteotomy in DDH (Developmental Dysplasia of the Hip).

Methods: This prospective cohort study included patients who underwent open reduction and salter osteotomy for DDH between 2014 and 2017. Patients were grouped based on age as follows: Group 1: 18 -30 months old (n=44), Group 2: 31-48 months old (n=41). Preoperative, postoperative, and final acetabular indexes, AVN and redislocation rates were compared.

Results: Among 85 patients included in the study, 20 were male and 65 were female. The mean ages of Groups 1 and 2 were 21.6 months and 38.5 months, respectively. Following surgery, Group 1 mean acetabular index reduced to 25.9 degrees from 35.1 degrees, while that of Group 2 decreased to 22.1 degrees from 33 degrees. AVN was present in 10 patients (22.72%) in Group 1 and 4 patients (9.75%) in Group 2.

Conclusion: The acetabular index was adequately corrected in both groups. AVN was more frequent in children who had early interventions. We believe that the higher rate of avascular necrosis in children who underwent early intervention is due to surgical technique and using tighter sutures in the hip joint capsule.

Keywords: Hip dislocation, Acetabular index, Avascular necrosis, Redislocation

Öz

Amaç: Yürüme dönemi çocuklarda gelişimsel kalça çıkığının cerrahi tedavisi oldukça zordur. Avasküler nekroz ve kalça çıkığı tekrarlaması, cerrahi sonrası en sık karşılaşılan problemlerdir. Bu çalışmadaki amacımız GKD (Gelişimsel Kalça Çıkığı) tedavisinde uyguladığımız açık redüksiyon ve Salter osteotomisi yönteminin 2 grup arasındaki ameliyat öncesi ve sonrası asetabuler indeks, avasküler nekroz (AVN) ve redislokasyon oranlarını karşılaştırmaktır.

Yöntemler: Bu prospektif kohort çalışmaya 2014-2017 yılları arasında GKD nedeniyle açık redüksiyon ve salter osteotomisi yapılan hastalardan elde edilen verilerle yapıldı. Grup 1: 18 ay -30 ay (44), Grup 2: 31 ay-48 ay arası (41) hasta mevcuttu. Grupların ameliyat öncesi, ameliyat sonrası ve final asetabuler indeksleri, AVN ve redislokasyon oranları karşılaştırıldı.

Bulgular: Çalışmaya alınan 85 kalçanın 20'si erkek, 65'i kadın idi. Grup 1 hastaların yaş ortalaması 21,6 ay, Grup 2 hastalarının yaş ortalaması ise 38.5 ay idi. Ameliyat sonrası Grup 1 asetabuler indeks ortalama 35.1 dereceden 25,9 dereceye düşürülürken, Grup 2 de ise 33 dereceden 22,1 dereceye kadar düşürüldü. Grup 1 de 10 hastada (%22,72), Grup 2 de ise 4 (%9,75) hastada AVN vardı.

Sonuç: Asetabular indeks her iki grupta da yeterince düzeltildiği gözlendi. AVN'in erken müdahale yapılan çocuklarda daha yüksek oranda olduğu görüldü. Erken müdahale yapılan çocuklarda AVN'in daha yüksek olmasının kalça eklemi kapsülünün daha sıkı sütüre edildiği ve yapılan cerrahi teknikten kaynaklandığına inanıyoruz.

Anahtar kelimeler: Kalça çıkığı, Asetabuler indeks, Avasküler nekroz, Redislokasyon

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Introduction

Developmental dysplasia of the hip (DDH) is one of the most critical and difficult orthopedic conditions. The term DDH includes broad-spectrum anomalies ranging from mild acetabular dysplasia and high hip dislocation. Treatment is quite difficult due to increased tightness of the joint capsule, the presence of extraarticular soft tissues, acetabular dysplasia, increased femoral anteversion, and inversion of the limbus. It may accompany congenital anomalies with acetabular dysplasia. When DDH is not diagnosed and treated early, it leads to progressive deformities in the hip joint and defective development of the acetabular cavity [1-3].

The aim of DDH treatment is to obtain a stable and painless hip joint, as well as provide a radiologically normal acetabular index [3,4]. Although DDH treatment is often successful in infants, it is still difficult to achieve success in late diagnoses [5].

While many surgical methods have been reported in DDH cases diagnosed at walking age, the most frequently used methods are Salter, Pemberton, and Dega [6]. Successful results have been reported with open reduction, capsulography, femoral shortening and pelvic osteotomies [7,8]. Although single-stage methods are used in late-diagnosed DDH surgeries, many unpredictable problems may arise in the treatment of older children [9]. In our study, we aimed to compare the acetabular index angle, frequency of avascular necrosis and redislocation rates of our patients in 2 different age groups that we treated with open reduction and salter osteotomy.

Materials and methods

Patients who were referred to our clinic, a tertiary healthcare institution, due to DDH between November 2014 and November 2016 and underwent Salter osteotomy, were included in this study. Inclusion criteria included patients with Tönnis grade 3-4 DDH we followed for at least 24 months who had not undergone any previous intervention due to hip dislocation. Exclusion criteria consisted of patients with bilateral hip dislocation, teratological hip dislocation, patients we could not follow up after treatment and Tönnis grade 1- 2 patients.

Table 1: Tonnis scoring system [10]

Grade 1	The femoral head is medial to the Perkin's line
Grade 2	The femoral head is lateral to the Perkin line, below the superolateral corner of the acetabulum.
Grade 3	The femoral head is at the level of the superolateral corner of the acetabulum.
Grade 4	The femoral head is above the superolateral corner of the acetabulum

The patients were categorized into two groups based on age as follows: Group 1 consisted of patients between 18-30 months of age, while Group 2 included patients between 31-48 months of age. The study was performed in accordance with the principles of Declaration of Helsinki and approved by the local Ethics committee (no: 2017/01).

All our patients were operated under general anesthesia and open reduction and the original osteotomy technique defined by Salter [11] were performed. For open reduction, Smith Peterson incision was utilized in some cases, while in others, a modified ilioinguinal anterior approach was used. Patients requiring femoral osteotomy were incised with a direct lateral approach. After the operation, pelvipedal cast was applied to all hips at 10-15 degrees of flexion and 20-30 degrees of abduction. Postoperative routine pelvis AP radiographs were obtained in a cast position. Casts of all patients were removed on the 45th postoperative day. After removing the pelvipedal cast, Dennis Brown splint was used for 45 days. The acetabular index measurement was performed on pelvis AP radiographs of patients who came to routine controls, and patients with avascular necrosis and redislocation were recorded. Revision surgery was planned immediately for the redislocated hips. Osteotomy was performed between the sciatic notch and the spina iliaca anterior inferior with the help of the Gigli saw. The triangular graft was taken from the superior of the iliac wing and placed between the proximal and distal ends of iliac osteotomy. After the graft was placed in the opened osteotomy line, it was attached with two K-wires directed from the edge of the iliac wing towards the back of the acetabulum.

Acetabular index

The acetabular index defined by Hilgenreiner in 1925 is a common method for evaluating the acetabular roof. In this measurement, the lowest side point of the ilium in the Y cartilage and the most lateral point of the sclerotic part of the acetabulum are determined. The angle between the line connecting these two points and the line (Hilgenreiner) connecting the two ilium points is defined as the acetabular index (Figure 1). Tönnis [12] defined acetabular index values until the age of seven.

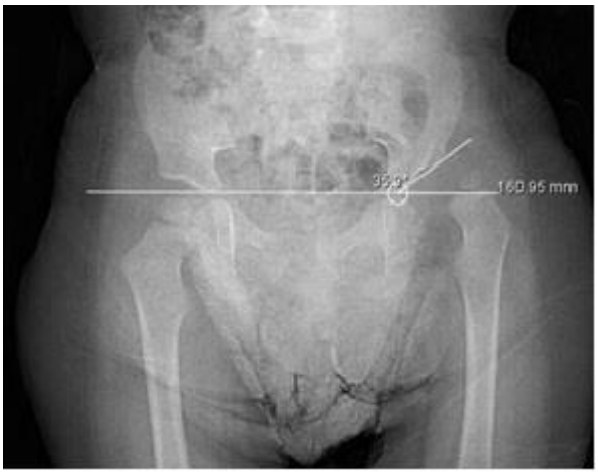

Figure 1: Measurement of the acetabular index in a pelvic anterior-posterior (AP) radiography of a patient with DDH

Statistical analysis

The differences between the groups were compared using the normal distribution values of the Student t-test. A Chi-square test was used to compare categorical variables. Results are presented as mean and range. *P*-value <0.05 was considered statistically significant. All analyses were performed using SPSS 11.0 version software (SPSS Inc. Chicago, IL, USA).

Results

Among 85 patients included in our study, Groups 1 and 2 comprised of 44 and 41 patients, respectively. The mean ages of Groups 1 and 2 were 21.6 months and 38.5 months, respectively. Thirty-seven patients had right hip dislocations and 48 had left hip dislocations (*P*=0.824). The demographic data of our patients is presented in Table 2.

A statistically significant difference was detected between the preoperative, early postoperative (Figure 2) and final acetabular (Figure 3) indexes of Groups 1 and 2. The degree of acetabular index correction was 9.2 degrees in Group 1 and

10.8 degrees in Group 2. Analysis of the final average acetabular indexes revealed that the average AI corrections in Groups 1 and 2 were 14.5 degrees and 16.3 degrees, respectively, the difference between which was significant (*P*=0.005).

Table 2: Demographic data of our patients

	Group 1	Group 2	*P*-value
Number of patients (n)	44	41	0.828
Male/Female ratio	6/38	14/27	0.04
Mean age (month) (SD)	21.6 (3.02)	38.5 (9.31)	0.001
Right hip/Left hip	20/24	17/24	0.824
Preoperative AI (SD)	35.1 (5.91)	32.9 (5.66)	0.109
Early postoperative AI (SD)	25.9 (7.39)	22.1 (5.89)	0.009
Final AI (SD)	20.6 (7.39)	16.6 (5.01)	0.005
Average follow-up period (SD)	49.3 (21.2)	46.5 (20.9)	0.538
Avascular necrosis	10	4	0.146
Redislocation	3	2	0.704

AI: Acetabular index

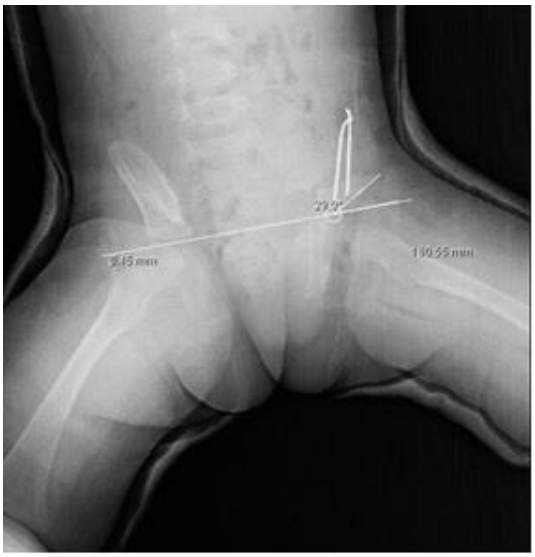

Figure 2: Measurement of the acetabular index on early postoperative pelvis anterior-posterior (AP) radiography

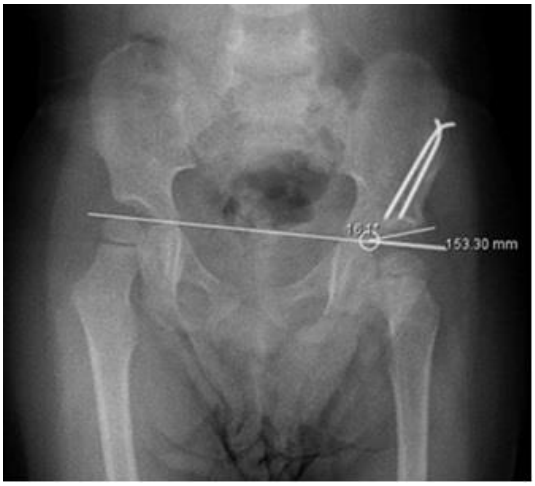

Figure 3: Final acetabular index measurement on pelvis anterior-posterior (AP) radiography of the same patient

The mean follow-up times of both groups were similar (*P*=0.538). Avascular necrosis was observed in 10/44 (22.72%) patients in Group 1 and 4/41 patients (9.75%) in Group 2. Three patients from Group 1 (6.8%) and 2 patients from Group 2 (4.8%) had redislocation, the difference between which was statistically insignificant (*P*=0.704).

Discussion

Although many methods have been described in developmental hip dislocation surgery, there are discussions about which to prefer [13,14]. In this study, we aimed to compare the results of open reduction and salter osteotomy technique, which we use most frequently in our clinic, in two groups of patients at different age groups. Lopez-Carreno et al. [15] reported that in patients undergoing salter osteotomy, the acetabular index decreased by 11 degrees on the radiographs after surgery. Barrett et al. [16] stated that in the 7-year follow-up of 4 different groups undergoing Salter osteotomy, they reduced the acetabular index by an average of 16 degrees. El-Sayed et al. [17] reported that they achieved 18-19-degree corrections in two different groups under and over 4 years of age using Salter osteotomy. In a study by Ahmed Essam et al. [18] it was stated that they reduced the preoperative mean acetabular index from 47.8 degrees to 26.7 degrees after Salter osteotomy in patients with DDH. Saqip et al. [19] reported that they reduced the preoperative mean acetabular index from 40.3 degrees to 23.4 degrees with Salter osteotomy in their study in which they followed patients for approximately 8 years. In our study, there was a statistically significant difference between the preoperative, mean early postoperative and final acetabular index measurements. Our acetabular index correction angles were compatible with the literature.

The most unfavorable complication in developmental hip dislocation surgery is avascular necrosis. In general, avascular necrosis rates of 1-13% have been reported in the literature after hip dislocation surgery [20,21]. Regardless of the treatment method used in DDH surgeries, surgical timing is important to avoid this complication. Some studies have reported that avascular necrosis is lower in the older age group [22]. In cases where femoral shortening is neglected, avascular necrosis is reportedly more frequent [23], and increased hip joint pressure has been reported to contribute to its development [24]. When pelvipedal plaster is made, difficult reduction, excessive internal rotation and abduction of the hip joint also increase avascular necrosis [25]. In our study, avascular necrosis occurred more in Group 1 (22.72%) than in Group 2 (9.75%).

In DDH, the femoral head is large, the acetabulum is shallow, femoral anteversion is increased, all of which are risk factors for dislocation, along with inadequate pelvic osteotomy [26,27]. In a study reporting that the rate of redislocation after hip dislocation is between 1-8 percent, it was concluded that the best results in pelvic osteotomies can be obtained between 2.5 years and 8 years of patient age [28]. In our study, 3 patients (6.8%) in group 1 and 2 patients (4.8%) in group 2 had redislocations.

Limitations

The small number of patients was one of the limitations of our study. Also, we could not compare the Salter osteotomy method with the other two frequently used methods, such as Dega and Pemberton, due to insufficient sample size. Further studies are needed to determine the association of Salter osteotomy results with age.

Conclusion

DDH treatment is highly challenging for children at walking age. Although the postoperative acetabular index values were compatible with the literature in both groups, avascular necrosis rates were particularly high in younger ages. We believe that the reason for high avascular necrosis in salter osteotomies performed in this group is related to the surgical technique rather than the age of the child.

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Impact of possible risk factors on pancreatic fistula development after pancreaticoduodenectomy: Prospective cohort study

Pankreatikoduodenektomi sonrası olası risk faktörlerinin pankreatik fistül gelişimi üzerine etkisi: Prospektif kohort çalışma

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Ethics Committee Approval: This study is approved by Ministry of Health, Istanbul Goztepe Training and Research Hospital Ethical Committee with the decision number 54/D, dated 2/10/2009. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: The most important complication that develops after pancreaticoduodenectomy is anastomosis leak and pancreatic fistula. Pancreatic fistula is thought to be the cause of major complications such as intra-abdominal abscess. The relationship between the development of fistula after pancreaticoduodenectomy and intraoperative risk factors (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure), along with the effect of pancreatic fistula on morbidity were investigated.

Methods: Forty-one patients who had undergone pancreaticoduodenectomy due to periampullary region tumors were included in this study. Patients were divided into two groups as with and without pancreatic fistula, and compared in terms of demographics, preoperative serum bilirubin and serum albumin values, and intraoperative risks (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure). In addition, the groups were evaluated for the development of post-operative complications.

Results: When both groups were compared in terms of intraoperative risk factors (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure), similar results were obtained for biochemical parameters (P=0.719, 0.599, 0.250, 0.906, respectively). A statistically significant association was found between the occurrence of pancreatic fistula and delay of gastric emptying (P=0.028). No significant relationship was detected between intraabdominal collection-abscess, intraabdominal hemorrhage, wound infection parameters and pancreatic fistula (P=0.204, 0.950, 0.116, respectively).

Conclusion: No factors were found to be solely associated with the development of pancreatic fistula following pancreaticoduodenectomy; however, it was concluded that pancreaticoenteric anastomosis technique and the consistency of pancreatic stump may be closely and significantly related.

Keywords: Pancreatic fistula, Pancreaticoduodenectomy, Pancreaticoenteric anastomosis

Öz

Amaç: Pankreatikoduodenektomi sonrası gelişen en önemli komplikasyon anastomoz kaçağı ve pankreas fistülüdür. Pankreas fistülünün karın içi apse gibi büyük komplikasyonların nedeni olduğu düşünülmektedir. Pankreatikoduodenektomi sonrası fistül gelişimi ile intraoperatif risk faktörleri (rezeksiyon tipi, pankreatik anastomoz tipi, pankreatik kanal çapı ve pankreatik güdük yapısı) arasındaki ilişki araştırıldı ve pankreatik fistülün morbidite üzerine etkisi araştırıldı.

Yöntemler: Bu çalışmada, periampuller bölge tümörleri nedeni ile pankreatikoduodektomi operasyonu uygulanan 41 hasta incelendi. Hastalar pankreatik anastomoz kaçağı olan ve olmayan olarak iki gruba ayrıldı. Her iki grup yüksek serum bilirübin ve düşük serum albumin değerleri ve intraoperatif riskler (rezeksiyon tipi, pankreatik anastomoz tipi, pankreatik kanal çapı ve pankreatik güdük yapısı) açısından karşılaştırıldı. Ayrıca gruplar post-operatif komplikasyon gelişimi açısından da değerlendirildi. Postoperatif komplikasyonlar: İntraabdominal koleksiyon-apse, intraabdominal hemoraji, yara yeri enfeksiyonu ve mide boşalma süresinin uzaması olarak kabul edildi.

Bulgular: Her iki grup da intraoperatif risk faktörleri (rezeksiyon tipi, pankreatik anastomoz tipi, pankreatik kanal çapı ve pankreatik güdük yapısı) açısından karşılaştırıldığında, biyokimyasal parametreler için benzer sonuçlar elde edilmiştir. (P=0,719, 0,599, 0,250, 0,906 sırasıyla). Gruplar, postoperatif komplikasyon parametreleri ile kıyaslandığında ise pankreatik fistül ile mide boşalma süresinin gecikmesi arasında istatistiksel olarak anlamlılık tespit edildi (P=0,028). İntra-abdominal apse, karın içi kanama, yara enfeksiyonu parametreleri ve pankreatik fistül arasında istatistiksel olarak anlamlı bir fark bulunmadı (sırasıyla P=0,204, 0,950, 0,116).

Sonuç: Pankreatikoduodenektomi sonrası pankreatik fistül gelişmesinde hiçbir faktör tek başına etkili bulunmadı. Ancak belirgin bir şekilde pankreatikoenterik anastomoz tekniği ve pankreatik güdüğün kıvamı ile yakından ilişkili olabileceği kanaatine varıldı.

Anahtar kelimeler: Pankreatik fistül, Pankreatikoduodenektomi, Pankreatikoenterik anastomoz

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Introduction

Pancreaticoduodenectomy (PD) is the only and a complex approach, which is believed to provide cure in the treatment of periampullary region tumors. Ever since PD series was published by Allen Whipple in 1935, this operation has been called the "Whipple Operation". In 1978, Pylorus-preserving pancreaticoduodenectomy (PPPD) was described by Longmire and Traverso [1,2]. Today, PPPD became more preferred than the standard Whipple intervention in periampullary malignity [3]. Besides providing a cure as much as the standard Whipple procedure, PPPD is also reported to have many advantages over Whipple surgery in terms of quality of life in the postoperative period [1,4]. 50-70% of periampullary region carcinomas originate from the pancreas, 15-25% from ampulla of Vater, 10% from duodenum, and 10% from the choledoch. Although ductus cells constitute 4% of all pancreas cells, more than 90% of exocrine cancers of pancreas are the adenocarcinomas, which originate from ductal epithelia [5]. The most crucial complication following PD is the development of pancreatic fistula (PF) since it can cause other complications. Activation of enzymes secreted from pancreatic leakage causes autodigestion, which leads to peripancreatic collection, intraabdominal abscess, delay of gastric emptying, and postoperative hemorrhage. PF ratio was reported in a wide range between 2-50%, the reason for which lies in the lack of an internationally accepted definition of fistula [1]. The most important risk factor in PF development is the pancreatic stump. If the protease enzymes secreted from this tissue are activated, they may digest the surrounding tissues, and cause partial or full diastasis of anastomosis. The fistulisation of pancreatico-enteric anastomosis leads to increased inflammation in the surrounding tissues, and even dramatic erosion of main veins in the retroperitoneal region. In such cases, complications such as intraabdominal and retroperitoneal collection, and delay of gastric emptying are mostly observed as the cause of hemorrhagic phenomenon. Intraabdominal abscess is closely related with pancreatic anastomosis leakage, and at least 50-60% of the abscesses develop upon pancreatic anastomosis leakage. All these complications lead to the development of sepsis, shock, single or multiple organ failure, or death [6]. Herein, we investigated the relationship between the development of fistula after pancreaticoduodenectomy and intraoperative risk factors (resection type, pancreatic anastomosis type, pancreatic duct diameter and pancreatic stump structure). In addition, the effect of pancreatic fistula on morbidity was investigated.

Materials and methods

This study was conducted in accordance with guidelines of the Declaration of Helsinki following the approval of the ethics committee of Ministry of Health, Istanbul Goztepe Training and Research Hospital (Decision number: 54/D, dated 2/10/2009). The patients, who had undergone PD due to periampullary region tumors between April 1996 and December 2008 at Istanbul Goztepe Training and Research Hospital, in the 4th General Surgery Clinic, were included in the study. Resection types were divided into two groups as standard PD and PPPD techniques. Cases in which total pancreatectomy is performed, are excluded from the study.

Forty-one patients were included in the study, sixteen of which were females. Standard PD and PPPD operations were performed in 20 and 21 patients, respectively. The patients were evaluated based on the type of PJ (invagination type or mucosal type), consistency of pancreatic stump (hard or soft) and dilation of the pancreatic duct (dilated or not dilated). The International Study Group of Pancreatic Fistula definition and grading of postoperative pancreatic fistula has been used in this study. The patients were divided into two groups as those with and without pancreatic fistula. The patients were examined in terms of intra-abdominal abscess, delay in gastric emptying time, wound infection, and intra-abdominal hemorrhage, as the main causes of morbidity.

Patients' age and gender distribution, symptoms and symptom frequency in the preoperative period, localization of tumor, preferred surgical techniques, postoperative early and late period complications, and mortality rates were investigated.

Statistical analysis

NCSS 2007&PASS 2008 Statistical Software (Utah, USA) program was used for statistical analysis. Besides descriptive statistical methods (mean, standard deviation, frequency), Chi-Square and Fisher's Exact tests were used for the comparison of qualitative data. The results were evaluated within a 95% confidence interval, and the significance was evaluated at $P<0.05$ level.

Results

Forty-one patients who had undergone PD due to periampullary region tumors between April 1996 and December 2008 were included in this study. The patients were followed for two years. Ages of the patients ranged between 15 and 75 years. There were 16 (39%) females and 25 (61%) males. The mean age of all patients was 61.92 (11.16) years. The tumor was located in the head of pancreas in 20 patients (48.8%), in the ampulla of Vater in 11 (26.8%), in the distal choledoch in 4 (9.8%), and in the duodenum in 2 patients (4.9%). One of the patients had a pancreatic cystadenoma (2.4%), one had chronic pancreatitis (%2.4), one had a pancreatic mass (2.4%), and one had an ampullary adenoma (2.4%) (Table 1).

While the preoperative serum albumin levels of 24 patients (58.5%) were normal, that of 17 patients (41.5%) were low. Serum bilirubin levels were high in 32 patients (78%) and normal in 9 (22%). No statistically significant relationship was detected between the development of a pancreatic fistula, low serum albumin levels ($P=0.837$) or high serum bilirubin levels ($P=0.350$) in the preoperative period (Table 2).

Standard PD technique (Whipple Operation) and PPPD were performed in 21 (51.2%) and 20 patients (48.8%), respectively. Evaluation of pancreatic anastomosis types revealed that invagination-style pancreaticojejunostomy (PJ) was performed 29 patients (70.7%) while PJ was done between the ductus and the mucosa in 12 (29.3%). While the parenchyma tissue of pancreatic stump was soft in 16 patients (39%), it was determined as hard in 25 (61%). The diameter of pancreatic duct (Wirsung) was dilated (≥3mm) in 28 cases (68.3%), and not dilated in 13 (31.7%) (<3mm).

There was no statistically significant relationship between the development of pancreatic fistula and PD resection

type (P=0.719), pancreaticoenteric anastomosis type (P=0.599), the parenchyma structure of the pancreatic stump (P=0.250) or the diameter of pancreatic duct (P=0.906) (Table 3).

Regarding the distribution of morbidity rates after the operation, 9 patients (42.8%) had PF, 4 patients (19.0%) had intraabdominal collection-abscess, 4 had extended gastric emptying time (19.0%), 3 had wound site infection (14.2%), and one patient (4.7%) had intraabdominal hemorrhage. No statistically significant relationship was determined between the PF development and development of intraabdominal collection and/or abscess, intraabdominal hemorrhage, or wound site infection within the following period (P=0.204, 0.950, 0.116 respectively). The difference between PF incidence rates between patients with longer and normal gastric emptying times were statistically significant (P=0.028) (Table 4).

Table 1: Distribution of patients' pathologic diagnosis

Pathologic diagnosis	n (41)	%
Tumor on pancreas head	20	48.8
Tumor on ampulla of Vater	11	26.8
Distal choledochal tumor	4	9.8
Duodenum tumor	2	4.9
Chronic pancreatitis	1	2.4
Pancreatic cystadenoma	1	2.4
Fibromatosis neoplasia	1	2.4
Ampulla adenoma	1	2.4

Table 2: Biochemical general risk factors in pancreatic fistula development evaluation

			Pancreatic fistula Present n (%)	Absent n (%)	*P*-value
Bilirubin Level	High	6	(18.8%)	26 (81.3%)	0.350
	Normal	3	(33.3%)	6 (66.7%)	
Albumin Level	Normal	5	(20.8%)	19 (79.2%)	0.837
	Low	4	(23.5%)	13 (76.5%)	

Chi-square test, Fisher's Exact test

Table 3: Comparison of intraoperative factors, which are considered as having effects on development of pancreatic fistula

Parameters		Pancreatic fistula Present n (%)	Absent n (%)	*P*-value
Resection type	Standard PD	4 (19.0)	17 (81.0)	0.719
	PPPD	5 (25.0)	15 (75.0)	
Anastomosis type	Invagination type PJ	7 (24.1)	22 (75.9)	0.599
	Duct-to-Mucosa PJ	2 (16.7)	10 (83.3)	
Parenchyma structure of pancreas stump	Soft	5 (31.3)	11 (68.8)	0.250
	Hard	4 (16.0)	21 (84.0)	
Diameter of pancreatic duct	Dilated >3 mm	6 (21.4)	22 (78.6)	0.906
	Nondilated <3 mm	3 (23.1)	10 (76.9)	

Chi-square test, Fisher's Exact test

Table 4: Comparison of complications which was developed after operation

Parameters		Pancreatic fistula Present n (%)		Absent n (%)		*P*-value
Intraabdominal collection/abscess	Present	2	(50.0)	2	(50.0)	0.204
	Absent	7	(18.9)	30	(81.1)	
Intraabdominal hemorrhage	Present	0	(0)	1	(100)	1.000
	Absent	9	(22.5)	31	(77.5)	
Wound site infection	Present	2	(66.7)	1	(33.3)	0.116
	Absent	7	(18.4)	31	(81.6)	
Gastric emptying time	Normal	6	(16.2)	31	(83.8)	0.028
	Extended	3	(75.0)	1	(25.0)	

Fisher's Exact test

Discussion

Today, the only potentially curative treatment type in periampullary tumors is PD. It is a highly complex and risky surgical approach. PD has become a routine method at experienced centers, and the mortality rate significantly reduced within the last 2 decades. Patient selection, increased surgical experience, development of preoperative and postoperative follow ups, and multidisciplinary approach allowed us to achieve better results. Nevertheless, the mortality is still 3-5% even in experienced centers, and the total morbidity is reportedly between 30-50%. This leads to increased hospitalization and cost [1].

The most important complication of PD is the development of a pancreatic fistula, which is thought to induce the development of other complications. PF is reported as 2-50% [1,6]. This wide range is due to the lack of an internationally accepted definition of a fistula [6]. In the study conducted by Duffas et al. [7], mortality and PF rates were 11% and 18%, respectively. The mortality, morbidity and PF rates reported by Andivot et al. [8] were 5.08%, 61% and 13.5%, respectively. Yang et al. [9] stated that the mortality, morbidity, and PF rates were 4.8%, 43.5% and 16.1%, respectively, while the evaluations of Fang WL et al. [10] yielded mortality, morbidity and PF rates of 8.9%, 56.4% and 17.6%, respectively. Our results were comparable to those reported in the literature.

Following PD, many risk factors for the development of PF were discussed in the literature: Among them are age, gender, degree of hepatitis, malnutrition, pathology of periampullary region tumor, resected part of the pancreas, consistency of the pancreatic stump, width of the pancreatic duct, time of operation, resection type, techniques of pancreatic anastomosis, and intraoperative hemorrhage [1,9]. Furthermore, novel studies in the literature reported the experience of the surgeon and the use of prophylactic somatostatin among the factors affecting PF [1,6,10]. High serum bilirubin and low albumin values were found not to pose a risk for PF development [1,11], just as in our study. Yeo CJ et al. [6] reported that preoperative low albumin value, which is not specific for PF, increases the complication rate for surgical procedures. Likewise, it has been reported that with a significantly high serum bilirubin level in the preoperative period, it may cause impaired liver, kidney, and immune systems, and increase the postoperative morbidity and mortality [12]. It was concluded that the used resection type was not a risk factor regarding the development of PF. Comparison with the literature revealed that the results were similar [9,13].

Kim et al. [14] found that PF rate was 3.2% in the group with wirsungojejunostomy and 17.5% in the group with intussusception. In addition, during postoperative follow-up, it was observed that the diameter of the pancreatic duct increased, and the pancreatic thickness decreased significantly in the intussusception group [14]. Poon et al. [15] found wirsungojejunostomy type anastomosis technique more effective than the invagination type. Marcus et al. [16] did not find wirsungojejunostomy anastomosis technique safe. They found the intussusception technique safer. In our study, 7 (24.1%) of 29 patients who underwent invagination type PJ developed PF, while 2 (16.7%) of 12 patients who underwent wirsungojejunostomy developed fistula. Although there was a difference between PJ and wirsungojejunostomy techniques in terms of PF development, it was not statistically significant. This result may be related to the scarcity of patients undergoing wirsungojejunostomy.

When the literature is examined, it was seen that the stiffness of the pancreatic stump tissue is considered as an important risk factor. Yang et al. [9] found the consistency of the remaining pancreatic tissue and the width of the pancreatic duct were related to the development of PF. PF rate was 4.8% in pancreatic duct widths of 3 mm and above, and 38.1% in those narrower than 3 mm. The rate of fistula development was 2.9% in patients with stiff remaining tissues, and 32.1% in soft ones.

Similarly, Yeo et al. [11] determined that there is a strong relationship between the structure of the remaining pancreatic tissue and PF. In his studies, none of 53 patients with hard pancreatic tissues (0%) developed fistula, while 19 of 75 (25%) patients with soft pancreatic tissue did. In conclusion, while fibrotic pancreatic tissue significantly facilitates pancreatico-enteric anastomosis in patients with chronic pancreatitis, it has been concluded that soft pancreatic parenchyma significantly complicates anastomosis [11]. Suziki et al. [17] determined the PF rate as 5 in 50 patients (8%) with their anastomosis techniques based on the width of the pancreatic duct and pancreatic tissue type. In our study, 5 (31.3%) of 16 patients with soft pancreatic stump parenchymal tissues and 4 (25.0%) of 25 patients with hard parenchymal tissues developed PF. Pancreatic stump softness caused an increase in the rate of PF development between the two parameters, but was not statistically significant.

Study of Suziki et al. [17] revealed that the internal and external drainage, which is performed by stenting the pancreatic duct to reduce PF after PD, had no benefit. The studies, defending the benefits of stenting, state that the stent shall reduce the damages to be caused by the exocrine secretion of pancreas, and decrease the fistula rate by securing the anastomosis. In some studies, they have found the inconvenience of stenting, and determined that the erosion caused by stent may increase the PF rate. Nonetheless, PF rate was found similar in patients to whom stents were and were not applied [9]. We did not use internal stents to any of our patients in this study.

It was thought that the inhibition of exocrine secretion of pancreas may decrease the PF rate after PD. The use of prophylactic somatostatin after PD has been emphasized in the recent years, however, a consensus could not be established. In the study conducted by Yang et al., while a decrease in PF rate was determined with the use of somatostatin in patients to which distal pancreatectomy and partial pancreatic resection were performed, the advantage of somatostatin use after PD over placebo could not be demonstrated [9]. Yeo et al. [11] performed PD on 211 randomized patients by using somatostatin and saline, and PF rate was determined as 11% in somatostatin group, and 9% in the control group. Yeo et al. [11] have determined that use of prophylactic somatostatin after PD did not decrease the fistula rate. Poon et al. [15] have conducted the meta-analysis of 6 ten-year prospective randomized studies and could not demonstrate any beneficial effects of the use of prophylactic somatostatin.

Limitations

Although pancreatic fistula studies are limited especially in one type of surgical technique, we think that we examined different surgical techniques in different pathologies in this study. We also think that by reflecting intra-operative risks to the study, we have revealed how pancreatic fistula affects morbidity. In the study, we statistically notice that the number of patients is insufficient. Poor identification of patients' co-morbidity is one of the weaknesses.

Conclusion

We found that no parameters were effective on pancreatic fistula development in patients undergoing standard PD, PPPD, end-to-end intussusception PJ and end-to-end Wirsungojejunostomy. The insufficient number of patients and many parameters (such as chronic diseases) have not been evaluated within the boundaries of the study. However, we think that we need larger studies to prove that the low serum albumin, high bilirubin values, the stiffness of the pancreatic parenchymal structure and the diameter of the pancreatic duct are effective in the development of PF.

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Investigating the role of nasal muscles in nasal obstruction after open technique rhinoplasty: A case-control study by electromyographic evaluation

Açık teknik rinoplasti sonrası nazal kasların burun tıkanıklığındaki rolünün araştırılması: Elektromiyografik değerlendirme ile bir vaka kontrol çalışması

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Ethics Committee Approval: This study was approved by the Istanbul Yeni Yuzyil University (IYYU), Non-Interventional Clinical Research Ethics Board (2/10/2020-2020/02). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma İstanbul Yeni Yüzyıl Üniversitesi (IYYU), Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu (10.02.2020-2020/02) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: Although the effects of rhinoplasty on nasal muscles by electromyography (EMG) or electroneuronography have been studied, the role of the nasal muscles in nasal obstruction after rhinoplasty operations has not yet been investigated. The aims of this study were to investigate the influence of the open rhinoplasty on nasal muscles and to reveal the role of the nasal muscles in post-operative nasal obstruction.

Methods: Thirty-five patients who underwent open technique rhinoplasty by a single surgeon due to external nasal deformity were included in the study. The patients were divided into two groups six months after the surgery: Study group with nasal obstruction and control group without nasal obstruction. EMG was performed to all patients for the activity of M. procerus, M. transversus nasalis and M. dilator before and after rhinoplasty.

Results: It was observed that the amplitudes of M. transversus nasalis and M. dilator muscles in the patients with nasal obstruction were significantly lower than the patients without nasal obstruction (P=0.01, P=0.003, respectively). Post-operative electromyographic activities of nasal muscles significantly decreased in all patients compared to pre-operative amplitudes.

Conclusion: This study demonstrated that nasal muscles or SMAS may be damaged during open technique rhinoplasty and as a result of this damage (especially in M. transversus nasalis and M. dilator) nasal respiration can be affected, which may lead to post-operative nasal obstruction. Preservation of these muscles and SMAS during rhinoplasty operations may reduce the incidence of post-operative nasal obstruction.

Keywords: Rhinoplasty, Intrinsic nasal muscles, Electromyography, Nasal obstruction

Öz

Amaç: Rinoplastinin nazal kaslar üzerine etkisi elektromyografi (EMG) veya elektronöronografi ile çalışılmış olsa da, rinoplasti operasyonu sonrası burun tıkanıklığında nazal kasların rolü henüz araştırılmamıştır. Bu nedenle bu çalışmanın amacı açık rinoplastinin nazal kaslar üzerine etkilerini incelemek nazal kasların operasyon sonrası burun tıkanıklığındaki rolünü ortaya koymaktır.

Yöntem: Çalışmaya eksternal nazal deformite nedeniyle tek bir cerrah tarafından açık teknik rinoplasti uygulanan otuz beş hasta dahil edilmiştir. Hastalar cerrahiden altı ay sonra; burun tıkanıklığı olan çalışma grubu ve burun tıkanıklığı olmayan kontrol grubu olmak üzere iki gruba ayrılmıştır. Tüm hastalara rinoplasti öncesi ve sonrasında m. procerus, m. transversus nasalis ve m. dilator aktivitelerinin ölçülmesi için EMG uygulanmıştır.

Bulgular: Burun tıkanıklığı olan hastalarda m. transversus nasalis ve m. dilator kaslarının amplitüdlerinin burun tıkanıklığı olmayanlara göre anlamlı düzeyde düşük olduğu saptandı (srasıyla; P=0,01, P=0,003). Cerrahi sonrası tüm hastalarda nazal kasların elektromiyografik aktivitesi cerrahi öncesi amplitüdleri ile kıyaslandığında anlamlı düşüş gösterdi.

Sonuç: Bu çalışma nazal kasların veya SMAS'ın açık teknik rinoplasti ile hasar görebileceğini; bu hasarın sonucunda (özellikle m. transversus nasalis ve m. dilator) nazal solunumun etkilenebileceğini ve cerrahi sonrası burun tıkanıklığı gelişebileceğini ortaya koymaktadır. Rinoplasti operasyonu süresince bu kasların ve SMAS'ın korunması cerrahi sonrası burun tıkanıklığı insidansını düşürebilir.

Anahtar kelimeler: Rinoplasti, İntrensek nazal kaslar, Elektromyografi, Burun tıkanıklığı

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Introduction

Although rhinoplasty is one of the most difficult aesthetic surgeries, the number of rhinoplasty operations has increased considerably in recent years. According to the annual report of American Society of Plastic Surgeon, rhinoplasty was the most common surgery performed among men in 2018, while it was the fourth most common surgical operation among women [1]. Because of aesthetic concern in rhinoplasty, more importance has been given to osseocartilaginous structure. However, both the aesthetic appearance and functional results must be considered when evaluating rhinoplasty outcomes. Recently, studies have increased investigating how nasal functions will be affected while achieving aesthetic outcome in rhinoplasty operations. Nasal obstruction is one of the most important post-operative (post-op) complaints in rhinoplasty. While 25 to 40% of rhinoplasty patients consult an aesthetic surgeon for revision surgery, 68% of patients complain of nasal obstruction after the operation [2-4].

The nose has many dynamic functions such as breathing and participating in facial mimic movements. The nasal muscles on the side walls of the nose provide these functions. These muscles are divided into two, intrinsic and extrinsic muscles. Intrinsic muscles including M. nasalis, M. dilatores naris anterior, M. procerus and M. depressor septi nasi are entirely within the nose and the bundles of extrinsic muscles including M. levator labii ala nasi, M. zygomaticus minor and M. orbicularis oris stretch out from the nose [5] (Figure 1). All these nasal muscles are located in a soft tissue called superficial musculoaponeurotic system (SMAS) [6]. The SMAS allows the distribution of forces resulting from contractions of multiple muscles. Each nasal muscle is interconnected by its fascia and a nasal SMAS component, thereby balancing the movement of the muscles [7]. It was stated that this layer may be damaged in rhinoplasty operations while it is dissected along with the dorsal nasal flap [8]. If this layer is damaged, the movement in these muscles, hence, the nasal movement will be affected, and the nose will become paralytic. This paralysis can be one of the causes of nasal obstruction, which is a complication of rhinoplasty.

Electromyography (EMG) is the best method to measure the functions of nasal muscles before and after surgery and to evaluate the muscular damage that may occur. In electromyographic evaluation using surface electrodes, it was possible to selectively distinguish the different electrical activities of each muscle despite the small size of the nasal muscles [9].

Although the effects of rhinoplasty on nasal muscles have been investigated by EMG or electroneuronography (ENoG) so far, the relationship between nasal obstruction after rhinoplasty and damage to nasal muscles in surgery has not yet been investigated. The aims of this study were to evaluate the influence of the rhinoplasty on nasal muscles, investigate the causes of post-op nasal obstruction in patients who underwent nasal hump reduction only because of aesthetic concern, reveal the role of the nasal muscles in post-op nasal obstruction and which muscle would have the greatest effect on this dysfunction.

Materials and methods

The study was conducted with 35 patients who underwent open technique rhinoplasty by a single surgeon due to external nasal deformity in Istanbul Yeni Yuzyil University and Bahat Hospital Otolaryngology and Throat Clinics between 2018 and 2019. After rhinoplasty operation the patients were divided into two groups as study group who had nasal obstruction complaints in the 6th post-operative month and control group who did not have any nasal obstruction complaints. The principles of the Declaration of Helsinki and Guidelines for Good Clinical Practices were followed during the study. The permission was obtained from the patient (in figure 2) to use her photograph in the article. This study was approved by Istanbul Yeni Yuzyil University (IYYU), Non-Interventional Clinical Research Ethics Board (2/10/2020-2020/02) and written informed consent was obtained from the patients after detailed explanations regarding the procedure were given.

Patients having complaints of nasal obstruction, dynamic nasal valve collapse by detailed nasal endoscopic examination, static nasal valve collapse by modified Cottle maneuver, nasal surgery prior to study, acute or chronic sinusitis, nasal polyps, facial paralysis, and myopathies were excluded from the study. Patients who were over 18 years of age and underwent planned open technique rhinoplasty due to external nasal deformity with only aesthetic concerns were included. All patients were evaluated by a neurologist and confirmed that they did not have any myopathies. The research was within the scope of seventy of our patients. 35 patients were excluded due to pre-op nasal congestion (n=12), sinusitis or nasal polyp (n=5), previous nasal surgery (n=11), static or dynamic nasal valve collapse (n=4) and missing control visits (n=3). Consequently 35 patients were included in the study.

Electromyography

Three major nasal intrinsic muscles (M. procesus, M. transversus nasalis, M. dilator naris anterior) were studied bilaterally in EMG preoperatively and in the 6th postoperative month. EMG was performed by our hospital neurologist using Medelec Syrerg N EP-EMG (EP monitoring system + Viasys Healthcare, Madisan, WI). During the analyses, the low filter was set at 500 Hz and the high filter at 1500 Hz. Recordings were studied bilaterally, and the arithmetic mean of bilateral amplitudes were calculated.

Functions of the nasal muscles were assessed in response to voluntary movements of the nose in these patients before and 6-7 months after open rhinoplasty. The EMG activities of the 3 intrinsic muscles (the procerus, transverse part of the nasalis muscle, and the dilator naris anterior) on both sides of the nose were recorded continuously. Three pairs of modified disposable bipolar surface electrodes were used after cleaning the skin with alcohol and ether. Short-circuiting was avoided with the application of the gel. Each pair of electrodes was placed on the nasal skin in such a way that they selectively recorded the activity of these muscles. Bipolar recordings were taken after the related electrodes were placed about 1 cm apart over the muscles to be investigated. As the muscle lengths were small, electrode placement was standardized on the subject as follows: For the procerus, active and reference electrodes were placed 0.5cm and 1.5cm below the glabella, respectively. The transverse part of the

nasalis muscle was tested with an active electrode placed at the rhinion and a reference electrode placed 1 cm below the rhinion. For dilator naris anterior muscle, an active electrode was placed on the ala close to the rim, and a reference electrode was attached 1 cm above the active electrode. The electrodes were fixated mechanically with the thin and short adhesive tape so that it did not interfere with nasal movements. EMG recording were made under the following conditions: a. Rhythmic widening of the nostril (nasal flaring), b. forced nasal inspiration, c. gentle closure of the eye, and d. lifting the nasal tip while frowning. Each movement was recorded 3 times for the each side of the nose. The highest amplitude levels of the bursts (interference pattern) were considered for the preoperative and postoperative measurements. At the end of each testing session, electromyographic recordings were also made in relaxed position to substantiate any spontaneous activity (Figure 2).

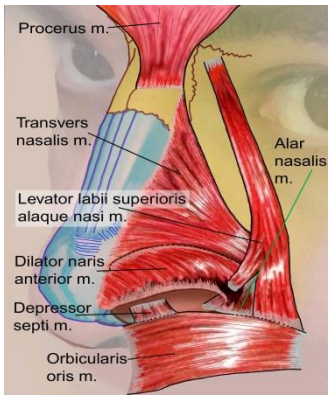

Figure 1: Intrinsic nasal muscles


Figure 2: Conducting an electromyographic test

Surgical technique

The open rhinoplasty operation was performed to all patients beginning with a transcolumellar V incision. The incision was extended by staying in the subcutaneous plane until the medial crura. Care was taken not to damage the soft tissue on the columellar flap and between the medial crura. The perichondrium of the middle crura was cut with sharp tip scissors. Elevation was extended in the subperichondral plane with the help of elevators. Caudal subperichondral dissection was continued until the fronto-nasal connection was reached while remaining in the subperiosteal plane. Facial nerve branches stimulating the nasal muscles were preserved under the SMAS layer. After completing the hamp resection and lateral osteotomies, the septal mucopericondrium was bilaterally elevated and septal cartilage graft was taken for use in nasal reconstruction and tip plasty. The incisions were closed by suturing and the operation was completed.

Statistical analysis

The analysis was performed using SPSS Statistics 20 software. The data were reported as mean (standard deviation) (SD). The normality analyses showed that the groups did not show normal distribution. Therefore, Mann Whitney U test was used to compare the means of independent groups and Wilcoxon test was used to compare the mean of dependent groups. *P*-value <0.05 was considered statistically significant.

Results

According to inclusion criteria, 35 patients were eligible for the study. Nineteen (54.3%) of them were included in the study group due to nasal obstruction after the 6th postoperative month and 16 (45.7%) were included in the control group due to lack of nasal obstruction complaints. The mean age of the patients in the study and control groups were 25.4 (5.25) years and 27.1 (6.83) years, respectively. The characteristics of the patients were given in Table 1.

Comparisons of the EMG amplitudes of M. procerus, M. transversus nasalis and M. dilator at the sixth postoperative months between the study group with post-op nasal obstruction and the control group without nasal obstruction were depicted in Table 2. While the amplitudes of the M. procerus muscle were not significantly different between the groups (P=0.39 at right, P=0.11 at left, P=0.15 at total), it was observed that amplitudes of M. transversus nasalis and M. dilator muscles decreased significantly in the study group (Figure 3) compared to the control group (P=0.01, P<0.01; respectively) (Figure 4) (Table 2). The post-op amplitude of M. transversus nasalis was 1.97 mV in the control group while it was 2.08 mV in the study group, and the post-op amplitude of M. dilator was 1.61 mV in the study group while it was 1.91 mV in the study group.

Comparisons of pre-op and post-op EMG results of the study group were depicted in Table 3. Right and left EMG amplitudes of all three muscles were significantly lower in post-op EMG values than pre-op values in study group (all P<0.001).

Comparisons of pre-op and post-op EMG results of the control group were depicted in Table 4. Right and left EMG amplitudes of all three muscles were significantly lower in the post-op EMG compared to the pre-op examination in the study group (all P<0.001 except left M. dilator P=0.03).

Table 1: Characteristics of the patients

	n	%	Age mean (SD) years
Study Group	19	54.3	25.4 (5.25)
Control Group	16	45.7	27.1 (6.83)
Total	35	100	26.3 (5.76)

SD: Standard deviation

Table 2: Comparison of post-op EMG results of study and control groups (Mann Whitney U)

		Study group mean (SD) mV	Control group mean (SD) mV	*P*-value
M. procerus	Right	1.98 (0.54)	1.98 (0.17)	0.39
	Left	2.06 (0.21)	1.91 (0.32)	0.11
	Total	2.08 (0.22)	1.97 (0.18)	0.15
M. transversus nasalis	Right	2.10 (0.20)	2.31 (0.25)	0.01
	Left	2.09 (0.21)	2.33 (0.23)	<0.001
	Total	2.10 (0.19)	2.32 (0.23)	0.01
M. dilator	Right	1.58 (0.29)	1.92 (0.25)	<0.001
	Left	1.63 (0.24)	1.90 (0.22)	0.003
	Total	1.61 (0.19)	1.91 (0.23)	<0.001

Table 3: Comparison of pre-op and post-op EMG results of the study group (Wilcoxon)

		Study group mean (SD) mV		Z	*P*-value
		Pre-op	Post-op		
M. procerus	Right	2.18 (0.26)	1.98 (0.54)	-3.62	<0.001
	Left	2.20 (0.23)	2.06 (0.21)	-3.72	<0.001
M. transversus nasalis	Right	2.21 (0.25)	2.10 (0.20)	-3.38	<0.001
	Left	2.17 (0.19)	2.10 (0.20)	-3.55	<0.001
M. dilator	Right	1.99 (0.29)	1.58 (0.29)	-3.85	<0.001
	Left	2.04 (0.22)	1.63 (0.24)	-3.86	<0.001

Table 4: Comparison of pre-op and post-op EMG results of the control group (Wilcoxon)

		Control group mean (SD) mV		Z	*P*-value
		Pre-op	Post-op		
M. procerus	Right	2.07 (0.22)	1.98 (0.17)	-3.07	<0.001
	Left	2.03 (0.22)	1.91 (0.32)	-2.97	<0.001
M. transversus nasalis	Right	2.38 (0.25)	2.31 (0.25)	-2.08	<0.001
	Left	2.47 (0.19)	2.33 (0.23)	-3.45	<0.001
M. dilator	Right	1.98 (0.27)	1.92 (0.25)	-2.88	<0.001
	Left	1.95 (0.21)	1.90 (0.22)	-2.11	0.03

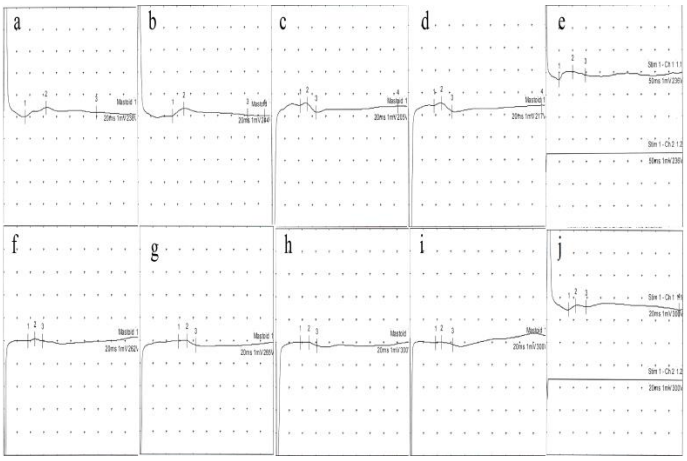

Figure 3: Electromyographic (EMG) results of study (nasal obstruction +) group: a)Pre-op.right m.transvers nasalis, b) Pre-op. left m.transvers nasalis, c)Pre-op. right m. dilator, d) Pre-op. left m. dilator, e) Pre-op. right m. procerus, f) Post-op.right m.transvers nasalis, g) Post-op. left m.transvers nasalis, h)Post-op. right m. dilator, i) Post-op. left m. dilator, j) Post-op. right m. procerus

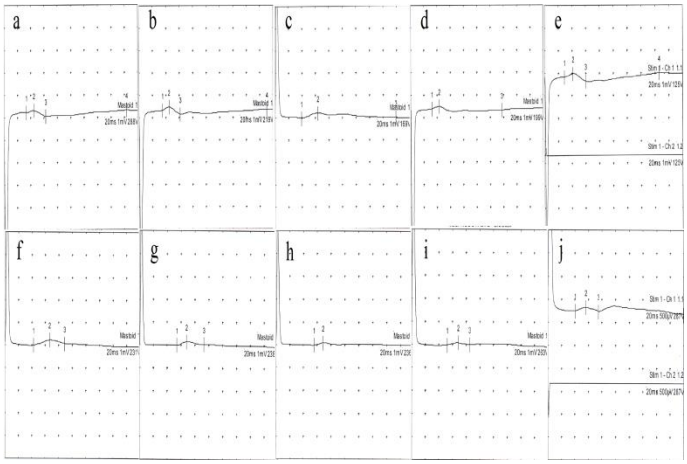

Figure 4: Electromyographic (EMG) results of control (nasal obstruction -) group: a)Pre-op.right m.transvers nasalis, b) Pre-op. left m.transvers nasalis, c)Pre-op. right m. dilator, d) Pre-op. left m. dilator, e) Pre-op. right m. procerus, f) Post-op.right m.transvers nasalis, g) Post-op. left m.transvers nasalis, h)Post-op. right m. dilator, i) Post-op. left m. dilator, j) Post-op. right m. procerus

Discussion

This is the first study to investigate the role of nasal muscles in post-op nasal obstruction. In our study, it was demonstrated that in all patients with nasal hump deformity who underwent open technique rhinoplasty for nasal hump reduction because of aesthetic concern, M. procerus, M. transversus nasalis and M. dilator could be damaged during the operation and particularly damage in M. transversus nasalis and M. dilator muscles could be related to post-op nasal obstruction. The results of present study indicate that the damage in M. transversus nasalis and M. dilator muscles or in the SMAS coordinating these muscles may contribute to post-op nasal obstruction in rhinoplasty cases.

Nose is important in cosmetic appearance and functions of the respiration. The nose is surrounded by nasal musculature, SMAS, perichondrium or periosteum. Nasal muscles have roles in determining phonation, respiration, and facial expression. The muscles that are strongly associated with the inspiratory phase of respiration are pars alaris and pars transversus of M. nasalis and M. dilator naris anterior. They work synergistically, balancing each other's effects [10]. Thus, these muscles can be considered as accessory muscles of respiration. They also take part in voluntary nasal movements [11]. On the other side there are M. procerus and M. levator labii alaquae nasi. These muscles are rarely activated in respiration but show high function in complex mimetic activities [10]. Although there are variations between individuals in intrinsic nasal muscles, M. proserus, M. transvers nasalis and M. dilator are major nasal muscles in humans [7]. Therefore, the protection of nasal muscles in rhinoplasty operations is important not only in cosmetics but also in mimic movements and protection of nasal respiration. However, while aesthetic results are desired in many rhinoplasty operations, the muscular layer and the structures associated with this layer are ignored. Increasing studies investigating the pre-op and post-op electromyographic functions of the nasal muscles will reveal the causes of functional disorders such as nasal obstruction after rhinoplasty and will increase the concern on these structures during the operations.

ENoG and EMG are very valuable methods that can be used to assess the functions of nasal muscles. The potentials of nasal motor units can be recorded from the skin using surface electrodes, although the size of the nasal muscles is very small and can be selectively discriminated between various electrical activities [9]. In the literature, EMG was used in some studies comparing muscle activities before and after rhinoplasty [11,12], while ENoG was used in others [13,14]. Although ENoG provides more information about muscle functions, patient compliance is more difficult because it is performed by external stimulation. In our study, EMG was applied to the patients using superficial electrodes over the skin. High compliance was achieved in all patients. Although there are several published studies about the functions of muscles before and after rhinoplasty with EMG or ENoG, there have been no report investigating the role of nasal muscles in post-op nasal obstruction after rhinoplasty. The function of nasal muscles after rhinoplasty was first investigated in 1983 by Thumfart et al. [12]. They compared the EMG findings of 42 patients before and 2 and 8 months after rhinoplasty and observed a significant decrease in the amplitudes of the nasal muscles in only 2 cases. However, there is not enough information about which technique is used during the operation. In 2001, Ozturan et al. [11] examined the activity of M. procerus, M. transversus nasalis and M. dilator in 21 patients who underwent open technique rhinoplasty and reported that amplitudes decreased significantly in all EMG recordings performed at the 3rd and 5th postoperative months. A study by Kirgezen et al. [13] reported the post-op EMG and ENoG results of 18 endonasal and 30 external rhinoplasty operations. About 6.6% of the closed rhinoplasty group and 11.1% of the open rhinoplasty group showed a decrease in EMG amplitudes of the nasal muscles and significant decreases in post-op amplitudes were found according to ENoG results. In a study by Batioglu-Karaaltin et al. [14] investigating the effect of open rhinoplasty on mimic movements involving 20 patients, a decrease was observed in all amplitudes of bilateral transverse nasal, levator labii superioris alaeque nasi and procerus muscles in the 3rd month following rhinoplasty. However, the significant decrease was found only in the left levator labii superioris alaeque nasi muscle. It was reevaluated at the sixth postoperative month and the values were improved. In our study, the EMG recordings of all patients were significantly decreased in the sixth month after surgery, along with the post-op measurements of the M. transversus nasalis and M. dilator

muscles, which were significantly lower in the nasal obstruction group compared to the group without nasal obstruction. This discrepancy between studies may be due to differences in surgical experience, types and localization of electrodes used in EMG technique, the temperature of the muscles, the means of the motor unit potential activation, the number of the fibers in the muscle and the concentration of the muscle fibers.

Since open rhinoplasty operations have many advantages over nasal muscles such as having a wide angle of view, easier preservation of related structures and no blinding of nasal dorsum elevation compared to closed rhinoplasty operations [13], open technique rhinoplasty operation was preferred in all patients in our study. However, all patients had a decrease in EMG amplitudes at the 6th month after surgery. One limitation of our study is that the observation period is as short as 6 months. As in the study of Batioglu-Karaaltin et al. [14], amplitudes could be increased during longer follow-ups, due to the fact that insufficient muscle contraction, positional changes in muscles and soft tissues, and edema all may cause lower EMG amplitudes during the postoperative period. All these factors are likely to improve in the future, allowing muscle amplitudes to increase [13].

Limitations

The main limitation of the present study was lack of objective evaluation and comparison of patients' nasal breathing with rhinomanometric examination before and after surgery. Short follow-up period and number of patients were the other limitations.

In future studies, we plan to increase the number of patients, investigate patients who underwent closed rhinoplasty, and to add rhinomanometric examination to the research protocol.

Conclusion

Even if an open technique rhinoplasty operation is performed, as a result of the damage to SMAS and nasal muscles during incision, elevation and other rhinoplasty stages, a decrease in the amplitudes of M. procerus, M. transversus nasalis and M. dilator which are the major muscles of the nasal function and the aesthetic appearance, may be observed. Furthermore, the damage of M. transversus nasalis and M. dilator during rhinoplasty may play an important role in post-op nasal obstruction. Preservation of these muscles and SMAS during operation may reduce the incidence of post-op nasal obstruction.

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Beating heart technique in tricuspid valve replacement among patients which have a TAPSE index lower than 15 mm

TAPSE değeri 15 mm altında olan hastalarda atan kalpte triküspit kapak replasmanı

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Abstract

Aim: Tricuspid valve replacement (TVR) has always been a compelling issue for cardiovascular surgeons due to the poor postoperative outcomes. Besides myocardial ischemia caused by aortic cross clamp, cardioplegia resulting in reperfusion injury is still one of the major problems in open heart surgery. In this study, we aimed to evaluate the benefits of TVR with beating heart (BH) in terms of decreasing mortality and morbidity rates among the patients with TAPSE indexes lower than 15 mm.

Methods: This research was designed as a retrospective cohort study. Twenty-nine patients with isolated tricuspid valve diseases with a TAPSE index lower than 15 mm and who underwent TVR consecutively between 2006 and 2012 were enrolled in this study. Among 29 patients, 13 underwent TVR with cardioplegic arrest (AH group) and 16 underwent TVR with a beating heart (BH group).

Results: There were 5 males in the AH group and 6 males in the BH group. The mean ages of the patients in AH and BH groups were 55.42 (11.6) years and 57.92 (8.43) years, respectively. Sixty-two percent of the AH group was in New York Heart Association (NYHA) Class III or IV heart failure in comparison to 56% of the BH group. Atrial fibrillation was present in 9 patients (69%) in the AH group and 11 patients (69%) in the BH group. Left ventricular functions were calculated as 57.23% (7.62) and 58.65% (8.02) in the AH and BH groups, respectively. Mean systolic pulmonary artery pressure was 38.45 (11.42) mmHg in AH group and 42.68 (13.01) mmHg in BH group. TAPSE score was 14.12 (1.78) in AH group and 13.67 (1.13) in BH group. Cardiopulmonary bypass times were 78.3 (19.8) minutes and 54 (14.6) minutes in the AH and BH groups, respectively, with respective total operation times of 167.4 (67.6) minutes and 132.2 (39.7) minutes (P=0.023). Positive inotropic drug use was observed in 9 patients (69%) in the AH group and in 7 patients (44%) in the BH group (P=0.029). The independent effect of BH in decreasing the mortality rates was calculated by logistic regression analysis (Odds ratio (OR) 0.43, 95% confidence interval (CI) 0.22–0.76, P=0.001).

Conclusion: Operative and postoperative outcomes of the BH technique in TVR encourage us to recommend using the BH technique in TVR among patients with a TAPSE score lower than 15 mm.

Keywords: TAPSE, Tricuspid valve replacement, Beating heart, Mortality

Öz

Amaç: Triküspit kapak replasmanı (TKR) her zaman için kalp damar cerrahları için zorlayıcı bir durum olmuştur. Bunun yanında, aortik kros klemp neticesinde oluşan miyokardiyal iskemi, reperfüzyon hasarı ile sonuçlanan kardiyopleji halen kalp cerrahisindeki major problemlerin başında gelmektedir. Bu çalışmada, TAPSE değeri 15 mm altında olan hastalardaki mortalite ve morbiditeyi azaltmak açısından atan kalpte (AK) TKR ameliyatının yararlarını değerlendirmeyi amaçladık.

Yöntemler: Bu çalışma retrospektif kohort çalışma olarak tasarlanmıştır. İzole triküspid kapak hastalığı olan ve TAPSE değeri 15 mm altındaki 2006 ve 2012 yılları arasında TVR yapılan 29 hasta çalışmaya dahil edildi. Bu hastalardan 13'üne TVR kardiyoplejik arrest (KA grubu) ve 16'sına atan kalpte (AK grubu) uygulandı.

Bulgular: KA grubunda 13 kişiden 5'i erkek ve ortalama yaş 55,42 (11,6) idi. AK grubunda 16 kişiden 6'sı erkek ve ortalama yaş 57,92 (8,43) idi. KA grubunun %62'sinde New York Kalp Vakfı (NYHA) sınıf III veya IV iken AK grubunda bu oran %56 idi. Atriyal fibrilasyon KA grubunda 9 (%69) hastada görülürken AK grubunda 11 (%69) hastada gözlendi. Sol ventrikül fonksiyonu AK grubunda %57,23 (7,62) ve KA grubunda %58,65 (8.02) idi. Sistolik pulmoner arterial basınç KA grubunda 38,45 (11,42) mmHg iken AK grubunda 42,68 (13,01) mmHg idi. TAPSE skoru KA grubunda 14,12 (1,78) mm iken AK grubunda 13,67 (1,13) mm idi. Kardiyo pulmoner baypas zamanı KA grubunda 78,3 (19,8) dakika iken AK grubunda 54 (14,6) dakika idi (P=0,015), ve toplam ameliyat süresi KA grubunda 167,4 (67,6) dakika iken AK grubunda 132,2 (39,7) dakika olarak ölçüldü (P=0,023). Pozitif inotropik destek kullanımı KA grubunda 9 (%69) hastada görülürken AK grubunda 7 (%44) hastada mevcut idi (P=0,029). AK tekniğinin mortalite oranını düşürmedeki bağımsız etkisi lojistik regresyon analizi ile değerlendirildi (Odds ratio (OR) 0,43, 95% confidence interval (CI) 0,22–0,76, P=0,001).

Sonuç: AK ile TVR uygulamasına ait operasyonel ve postoperatif veriler bizleri TAPSE skoru 15 mm altında olan hastalarda AK tekniğinin kullanılmasını önermekte cesaretlendiriyor.

Anahtar kelimeler: TAPSE, Triküspit kapak replasmanı, Atan kalp, Mortalite

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Introduction

Despite the valuable impairments in surgical techniques, tricuspid valve replacement (TVR) has always been a compelling issue for the cardiovascular surgeons due to the poor postoperative outcomes. However, under certain circumstances TVR may be the first option in consideration of the elevated risks of mortality and morbidity.

Right ventricle dysfunction (RVD) is one of the major risk factors increasing the operative and postoperative mortality rates in tricuspid valvuloplasty operations [1]. Fractional area change (RVFAC) and ejection fraction (RVEF) are two main parameters of trans-thoracic echocardiography (TTE) in defining right ventricle function. However, they have a limited value in clinical practice due to the lack of inadequate right ventricle endocardial examination [2,3]. Tricuspid annular plane systolic excursion (TAPSE) shows apex to base shortening diameter of right ventricle and is used to define right ventricle function [4-6]. Patients which have a TAPSE index lower than 15 mm are considered to have a high risk of peroperative mortality and morbidity due to remarkable RVD [7].

Due to the negative systemic effects of cardiopulmonary bypass (CPB) and myocardial ischemic duration (cross clamp time), in recent years, performing TVR operations with beating heart technique (BH) has become popular to avoid additional elevated morbidity and mortality rates [8].

This study was designed to evaluate the benefits of TVR with BH in terms of decreasing mortality and morbidity rates among the patients with TAPSE indexes <15 mm.

Materials and methods

This retrospective cohort study, which complies with the standards defined by the Declaration of Helsinki, was conducted in the Cardiovascular Surgery Department of Akay Hospital. Twenty-nine consecutive patients with isolated tricuspid valve diseases who underwent TVR between 2006 and 2012 were enrolled. Patients who have a TAPSE index>15 mm, a history of coronary artery bypass operation and those who were reoperated were not included. Among 29 patients, 13 underwent TVR with cardioplegic arrest (AH group) and 16 underwent TVR with BH (BH group).

The computerized institutional database was used to obtain demographic data and record co-morbidities. Age, gender, history of coexisting diseases, and intra-postoperative parameters of the patients were noted.

A preoperative TEE exam was performed using multiplane TEE probes (Acuson, Mountain View, CA) by an experienced cardiologist certified in perioperative TEE. TAPSE was measured in a mid-esophageal four chamber view. 2D cursor was placed at the tricuspid lateral annulus and the distance of systolic annular RV excursion along a longitudinal line was measured defining the end of systole as the end of the T wave in the electrocardiogram [9].

The indications of TVR were as follows: One patient due to tricuspid valve endocarditis, one patient due to tricuspid valve stenosis and 27 patients due to severe tricuspid valve insufficiency. Mortality occurring in the first postoperative 30 days were considered hospital mortality.

Operational technique

A midline sternotomy was performed on 8 patients in the AH group and 7 patients in the BH group. Arterial cannulation of ascending aorta and bicaval venous cannulation of right atrium were done. Right anterolateral thoracotomy was performed to the remaining patients of both groups following arterial cannulation of femoral artery and bicaval venous cannulation from femoral vein by means of transesophageal echocardiography (TEE). CPB was initiated. Tape strips were placed to Vena Cava Inferior and Superior. In the AH group, following mild systemic hypothermia (30°C) and application of topical ice slush, heart was arrested by means of cold cardioplegia solution. BH group patients had systemic normothermia (36.5 °C). In both groups, a right atriotomy was performed after tightening the snares of caval tape strips. Tricuspid valve was replaced with a mechanical prosthetic valve in 7 patients of the AH group and 11 of the BH group, and with a bioprosthetic valve in 6 patients in the AH group and 5 in BH group by preserving tricuspid valve tissue and sub-valvular apparatus in order to decrease the risk of damaging signal transduction pathways and support right ventricle function. Antegrade hot cardioplegia was applied before declamping the aorta in the AH group. Blood samples were obtained in the postoperative 1^{st}, 4^{th}, 12^{th} and 24^{th} hours to monitor serum lactate, troponin-T and CK-MB levels.

Postoperative follow-up

Peroperative and follow-up data were recorded in a computerized database. Death within postoperative 30 days was defined as mortality. All patients were followed up via transthoracic echocardiographic evaluation, which was performed at discharge, at the end of first and sixth months, and annually thereafter.

Statistical analysis

Statistical analysis was conducted using the SPSS for Windows software package (ver. 17; SPSS Inc., Chicago, IL, USA). All variables were evaluated using visual (histograms, probability plots) and analytical (Kolmogorov Smirnov test) methods to determine whether they were normally distributed. Continuous variables are reported as means (SDs) for normally distributed variables, and as medians with interquartile ranges for non-normally distributed variables. Categorical variables are presented as numbers and percentages.

Group comparisons were performed using chi-squared or Fisher's exact tests for qualitative variables, independent t-tests for normally distributed continuous variables, and the Mann-Whitney U test for non-normally distributed continuous variables.

Logistic regression analysis was used to evaluate the effect of BH and cardioplegic arrested heart techniques on the mortality rates of the patients undergoing TVR. Potential risk factors and predictor variables with a *P*-value lower than 0.25 in the univariate analysis were included as covariates in the multivariate model. The multivariate model was regulated for age, sex, operational and CPB time, intensive care unit stay duration. *P*-values <0.05 were considered to indicate statistical significance.

Results

The demographic data of AH group (n=13, 5 males, mean age: 55.42 (11.6) years) and BH group (n=16, 6males, mean age: 57.92 (8.43) years) are presented in Table 1. Sixty-two percent of the AH group was in New York Heart Association (NYHA) Class III or IV heart failure in comparison to 56% of the BH group. Atrial fibrillation was present in 9 patients (69%) in the AH group and 11 patients (69%) in the BH group. Left ventricular functions were calculated as 57.23% (7.62) and 58.65% (8.02) in the AH and BH groups, respectively. Mean systolic pulmonary artery pressure was 38.45 (11.42) mmHg in AH group and 42.68 (13.01) mmHg in BH group. TAPSE score was 14.12 (1.78) in AH group and 13.67 (1.13) in BH group. There was no statistically significant difference between the two groups in terms of age, gender, preoperative atrial fibrillation, left ventricular function, NYHA functional class, and preoperative cardiac surgery history. However, EuroSCORE II risk scoring system of BH group had a significantly higher predicted mortality rate than AH group (P=0.03) (Table 1).

According to intraoperative data given in Table 2, cardiopulmonary bypass times were 78.3 (19.8) minutes and 54 (14.6) minutes in the AH and BH groups, respectively, with respective total operation times of 167.4 (67.6) minutes and 132.2 (39.7) minutes (P=0.023). In AH group, X-clamp time was 48.27 (17.2) minutes and total amount of cardioplegia was 1057 (467) ml.

Positive inotropic drug use was observed in 9 patients (69%) in the AH group and in 7 patients (44%) in the BH group (P=0.029). The AH group required significantly prolonged inotropic support (Table 3).

Mechanic ventilator support time was 33 (17) hours in AH group and 13 (4) hours in BH group (P=0.047). Intensive care unit stay time was 6.1 (2.7) days in AH group and 3.4 (1.7) in BH group (P=0.035). The total hospital stay times were similar in both groups (P=0.089).

Although the postoperative tube drainage amounts were similar in both groups (575.6 (263.1) mL in AH group vs. 512.3 (178.5) mL in BH group, P=0.398), RBC transfusion amount was 6.31 (6.83) Units in AH group and 5.27 (5.1) Units in BH group (P=0.003). The amount of plasma transfusion was 725.54 (632.76) mL in AH group and 570.12 (532.12) in BH group (P=0.008). Only one patient was re-explored in AH group and none were re-operated in the BH group (P=0.854). The causes of death were heart failure in three, ventricular arrhythmias in one, and multi-organ dysfunction in two patients. In-hospital mortality was 30.7% with four patients of the AH group and 12.5% with two patients of the BH group (P=0.011) (Table 3).

Postoperative CK-MB and Troponin-T levels are given in Table 4. CK-MB levels within the first postoperative four hours were 26.2 (2.8) IU/L and 18.4 (3.4) IU/L in the AH and BH groups, respectively (P=0.041). However, CK-MB levels at the end of the 12^{th} and 24^{th} hours were similar in both groups (P=0.723 and P=0.265, respectively). Peak CK-MB levels were 31.7 (10.1) IU/L and 21.4 (6.7) IU/L in the AH and BH groups, respectively (P=0.015). Troponin-T levels at the 4^{th}, 12^{th} and 24^{th} postoperative hours were all significantly lower in the BH group (Table 4).

Peak Troponin-T levels were 0.23 (0.08) ng/mL in AH group and 0.11 (0.05) ng/mL in BH group (P=0.001). Peak Lactate levels were 4.7 (2.2) mmol/L x and 3.3 (1.6) mmol/L in the AH and BH groups, respectively (P=0.023). The independent effect of BH in decreasing the mortality rates was calculated by logistic regression analysis (Odds ratio (OR) 0.43, 95% confidence interval (CI) 0.22–0.76, P=0.001) (Table 5).

Table 1: Preoperative data

	AH Group (13)	BH Group (16)	*P*-value
Age	55.42 (11.6)	57.92 (8.43)	0.403
Gender (Male/Female)	5/8	6/10	0.361
SPAP	38.45 (11.42)	42.68 (13.01)	0.792
TAPSE	14.12 (1.78)	13.67 (1.13)	0.915
LVEF	57.23 (7.62)	58.65 (8.02)	0.877
Atrial fibrillation	9	11	0.743
NYHA class 3-4	8 (%62)	9 (%56)	0.885
Euro SCORE II (%)	12.4 (9.1)	18.3 (12.4)	0.03
AST (IU/L)	53 (47)	59 (51)	0.501
ALT (IU/L)	57 (68)	62 (71)	0.622
Albumin (g/dl)	3.6 (0.9)	3.7 (1.1)	0.718
Total bilirubin (mg/dl)	3.3 (2.4)	3.5 (3.2)	0.641
Hb (g/dl)	12.1 (1.7)	12.5 (1.8)	0.867
Creatinine (mg/dl)	1.07 (0.2)	1.08 (0.2)	0.906
Preoperative cardiac surgery history			
AVR	0	2	0.552
MVR	3	4	0.855
AVR+MVR	2	2	0.916
MVR+TV Repair	3	4	0.855
No history of prior cardiac surgery	5	4	0.922

AH: Arrested heart, BH: Beating heart, SPAP: Systolic pulmonary artery pressure, TAPSE: Tricuspid annular plane systolic excursion, LVEF: Left ventricle ejection fraction, NYHA: New York Heart Association. AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, Hb: Hemoglobin, AVR: Aortic valve replacement, MVR: Mitral valve replacement, TV: Tricuspid valve

Table 2: Operative data

	AH Group (13)	BH Group (16)	*P*-value
Midline sternotomy	8	7	0.667
Right anterolateral thoracotomy	5	9	0.241
Mechanical valve	7	11	0,188
Bioprosthetic valve	6	5	0,442
CPB duration (min)	78.3 (19.8)	54 (14.6)	0.015
Cross-cl amp duration (min)	48.27 (17.2)	NA	
Total operation duration (min)	167.4 (67.6)	132.2 (39.7)	0.023
Amount of cardioplegia (ml)	1057 (467)	NA	

AH: Arrested heart, BH: Beating heart, CPB: Cardiopulmonary bypass, NA: not applicable

Table 3: Postoperative data

	AH Group (13)	BH Group (16)	*P*-value
Positive İnotropic drug use (dopamine, dobutamine, adrenaline)	9 (69%)	7 (44%)	0.029
Intubation duration (hr)	33 (17)	13 (4)	0.047
Intensive care unit stay duration (day)	2.7 (6.1)	1.7 (3.4)	0.035
Total hospitalization duration (day)	14 (13)	8.7 (6.7)	0.089
Chest tube drainage amount (ml)	575.6 (263.1)	512.3 (178.5)	0.398
Total Transfusion			
RBC (U)	6.31 (6.83)	5.27 (5.1)	0.003
Plasma (mL)	725.54 (632.76)	570.12 (532.12)	0.008
Re-exploration	1	0	0.854
Tracheostomy	2	1	0.116
Mortality	4 (%30.7)	2 (%12.5)	0.011

AH: Arrested heart, BH: Beating heart, RBC: Red blood cell

Table 4: Postoperative CK-MB and Troponin-T levels

	AH Group (13)	BH Group (16)	*P*-value
CK-MB(IU/L) (normal reference 0–25 IU/L) 4.h	26.2 (2.8)	18.4 (3.4)	0.041
CK-MB(IU/L) (normal reference 0–25 IU/L) 12.h	18.8 (3.2)	17.6 (3.9)	0.723
CK-MB(IU/L) (normal reference 0–25 IU/L) 24.h	17.4 (2.6)	15.4 (2.7)	0.265
Troponin-T(ng/mL) (upper reference limit=0.1 ng/mL) 4.h	0.72 (0.38)	0.17 (0.14)	0.023
Troponin-T(ng/mL) (upper reference limit=0.1 ng/mL) 12.h	0.55 (0.22)	0.18 (0.15)	0.012
Troponin-T(ng/mL) (upper reference limit=0.1 ng/mL) 24.h	0.47 (0.22)	0.14 (0.11)	0.028
Peak CK-MB (IU/L) (normal reference 0–25 IU/L)	31.7 (10.1)	21.4 (6.7)	0.015
Peak Troponin-T (ng/mL) (normal reference <0.1 ng/mL)	0.23 (0.08)	0.11 (0.05)	0.001
Peak Lactate (mmol/L)	4.7 (2.2)	3.3 (1.6)	0.023

AH: Arrested heart, BH: Beating heart, CK-MB: Creatine kinase myocardial band

Table 5: Results of the logistic regression analysis

	OR	95% CI	*P*-value
Age	0.86	0.83–0.94	0.178
Female sex	1.01	0.69–2.29	0.242
CPB time	0.93	0.9–1.01	0.752
Beating heart technique with CPB	0.43	0.22–0.76	0.001

OR: Odds ratio, CPB: Cardiopulmonary bypass, CI: Confidence interval

Discussion

Among the literature, this study is first to compare the early postoperative results of BH and cardioplegic arrested heart techniques (CAH) of TVR among the patients having a TAPSE score under 15 mm. Enrolling these patients only helped us obtain a more homogenized patient group in comparison to similar studies. Forfia et al. [10], evaluated 63 consecutive patients with pulmonary hypertension by a right heart catheterization and TAPSE measurement. They demonstrated that patients with a TAPSE score lower than 18 mm had an increased risk of mortality compared to those with a TAPSE score higher than 18 mm. ROC analysis showed that the TAPSE cut-off of 18 mm was highly sensitive of impending death and useful in ruling out the risk of perioperative death (Negative predictive value: 31/31=100%).

Although many improvements have been made in myocardial protection, myocardial ischemia caused by aortic cross clamp and cardioplegia resulting with reperfusion injury are still some of the major problems in open heart surgery. BH cardiac surgery without the use of cross-clamp results in shortened cross-clamp and CPB times, helping the patient avoid systemic inflammatory response caused by extracorporeal circulation and associated negative effects such as myocardial hypoxemia, malnutrition, and electronic imbalance, which may strongly increase morbidity and mortality [1,11-14]. Patients with a poor right ventricle dysfunction such as a TAPSE score lower than 15 mm would benefit from BH the most [7,10,15].

Matsumoto et al. [15] evaluated the catecholamine, CK-MB and Troponin levels released postoperatively in their randomized study involving 50 patients who underwent left cardiac valve surgery. According to their study, shorter CPB times accompanied decreased catecholamine release and resulted in lower CK-MB and troponin release during the postoperative period. In our study, CK-MB levels within the first postoperative four hours and Troponin-T levels at the end of 4^{th}, 12^{th} and 24^{th} hours were lower in the BH group compared to the AH group.

Performing TVR with the arrested heart technique results in CPB with a hemodiluted blood and an increased number of blood transfusions, which bring about transfusion-related complications like plasma and erythrocyte hemolysis, acute pulmonary injury, allergic reactions, metabolic and coagulative abnormalities, volume overload, alloimmunization, immunosuppression, ferrum overload, graft versus host reaction and a remarkable increase in hospitalization costs [16]. In our study, the need of blood transfusion was significantly less in the BH group despite the similar amounts of chest tube drainage. Intensive care unit stay, and intubation times were also lower in the BH group.

Performing TVR with CAH provides an easier surgical exposure and bloodless operative field due to less amount of blood flow of coronary sinus and the lack of leaflet movement (especially in case of thrombus, vegetation or tumoral tissue). However, TVR with BH is a more complicated process for the patient due to limited surgical vision resulting in a more difficult surgical manipulation [1,6,8,15]. There are also some advantages of BH. For example, an atrioventricular block caused by the sutures placed on the septal side would easily be observed by the surgeon and early manipulation would prevent the patient from needing a permanent pacemaker.

In a beating heart, tricuspid valve environment decreases by 19% and tricuspid valve area decreases by 30% during systole, which may cause a reasonable shearing force improvement on posterior annulus resulting with the dehiscence of prosthetic valve [17-19]. On the follow-up, we did not observe any case with dehiscence of the prosthetic valve. However, for more reliable results a longer follow-up duration would be beneficial.

Limitations

The main limitation of our study is the small number of the cases. Further, multi-center studies involving larger number of cases would provide more realistic and meaningful statistical results.

Conclusion

Tricuspid valve insufficiency in patients having a TAPSE index lower than 15 mm is a strongly challenging process to operate and manage peroperative times both for the patients and clinicians. Therefore, as clinicians, it is our duty to use recent operational technique improvements. In our study, CPB and total operational time, the need of positive inotropic drug, intubation and intensive care unit stay duration, and mortality rate were significantly lower in the BH group. Operative and postoperative outcomes of BH technique in TVR process encourages us to recommend using the BH technique in TVR among the patients with a TAPSE score lower than 15 mm.

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Bacterial profiles and antibiotic susceptibility pattern in patients with chronic dacryocystitis

Kronik dakriyosistitli hastalarda bakteri profili ve antibiyotik duyarlılık paterni

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Ethics Committee Approval: Non-Interventional Clinical Research Ethics Committee of Karabuk University (Date: 12/8/2019; No:2019/60). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Dacryocystitis is an infection of the lacrimal apparatus, and without appropriate treatment, it can lead to serious complications such as orbital cellulitis and meningitis. In this study, we aimed to determine the frequency and antibiotic susceptibility of the bacterial pathogens in chronic dacryocystitis.

Methods: This cross-sectional study included 60 patients diagnosed with chronic dacryocystitis in the Ophthalmology department of Karabuk Training and Research Hospital between December 2019 and February 2020. Aerobic culture tests were performed using swab samples obtained from the lacrimal punctum of the patients. Identification and antibiotic susceptibility of isolates were determined using Phoenix-100™ (Becton Dickinson, Sparks, MD, USA) fully automated system.

Results: In total, 43 of 60 (71.7%) of patients were females, and the mean age was 56.78 (12.67) years. Aerobic bacteria were isolated from 51 (85%) of 60 samples. The most common pathogens were *Pseudomonas aeruginosa* (45%), *Staphylococcus epidermidis* (15.7%), and *Staphylococcus aureus* (11.8%) respectively. The most effective antibiotics against Gram-negative bacteria were aminoglycosides with a susceptibility of >90%. Gentamicin was also active against 85.7% of Gram-positive bacteria. Although in-vitro efficacy of ciprofloxacin was 81.5% against Gram-negative bacteria, it was mildly active against Gram-positive bacteria (52.5%). Methicillin resistance was detected in 33% of *Staphylococcus* species.

Conclusion: In our region, aminoglycosides may be preferred instead of fluoroquinolones for the empirical treatment of chronic dacryocystitis. However, since our study is single-centered and small-sized, these findings should be supported by large-scale studies in the future.

Keywords: Dacryocystitis, *Corynebacterium striatum*, *Pseudomonas aeruginosa*, Antibiotic, Ciprofloxacin, Gentamicin

Öz

Amaç: Dakriyosistit lakrimal aparatusun enfeksiyonu olup, uygun şekilde tedavi edilmezse orbital sellülit, menenjit gibi ciddi komplikasyonlara yol açabilir. Bu çalışmada kronik dakriyosistitte, bakteriyel patojenlerin sıklığını ve antibiyotik duyarlılık profilini saptamayı amaçladık.

Yöntemler: Bu kesitsel çalışmaya Aralık 2019- Şubat 2020 tarihleri arasında Karabük Eğitim ve Araştırma Hastanesi Göz hastalıkları bölümünde kronik dakriyosistit tanısı almış 60 hasta dahil edilmiştir. Hastaların punktumundan alınan sürüntü örneklerinden aerop kültür yapılmıştır. İzolatların identifikasyonu ve antibiyotik duyarlılığı Phoenix-100 (Becton Dickinson,MD, PA,USA) tam otomatize sistemle saptanmıştır.

Bulgular: Kronik dakriyosistitli toplam 60 hastanın 43'ü (%71,7) kadın olup yaş ortalaması 56,78 (12,67) idi. Altmış örneğin 51 inde aerop bakteri üredi (%85). En sık izole edilen patojenler *Pseudomonas aeruginosa* (%45), *Staphylococcus epidermidis* (15,7) ve *Staphylococcus aureus* (%11,8) idi. Gram negatif bakterilere en etkili antibiyotikler aminoglikozidler olup, duyarlılık %90'ın üzerinde idi. Gentamisin, Gram-pozitif bakterilere de %85,7 oranında etkili idi. Siprofloksasinin etkinliği Gram- negatiflerde %81,5 iken, Gram-pozitif bakterilere düşük etkili idi (%52,5). Stafilokok türlerinin %33' ünde ise metisilin direnci saptandı.

Sonuç: Yöremizde kronik dakriyosistitin ampirik tedavisinde florokinolonlar yerine aminoglikozidler tercih edilebilir. Bununla birlikte, çalışmamız tek merkezli ve küçük boyutlu olduğundan, bu bulgular gelecekte büyük ölçekli çalışmalarla desteklenmelidir.

Anahtar kelimeler: Dakriyosistit, *Corynebacterium striatum*, *Pseudomonas aeruginosa*, Antibiyotik, Gentamisin, Siprofloksasin

Introduction

Dacryocystitis is the most common inflammatory disease of the lacrimal system. It may occur due to primary or secondary obstructions. Primary obstruction is usually idiopathic, whereas secondary obstruction occurs as a result of infection, trauma or neoplasm [1,2].

In acute dacryocystitis, obstruction of the lacrimal sac leads to the accumulation of tears, predisposing for infection. Clinical symptoms include pain, swelling, and redness in the lacrimal sac region [2]. In chronic dacryocystitis, there is chronic inflammation of the lacrimal sac, connective tissue, and nasal mucosa associated with dilation of the lacrimal sac due to nasolacrimal duct stenosis [1,3]. Also, there is no sign of infection; however, compression of the inflamed sac results in discharge of purulent material from the lacrimal punctum [4]. Insufficient lacrimal drainage leads to the colonization of microorganisms, leading to infection in the lacrimal sac. In previous studies, it has been shown that inflammation and fibrosis occur secondary to bacterial colonization in the lumen of the lacrimal sac in chronic cases [1,5]. Chronic dacryocystitis poses a potential risk of infection to the cornea and other neighboring tissues [6]. Without proper treatment, it can lead to life-threatening complications including orbital cellulitis, cavernous sinus thrombosis, and meningitis [2]. Although treatment guidelines recommend bacterial culture testing in patients with dacryocystitis, empirical antibiotic treatment is generally preferred [6,7]. However, the microbial spectrum of chronic dacryocystitis may change over time and lead to treatment failures [2,8]. Therefore, identification and antibiotic susceptibilities of microorganisms should be determined in patients with dacryocystitis.

In this study, we aimed to contribute to the empirical antibiotic treatment options by determining the frequency and in vitro antibiotic susceptibility profiles of bacterial pathogens in patients with chronic dacryocystitis.

Materials and methods

This cross-sectional study included 60 patients who were admitted to the ophthalmology department of Karabuk Training and Research Hospital between December 2019 and February 2020 and diagnosed with chronic dacryocystitis. Patients who underwent surgery for dacryocystitis, who were treated using topical or systemic antibiotics within the last 10 days, or those not wanting to participate in this study were excluded. Informed consent was obtained from all patients before the study. This study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the Karabuk University Non-Interventional Ethics Committee (Date: 12/8/2019; No:2019/60).

Nasolacrimal duct irrigation was performed using sterile saline by inserting a lavage cannula from the lower punctum of the patients. Swab samples were obtained from the fluid and pus draining from the lower and upper puncti, transferred onto the Stuart transport medium (COPAN, Brescia, Italy), sent to the microbiology laboratory, inoculated onto 5% sheep blood agar (RTA laboratories, Kocaeli, Turkey), chocolate agar (RTA), and eosin methylene blue agar (RTA) and then incubated at 35 °C for 24–48 hours under aerobic conditions. Identification and antibiotic susceptibility testing of the isolates were performed using BD -Phoenix 100 (Becton Dickinson Diagnostic Systems, Sparks, MD, USA) fully automated system. Kirby–Bauer disc diffusion method was used for *Corynebacterium striatum*. Antibiotic susceptibility results were evaluated according to the European Committee on Antimicrobial Susceptibility Testing guidelines [9]. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 were used as quality control strains.

Statistical analysis

Statistical analysis of the data was performed using Minitab 17 (Minitab, Inc., PA, USA) program. Descriptive statistics were expressed as number, percentage, and mean (standard deviation: SD). Anderson–Darling test was used to determine whether the data were normally distributed. Two-sample t-test was used to compare continuous variables. Pearson chi-square or Fisher's exact test were used for evaluation of categorical variables. A *P*-value ≤ 0.05 was considered statistically significant at 95% confidence interval.

Results

The mean age of patients was 56.78 (12.67) years. Among 60 patients, 43 (71.7%) were females and 17 (28.3%) were males. The mean ages of females and males were similar with 55.67(13.59) years and 59.59 (9.79) years, respectively *(P*=0.221). Bacterial growth was detected in 51 (85%) of 60 samples, of which 37 (72.5%) were isolated from females and 14 (27.5%) from males. Gram negative bacterial growth was detected in 21 of 37 females and 6 of 14 males, while 8 males and 16 females were found to have Gram positive bacterial growth. There was no significant difference between gender and bacterial species (Gram-positive/Gram-negative) (*P*=0.375). The distribution of bacterial pathogens isolated from the samples are presented in Table 1. Among 51 isolates, 27 (53%) were Gram-negative and 24 (47%) were Gram-positive bacteria. The most common pathogens were *Pseudomonas aeruginosa* (45%), followed by *S. epidermidis* (15.7%), and *S. aureus* (11.8%). Twenty-three (85.2%) of 27 Gram-negative bacteria were *P. aeruginosa* and 4 other isolates were *Enterobacterales* species (spp.) (2 *Klebsiella pneumonia*e and 2 *Proteus mirabilis*). Antibiotic susceptibilities of Gram-negative strains are presented in Table 2. They were susceptible to more than 80% of all evaluated antibiotics. The most active antibiotics were amikacin, gentamicin, and netilmicin, with susceptibility rates of 96.3%, 92.6%, and 92.6%, respectively. The lowest susceptibility was detected for ciprofloxacin (81.5%). In other words, approximately 20% of the Gram-negative isolates were resistant to ciprofloxacin.

Antibiotic susceptibility rates of Gram-positive bacteria are shown in Table 3. Eighteen (75%) of 24 Gram-positive bacteria were *Staphylococcus* spp., 6 of which (33.3%) were resistant to methicillin. Four of the methicillin-resistant strains were coagulase-negative staphylococcus (CNS) and 2 were *S. aureus*. The most effective antibiotics were vancomycin, trimethoprim/sulfamethoxazole (TMP-SMX), and gentamicin, with susceptibility rates of 100%, 95.2%, and 85.8%, respectively. On the other hand, almost half of the isolates

(47.6%) were resistant to ciprofloxacin, levofloxacin, and erythromycin.

Table 1: Distribution of bacterial pathogens isolated from patients with chronic dacryocystitis (n=51)

Bacterial species	n (%)
Gram-negative bacteria	
Pseudomonas aeruginosa	23(45)
Klebsiella pneumoniae	2(3.9)
Proteus mirabilis	2(3.9)
Gram-positive bacteria	
Staphylococcus species	18(35.3)
S.epidermidis	8(15.6)
S. aureus	6(11.8)
S.schleiferi	3(5.9)
S. saprophiticus	1(2)
Corynebacterium striatum	3(5.9)
Streptococcus pyogenes	3(5.9)
Total	51(100)

Table 2: Antibiotic susceptibilities of Gram-negative bacterial strains (n=27)

	P.aeruginosa (n=23)	Enterobacterales spp. (n=4)	Total % (susceptible/total)
Amikacin	23	3	96.3 (26/27)
Netilmicin	22	3	92.6 (25/27)
Gentamicin	22	3	92.6 (25/27)
Ciprofloxacin	20	2	81.5 (22/27)
Cefepime	22	2	88.9 (24/27)
Ceftazidime	22	2	88.9 (24/27)
TZP	21	3	88.9 (24/27)
TMP-SMX	*	3	
Levofloxacin	*	2	
Moxifloxacin	*	2	

TZP: Piperacillin-tazobactam, TMP-SMX: Trimethoprim-sulfamethoxazole, * no EUCAST recommendation

Table 3: Antibiotic susceptibilities of Gram-positive bacterial strains (n=24)

Antibiotic	CNS (n=12)	*S.aureus* (n=6)	*S.pyogenes* (n=3)	*C.striatum* (n=3)	Total % (susceptible/total)
Ciprofloxacin	6	4	*	1	52.4 (11/21)
Clindamycin	10	5	3	1	79.2 (19/24)
Erythromycin	5	3	3	*	52.4 (11/21)
Gentamicin	10	5	*	3	85.8 (18/21)
Levofloxacin	6	3	2	*	52.4 (11/21)
Tetracycline	4	6	3	2	62.5 (15/24)
Tobramycin	6	6	*	*	66.6 (12/18)
TMP-SMX	10	5	**	*	83.3 (15/18)
Vancomycin	12	6	3	3	100 (24/24)
Moxifloxacin	8	4	2	2	66.6 (16/24)
Methicillin (Oxacillin)	8	4	**	**	66.6 (12/18)

CNS: coagulase-negative staphylococcus, TMP-SMX: Trimethoprim-sulfamethoxazole, * no EUCAST recommendation, ** not applicable

Discussion

Dacryocystitis is the most common infection of lacrimal apparatus with unknown etiology. In the literature, it has been reported that female gender is a risk factor for the development of dacryocystitis [9]. Narrower nasolacrimal canal in females compared to males and hormonal changes may play a role [9-11]. Indeed, in our study, 70% of patients were females. In previous studies, 63.3%–78% of patients with dacryocystitis were reportedly females [2,9,10,12].

In this study, we have included 60 patients with chronic dacryocystitis. To prevent the development of a possible infection in neighboring tissues, dacryocystitis should be treated for a sufficient period of time with effective antibiotics. It is important to define the current microbiological profile, because the causative agents can change over time. Although Gram-positive bacteria have been reported as a common cause in many studies, Gram-negative bacteria were isolated more frequently in this study. In fact, Gram-negative bacteria are increasingly reported as the cause of chronic dacryocystitis [13,14]. For instance, Briscoe et al. [14] have reported that 25 of 41 bacteria (61%) isolated from 39 patients with dacryocystitis were Gram-negative, with the most frequently isolated species being *P. aeruginosa* (22%), similar to our study. In a study from Turkey conducted by Gümüşsoy et al. [12] in 150 samples obtained from 50 patients with chronic dacryocystitis, *P. aeruginosa* (10.8%) was the most frequently isolated Gram-negative pathogen. In the literature, the frequency of *Pseudomonas* spp. in patients with dacryocystitis has been reported in highly varying rates between 9.6% and 61% [1,2,9,14]. This may be due to regional differences and preferences of antibiotic prescription. In addition, overuse of antibiotics in patients with chronic dacryocystitis can lead to the selection of resistant strains. *Pseudomonas* aeruginosa is one of the opportunistic pathogens occurring particularly in hospitalized patients with chronic diseases who have had long-term antibiotic treatments. The fact that *P. aeruginosa* is naturally resistant to many routinely used antibiotics and that antimicrobial resistance is increasing limits the treatment options. Indeed, Infectious Diseases Society of America (IDSA) grouped six bacterial species in 2009 with the acronym ESKAPE [16], *Enterococcus faecium*, *S. aureus*, *K. pneumoniae*, *Acinetobacter baumanni*, *P. aeruginosa*, and *Enterobacter* spp., all of which show multidrug resistance and can escape via different resistance mechanisms from the biocidal effect of antibiotics. However, IDSA does not recommend antibiotics with local antibiotic resistance above 20% in empirical treatment [20]. Thus, empirical treatment protocols should be established according to the regional antibiotic resistance profiles.

In this study, the susceptibility of Gram-negative isolates to aminoglycoside antibiotics was over 90%. Similarly, 93%–99% susceptibility to amikacin [18-20] and 75%–91% susceptibility to gentamicin [12,18,19] have been reported in various studies in Turkey. In our study, Gram-negative strains were 81.5% susceptible to ciprofloxacin. In the national ARMOR surveillance study conducted in the USA, ciprofloxacin susceptibility was 94.9 % in 389 ocular *P. aeruginos*a strains [21]. Turkey-based studies have reported that susceptibility to ciprofloxacin was 51%–70% [12,22,23]. In this study, ciprofloxacin resistance (18.5%) was close to the empirical treatment limit (20%). Hence, aminoglycosides should be preferred instead of quinolones against infections caused by Gram-negative bacteria. Besides, 88.9% susceptibility was detected against cefepime, ceftazidime, and piperacillin/tazobactam. However, these antibiotics are not available in topical form and can only be administered parenterally, which makes them less preferred in the treatment of dacryocystitis in our region.

In this study, *Staphylococcus* spp. (35.2%, 18/51) were the second most common isolates. In previous studies, *Staphylococcus* spp. had been reported as the causative pathogens in dacryocystitis with a frequency ranging from 39%–75% [12,14,24,25]. In our study, 6 (33.3%) of 18 *Staphylococcus* strains were resistant to methicillin. Among these 6 strains, 4 were methicillin resistant CNS, and 2 were methicillin resistant *S. aureus* (MRSA). MRSA was first described in the United Kingdom In 1961 [26]. Recently, MRSA prevalence is below 5% in Nordic countries, but it is 25%–50% in southeast Europe. In Turkey, it has been reported as 30% [27]. Mills et al. [1] reported that the rate of MRSA in dacryocystitis cases is 21.7%. This rate was 20% in a study by Chung et al. [2] and 42.2% in the ARMOR surveillance study [21]. In this study, the most effective antibiotics for *Staphylococcus* spp. were vancomycin,

gentamicin, clindamycin, and TMP-SMX. Almost half of the strains were resistant (47.6%) to ciprofloxacin, which is commonly used. Fluoroquinolones, which are broad-spectrum antibiotics effective against many Gram-positive and Gram-negative bacteria, are often prescribed in ocular infections owing to their availability in both oral and eye drops forms, good ocular penetration, and low toxicity [26,28]. Ciprofloxacin, which is a second-generation quinolone derivative, has greater efficacy against Gram-negative microorganisms, whereas limited efficacy of ciprofloxacin has been demonstrated against Gram-positive bacteria [28]. It was approved for the topical treatment of bacterial corneal ulcers in 1990 [26]. Compared with ciprofloxacin, moxifloxacin, which is a fourth-generation quinolone, has been reported to have a broader efficacy against Gram-positive pathogens [28]. In this study, the susceptibility rates to ciprofloxacin and moxifloxacin were 52.4% and 66.6% respectively. In the literature, ciprofloxacin susceptibility of *Staphylococcus* spp. ranged from 60.2%–93.8% [15,21,23,26]. Moreover, a trend of increase in resistance of ocular pathogens against fluoroquinolones has been emphasized [26,28]. The ARMOR surveillance study reported that ciprofloxacin resistance of *S. aureus* strains was 39.8%, whereas this rate was 76.1% in MRSA. In addition, moxifloxacin resistance was 56.8% among MRSA strains [21]. In this study, the susceptibility of Gram-positive bacteria against gentamicin was 85.8%. In the literature, susceptibility rates of gentamicin have been reported as 79.1%–90.9% [12,23,29,30]. Although gentamicin has been frequently used in ocular infections for a long time, the resistance rate is still low, therefore, it can be preferred instead of quinolones in empirical treatment of ocular infections.

In the present study, three *C. striatum* were isolated as ocular pathogens. All strains were susceptible to vancomycin and gentamicin, but one strain was resistant to ciprofloxacin and erythromycin. Antibiotic resistance is gradually increasing in *C. striatum* strains. In the literature, among clinical *C. striatum* isolates, resistance to gentamicin and ciprofloxacin were 7.2%–75% [31-34] and 83%–100% [31.32, 35], respectively. In ocular *Corynebacterium* isolates, ciprofloxacin resistance has been reported as 50% [3,36]. *Corynebacterium* spp. are inhabitants of the skin and mucous membranes which can cause opportunistic infections. Resistance to fluoroquinolones in *Corynebacterium* spp. is caused by point mutations occurring in the gyrase gene. After exposure to fluoroquinolones, spontaneous mutations have reportedly occurred in skin and mucous membrane colonizers such as *Corynebacterium* spp., with the consequential emergence of quinolone-resistant strains [37]. Therefore, gentamicin may be preferred instead of ciprofloxacin in infections of *C. striatum*.

Limitations

This study has some limitations. It is a single-center study with a small sample size; therefore, our study results cannot be generalized. In addition, only aerobic culture testing was performed, and the presence of anaerobic bacteria was not investigated.

Conclusions

In this study, *P. aeruginosa* and *S. epidermidis* are most frequently isolated pathogens from patients with chronic dacryocystitis. Based on our study results, aminoglycoside antibiotics are highly effective against both Gram-negative and Gram-positive bacteria; however, quinolones showed reduced efficacy against Gram-positive bacteria. Thus, in our region, in patients with chronic dacryocystitis, aminoglycosides may be preferred instead of quinolones for empirical antibiotic treatment. On the other hand, these study results are preliminary, so they should be supported by large-scale studies. Bacterial profiles and antibiotic susceptibility can change over time in patients with chronic dacryocystitis. They should be monitored with active surveillance.

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Serum RANKL levels and bioelectric impedance assessments in knee osteoarthritis patients

Diz osteoartritli hastalarda serum RANKL düzeyleri ve biyoelektrik empedans değerlendirmeleri

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Abstract

Aim: Osteoarthritis (OA) is a common joint disease that is caused by mechanical, genetic, and biochemical factors, and knee OA is one of the reasons of mobility limitation and disability. The receptor activator of NF-κB ligand (RANKL) is directly involved in the differentiation of osteoclasts through its receptor RANK. In this study, we aimed to study circulating serum levels of RANKL, and assess knee bioelectric impedance in control and patients with knee OA.

Methods: In this case-control study, OA severity was evaluated by the Kellgren–Lawrence grading scale, based on which we categorized patient groups. There were 22 control individuals (Grades 0 and 1), 11 early (Grade 2) and 30 late OA patients (Grades 3 and 4). We evaluated the performance of the bioimpedance phase angle values at 50 kHz. The RANKL protein levels in the serum were quantified using Enzyme-Linked Immunosorbent Assay (ELISA).

Results: It was observed that the control group could not be differentiated from the study group by using phase angle values (P=0.925). Concerning the RANKL levels, although it shows a relative increase in the study group, it did not reach a significant level (P=0.116).

Conclusion: The phase angle values at 50 kHz and RANKL levels may not be used in predictive detection of knee OA. Additional studies with larger sample sizes are needed to interpret if these changes are consistent and clinically related.

Keywords: RANKL, Bioimpedance, Knee osteoarthritis

Öz

Amaç: Osteoartrit (OA), mekanik, genetik ve biyokimyasal faktörlerin etkilerinden kaynaklanan yaygın bir eklem hastalığıdır ve diz OA'i, hareket kısıtlaması ve engel nedenlerinden biridir. Bu çalışmada NF-κB ligandının (RANKL) reseptör aktivatörünün dolaşımdaki serum seviyelerini incelemeyi ve kontrolde ve diz OA'i olan hastalarda biyoelektrik empedansını değerlendirmeyi amaçladık.

Yöntemler: Çalışmamız bir vaka-kontrol çalışması olarak tasarlanmıştır. OA şiddeti Kellgren-Lawrence derecelendirme skalası ile değerlendirildi, gruplar 22 sağlıklı kontrol (derece 0 ve 1), ve çalışma grubu 11 erken (derece 2) ve 30 geç OA (derece 3 ve 4) olarak tanımlandı. 50kHz'te biyoimpedans faz açısı değerlendirildi. Serumdaki RANKL protein seviyeleri Enzyme Linked Immunosorbent Assay (ELISA) metodu ile ölçüldü.

Bulgular: Kontrol grubunun faz açısı değerleri kullanılarak diz OA grubundan ayırt edilemediği gözlendi (P=0,925). RANKL düzeyleri ile ilgili olarak, çalışma grubunda göreceli bir artış tespit edilse de, anlamlı bir seviyeye ulaşmadı (P=0,116).

Sonuç: 50 kHz faz açısı değerleri ve RANKL seviyeleri, diz OA'sının tespitinin öngörülmesinde kullanılamayabileceği belirlenmiştir. Bu değişikliklerin tutarlı ve klinik olarak ilişkili olup olmadığını yorumlamak için daha büyük örnek büyüklüklerine sahip ek araştırmalara ihtiyaç vardır.

Anahtar kelimeler: RANKL, Biyoimpedans, Diz osteoartiriti

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Introduction

Knee osteoarthritis (OA) is a common and disabling condition in middle-aged adults and the elderly, and its predominance has been growing with the advancing age of the population [1,2]. OA of the knee begins with the degeneration of articular cartilage and modifications to subchondral bone. As the disease progresses, destruction and deformation of cartilage occurs and is sometimes associated with reactive changes to bone and secondary synovitis [3].

Bioimpedance is characterized by the passive electrical components of biological tissues. It defines the capacity of biological structures to resist the flow of an alternating current. It is also incorporated with conductivity and permeability intracellular and extracellular electrolytes at different frequencies [4]. Hence, bioimpedance can be used for researching electrochemical processes that occur in biological tissues and examining physiological alterations associated with diseases [5]. Bioimpedance spectroscopy is a non-invasive, and inexpensive method that had been practiced in a high number of biomedical researches.

Osteoblastic lineage cells produce receptor activator of NF-κB ligand (RANKL), which is required to mediate bone resorption by regulating osteoclastogenesis. Osteoclastogenesis and osteoclast activity stimulates RANKL via connecting to the cell surface receptor RANK, which is located on precursor and mature osteoclasts [6-8]. Systemic changes like sex steroids, parathyroid hormone, and growth factors cause age-related bone degeneration, and can modulate RANKL in-vivo [9].

Magnetic resonance imaging and arthroscopy are essential methods to evaluate the severity of the OA. However, these methods have a limited role in diagnosis, Favero et al. [10] reported that knee articulation radiography could be normal in the initial stages of OA. Therefore, it is necessary to explore quantitative and sensitive methods for the examination of this disease. We aimed to study circulating serum levels of RANKL and assess knee bioelectric impedance in patients with different stages of knee OA, in addition to correlating these parameters with disease severity to combine all results and reveal if these parameters could be used as markers for the evaluation of knee OA.

Materials and methods

Study population

This clinical study was conducted at SANKO University, Department of Physiotherapy and Rehabilitation with the approval of the SANKO University Ethics Committee (2019/05-02). Written informed consent was acquired from all patients who agreed to participate in our study. Between May 2019 and February 2020, a total of 63 participants, including 41 knee OA patients diagnosed according to the American College of Rheumatology criteria [11] and 22 controls, were selected for the study. All participants included in the study were examined in terms of age, gender, BMI and any medications used. The patients with inflammatory rheumatic diseases, infectious/endocrine-related arthropathies, previous knee injuries, clinically unstable medical diseases, and those receiving chronic drug treatment that may alter body fluid balance were excluded. Blood samples were collected from the study and control groups at the time of diagnosis before any treatment was started. Bioimpedance measurements were performed on all volunteers in cooperation with the Physiotherapy and Rehabilitation Department. The OA severity was evaluated and classified by the Kellgren–Lawrence (KL) grading scale [12]. Grades were classified as 0 (normal), 1 (possible osteophyte), 2 (absolute osteophyte and possible joint space narrowing), 3 (mild osteophyte and/or absolute joint space narrowing), and 4 (dominant osteophyte, severe joint space narrowing and/or bone sclerosis). Patients with grade 0 and 1 were included in the control group (n=22), whereas the study group was classified as grade 2 (n=11) early knee OA, and grade 3 and 4 late knee OA (n=30).

Bioimpedance measurements

Bioimpedance analyzer (Quadscan 4000, Bodystat Inc.) was connected to the 1.0 cm disposable Ag/AgCl disc electrodes (3M, Brazil). The electrode placement protocol was set to maximize the current pathway in synovial fluid and minimize the variable's influence [13]. For this reason, two-disc electrodes were placed on the lateral and medial sides of the interarticular line of the knee, the volunteers were seated, and their knee was flexed 90 degrees. The purpose of electrode usage is to send an electrical signal to the synovial fluid and to collect its response [14]. The current was sent in multiple (5, 50, 100, and 200 kHz) frequencies for bioimpedance measurements. Many bioimpedance systems utilize 50 kHz as a frequency where the capacitor's reactance (X_C) becomes relatively small so that the current is defined mostly by resistance (R). The frequency of 50 kHz is one of the most essential and optimal frequencies. Besides, most published studies have been conducted using devices at a frequency of 50 kHz to differentiate the structures. Due to the logic of this reasoning, we have chosen to illustrate our results only for 50 kHz. We calculated the phase angle values by using arctan (X_C/R) formulas and investigated its values in this frequency [15]. Five phase angle measurements were obtained from each volunteer within 1-2 minutes, and their mean values were used for analysis.

ELISA for RANKL in serum

Total serum RANKL levels were quantified using a direct competitive chemiluminescent enzyme-linked immunosorbent assay (ELISA), RANKL kit (Cloud Clone Corp, TX, USA) considering the manufacturer's instructions. Absolute values were obtained based on a standard curve. The absorbance of the reaction mixture was measured at 450 nm. The sample concentrations (ng/ml) of RANKL were calculated from the standard curve.

Statistical analysis

IBM SPSS Statistics 23 was utilized for statistical analyses. Descriptive statistics were presented as mean and standard deviation or median and minimum-maximum values and percentages. For continuous variables, the Kolmogorov-Smirnov test was used to assess the normality of the data. Independent sample t-test and Mann Whitney U tests were used to compare normally and non-normally distributed two groups, respectively. Kruskal-Wallis test was utilized for comparing more than two groups with non-normally distributed data. Chi-

square test was used for comparison of categorical data. *P*-value <0.05 was considered statistically significant.

Results

This research was conducted on a total of 63 volunteers. The demographic data, RANKL levels and bioimpedance characteristics of the study and control groups are presented in Table 1. Age and BMI values were significantly lower in the control group than the study group (P<0.001). The phase angle values of the two groups were similar (P=0.925) (Figure 1). Concerning the RANKL levels, although it shows a relative increase in the study group, the difference was not significant (P=0.116). Kruskal-Wallis test was performed to compare RANKL levels and phase angle values between the control, early and late knee OA groups. There were no significant differences between these three groups, and the pairwise comparison was not done.

Table 1: Demographic and bioimpedance characteristics of the study and control groups

	Control group (n=22)	Study group (n=41)	*P*-values
Age[a] (years)	56.3 (6.41)	65.3 (8.66)	<0.001
Gender[b] (M/F)	36.4/63.6	17.1/82.9	0.160
BMI[a] (kg/m^2)	24.7 (4.61)	31.3 (4.65)	<0.001
RANKL[c] (ng/ml)	9.27[9.2-11.4]	9.52[9.2-13.6]	0.116
Phase angle[c] (degree)	14.8[4.8-41.3]	15.4[6.6-42.2]	0.925

[a] Measurements are presented as mean (SD), [b] Measurements are presented as percentage, [c] Measurements are presented as median [minimum-maximum]

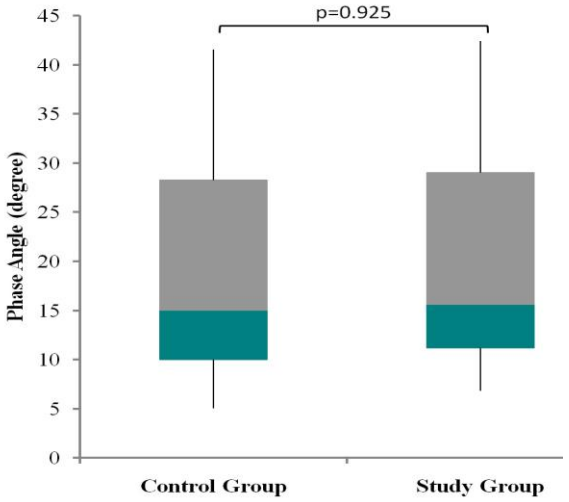

Figure 1: Box plot of phase angle results. The box border represents the interquartile range, the horizontal line in the box is the median. Insignificant differences between control and study groups of phase angle was shown.

Discussion

OA is a common form of degenerative joint disease that affects the western population. The knee is the main peripheral joint that is affected by age-related factors and OA in the knee results in progressive loss of function, pain, and stiffness [16]. Approximately one-tenth of the population over 50 years is estimated to be affected by this disease [17]. The effect of genetic components is evident in the prevalence of knee OA, but the responsible gene is not exactly known. Spector et al. [18] revealed that the effect of genetic factors on hand and knee radiographic OA is between 39% and 65% in women. Radiological evaluation of joint OA is based on plain films as gold standard research with high-resolution MRI evaluation [19]. These investigations are ineffective for the early detection of the condition, which is not always associated with patients' observing symptoms or progression of the disease [20-22]. Symptomatic OA patients often have significant and irreparable cartilage damage, resulting in knee arthroplasty as a final solution. It would be valuable for patients and health care systems if it were the potential to scan high-risk patients by using a biomarker examination. The success of the biomarkers utilized in this context will depend on their ability to identify the beginning of this biological process and respond to interventions in a timely manner [23].

RANKL originates from the surface of osteoblasts that bind to RANK, plays a crucial role in the improvement of osteoclastogenesis, osteoclast maturation, and activation and prevention of apoptosis of osteoclastic cells [24]. Cooperation between RANKL and RANK manages to improve bone loss and resorption [6]. The RANKL activity is the necessary factor in the improvement of bone damage in inflammatory joint diseases and defines the extent of bone destruction mediated by osteoclasts [25]. In our study, the BMI levels of the study group were higher compared to the control group. It is already known that BMI is a significant risk factor for OA [26]. Also, there was no significant differences between BMI categories and serum RANKL levels [27]. There are some studies in the literature concerning serum RANKL levels in knee OA patients. Pilichou et al. [28] evaluated 37 patients with primary knee OA and demonstrated that patients had higher serum RANKL levels compared to 20 controls. In another study, comprising 105 patients suffering from knee OA, transcript levels of the RANKL mRNA were measured using real-time quantitative RT-PCR, and it was shown that RANKL mRNA may be used to diagnose this disease at an early stage when radiological features do not reflect the degradation of articular cartilage [29]. In terms of this protein level, we did not find any significant differences between these two groups.

There are a lot of studies in the literature that use phase angle value to differentiate healthy and diseased states, according to which this value increases with improving clinical status [30,31]. In a study that used phase angle to differentiate structures, it was shown that low PA was associated with tumor, cell death or decreased cell integrity, but high PA was associated with the healthy cell or cell membrane [32]. We did not detect any significance to differentiate the study group from controls. Some limited studies investigated the application of a bioimpedance spectroscopy technique to diagnose knee OA. In a study that consisted of 14 knee OA patients and seven controls in which electrode placement was in the same pattern as ours, the authors suggested that bioelectrical impedance resistance evaluation is a valid method to determine the inflammatory pathological conditions of this joint [33].

Limitations

Electrode placement, electrode sizes and the position of the patient's knee may affect the penetration depth of the signal in bioimpedance measurements. To overcome these limitations electrode sizes are required to clarify whether these changes are clinically relevant and consistent. The placements of electrodes and the knee position with different angles should be considered.

Conclusions

Our results indicate that serum RANKL and phase angle values may not be a predictive marker of knee OA progression. Further controlled clinical researches with larger samples are needed.

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The relationship between alexithymia, anxiety, depression, and severity of the disease in psoriasis patients

Psoriasis hastalarında aleksitimi, anksiyete ve depresyonun hastalığın şiddeti ile ilişkisi

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Abstract

Aim: It is known that psychological factors are significant in the onset and exacerbation periods of psoriasis. The purpose of this study is to evaluate the levels of anxiety, depression, and alexithymia in psoriasis patients and to determine their relationship with the severity of disease and quality of life.

Methods: In this case-control study, 71 patients with psoriasis and 86 healthy people constituted the study and control groups, respectively. The clinical severity of psoriasis was determined by the "Psoriasis Area Severity Index" (PASI). "Dermatological Life Quality Index" (DLQI) form was conducted on the patients, and the "Toronto Alexithymia Scale", "Beck Depression Scale" and "Beck Anxiety Scale" questionnaires were used for both the patients and the controls.

Results: Anxiety and depression scores in psoriasis patients were significantly higher than controls (P=0.029, P=0.003, respectively), but there was no significant difference between alexithymia scores (P=0.158). A positive correlation was found between PASI and alexithymia scores (P=0.004), and between the DLQI score of psoriasis patients and anxiety, depression, alexithymia, and PASI scores (P<0.001, P=0.006, P=0.004, P=0.001, respectively).

Conclusion: In our study, anxiety and depression levels were high in psoriasis. As the levels of anxiety, depression, and alexithymia increased, the quality of life deteriorated. Psoriasis patients should be not evaluated dermatologically only, but also be assessed psychologically and directed to the psychiatry outpatient clinic when necessary.

Keywords: Anxiety, Depression, Alexithymia, Psoriasis, Quality of life

Öz

Amaç: Psoriasis hastalığının başlangıcında ve alevlenme dönemlerinde psikolojik faktörlerin önemli olduğu bilinmektedir. Bu çalışmanın amacı psoriasis hastalarında anksiyete, depresyon ve aleksitimi düzeylerinin değerlendirilmesi ve bunların hastalığın şiddeti ve yaşam kalitesi ile ilişkisinin saptanmasıdır.

Yöntemler: Bu vaka-kontrol çalışmasında, 71 psoriasis tanılı hasta çalışma grubumuzu, 86 sağlıklı kişi ise kontrol grubumuzu oluşturdu. Psoriasis hastalığının şiddeti Psoriasis Alan Şiddet İndeksi (PAŞİ) ile belirlendi. Psoriasis hastalarına "Dermatolojik Yaşam Kalite İndeksi" (DYKİ) formu, tüm katılımcılara ise "Toronto Aleksitimi Ölçeği", "Beck Depresyon Ölçeği" ve "Beck Anksiyete Ölçeği" anket formu uygulandı.

Bulgular: Psoriasis hastalarında anksiyete ve depresyon puanları kontrollerden anlamlı düzeyde yüksekti (sırasıyla P=0,029, P=0,003), ancak aleksitimi puanları arasında anlamlı bir fark yoktu (P=0,158). PAŞİ ile aleksitimi puanları arasında pozitif korelasyon saptandı (P=0,004). Ayrıca psoriasis hastalarının DYKİ puanı ile anksiyete, depresyon, aleksitimi ve PAŞİ arasında pozitif korelasyon mevcuttu (sırasıyla P<0,001, P=0,006, P=0,004, P=0,001).

Sonuç: Çalışmamızda psoriasisde depresyon ve anksiyete düzeyi yüksek olarak saptandı. Ayrıca anksiyete, depresyon ve aleksitimi düzeyleri arttıkça yaşam kalitesinin bozulduğu belirlendi. Sonuçlarımıza göre psoriasis hastaları sadece dermatolojik açısından değerlendirilmemeli, psikolojik olarak da değerlendirilmeli ve gerekli durumlarda psikiyatri polikliniğine yönlendirilmelidir.

Anahtar kelimeler: Anksiyete, Depresyon, Aleksitimi, Psoriasis, Yaşam kalitesi

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Introduction

Psoriasis is a chronic inflammatory disease that influences about 1-3% of the population [1]. Although the etiopathogenesis of the disease has not been fully elucidated, genetic, environmental, and immunological factors are considered significant. Presentation can often range from localized, erythematous, white-scaled papules and plaques to generalized severe involvement. Due to the comorbidities associated with psoriasis, it is now defined as a disease spectrum or a systemic disease rather than a limited disease in the skin [2].

The significance of psychological factors is known at the beginning of psoriasis and in periods of exacerbation. Therefore, psoriasis is considered a psychosomatic disease [3]. Psychiatric diseases or psychosocial factors accompany at least 25-30% of dermatological diseases [4]. Psoriasis is one of the most frequently investigated psychosomatic skin diseases. In 40-80% of the patients, psychosocial factors have been defined during the onset of disease or periods of exacerbation [5]. In a study, the rates of depression and anxiety are reported as 44% and 55%, respectively [6]. Depression is more widespread in psoriasis patients than in many other dermatological diseases. It may be a disease-independent diagnosis, or it may develop secondary to the disease [7,8]. Anxiety is characterized by feelings such as worry, and an expectation that something bad will happen. Anxiety disorders are more common in psoriasis than other dermatological illnesses [8,9].

Alexithymia is defined as difficulty in distinguishing, recognizing, identifying, and expressing the feelings of the individual and other people [10,11]. In some studies, it has been reported that alexithymia is observed not only in psychosomatic diseases but also in various medical and psychiatric diseases and the general population [12]. Alexithymic properties were found most frequently in psoriasis patients among those with other dermatological diseases [11,13].

While they are not life-threatening, chronic skin diseases in the visible areas of the skin generally affect patients' appearances, and embarrassment, distress, depression, and restriction from social and physical activities occur in these patients due to chronic stress. For these reasons, their psychosocial statuses, personal relationships, and daily activities are adversely affected, and their quality of life deteriorates [3,8]. Studies have reported that quality of life is impaired in psoriasis [3,9]. In these patients, along with the management of skin lesions, depression, anxiety and alexithymic properties should be evaluated and psychological support should be given when necessary. It will then be possible to increase the quality of life with treatment. In this study, we aimed to evaluate anxiety, depression and alexithymic features in psoriasis patients and determine their relationship with severity and quality of life.

Materials and methods

This case-control study was conducted between August 2017 and December 2017 at the Dermatology outpatient clinic of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital after obtaining the approval of the local ethics committee (19.07.2017, No=2017-9/9). Our study group consisted of patients diagnosed with psoriasis, and our control group consisted of age and sex-matched healthy subjects. Power analysis G*Power 3.1.9.2 software was used to determine the sample size. The power of this data was calculated as 1-β=0.90 with n_1=86, n_2=86, α=0.05 and an effect size of d=0.5. According to this calculation, we planned to include 86 people in each group, but 15 patients who did not answer more than 50% of the questionnaire in the study group were excluded. Consequently, the data of 71 psoriasis patients and 86 individuals in the control group were evaluated. Those who previously had psychiatric diagnoses and treatment and those with neurological diseases were excluded from the study. The gender, age, marital status, education level, duration of the disease of the psoriasis patients were noted, and the "Psoriasis Area Severity Index" (PASI) was conducted by the same doctor to assess the severity of the disease. The patients filled the "Dermatological Life Quality Index" (DLQI). All participants in the study filled the "Beck Depression Scale" (BDI), the "Beck Anxiety Scale" (BAI), and 20 question-long "Toronto Alexithymia Scale" (TAS-20).

Psoriasis Area Severity Index (PASI)

It is the most frequently used scale to determine the severity of the disease. It is calculated by grading the psoriasis lesions according to degrees of erythema, infiltration and desquamation and the involvement percentages of the affected areas in the body [3].

Beck Depression Inventory (BDI)

It is a self-assessment scale used to determine depressive symptoms and attitudes. It consists of 21 items; and each item gets is scored from 0 to 3. A high total score indicates increased severity of depression experienced by the person. The validity and reliability study of the scale developed by Beck et al. [14] was conducted by Hisli [15] in our country.

Beck Anxiety Inventory (BAI)

It is a self-assessment scale applied to evaluate the level of anxiety experienced by the person. In the scale comprising 21 items, each item scores between 0 and 3. The higher the total score, the higher the level of anxiety [16]. The validity and reliability study in our country was done by Ulusoy et al. [17].

Toronto Alexithymia Scale (TAS-20)

It is a scale of 20 questions evaluating alexithymia, and each item is scored between 1 and 5. High scores indicate a high alexithymic level [18]. In this scale, there are subgroups of difficulty in recognizing emotions, difficulty in expressing emotions, and extrovert thinking. Since the cutoff score of the Turkish version of the scale was 59, individuals scoring 59 and above were evaluated as alexithymic [19,20]. In our study, as in some studies, only a general alexithymia score was calculated [20].

Dermatology Life Quality Index (DLQI)

Consisting of a total of 10 questions evaluating the patient's quality of life, DLQI is a common test specific to dermatological diseases. Each question scores between 0 and 3, the height of the total score is related to poor quality of life [21,22].

Statistical analysis

Kolmogorov-Smirnov test was used to evaluate the conformity of the data to normal distribution. Descriptive statistical methods were used to evaluate frequency, percentage,

mean (standard deviation (SD)). Chi-square test was used for univariate analysis. A non-parametric test, Mann-Whitney U test, was used to compare mean values between the groups, and Spearman's correlation analysis was utilized to evaluate correlation. *P*-value <0.05 was considered statistically significant.

Results

In our study, there were 157 people, 55% constituted by the control group and 45% by the psoriasis patients. The mean age of the participants was 35.8 (13.9) years. Among them, 46.5% were male and 53.5% were female. There was no significant difference between the study and control groups in terms of age, gender, and marital status (*P*>0.05). Control individuals were found to have a higher education level than the study group (*P*=0.001) (Table 1).

Anxiety and depression scores in the study group were significantly higher than that among the controls (*P*=0.029, *P*=0.003, respectively), but there was no meaningful differentiation between alexithymia scores (*P*=0.158) (Table 2). According to the Alexithymia cut-off scores, 25.3% of psoriasis patients and 21.7% of the whole study group were alexithymic. There was no statistical difference between both groups in terms of alexithymia status (*P*=0.307) (Table 2). Alexithymic and non-alexithymic groups were similar in terms of gender, age, education period and marital status (*P*>0.05) (Table 3).

The mean (SD) PASI scores of psoriasis patients in our study was 5.8 (4.0). There was no significant correlation between the PASI, BDI and BAI scores. PASI score and TAS scores were positively correlated (r=0.34; *P*=0.004). The mean DLQI score of psoriasis patients was 8.9 (6.6). There was a positive correlation between the DLQI score of psoriasis patients and anxiety, depression, alexithymia and PASI (*P*<0.001, *P*=0.006, *P*=0.004, *P*=0.001 respectively). No significant correlation was found between the disease duration of the patients and DLQI, BDI, BAI, and TAS scores (*P*>0.05) (Table 4).

There was a significant positive correlation between the total TAS score of the study group and the BDI and BAI scores (*P*<0.001, *P*<0.001 respectively). A significant positive correlation was also found between DLQI scores and the TAS score of the study group (*P*=0.004).

Table 1: Sociodemographic characteristics of the study and control groups

	Control group (n=86) n(%)	Study group (n=71) n(%)	Total (n=157)	Statistics
Age (Year) mean (SD)	37.1 (13.6)	34.1 (14.1)	35.8 (13.8)	*Z*=-1,512 *P*=0.131
Gender				
Male	37 (50.7)	36 (49.3)	73 (46.5)	X^2=0.922
Female	49 (58.3)	35 (41.7)	84 (53.5)	*P*=0.337
Marital status				
Single	38 (61.3)	24 (38.7)	62 (39.5)	X^2=1.755
Married	48 (50.5)	47 (49.5)	95 (60.5)	*P*=0.185
Educational level				
Primary school	18 (36.0)	32 (64.0)	50 (31.8)	X^2=15.718
Secondary school	24 (51.1)	23 (48.9)	47 (29.9)	*P*=0.001
University	44 (73.3)	16 (26.7)	60 (38.3)	

Table 2: Scores of study and control group questionnaires

	Control group	Study group	Total	Statistics
BDI mean (SD)	11.3 (10.7)	15.2 (9.8)	13.0 (10.5)	*Z*=-2.942 *P*=0.003
BAI mean (SD)	9.1 (8.1)	12.6 (10.7)	10.9 (9.9)	*Z*=-2.188 *P*=0.029
TAS mean (SD)	48.8 (9.8)	51.3 (9.5)	49.9 (9.7)	*Z*=-2.412 *P*=0.158
Alexithymia* n (%)				
No	70 (56.9)	53 (43.1)	123 (78.3)	X^2=1.04
Yes	16 (47.1)	18 (52.9)	34 (21.7)	*P*=0.307

* Row percentage taken, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, TAS: Toronto Alexithymia Scale

Table 3: Comparison of demographic characteristics of the group with and without alexithymia

	Non-Alexithymia (n=123) n (%)	Alexithymia (N=34) n (%)	Total (N=157)	Statistics
Age (Year) mean (SD)	36.3 (13.9)	33.8 (13.7)	35.8 (13.9)	*Z*=-0.944 *P*=0.345
Gender				
Male	55 (75.3)	18 (24.7)	73 (46.5)	X^2=0.724
Female	68 (81.0)	16 (19.0)	84 (53.5)	*P*=0.395
Marital status				
Single	47 (75.8)	15 (24.2)	62 (39.5)	X^2=0.389
Married	76 (80.0)	19 (20.0)	95 (60.5)	*P*=0.533
Educational level				
Primary school	40 (80.0)	10 (20.0)	50 (31.8)	X^2=1.470
Secondary school	34 (72.3)	13 (27.7)	47 (29.9)	*P*=0.480
University	49 (81.7)	11 (18.3)	60 (38.3)	

Table 4: Relationship between PASI, disease duration, DLQI and BDI, BDI, TAS in patients with psoriasis, correlation

	PASI		Disease duration		DLQI	
	r	*P*-value	r	*P-value*	r	*P*-value
DLQI	0.389	0.001	0.156	0.200	-	-
BDI	0.138	0. 254	-0.117	0.335	0.327	0.006
BAI	0.127	0. 291	0.130	0.280	0.432	<0.001
TAS	0.340	0.004	0.023	0.849	0.341	0.004

DLQI: Dermatology Life Quality Index, BDI: Beck Depression Inventory, BAI: Beck Anxiety Inventory, TAS: Toronto Alexithymia Scale, PASI: Psoriasis Area Severity Index

Discussion

Since psoriasis is considered a psychosomatic disease, its relationship with psychiatric disorders has been examined by researchers for a long time. It was found that stress was important at the onset and during psoriasis episodes, and anxiety and depression levels were higher in psoriasis patients [3,7,9]. Similarly, we found elevated levels of depression and anxiety in our study group. On the contrary, Güleç et al. [23] reported that depression is common among psoriasis patients, but not significantly higher than healthy controls.

Different results have been reported in studies investigating the relationship between psoriasis severity, depression, and anxiety. Ozguven et al. [24] found that there is a relationship between depression and psoriasis severity, but not anxiety and psoriasis severity. In their study, Kılıç et al. [25] reported that there was no link among the severity of psoriasis, anxiety, and depression, a finding akin to our study. Similar to the studies in the literature, we found no relationship between the duration of psoriasis disease, depression and anxiety [25].

Studies investigating alexithymia are increasing in psoriasis patients. Different rates ranging from 21% to 42.2% have been found in studies for alexithymia among various clinical groups [20]. We found alexithymia in 25.3% of patients with psoriasis, but the difference was not significant compared to the controls as in the other two studies conducted in our country [11,23]. However, some studies have found a relationship between psoriasis and alexithymia [26]. In the study of Richards et al., the rate of alexithymia was 33% among psoriasis patients, while it was reportedly not related to the severity and duration of the disease [27]. Similarly, in another study conducted in our country, it was stated that there was no relationship between the total score of alexithymia and the severity and duration of the disease [23]. In our study, while a relationship was found between alexithymia score and the severity of the disease, the duration of the disease was not related. In addition, there was a relationship between alexithymia, depression, and anxiety in our study. This result makes us think that we should pay attention to the possibility of alexithymia in patients with depression and anxiety.

Although different scales have been used in studies regarding the quality of life in psoriasis patients, it has been found that it is frequently decreased [3,9,28]. In one study, the effect of psoriasis on quality of life was reported to be similar to those of serious medical conditions such as hypertension, cancer, diabetes, and depression [28].

Different results have been reported in studies on the relation between quality of life and severity of the disease. In a study conducted in our country, the mean PASI score was 5.76 and a negative correlation was found between the PASI score and quality of life [29]. Similarly, in our study, we found the mean PASI value of 5.87, and as the PASI score increased, the quality of life decreased. However, in two studies conducted in our country, no significant relationship was found between the quality of life and the severity of the disease [3,9]. In our study, we also found a negative correlation between patients' quality of life and depression and anxiety, that is, the quality of life deteriorated as the level of depression and anxiety increased. Sesliokuyucu et al. [9] found a relationship between quality of life, depression and anxiety in their studies using different questionnaires in psoriasis patients. In another study, it was reported that depression is highly effective in the quality of life in psoriasis patients and affects the quality of life as much as the severity of the disease [7].

Limitations

This study had several limitations. Firstly, the sample group was relatively small. Secondly, the data obtained depend on the participants' own statements, and no psychiatric interviews were conducted. Therefore, we believe that our results should be supported by prospective studies with a larger population and diagnostic psychiatric interviews.

Conclusion

Psoriasis, considered a psychosomatic disease, negatively affects patients' lives in most aspects. These patients should be managed both dermatologically and psychologically. In addition, we believe that methods which will likely improve the quality of life will increase the compliance of the patients, rendering the treatment more successful and reducing the severity of the disease. In this respect, we believe that the levels of depression, anxiety, and alexithymia, all of which are related to the quality of life in psoriasis patients, should be evaluated in each patient during follow-up and treatment.

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Evaluation of factors affecting the success of percutaneous nephrolithotomy in kidney stones sized 2 cm and above

2 cm ve üzeri böbrek taşlarında perkütan nefrolitotomi başarısını etkileyen faktörlerin değerlendirmesi

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Abstract

Aim: Although percutaneous nephrolithotomy (PNL) is the preferred minimally invasive treatment method for large and complex kidney stones, complications may develop, and the operation may fail. In this study, we aimed to evaluate the factors affecting the success of PNL as well as the significance of surgical experience.

Methods: In this retrospective cohort study, the reports of 106 patients who underwent PNL between September 2017 and August 2019 were analyzed. The features of the stones and urinary system, operation parameters and postoperative findings of all patients were noted. The surgical experience was divided into two groups as the first 53 and the last 53 cases. The stones were classified as simple stones and complex stones by their location in the kidney. The patients were evaluated with kidney ureter bladder (KUB) x-ray on the first day after the operation and by non-contrasted computed tomography (CT) in the 3rd postoperative month.

Results: Among 106 patients who underwent PNL, 64 (60.3%) were male, 42 were female (39.7%), and the mean age was 52.65 (9.36) years. The mean size of the stones in the patients was 4.25 (1.37) cm, and 48 of them had simple stones and 58 had complex stones. The mean operation time was 58.70 (9.41) minutes, and the mean duration of hospitalization was 52.11 (8.62) hours. KUB was successful in 90 (84.9%) of 106 kidney stone cases in the first postoperative day. Following additional treatment administration in 8 cases, this rate increased to 92.4% in the 3rd postoperative month, in which the rate of stone-free cases was 91.7% in simple kidney stones, and 79.3% in complex kidney stones. Assessment of surgical experience revealed that failure rate was 22.7% in the first 53 cases and 7.6% in the last 53 cases (P=0.016).

Conclusion: PNL is a minimally invasive treatment method that may be preferred in simple and complex kidney stones of 2 cm and above. The size of the stone, the localization of the stone, the number of percutaneous interventions and surgical experience are crucial factors affecting success rates.

Keywords: Percutaneous nephrolithotomy, Kidney stones, Surgical experience

Öz

Amaç: Perkütan nefrolitotomi (PNL), büyük ve karmaşık böbrek taşları için tercih edilen minimal invaziv tedavi yöntemi olmasına rağmen, komplikasyonlar gelişebilir ve operasyon başarısızlıkla sonuçlanabilir. Bu çalışmada PNL'de başarıyı etkileyen faktörleri ve cerrahi tecrübenin PNL'ye etkisini değerlendirmeyi amaçladık.

Yöntemler: Bu retrospektif kohort çalışmasında, Eylül 2017 ve Ağustos 2019 tarihleri arasında PNL operasyonu yapılan toplam 106 hastanın kayıtları incelendi. Bütün hastaların taş ve üriner sistem özellikleri, operasyon parametreleri ve postoperatif bulguları kaydedildi. Cerrahi tecrübe sırasıyla ilk 53 ve son 53 vaka olmak üzere iki gruba ayrıldı. Taşlar böbrekteki yerleşimine göre basit taşlar ve kompleks taşlar olarak sınıflandırıldı. Hastalar operasyon sonrası 1. gün çekilen direk üriner sistem grafisi (DÜSG) ve 3. ayda çekilen kontrastsız bilgisayarlı tomografi (BT) ile değerlendirildi.

Bulgular: PNL uygulanan 106 hastanın 64'ü (%60,3) erkek, 42'si kadın (%39,7), ortalama yaş 52,65 (9,36) yıl idi. Hastaların taş boyutları ortalama 4,25 (1,37) cm idi ve 48'i basit taşlara, 58'i kompleks taşlara sahipti. Ortalama operasyon süresi 58,70 (9,41) dk., ortalama yatış süresi 52,11 (8,62) saat idi. 106 böbrek taşı vakasının 90'ında (%84,9) postoperatif birinci günde çekilen DÜSG'de başarı elde edildi. Olguların 8´ine uygulanan ek tedavi sonrası postoperatif 3. ayda bu oran %92,4'e yükseldi. Operasyon sonrası 3. ay basit böbrek taşlarındaki taşsızlık oranı %91,7 iken, kompleks böbrek taşlarında bu oran %79,3 olarak bulundu. Cerrahi tecrübenin etkisi değerlendirildiğinde ilk 53 vakada %22,7, son 53 vakada %7,6 başarısızlık saptandı (P=0,016).

Sonuç: PNL, 2 cm ve üzeri basit ve kompleks böbrek taşlarında tercih edilebilecek minimal invaziv bir tedavi yöntemidir. Taşın boyutu, taşın lokalizasyonu, perkütan girişim sayısı ve cerrahi tecrübe başarı oranlarını etkileyen önemli faktörlerdir.

Anahtar kelimeler: Perkütan nefrolitotomi, Böbrek taşları, Cerrahi tecrübe

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Introduction

Percutaneous nephrolithotomy (PNL), a minimally invasive surgical method that is used in the treatment of urinary system stone disease, was first defined by Fernstrom and Johansson in 1976 [1].

Today, extracorporeal shock wave lithotripsy (ESWL), PNL, retrograde intrarenal surgery (RIRS), their combinations and laparoscopic techniques are used in the treatment of kidney stones in the adult and pediatric patients [2]. The purpose of the treatment is to remove stones maximally with minimal damage to the patient. PNL is recommended as a first line treatment for >2 cm, ESWL resistant, complex, and staghorn kidney stones with various abnormalities. Due to short operation times, low morbidity rates, short hospitalization duration, and its minimally invasive nature, it has been a feasible treatment option for indicated kidney stones, replacing open stone surgery [3].

Improvements in instruments as well as lithotripsy (stone destruction) technology have increased the efficacy of percutaneous stone destruction and the rate of stone-free cases to above 90% [4].

A successful PNL operation depends on factors related to patient and the stone, such as bleeding degree, complication rate, fluoroscopy, and duration of surgery.

The aim of this study is to evaluate the factors which may predict success and development of various complications, when success is considered as "removing the stone completely or the presence of a residual stone smaller than 4 mm following PNL operation".

Materials and methods

A total of 106 patients who underwent PNL in our clinic between September 2017 and August 2019 were included in the study. All patients were evaluated with detailed a history form before the operation. A general internal examination was performed, and systemic diseases were investigated. Hemogram, blood biochemistry and urine culture were obtained preoperatively. Patients with urine culture growth were operated following the administration of appropriate antibiotherapy. Operations of patients using aspirin and other anticoagulant drugs were postponed for 7-10 days after drug discontinuation. Patients with bleeding diathesis or comorbidities were operated following necessary treatments. The patients over the age of 18 years who were operated for simple or complex kidney stones larger than 2 cm were included in the study. Patients with kidney stones smaller than 2 cm, those with spinal deformity, neuromuscular diseases, coagulation disorders and the patients with sensitivity to anesthetic drugs were excluded, in addition to patients under the age of 18, patients with renal abnormalities or solitary kidney.

Demographic data including age, gender, features of the stones and urinary system (stone size, surgical history and/or ESWL history), operation parameters (operation time, fluoroscopy duration, number and location of insertion, blood transfusion, complications) and postoperative findings (hospitalization duration, blood transfusion, complications, the rate of stone-free cases) as well as the medical records of the patients were evaluated retrospectively. Maximum stone length measured by non-contrast computed tomography (CT) was defined as stone size. In the kidney-ureter-bladder (KUB) X-ray performed after the operation, stones that were 4 mm and below were considered clinically insignificant residual fragments (CIRF). The complications were graded by the Clavien classification. The patients were evaluated by non-contrasted CT at the 3rd postoperative month. Success was defined as complete removal of stones (Stone Free/SF) or the presence of clinically insignificant residual stones (CIRF, smaller than 4 mm, asymptomatic).

Demographic data, stone sizes, operative parameters and postoperative findings were evaluated. The operation duration was defined as the time from the initiation of the cystoscopy until nephrostomy was inserted and fixed to the skin. The duration of hospitalization began with surgery date and ended at date of discharge.

In our study, stone size, stone location, number of accesses and surgical experience were evaluated as the factors affecting success in PNL operations. Stone size was divided into two groups, as those between 2-4 cm and >4 cm. The stones were classified as simple stones (single calyx or pelvis stone) and complex stones (coraliform or multiple calyx stones) based on their location in the kidney. The number of accesses was divided into two groups as 1 and >1. The surgical experience was divided into two groups, the first 53 and the second 53 cases.

All procedures in the studies involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

PNL technique

All operations were performed under general or spinal anesthesia. In both groups, a 6 Fr ureter catheter was inserted by a cystoscope to the relevant ureter in the lithotomy position and then fixed to a 16 Fr foley catheter. Then, patients were placed in prone position. After the opaque substance was delivered to the targeted calyx through the ureter catheter accompanied by C-arm fluoroscopy, an 18-gauge percutaneous insertion needle was advanced into the renal collector system by a 0.038-inch guidewire. The insertion site was dilated on the guide wire with a 30Fr Amplatz dilator and a sheath (30 Fr) was inserted. A 26 Fr nephroscope was inserted into the renal collector system, and the stone(s) were broken by pneumatic lithotripter and extracted by a grasper. Stone-free status was confirmed by either direct nephroscope or fluoroscopy. In patients with stones in different calyxes, an additional insertion was performed to obtain the maximum stone-free status in cases when a single insertion was not sufficient. After the operation was completed, a 14 Fr nephrostomy tube was placed in the insertion sheath and the operation was terminated after checking by fluoroscopy. The next morning, the foley catheter was removed according to the color of the urine bag.

Statistical analysis

The data were analyzed using the IBM SPSS version 20.0 software (IBM Inc., Chicago, IL, USA). Data were presented as mean (SD) values. Conformity of the variables to normal distribution was determined with Kolmogorov-Smirnov and Shapiro-Wilk tests. As the patient numbers did not show normal distribution, Mann Whitney U test was used to compare both groups. The Chi-square test was used to compare values in

different groups. *P*-value of <0.05 was considered statistically significant.

Results

The demographic variables and stone characteristics are shown in Table 1. Among all patients, 64 (60.3%) were men, 42 were women (39.7%), and the mean age was 52.65 (9.36) years. Fifty-seven (53.8%) had right-sided and 49 (46.2%) had left-sided kidney stones. Before the operation, grade 2 or grade 3 hydronephrosis was detected in 64.2% of the patients.

Subcostal insertion was optimal in 102 patients, while intercostal insertion was performed in 6 patients. The lower calyx, middle calyx and the upper calyx insertion were performed in 88 (83%), 10 (9.4%) and 2 (1.9%) patients, respectively. Six cases (5.7%) underwent insertion through multiple calices. The mean size of the stones was 4.25 (1.37) cm, with 48 simple and 58 complex stones. The mean operation and hospitalization durations were 58.70 (9.41) minutes and 52.11 (8.62) hours, respectively.

Ninety (84.9%) of 106 renal stone cases underwent successful PNL, as observed in direct radiographs on the first postoperative day. This rate increased to 92.4% in 8 cases with additional treatment in the 3rd postoperative month. For this purpose, 5 cases were treated with ESWL, 2 cases were treated with ureterorenoscopy and 1 case was re-treated with PNL.

The complications were determined by the modified Clavien classification system and presented in Table 2. In 8 (7.5%) patients, double j catheter was placed due to prolonged drainage and/or extravasation after nephrostomy tube was removed. Blood transfusion was administered to 3 patients due to decreased hemoglobin. None of the patients had major vascular and visceral organ injuries.

In the third postoperative month, the rate of stone-free cases was 91.7% in simple kidney stones, and 79.3% in complex kidney stones. Success was achieved in 91.9% of the cases with 2-4 cm stones and in 75% in those with stones over 4 cm (*P*=0.034) (Figure 1). The success rates by mean sizes and localization of the stones are presented in Table 3 in detail.

Ninety-four patients had single access surgeries while 12 patients were operated with two or more accesses. Success rates were found to decrease with increased number of accesses (*P*=0.042). Failure rate was 22.7% in the first 53 cases and 7.6% in the last 53 cases (*P*=0.016).

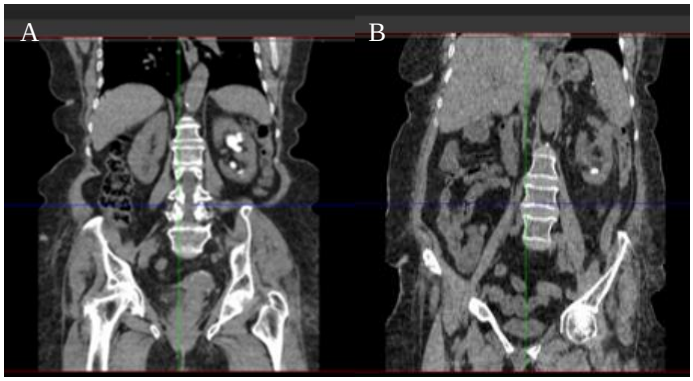

Figure 1: A: Preoperative complex kidney stones, B: Postoperative 3rd month, residual fragment larger than 4 mm

Table 1: Patient demographics and stone characteristics

Variables	Value
Patients, n	106
Mean (SD) age, years	52.65 (9.36)
Gender, n (%)	
Male	64 (60.3)
Female	42 (39.7)
Mean (SD) stone size, cm	4.25 (1.37)
Laterality, n (%)	57:49
Right	57 (53.8%)
Left	49 (46.2%)
Site of stone, n (%)	
Pelvis	52 (49%)
Upper calyx	4 (3.8%)
Middle calyx	11 (10.4%)
Lower calyx	39 (36.8%)
Stone location, n (%)	
Simple stone	48 (45.3%)
Complex stone	58 (54.7%)
Previous surgery	14 (13.2%)
Previous ESWL	19 (17.9%)

SD: Standard deviation, n: Number, ESWL: Extracorporeal shock wave lithotripsy

Table 2: Intraoperative and postoperative variables

Variables	Value
Operation time, minutes mean (SD)	58.70 (9.41)
Postoperative complications, n (%)	25 (23.5%)
Hematuria (Clavien I)	12 (11.3%)
Fever (Clavien I)	5 (4.7%)
Postoperative double-J stenting, n (%)	8 (7.5%)
Hemoglobin drop g/dl mean (SD)	1.36 (0.81)
Hospital stay, hours mean (SD)	52.11 (8.62)

SD: Standard deviation, n: Number

Table 3: Factors affecting of success

Variables	Successful n (%)	Unsuccessful n (%)	*P*-value
Stone size, cm			0.034
2-4 cm	57 (91.9%)	5 (8.1%)	
>4 cm	33 (75%)	11 (25%)	
Stone location			0.026
Simple stone	44 (91.7%)	4 (8.3%)	
Complex stone	46 (79.3%)	12 (20.7%)	
Number of access			0.042
1	81 (86.1%)	13 (13.9%)	
>1	9 (75%)	3 (25%)	
Surgical experience			0.016
First 53 cases	41 (77.3%)	12 (22.7%)	
Last 53 cases	49 (92.4%)	4 (7.6%)	
Total, n (%)	90 (84.9%)	16 (15.1%)	

n: Number

Discussion

PNL is a minimally invasive surgical treatment method with advantages such as low morbidity, high success rate and short duration of hospitalization in the treatment of multiple, larger than 2 cm and complex stones in the upper urinary system. PNL procedure is contraindicated in patients with uncontrolled bleeding diathesis, pregnancy, active urinary infection, and suspected renal tumor [3,5].

A nephrolithometric nomogram has been developed by the Clinical Research Office of Endourological Society (CROES) PNL working group to predict the success of PNL. Using multivariate variations, the relationship between preoperative markers and stone-free rate was determined and it was concluded that the stone burden is the most effective factor affecting success. Other factors include surgical experience, previous stone treatment, the presence of staghorn stones, stone localization, and number of stones [6].

According to European guidelines, PNL is the first-line treatment option for the treatment of pelvic, upper and middle calyx group stones over 2 cm. PNL and flexible URS are recommended for stones over 1.5 cm in the bottom pole, because ESWL activity is limited due to factors such as resistant stones, vertical infundibular-pelvic angle, narrow infundibulum (<5mm), long lower pole calyx (>10mm) [3].

As a result of the PNL operation, the concept of Clinical Insignificant Residual Fragments (CIRF) has been introduced for

stones that are not clinically significant since they do not cause obstruction, pain, and infection in the urinary system. Eighty-five percent of stones of this size may fall spontaneously without causing any clinical symptomatic pain, and detection of residual stones of this size following PNL have been considered surgical success [7].

The success of PNL operation varies between 72-98% in large series [8,9]. Segura [10] reported the success rate as 98% in 1000 cases. In the first PNL studies conducted in our country, the rate of stone destruction was reported as 60% by Muslumanoğlu et al. [11] and as 77% by Unsal et al. [12]. In our 106-case series, success rate was 84.9%, and this rate increased to 92.4% in the postoperative 3rd month after additional treatments were administrated in 8 cases. Lingeman et al. [13] reported PNL success (88-91%) in 1-3 cm stones; and reported that this rate may decrease to 75% in the stones above 3 cm. In our study, success was achieved in 91.9% of the cases with 2-4 cm stones and in 75% with stones over 4 cm.

One of the most important steps of a successful PNL surgery is to achieve optimal access, preferably from the right. Choosing the most suitable tract for the method is very important and the preferred approach is the posterior calyx route. In some cases, more than one access may be required in the same session. Lee et al. [14] and Merhej et al. [15] used multiple accesses in 73% and 78% of patients with staghorn stones. The success rate decreases in staghorn or complex stones accessed multiple times compared to simple stones. Stone-free rate (SFR) after PCNL monotherapy for staghorn stone is reported to range between 49% and 78% [16]. SFR in our study was not very different from the research conducted by El-Nahas et al. [17] (56.6%) and Desai et al. [18] (56.9%). Single access was performed in 94 patients, and 2 or more accesses were used in 12 patients in our study. As the number of accesses increased, success rates decreased. Again, success rate was 79.3% in patients with 58 complex stones. When evaluated in terms of complete stone-free cases, the lowest success rate was obtained in complete coraliform stones and multiple calyx stones concomitant with pelvis stones.

Our study showed that the history of renal stone surgery did not affect PNL success negatively. The data we obtained were similar to the results of the study conducted by Kurtulus et al. [19], in which the patients who had undergone PNL surgery for the first time due to kidney stones were compared with those who had previously undergone open kidney stone operations. No statistically significant difference was found in CIRF rates. In some other studies, it had been reported that open stone surgery may increase PNL failure rate [20].

Another factor affecting the success of PNL is surgical experience. Sofikerim et al. [21] reported that surgical experience was one of the most important factors affecting success. How many cases should be done to ensure adequate surgical experience in PNL operations is an especially important issue. Tanriverdi et al. [22] defined the learning curve for PNL and showed that the average operating times may be achieved after an average of 60 cases. According to the common results obtained from these two studies, the surgeon may determine his own average value after reaching a certain number of cases. In our study, success rate was 77.3% in the first 53 cases, and it increased to 92.4% in the last 53 cases.

PNL is a remarkable treatment alternative with high success rates, however, it should be noted that serious and even life-threatening complications may develop during or after this operation. In the study of Segura et al. [23] published in 1985 conducted on 1000 PNL cases, one of the first series on this field, the major complication rate was 3.2%. In this study, peroperative bleeding was the most common complication which required the termination of the operation, occurring in a total of 6 (0.6%) patients. In Lee et al.'s [24] comprehensive study published in 1987 on 582 patients who underwent PNL operation, the major and minor complication rates were 6.8% and 50%, respectively. The complication data of our study showed that a double j catheter was placed in 8 (7.5%) patients due to prolonged drainage and/or extravasation after nephrostomy tube was removed. Blood transfusion was administered to 3 patients due to decreased hemoglobin.

Limitations

This study has various limitations, the major one being its retrospective nature. Other limitations are the relatively low number of patients, and its single centered design. Also, we did not compare body mass index values.

In this study, we demonstrated which factors affect success in PNL operation. We observed that as the size of the stone, the localizations, and the number of accesses increased, the success of the operation decreased. In addition, we showed that the increase of surgical experience increased stone-free rates following the operation. These findings were consistent with the literature [17,21,22]. This article will lead future, multicenter prospective studies with more patients.

Conclusion

In conclusion, the size and the localization of the stone, the number of percutaneous interventions, surgical experience and need for additional treatment are statistically significant factors affecting the success rates. PNL is a minimally invasive treatment method that may be preferred for simple and complex kidney stones of 2 cm and above due to its shorter duration of hospitalization, lower postoperative care costs and less labor loss as compared to open operation. Further, prospective studies with large patient series are required to shed light on the issue.

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Association between fibromyalgia syndrome and MTHFR C677T genotype in Turkish patients

Türk hastalarda fibromiyalji sendromu ile MTHFR C677T genotip arasındaki ilişki

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Abstract

Aim: Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and tender points. Among the several suggested mechanisms, most reports strongly emphasize the importance of the molecular mechanisms. It is known that the disorder is accompanied by various mental disorders, the most common being depression. Methylenetetrahydrofolate reductase (MTHFR) gene polymorphism was also associated with psychiatric disorders such as depression, anxiety, bipolar disorder and schizophrenia. This study aimed to evaluate the association between C677T genotype of methylenetetrahydrofolate reductase (MTHFR) gene, FMS risk and symptom severity in Turkish patients.

Methods: One hundred (n=100) patients with FMS diagnosed according to the 1990 American College of Rheumatology Classification Criteria were included in our case-control study. Control group consisted of 100 patients of similar age and gender. Genomic DNA was extracted from peripheral blood leukocytes obtained from the participants and MTHFR C677T mutation was detected with real-time polymerase chain reaction. FMS disease activity was evaluated by Fibromyalgia Impact Questionnaire (FIQ) and presence of depression was assessed by Beck Depression Inventory (BDI).

Results: The study and control groups were all female. Depression was detected in 42% of the study group. Results of statistical evaluation have shown that those who carry the 677 C allele are 2.111 times more likely to have FMS than those with the T allele of MTHFR (P<0.001). There was no relationship between distribution in the MTHFR gene C677 polymorphisms, functional status (P=0.107), or BDI scores (P=0.848) in study group.

Conclusion: Our study found that the presence of the MTHFR C677T variant was protective against FMS. Based on these results, comprehensive studies in rare types of polymorphisms of MTHFR should be conducted.

Keywords: Fibromyalgia Syndrome, Methylenetetrahydrofolate reductase gene, C677T mutation, Depression

Öz

Amaç: Fibromiyalji sendromu (FMS); etiyolojisi belli olmayan, yaygın vücut ağrıları ve hassas noktalar ile karakterize bir hastalıktır. Oluşumunda pek çok mekanizma öne sürülmüş olup bunlardan biri de kalıtsal mekanizmadır. Hastalığa, en sık depresyon olmak üzere çeşitli ruhsal bozuklukların eşlik ettiği bilinmektedir. Metilentetrahidrofolat redüktaz (MTHFR) gen polimorfizmiyle de depresyon, anksiyete, bipolar bozukluk ve şizofreni gibi psikiyatrik hastalıklar ilişkili bulunmuştur. Bu bilgilerden yola çıkarak FMS tanılı hastalarda etyolojik açıdan MTHFR geni C677T genotipi ve allel sıklığını ve bu genotip ile fibromiyalji kliniği arasındaki olası ilişkiyi belirlemeyi amaçladık.

Yöntemler: Vaka-kontrol çalışmamıza 1990 American College of Rheumatology sınıflama kirterlerine göre tanı konmuş 100 FMS tanılı hasta dahil edildi. Kontrol grubuna ise aynı cinsiyet ve yaş aralığında 100 sağlıklı gönüllü dahil edildi. Katılımcılardan elde edilen periferal kan lökositlerinden genomik DNA ekstrakte edildi ve gerçek zamanlı polimeraz zincir reaksiyonu kullanılarak MTHFR C677T mutasyon tespiti yapıldı. FMS hastalık fonksiyonel durumu Fibromiyalji Etki Anketi (FEA) ve depresyon varlığı Beck Depresyon Envanteri (BDE) ile belirlendi.

Bulgular: Çalışmaya alınan 100 FMS tanılı hasta ve 100 kontrol grubunun hepsi kadındı. Çalışmamızda FMS'lu 100 hastanın 42'sinde (%42) depresyon saptandı. Yapılan istatistiki değerlendirmeler sonucu C allelini taşıyanların T allelini taşıyanlara göre hastalığa yakalanma olasılığı 2,111 kat daha fazla olarak hesaplandı (P<0,001). Hasta grubunda MTHFR geni C677T genotipi polimorfizmi dağılımı ile FEA ve BDE skorları arasında herhangi bir ilişki bulunamadı.

Sonuç: Çalışmamıza göre MTHFR C677T varyantının varlığının FMS'ye karşı koruyucu olduğunu bulundu. Bu sonuçlara dayanarak, MTHFR'nin nadir görülen polimorfizm tiplerinde kapsamlı çalışmalar yapılmalıdır.

Anahtar kelimeler: Fibromiyalji sendromu, Metilentetrahidrofolat redüktaz geni, C677T mutasyonu, Depresyon

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Introduction

Fibromyalgia syndrome (FMS) is characterized by presence of chronic widespread pain, persisting for more than 3 months, without any obvious organic lesion. FMS is often accompanied by additional symptoms such as fatigue, uncomfortable sleep, joint stiffness, cognitive dysfunction, psychological distress, abdominal disturbance, and headache [1-3]. This list also includes depressive symptoms, with a life-time prevalence of 90% for depression and 62-86% for major depressive disorder [4]. The high incidence of depression in FMS suggests that there may be a common pathophysiological mechanism [5]. The etiopathogenesis of FMS is complex and still not fully understood. The strong familial aggregation reported in FMS, though not excluding a possible contribution by environmental factors, appears to point to molecular basis as an important contributor to its etiology [6].

One of the best strategies for evaluating genetic relationships is the analysis of a relatively large number of candidate genes. One of the candidate genes for the development of FMS is methylenetetrahydrofolate reductase (MTHFR), which is a regulatory enzyme of homocysteine (Hcy) metabolism. The MTHFR gene is located on the short arm of chromosome 1 at 1p36.22. The enzyme plays a central role in folate metabolism by irreversibly converting 5,10-methylenetetrahydrofolate to 5-methylenetetrahydrofolate, the predominant circulating form of folate. 5-Methylenetetrahydrofolate donates a methyl group to Hcy in the generation of S-adenosyl methionine, a major source of methyl groups in the brain [7]. A common mutation of MTHFR C677T has been shown to cause increased plasma Hcy levels which in turn is associated with an increased risk of vascular disease and hypercoagulability [8]. Particular emphasis has been placed on two common mutations in MTHFR genes: C677T and A1298C. These mutations have been associated with diseases such as cerebrovascular disease, venous thrombosis, neural tube defects, diabetes, cancer, migraine, depression, cognitive impairment, bipolar disorder, and schizophrenia [9,10]. It has been suggested that the mutations in MTHFR gene may be associated with chronic widespread pain [11]. Since FMS is associated with depression, we aimed to investigate the association of FMS and MTHFR genotype.

Whether FMS and some neuropsychiatric disorders share the same etiopathogenesis and they are separate entities that coincidentally have the same alterations in gene locus are unknown. The purpose of this study was to establish the relationship between FMS and C677T genotype of MTHFR gene.

Materials and methods

Patient selection

One-hundred patients with FMS admitted to the Department of Physical Medicine and Rehabilitation at Başkent University Medical Faculty Ankara Hospital between 2013 July and 2014 January were included in the study. The American College of Rheumatology (ACR) 1990 classification for FMS was used in the diagnosis (widespread pain over three months, and tenderness in at least 11 of 18 tender point sites) of FMS. Control group consisted of 100 healthy volunteers, randomly selected among people who visited general health clinics and had no FMS or chronic pain. The FMS and the control groups were all female. All patients provided written informed consent after being informed of the details of the study.

Exclusion criteria included: being under 18 years of age, pregnancy, and chronic diseases such as chronic kidney disease, hypothyroidism, polyneuropathy, and rheumatoid arthritis. All participants were of Turkish descent and shared common ethnogeographic origin.

Clinical evaluation protocol

All participants underwent a complete clinical evaluation. All patients completed a detailed form on demographic characteristics, body mass index and systemic diseases. In addition, peripheral venous blood samples were obtained from all participants for genotyping.

The functional status of the patients included in the study group was assessed using the Fibromyalgia Impact Questionnaire (FIQ) [12], which measures physical function, work status (days of work and work difficulties), depression, anxiety, morning fatigue, pain, stiffness, fatigue and well-being. The FIQ is completed by the patients themselves and the maximum score is 100. In this questionnaire, while a patient with fibromyalgia averages 50 points, a highly affected patient usually obtains more than 70 points. It has been found valid and reliable in Turkish fibromyalgia patients [13].

The participants were also evaluated for depression and health-related quality of life. Depressive symptoms were assessed using the Beck Depression Inventory (BDI), whose validity and reliability in Turkish patients has been proven [14]. A 36-item Short Form Health Survey (SF-36) was used to assess the health-related quality of life of patients and their general health status. The SF-36 is a generic health survey that measures the physical and mental health status of patients. Responses to each of the SF-36 items are scored and summed according to a standardized scoring protocol and expressed as a score on a 0-100 scale for each of the eight health concepts. The higher the score, the better the person perceives his or her health. The SF-36 questionnaire was shown valid and reliable in Turkish patients [15].

Molecular analysis

All patients included in this study gave their informed consent to having a blood sample drawn for DNA analysis. Genomic DNA was extracted from peripheral blood leukocytes by means of a highly pure polymerase chain reaction (PCR) template preparation kit (Roche Diagnostics GmbH, Mannheim, Germany). MTHFR C677T mutation detection was performed by real-time polymerase chain reaction (RT-PCR) using the LightCix Kit and Light Cycler Fast Start DNA Master HybProbe in Light Cycler 2.0 (Roche Diagnostics, Germany). A 233 bp fragment of the MTHFR gene was amplified with specific primers. The resulting PCR fragments were analyzed with hybridization probes and the genotype was identified by melting curve analysis. Melting temperatures were 63.0 °C for 677 C and 54.5. °C for 677 T. CC (Alanin/Alanin) homozygous normal, CT (Alanin/Valin) heterozygote and TT (Valin/Valin) homozygote mutant genotypes are observed in the C677 genotype of MTHFR.

This study was approved by Baskent University Medical and Health Sciences Research Board and Ethics Committee on 09/01/2013 (Project no: KA12 / 274) and supported by Baskent University Research Fund. All subjects understood the purpose of this study and provided their written informed consent prior to their participation. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The data set was evaluated using the SPSS program (SPSS version 17.0; SPSS Inc., Chicago, IL, USA). The normal distribution of continuous variables was controlled using the Shapiro-Wilk test. The homogeneity of the variances was analyzed using the Levene test. It has been observed that there are no preconditions for parametric tests. Therefore, the Mann-Whitney U test was used to compare two groups of the subject variables. The results were expressed as mean (standard deviation) and median values. Bi-directional tables were assessed using the Monte Carlo simulated Pearson Chi-square test and Fisher's Exact test. Results were expressed in n and %. *P*-value less than 0.05 was regarded statistically significant.

Results

The demographic characteristics of the patients and controls are given in Table 1. The patients and the controls included in the study were all female, with mean ages of 39.16 (11.62) years in study group and 36.76 (8.74) years in the control group. Symptoms were significantly more (P=0.04) in the study group than in the control group except for Raynaud's phenomenon (P=0.735) (Table 2). According to the FIQ score, 78% of the patients were mildly affected and 22% of the patients were severely affected by FMS. Depression was detected in 42% of FMS patients. There was a statistically significant difference between study and control group in SF-36 health survey scores (P<0.001) (Table 3). The distribution of the C677T genotype of the MTHFR gene in the study and control groups is shown in Table 4. It was found that those who carry the 677 C allele are 2.111 times more likely to have FMS than those carrying the 677 T allele of the MTHFR gene (P<0.001). There was no relationship between distribution in the MTHFR gene C677 polymorphisms and functional status (P=0.107) in study group (Table 5). Similarly, there was no relationship between distribution in the MTHFR gene C677 polymorphisms and BDI scores (P=0.848) in study group (Table 6).

Table 1: The demographic features of FMS patients and controls

	Study group (n = 100)	Control group (n = 100)	*P*-value
Age (years) [mean (SD)]	39.16 (11.62)	36.76 (8.74)	0.289
Body mass index (kg/m²) [mean (SD)]	25.17 (3.82)	25.11 (4.47)	0.715
Education [n (%)]			0.587
Illiterate	1 (1%)	0	
Primary School	25 (25%)	18 (18%)	
Secondary School	7 (7%)	8 (8%)	
High School	28 (28%)	27 (27%)	
University	39 (39%)	47 (47%)	
Marital status [n (%)]			0.860
Single	18 (18%)	21 (21%)	
Married	77 (77%)	74 (74%)	
Widow	3 (3%)	4 (4%)	
Divorced	2 (2%)	1 (1%)	

FMS: Fibromyalgia syndrome, SD: Standard deviation

Table 2: The clinical characteristics of FMS patients and controls

	Study group (n = 100)	Control group (n = 100)	*P*-value
Morning stiffness	77 (77)	5 (5)	0.002
Sleep disorder	79 (79)	15 (15)	0.003
Fatigue	100 (100)	45 (45)	0.004
Morning fatigue	93 (93)	22 (22)	0.003
Irritable bowel syndrome	55 (55)	20 (20)	0.004
Sicca symptoms	21 (21)	5 (5)	0.003
Swelling sensation	67 (67)	7 (7)	0.003
TMJ dysfunction	21 (21)	6 (6)	0.003
Reynaud's phenomena	2 (2)	1 (1)	0.735

FMS: fibromyalgia syndrome, TMJ: temporomandibular joint

Table 3: Comparison of SF-36 health survey outcomes in FMS patients and controls

SF-36	Study group [mean (SD)]	Control group [mean (SD)]	*P*-value
Physical function	60.48 (20.44)	81.66 (15.19)	<0.001
	60.00 (5.00-100.00)	84.00 (50.00-100.00)	
Role physical	74.50 (30.97)	44.50 (47.97)	<0.001
	25.00 (0-100.00)	100.00 (0-100.00)	
Bodily pain	65.69 (21.28)	37.47 (17.00)	<0.001
	41.00 (0-88.00)	63.00 (22.00-100.00)	
General health	44.28 (14.97)	62.85 (15.65)	<0.001
	45.00 (0-80.00)	65.00 (25.00-100.00)	
Vitality	32.6 5 (18.56)	50.73 (18.49)	<0.001
	30.00 (0-75.00)	50.00 (5.00-90.00)	
Social functioning	49.42 (18.94)	68.77 (20.96)	<0.001
	50.00 (0-100.00)	68.75 (12.5-100.00)	
Role emotional	43.65 (29.10)	62.49 (30.10)	<0.001
	33.30 (0-100.00)	66.70 (0-100.00)	
Mental health	50.52 (16.44)	62.36 (17.67)	<0.001
	52.00 (8.00-80.00)	68.00 (20.00-100.00)	

FMS: fibromyalgia syndrome, SF-36: 36-item short form health survey

Table 4: Distribution of the C677 genotypes in study and control groups

	MTHFR (C677) Genotype			
	CC n (%)	TT n (%)	CT n (%)	*P*-value
Study group	58 (58)	6 (6)	36 (36)	<0.001
Control group	37 (37)	17 (17)	46 (46)	

FMS: fibromyalgia syndrome, MTHFR: methylenetetrahydrofolate reductase

Table 5: The relationship between distribution in the MTHFR gene C677 polymorphisms and FIQ scores in study group

	MTHFR (C677) Genotype			
	CC n (%)	TT n (%)	CT n (%)	*P*-value
FIQ<70 (Mild clinical involvement)	39 (39)	3 (3)	30 (30)	0.107
FIQ>70 (Severe clinical involvement)	19 (19)	3 (3)	6 (6)	

FMS: fibromyalgia syndrome, MTHFR: methylenetetrahydrofolate reductase, FIQ: fibromyalgia impact questionnaire

Table 6: The relationship between distribution in the MTHFR gene C677 polymorphisms and depression in study group

	MTHFR (C677) Genotype			
	CC n (%)	TT n (%)	CT n (%)	*P*-value
No depression	33 (33)	3 (3)	22 (22)	0.848
Depression	25 (25)	3 (3)	14 (14)	

FMS: fibromyalgia syndrome, MTHFR: methylenetetrahydrofolate reductase

Discussion

This study aimed to investigate the genetic basis of FMS etiopathogenesis. Therefore, all participants included in the study were female so to exclude the possible differences in genetic and clinical parameters that gender causes. There were no significant differences in the demographical characteristics between FMS patients and controls.

The findings obtained from previous studies show that both genetic factors and abnormal peripheral and/or central pain mechanisms play a role on the development of widespread and chronic pain in FMS patients. According to recent genetic studies, the fact that pain severity is unique to each individual, even though the disease or damage are the same, is explained by genetic polymorphisms [16]. Recent studies have shown that the number of polymorphisms in the serotonin 5-HT2A receptor, dopamine D4 receptor, catechol-O-methyltransferase, adrenergic receptor, IL-4, guanosine triphosphate cyclohydrolase-1 and alpha-1 antitrypsin genes were high in patients with FMS. On the

other hand, these gene variants are not specific to FMS and can also be observed in other somatic disorders [17,18].

It has been suggested that in those who are genetically predisposed to FMS, psychological factors trigger the development of fibromyalgia [19]. It has also been reported that FMS is more common in families with mood disorders and it is suggested that these two conditions may result from a common genetic predisposition [20]. According to some investigators, irritable colon, panic disorders and major affective disorder are different clinical manifestations that originate from the same pathology [2,21,22].

In various studies, the incidence of psychiatric comorbidity in FMS has been reported between 30% and 60% [4,23,24]. In these patients, specific disorders such as depression and anxiety, somatization, panic disorder are seen [4]. In the studies in our country, Guven et al. [25] evaluated the depressive symptoms of FMS patients using BDI and detected mild (50%), moderate (38%) and severe (2%) depression in the patients. In our study, depression was found in 42% of FMS patients, consistent with these results.

There is compelling evidence that mood disorders including depression are significantly affected by polygenic and multifactorial genetic factors. MTHFR enzyme catalyzes the transformation of methylenetetrahydrofolate into tetrahydrofolate. The point where this reaction takes place is a junction which affects DNA methylation, folic acid, homocysteine, and nucleotide synthesis. Several mutations have been reported in the MTHFR gene. The most common, MTHFR C677T, is the transition of cytosine to thymine in 4th exon, 677th position. In patients with MTHFR mutations, reduced enzyme activity and decreased remethylation of hcy to methionine leads to elevated total Hcy. As Hcy promote oxidant injury to vascular cells, hyperhomocysteinemia may play an important role in oxidative stress [26].

Clinical characteristics such as peripheral neuropathy, developmental deficiency, hypotonia, stroke and thrombosis are observed in serious MTHFR deficiency in which hyperhomocysteinaemia and homocysistinuria occur. Mild and moderate MTHFR deficiency is common, reported in 10-15% of the general population. Such patients suffer from various diseases such as neurological diseases like dementia, Alzheimer, Parkinson's disease and migraine, chronic fatigue syndrome, and psychiatric disorders such as depression, anxiety, schizophrenia, and bipolar disorder. Furthermore, Schmechel and Edwards stated that MTHFR mutation may be associated with chronic widespread pain and FMS [11].

Arinami et al. [27] found that there was a significant relationship between the MTHFR C677T, in particular the homozygous TT (T allele) variant, and patients with depression and schizophrenia. Almeida et al. [28] investigated the relationship between MTHFR C677T genotype and depression, anxiety and cognitive disorders and observed that TT genotype patients were inclined to becoming depressed. However, there was no correlation between MTHFR genotype, anxiety and cognitive impairment. Similarly, in this article, the relationship between MTHFR C677T and depression is explained by mechanisms involving impaired cellular methylation, critical for the synthesis and metabolism of norepinephrine, serotonin, and dopamine. In our study, we did not find any relationship between polymorphism and patients diagnosed with depression (P=0.848) in the study group (Table 6).

A meta-analysis by Gilbody et al. [29] showed that subjects with the TT genotype of MTHFR had an increased risk of depression. On the other hand, there was no correlation between MTHFR C677T and anxiety disorders in this meta-analysis. In another meta-analysis, the relationship between MTHFR gene variants and psychiatric disorders such as schizophrenia, bipolar disorder and unipolar depressive disorder was investigated, and TT genotype carriers were found to be more at risk than CC genotype carriers [9].

The first study published in the literature investigating the relationship between FMS and MTHFR C677T was performed by Inanir et al. [26]. This study, conducted among Turkish patients, showed that there was no significant correlation between MTHFR C677T mutation and FMS, but that MTHFR C677T mutation was significantly associated with findings of dry eye and feelings of stiffness. The authors emphasized that the MTHFR C677T mutation was also reported in patients with Sjögren's syndrome and eye involvement in Behçet's disease. They stated that this mutation may be involved in the complex mechanism of dry eye, which in turn may be related to FMS.

In our study, we found that the likelihood of developing FMS in 677 C alleles was 2.111-fold higher than that of the 677 T allele carriers of the MTHFR gene. That is, CC genotype carriers (normal genotype) were more prone to FMS when compared to TT genotype carriers (homozygous mutant) of the MTHFR gene. Also, when the distribution in C677T genotype of MTHFR was compared to FIQ points, no relationship was found between genotype distribution and severity of fibromyalgia. Although there is a relationship between MTHFR C677T homozygosity and depression in the literature, there is no study showing that it is associated with anxiety disorders [28,29]. However, as in our study, we did not observe a study showing protection in TT genotype carriers. Our results may be explained by the fact that normal genotype pattern (CC) is more common in the population.

Limitation

In this study, C677T, the most frequent genotype of the MTHFR gene, was investigated, however the second frequent polymorphism of the MTHFR gene, 1298C, was not. This may be considered a limitation of the study. Another limitation of the study is that the number of participants was relatively small.

Conclusion

Our study was based mainly on the fact that MTHFR C677T gene polymorphism is considered an etiological factor in the development of depression and the frequent coexistence of psychiatric diseases in fibromyalgia syndrome patients. However, while MTHFR C677 TT carriage is thought to predispose to depression and other psychiatric diseases, it was found to be protective against FMS in our study. Based on these results, future comprehensive studies on rare types of polymorphisms of MTHFR should be conducted.

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Right amelia in a patient with neurofibromatosis type 1

Nörofibromatozis tip 1'li hastada sağ amelia

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Abstract
Neurofibromatosis type 1 (NF1) affects many different systems such as the skeletal, endocrine, gastrointestinal systems, as well as the skin, peripheral and central nervous systems (CNS). The NF-1 gene, located in the 11p12 region of chromosome 17, encodes a tumor suppressor protein, called neurofibromin, and is expressed in a diverse range of cell and tissue types. Neurofibromin negatively regulates the activity of an intracellular signaling molecule, p21ras (Ras), acting as a GTPase-activating protein (Ras-GAP). The Ras-GAP function of neurofibromin has been associated with various NF1-related clinical symptoms. We aimed to present a case of clinically and genetically diagnosed neurofibromatosis type 1 with a developmental anomaly in the right hand (right hand amelia). Our knowledge about whether the coexistence of these two conditions is coincidental or a result of neurofibromatosis is limited. We wanted to present this case since the coexistence of amelia and neurofibromatosis is a first.
Keywords: Neurofibromatosis type 1, Amelia, Neurofibromin

Öz
Nörofibromatozis tip 1 (NF1); deri, periferal ve santral sinir sistemi (SSS) yanında kemik, endokrin, gastrointestinal sistem gibi bir çok değişik sistemi etkiler. Otozomal dominant geçişli olup görülme sıklığı 1/3000-1/4000 olarak saptanmıştır. NF-1 geni 17. kromozom 11p12 bölgesindedir, bu gen nörofibromin olarak adlandırılan tümor supresor bir proteini kodlamaktadır. NF1 geni, nörofibromin proteini kodlar, çok çeşitli hücre ve doku tiplerinde eksprese edilir. Nörofibromin, bir GTPaz aktive edici protein (Ras-GAP) olarak işlev görerek hücre içi bir sinyal molekülü p21ras'ın (Ras) aktivitesini negatif olarak düzenler. Nörofibrominin Ras-GAP fonksiyonu, NF1 ile ilişkili çeşitli klinik semptomlarla ilişkilendirilmiştir. Bu yazıda Nörofibramatozis tip 1 klinik ve genetik olarak tanısı konulan ve sağ elde gelişimsel anomalisi (sağ el amelia) olan bir vakayı sunmayı hedefledik. Bu iki durum birlikteliğinin koinsidental mi olduğu yada nörofibramatozis sonucu mu olduğu konusunda bilgilerimiz yetersiz kalmaktadır. Amelia ve nörofibramatozis birlikteliği bir ilk olduğu için bu vakayı sunmak istedik.
Anahtar kelimeler: Nörofibromatozis tip 1, Amelia, Nörofibromin

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Introduction

Neurofibromatosis type 1 (NF1) affects many different systems such as the skeletal, endocrine, gastrointestinal systems, as well as the skin, peripheral and central nervous systems (CNS). It is an autosomal dominant disease with an incidence of 1 in 3000-4000 individuals [1]. The NF-1 gene, located in the 11p12 region of chromosome 17, encodes a tumor suppressor protein, called neurofibromin, and is expressed in a diverse range of cell and tissue types [2]. The diagnosis of NF1 is made based on the coexistence of at least two of the diagnostic criteria defined by the National Institute of Health (NIH): 1-6 or more café au lait macules of 5 mm in prepubertal individuals and >15 mm in post-pubertal individuals, 2- Freckling in the axillary or inguinal regions, 3- Two or more neurofibromas or one plexiform neurofibroma, 4- Optic glioma, 5- Osseous lesion, 6- At least two iris hamartomas (Lisch nodule), 7- A first-degree relative diagnosed with NF1 [1]. In this article, we aimed to present a case of clinically and genetically diagnosed Neurofibromatosis type 1 with a developmental anomaly in the right hand (right hand amelia).

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Case presentation

A 7.5-year-old girl presented with café au lait macules on her body. The patient's prenatal and natal history were insignificant, her neuromotor development was normal and she underwent surgery for pseudoarthrosis of the left tibia at the age of 4 years. There was no history of consanguinity. It was stated that the mother of the patient was diagnosed with neurofibromatosis type 1 and did not go to control visits regularly. When the history of the patient was detailed, it was learned that genetic analysis was ordered with the pre-diagnosis of neurofibramatosis, but the result was not pursued by the family. On her physical examination, her general condition was good, vital signs were stable, head circumference was 52 cm (0, +2SD), she was cooperative, orientated, and other systemic examinations were normal except for multiple café au lait macules on the body, developmental anomaly in the right hand (right hand amelia), and kyphoscoliosis (Figure 1). The abdominal ultrasonography, echocardiography, fundus, and hearing tests of the patient were performed, and all were found normal. The laboratory tests including hemogram, transaminases, renal function tests, the electrolytes, 25-OH vitamin D, thyroid function test, folate, and vitamin B12 levels were normal. The cranial imaging revealed T2A and FLAIR hyperintensity in bilateral basal ganglia. She was referred to orthopedics because of kyphoscoliosis. No additional pathology was identified in the follow-ups of the patient who was closely monitored.

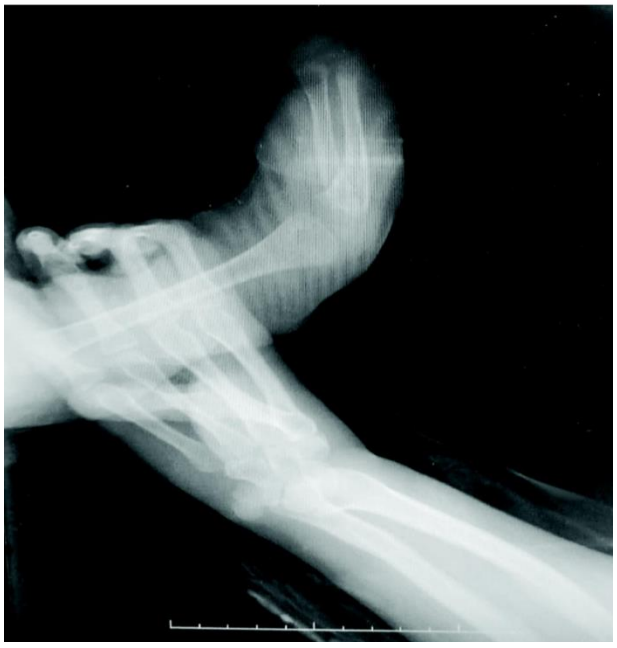

Figure 1: Developmental anomaly in the right hand (right hand amelia) of Neurofibromatosis Type 1 patient

Discussion

The incidence of congenital anomalies is expected to be high in NF1. The common congenital anomalies include spina bifida, fusion of vertebral bodies, congenital hip dislocation, club-foot deformities and spondylolysis [3]. Although congenital skeletal anomalies are not characteristic of neurofibromatosis, they probably represent one aspect of the disease in which mesodermal dysplasia is manifested. Osseous abnormalities are present in 40% of patients with NF1. The most common skeletal deformity is kyphoscoliosis [4]. Although about 50% of cases with congenital pseudoarthrosis are due to NF, only 0.5 to 1% of NF patients have pseudoarthrosis. Congenital pseudoarthrosis most commonly occurs in the tibia [5].

The NF1 gene encodes the neurofibromin protein and is expressed in a diverse range of cell and tissue types. Neurofibromin negatively regulates the activity of an intracellular signaling molecule, p21ras (Ras), acting as a GTPase-activating protein (Ras-GAP). The Ras-GAP function of neurofibromin has been associated with various NF1-related clinical symptoms [6]. The difficulties in understanding the human pathophysiology of skeletal defects in NF1 have led to the development of mouse models to determine the role of NF1 in bone cells and to facilitate preclinical studies. NF1 mRNA and neurofibromin are expressed during puberty and development in mouse bone and cartilage, and more specifically in mesenchymal stem cells, corneocytes, osteoblasts and osteoclasts. This expression pattern has shown that NF1-related skeletal defects are caused by primary bone defects resulting in bone cellular dysfunction and/or partially generalized NF1 heterozygosity due to loss of NF1 function in specific bone cells [7]. The Ras/MAPK pathway interacts with the FGF signaling pathway, including targets such as SHH (sonic hedgehog), a crucial factor in bone formation and limb development. In the literature, the association of polydactyly and NF was investigated, and Kimes et al. stated that neurofibromin deficiency disrupts Ras / MAPK pathway, affects downstream SHH targets and ultimately causes extra finger formation. In the literature, there are publications indicating whether the association of NF1 and polydactyly is coincidental or related to pathogenesis [8].

Congenital anomalies affect approximately 1-2% of newborns. About 10% of these malformations involve the upper extremities. The congenital transverse deficiency is defined according to the last remaining bone segment from aphalangia to amelia. These defects are partial or complete absence due to disruption of apical ectodermal ridge, its signaling or vascular abnormalities. Amelia is a birth defect characterized by the absence of one or more limbs. It is a rare condition with an incidence ranging from 0.053 to 0.095 in 10,000 live births. Although it is usually sporadic, it is less frequently involved in autosomal recessive/dominant or sex-linked inheritance. Amelia can be identified as an isolated defect, but it can often coexist with major malformations of other organ systems [9], including cleft lip and/or palate, body wall defects, head shape anomalies, kidney, diaphragm and spinal canal defects. It may coexist with facial clefts and facial anomalies. Diaphragm may or may not be herniated and one or both kidneys may be small or absent. Infants with only amelia have a good prognosis, while patients with organ malformations are lost at the first age due to complications [10]. Although our patient had isolated amelia, all abdominal ultrasonography, echocardiography, eye, and hearing tests performed for concomitant pathologies were normal.

Conclusions

Considering the literature, it is seen that patients with neurofibromatosis type 1 have a variety of skeletal deformities. However, the coexistence of amelia and neurofibromatosis has not been found in the literature. The Ras/MAPK pathway interacts with the FGF signaling pathway, including targets such as SHH (sonic hedgehog), a crucial factor in bone formation,

limb development. Neurofibromin deficiency also causes disruption of the RAS/MAPK pathway. Our knowledge about whether the coexistence of these two conditions is coincidental or a result of neurofibromatosis is limited. Further molecular and functional genetic studies are needed in this aspect.

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Carotid-cavernous fistula: A case report

Karotiko-kavernöz fistül: Olgu sunumu

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Abstract
Carotid-cavernous fistula is an abnormal arteriovenous communication between the carotid arteries and the cavernous sinus. Imaging studies are the most important step of diagnosis. We herein report a 50-year-old woman with a carotid cavernous fistula, who presented with double vision, right ptosis and ipsilateral pain. All imaging studies were normal except digital subtraction angiography, which revealed a carotid cavernous fistula arising from the meningohypophyseal trunk of right internal carotid artery, internal maxillary artery and middle meningeal artery. The patient underwent endovascular coiling of the fistula. She had an excellent recovery after intervention. In rare situations, carotid cavernous fistula cannot be revealed by computerized brain tomography or magnetic resonance imaging. If there is a strong suspicion of carotid cavernous fistula, digital subtraction angiography must be obtained for diagnosis and treatment.
Keywords: Carotid artery, Fistula, Angiography

Öz
Karotiko-kavernöz fistül, karotis sistemi ile kavernöz sinüs arasındaki anormal arteriyovenöz bağlantıdır. Görüntüleme yöntemleri tanıda en önemli basamağı oluşturmaktadır. Karotiko-kavernöz fistülü olan 50 yaşındaki kadın hastayı sunmaktayız. Hastanın çift görmesi, sağda göz kapağı düşüklüğü ve sağ göz çevresinde ağrısı mevcuttu. Yapılan diğer görüntüleme yöntemleri normal saptanan hastanın dijital subtraksiyon anjiografisinde sağ internal karotis arterin meningohipofisyal arterinden, internal maksiller arterden ve orta meningeal arterden köken alan karotiko-kavernöz fistülü tespit edildi. Hastanın fistülünün koillenmesinin ardından kişi eski sağlığına kavuştu. Nadir durumlarda, karotiko-kavernöz fistül manyetik rezonans görüntüleme ya da bilgisayarlı tomografi ile tespit edilemeyebilmektedir. Eğer hastada fistül olduğuna dair kuvvetli şüphe var ise, dijital subtraksiyon anjiografi yapılması konusunda ısrarcı olunmalıdır.
Anahtar kelimeler: Karotis arteri, Fistül, Anjiografi

Introduction

Carotid cavernous fistula (CCF) is a type of abnormal shunt from the carotid artery to the cavernous sinus [1]. Its symptoms are mainly due to important structures residing in the cavernous sinus [2]. CCFs are classified based on hemodynamics (high flow or low flow), pathogenesis (spontaneous or traumatic), and angiographic anatomy (direct or indirect) [3]. Its main treatment is ligation. We herein report a case of CCF with radiologic findings.

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Case presentation

A 50-year-old woman with a history of falling down the stairs and suspected trauma to the head one month earlier presented with double vision, right ptosis and ipsilateral retro-orbital pain. She had bilateral cataract surgery fifteen days before. Examination of right eye revealed ptosis, near complete ophtalmoplegia, poor light response and midriasis (6mm). She had hypoesthesia on cranial nerve V_1(ophthalmic nerve). There was no oscultation finding over the globe. Fundoscopic examination was also normal. Further general physical examination showed no abnormalities. Her blood tests including infectious disease testing and vasculitis panel were normal. Computed brain tomography (CT), contrast-enhanced cranial magnetic resonance images (C-MRI), cranial magnetic resonance angiography (CMRA), constructive interference in steady state (CISS) sequence cranial MR were all normal. Sterile lumbar puncture was performed with an opening pressure of 17 cm CSF, analyses of which were normal. Due to neurological examination findings pointing out cavernous sinus pathologies, cavernous sinus focused cranial MRI was performed, which revealed nothing. Because vascular pathology was suspected, digital subtraction angiography was planned, which revealed a carotid cavernous fistula arising from meningohypophyseal trunk of right internal carotid artery, internal maxillary artery and middle meningeal artery (Figure 1). The patient underwent endovascular coiling of the fistula under general anesthesia (Figure 2). On the visit a month after surgery, her examination was all normal.

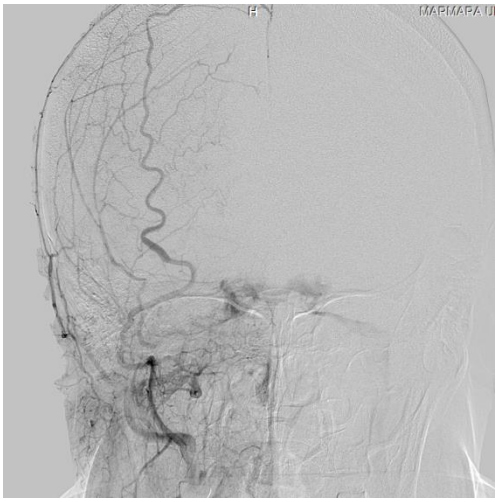

Figure 1: Carotid cavernous fistula arising from the meningohypophyseal trunk of right internal carotid artery, internal maxillary artery and middle meningeal artery

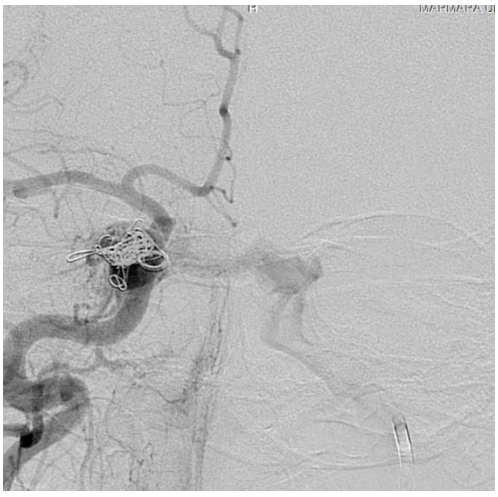

Figure 2: Endovascular coiling of the fistula

Discussion

Carotid cavernous fistula is an abnormal arteriovenous communication between the carotid arteries and the cavernous sinus [1]. It can arise spontaneously or from secondary causes (e.g. head trauma). If there is a direct connection between intracavernous carotid artery and sinus, it is termed “a direct fistula” and has high flow. Indirect or dural fistula implies that a fistula is located between the internal or external carotid artery branches and the sinus, and it has low flow. As arterial blood enters the cavernous sinus under high pressure, main pathology is arterialization of orbital veins. The symptoms of direct CCFs are proptosis, chemosis, painful ophthalmoplegia, and conjunctival injection. The onset of symptoms is almost always acute and rapidly progressive [3]. On the other hand, indirect CCFs have slower progression than direct CCFs. Symptoms depend on the venous drainage type. If it drains anteriorly by the superior ophthalmic vein, orbital symptoms like chemosis, proptosis can be observed, but if the drainage is posterior through the inferior or superior petrosal sinus, orbital symptoms and signs are usually absent [1,4]. Patients with low flow CCFs usually have mild signs and symptoms and may be misdiagnosed [5].

The disorders causing painful ophthalmoplegia may be considered for differential diagnosis, which include trauma, infection, neoplasms, vascular problems or miscellaneous. A detailed history, examination findings and imaging studies help the clinician to rule out these conditions.

Imaging studies include computed tomography (CT), CT angiography (CTA), magnetic resonance imaging (MRI), MR angiography (MRA) and sometimes orbital ultrasonography. Both CT and MRI show proptosis, extraocular muscle enlargement, and dilation of the cavernous sinus and superior ophthalmic vein. Although CTA has better sensitivity than MRA in detecting CCFs, especially in cases where the fistula lies in the proximal portion of the cavernous sinus, 3-D time of flight (3-D TOF) MRA has a 100% specificity in revealing a fistula[6]. Digital subtraction angiography should be used if the diagnosis cannot be made through other imaging techniques. It is both a diagnostic and a therapeutic test.

The goals of therapy are treatment of ophthalmologic complications and closure of CCF. The mainstay of therapy is endovascular occlusion of the affected cavernous sinus with coils, glue, or balloons. Transarterial embolization is the main method for direct CCFs and transvenous embolization is preferred for indirect CCFs [7]. Surgery and other interventions (e.g stereotactic radiosurgery) can be considered when the endovascular treatment is not possible or is unsuccessful. In one series, 9% of patients had a recurrence [8], but in general the success of treatment is pretty high.

Conclusion

CCFs are a rare but treatable cause of orbital injury and vision loss. Obtaining an accurate history of the onset of symptoms is important as they can explain the etiology of the CCFs. Some options are available for the management of the shunt and the goal is to achieve complete occlusion of the fistula while preserving normal carotid flow. Since most CCFs are not life-threatening, treatment as quickly as possible is necessary to prevent permanent injury to the involved eye.

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Neuroplay method combined with home-based Ayres sensory integration for autism: A case report

Otizmde ev temelli Ayres duyusal bütünleme müdahalesi ile birleştirilmiş nöroplay metodu: Bir vaka sunumu

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Abstract

Autism is a neurodevelopmental disease that occurs in early childhood. As the frequency of early detection of autism findings increases, intervention programs involving families become common. We herein present a boy who was diagnosed with autism at 19 months of age and followed up with Neuroplay Method integrated with home-based Ayres Sensory Integration intervention, which significantly improved his autism findings.

Keywords: Autism, Early intervention, Social interaction, Neuroplay method, Ayres sensory integration therapy

Öz

Otizm erken çocuklukta görülen nörogelişimsel bir bozukluktur. Otizm bulgularının erken dönemde saptanma sıklığı arttıkça, ailelerin dahil edildiği müdahale programları yaygın hale gelmektedir. Bu olgu sunumunda, 19 aylıkken otizm tanısı almış, ev temelli Ayres Duyusal Bütünleme müdahalesi ile birleştirilmiş Nöroplay Metodu ile izlendikten sonra otizm bulguları önemli ölçüde sağaltılan bir erkek çocuk sunulacaktır.

Anahtar kelimeler: Otizm, Erken müdahale, Sosyal etkileşim, Nöroplay yöntemi, Ayres duyusal bütünleme terapisi

Introduction

Autism is a developmental disability characterized by social and communication impairments, restricted interests, and repetitive behaviors [1]. Symbolic play implies the social use of an object in accordance with its function and features and is an important indicator of social interaction during childhood. Examination of symbolic play in children reveals that they often show repetitive behaviors and lack diversity [2]. The play behavior of some parents who have children with autism involves similar repetitive play patterns like their children [3]. Similar parallelism exists between sensory problems of the parents and the child. The prevalence of sensory problems of people with autism reportedly ranges from 69% to 93% among children and adults [4].

The Neuroplay Method (Neuroplay) is an intensive parent-mediated early intervention approach for children with autism between 12-42 months of age. The method aims to teach strategies of social interaction to parents about their children. After initial intensive training, parents are encouraged to play with their child for at least 4 hours a day. The therapist also helps them improve the home environment and choose the right toys for the child. During weekly visits, the therapist monitors the progress. This therapeutic approach, also known as Ayres Sensory Integration (ASI), was developed by A. Jean Ayres, who defined sensory integration as the process by which people register, modulate, and discriminate sensations received through the sensory systems to produce purposeful, adaptive behaviors in response to the environment [5].

In this case report, we aim to present a male patient diagnosed with autism and discuss the effectiveness of Neuroplay and ASI combinations.

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Case presentation

A two-year old male was born by normal spontaneous childbirth after an uneventful pregnancy as the only child of parents with bachelor's degrees. His parents stated that he was very restless during infancy, and he had been exposed to the screen for at least four hours a day. His motor development was normal. Later he had tended to play alone, made limited eye contact, and displayed obsessive playing behavior. Also, he reportedly avoided pressing on surfaces such as grass and sand and had not yet consumed solid food. Examination revealed that eye contact was indeed limited, and he did not respond when his name was called. The patient was diagnosed with autism in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. His Childhood Autism Rating Scale (CARS) score was 36. His neurodevelopmental level was evaluated with the Denver II Development Screening Test. Accordingly, his social age was determined as 6-8 months, lingual age, 6-8 months, fine motor development age, 10-12 months and gross motor development age, 17-18 months. The patient had atypical responses to the tactile stimuli of the oral and general areas. The patient could not consume solid food. He was started on Neuroplay and Ayres Sensory Integration therapy for three months, receiving 12 sessions of Neuroplay therapy and Ayres Sensory Integration therapy each.

During the therapy sessions, the Neuroplay therapist did not aim for the patient to gain any developmental skills. Instead, the parents learned social play strategies, some of which include how to make an eye contact, interact and communicate, prevent inappropriate behaviors and obsessions, support child's symbolic play, choose the right toy, use the toys while playing and improve joint attention. Ayres Sensory Integration sessions focused primarily on alleviating tactile defensiveness in the oral region. Home-based sensory activities were taught in therapy sessions. Oral massage was described to the parents to improve oral awareness. The parents were expected to massage the patient twice per day. Additionally, the child was encouraged by parents for oral-motor play before meals with non-food items like biting hard on oral toys, blowing bubbles, etc.

After 3 months of home-based intervention, Denver II scores for the social area was 14-15 months, language area, 10-13 months, fine motor area, 21-23 months, and gross motor area was normal. His latest CARS score was 26. It was observed that the patient started to gain developmental milestones while playing with his parents. His repetitive behaviors decreased, while his symbolic play and attention span increased. Although he began to respond to his name, receptive language skills were below the normal level for his age. The case was re-evaluated after treatment and he gave typical responses in all sensory areas. He started to consume solid foods.

Discussion

Low-intensity parent-mediated early intervention approaches can yield immediate effects on children's social behavior and communication. These effects can also be transmitted through late childhood [6]. These methods support caregivers to establish eye contact and joint engagement, avoid directive play and create opportunities for shared attention and social play [7]. However, social interaction with their children with autism could be difficult for their parents as they may also have social communication problems [3]. During Neuroplay therapy, parents send the practice videos to the therapist, which in turn leads to continuous supervision. Unlike low-intensity approaches, Neuroplay recommends intensive social interaction between the parents and the child at least 4 hours per day. This approach shows similarities with naturalistic behavioral developmental interventions like Applied Behavior Analysis. Neuroplay supports children with autism in their natural environment as a novel intensive therapy and it could prove to be a very beneficial approach, especially for families who have no access to high-quality therapy. Furthermore, the risk of autism in siblings is increased 20-25 times [6,8]. Therefore, Neuroplay can be also protective for high-risk siblings.

Atypical sensory reactivity is a core feature of autism and in some cases, sensory problems may hinder social interaction [4]. Sensory-oriented treatments are usually delivered by occupational therapists. However, Ayres Sensory Integration is a play-based approach and follows the child's lead, so it could be integrated into a parent-mediated intervention such as the Neuroplay method. In our case, home-based sensory activities improved tactile defensiveness and feeding problems.

Conclusion

Patients with autism and sensory issues can improve with home-based intervention. The efficiency of Neuroplay, when combined with sensory integration therapy, may increase for such cases. This approach will prove cost-saving for many families.

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Unexplained pellets in heart after shotgun wound through the hip: A case report

Kalçadan tüfekle vurulma sonrası kalpte açıklanamayan saçma taneleri: Olgu sunumu

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Informed Consent: Written consent was obtained from the parents of the patient presented with images in this study.
Hasta Onamı: Yazar çalışmada görüntüleri sunulan hastanın ebeveynlerinden yazılı onam alındığını ifade etmiştir.

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Abstract
The replacement of foreign materials in the human body is rare and the exact mechanism of migration has never been entirely explained. This case was found worth reporting because of the pellets found in the heart of a patient injured by a shotgun through the hip region. The patient was brought to the emergency service because of a hunting rifle injury. Examination revealed numerous entry holes in the gluteal region but there was no sign of injury in the chest or back. On radiographs, there were numerous pellets in the hip and thigh regions. Routine chest X-ray showed four pellets within the mediastinum, probably within the heart, so patient was followed up to prevent probable complications. It should be considered that unexpected complications may be encountered in shotgun injuries due to migration of pellets regardless of the region of injury.
Keywords: Shotgun wound, Pellet migration, Foreign body embolism, Chest X-ray

Öz
Yabancı maddelerin insan vücudu içinde yer değiştirmesi nadir görülen bir durum olup, göç mekanizması hiçbir zaman tam olarak açıklanamamıştır. Kalça bölgesinden av tüfeği ile yaralanan hastanın kalbinde dört adet saçma tanesine rastlanması nedeniyle bu olgu rapor edilmeye değer bulunmuştur. Av tüfeğiyle yaralanma tanısıyla acil servise getirilen hastanın muayenesinde; gluteal bölgede çok sayıda saçma giriş deliği olduğu, göğüs ve sırt bölgelerinde herhangi bir yaralanma izi olmadığı tespit edildi. Çekilen radyografilerde; kalça ve uyluk bölgelerinde çok sayıda saçma tanesi mevcuttu. Rutin olarak çekilen akciğer grafisinde mediastende kalbe uyan bölgede, dört adet saçma tanesi izlendi ve bu nedenle oluşabilecek komplikasyonlar açısından takip edildi. Özellikle saçma ile olan ateşli silah yaralanmalarında, yaralanma bölgesi fark etmeksizin saçma tanelerinin yer değiştirebileceği göz önüne alınarak beklenmedik komplikasyonlarla karşılaşılabileceği göz önüne alınmalıdır.
Anahtar kelimeler: Av tüfeği yaralanması, Saçma migrasyonu, Yabancı cisim embolisi, Akciğer filmi

Introduction

The migration of foreign bodies within the human body is a rare phenomenon. It has been reported that materials such as Kirshner or cerclage wire, which are frequently used in orthopedic surgeries, migrate to different regions from the areas where they are applied, such as the clavicle, patella or olecranon [1-7]. In some rare cases, bullets have been observed to migrate to different regions of the body following a gunshot injury [8-11]. The common feature of these cases is that the migration mechanism is never fully explained.

This case was found worthy of reporting due to four pellets which were displaced into the heart of the patient who had been injured by a shotgun from the gluteal region.

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Case presentation

A 36-year-old male patient was brought to the emergency room after a hunting rifle injury. During his examination, many open wounds, all posteriorly located and consistent with the entry wounds of the pellet, were seen in both hips and thighs (Figure 1). On the other hand, there were no signs of injury in the chest and back (Figure 2). It was found that the range of motion of the lower extremities of the patient was painful but complete and there was no neurovascular deficit.

On the radiographs, many radio-opacities, consistent with pellets, were observed in the hip and thigh regions. The patient was hospitalized for follow-up, before which a chest radiograph was obtained that showed four more pellets in the mediastinum in the heart-matching region (Figure 3). Computed tomography images confirmed that two of the pellets were attached to the pericardium and two of them adhered to the ventricular wall (Figure 4). Bedside echocardiography performed in the emergency department showed no pericardial fluid and no wall motion abnormality. Since there was no entry wound in the chest or back, it was concluded that the pellets detected on chest x-ray had migrated from the gluteal region into the mediastinum. Transthoracic echocardiography, performed after hospitalization, showed no pathology. It was confirmed via daily chest radiographs that the particles were not mobile. No surgical intervention was planned for the patient in the evaluation made by the Cardiovascular Surgery Clinic. On the fifth day of hospitalization, the patient was discharged with antibiotic treatment.

The patient was followed-up for one year by monthly checks within the first three months and then once every three months. Pelvic, thigh and chest radiographs were obtained at each follow-up. It was confirmed that the particles in the heart were not mobile. On the first year of follow-up, 3 of these particles were seen in the same location and 1 was minimally displaced in the ventricular wall. Because this replacement was not clinically important and the other pellets remained constant, no intervention was needed, and the patient was invited for control visits at one-year intervals. Patient's written consent and ethical approval were obtained (Decision No: E-18-1815).

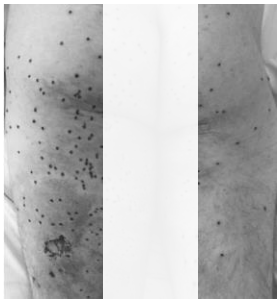

Figure 1: Multiple open wounds were seen in both hip and thigh regions of the patient, all posteriorly located and compatible with the entry wounds of the rifle injury.

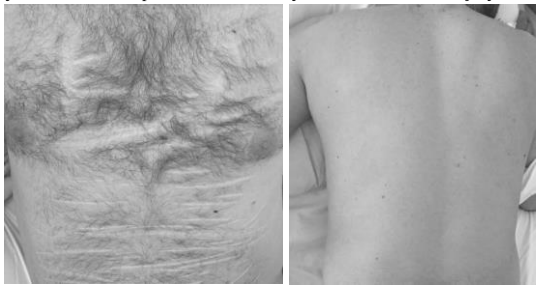

Figure 2: Patient had no injuries on his chest and back.

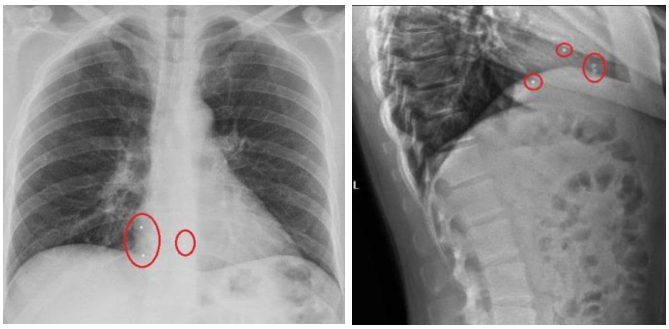

Figure 3: Hyperdense foreign bodies in the middle mediastinum on anteroposterior and lateral chest x-ray

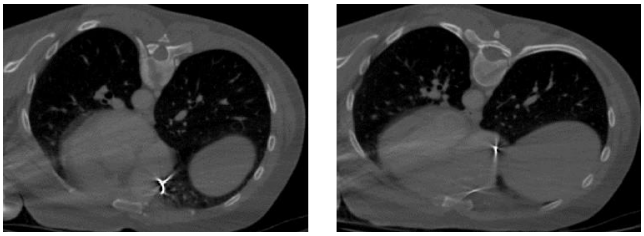

Figure 4: Hyperdense foreign bodies in the middle mediastinum on axial computed tomography images

Discussion

Foreign body migration, although not quite common in the literature, happens through different mechanisms and implants. Implanted materials such as pacemaker and shunts may reportedly migrate from their original locations to distant sites; however, the exact mechanism of such migration is not always clear. There are case reports in the literature of materials such as Kirschner and cerclage wire are migrating various regions to other locations in the body [12,13]. Although it is a relatively rare event, the migration of bullets or pellets into the heart has also been reported. When a pellet enters the soft tissue and loses its kinetic energy, it can either penetrate the tissue or remain inside. Richve et al. [14], who examined 7500 firearm injuries in the Vietnam War, encountered 22 patients with embolism of bullets. In 2001, two cases of gunshot injury from the upper extremity, one of which migrated to the heart and the other to a peripheral vein, were reported in Australia [15]. Although these migrations are explained with different theories, such as replacement of foreign bodies by blood flow after entering the vein, abdominal pressure change by coughing etc., or replacement via macrophage response caused by body defense mechanisms, the mechanism of the replacement has not yet been fully elucidated [3,5,13]. Because the mechanism of replacement is not clear, there is no possible way to know where the migrating bullet or pellet will migrate to in the human body.

Replacement of foreign bodies in the body, although a rare phenomenon, should always be kept in mind because of potential unexpected complications. Therefore, especially in firearm injuries, chest x-ray should be obtained routinely, considering that bullets or pellets can be replaced.

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