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Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

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Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

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The Importance of Arcuate Foramen, A Variation of the Atlas: A Microsurgical Cadaveric Study and Review of the Literature

Atlasın Varyasyonu Arkuat Foramenin Önemi: Bir Mikroşirürjikal Kadavra Çalışması ve Literatürün Gözden Geçirilmesi

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ABSTRACT

Introduction: Arcuate foramen (AF) is an osseous variation located on the vertebral artery (VA) groove (sulcus arteriae vertebralis) at the posterior arch of the atlas. Its prevalence may vary due to regional and ethnic factors. Although it is thought that it causes compression of the structures inside AF and causes vertebrobasilar insufficiency, there are not enough cadaver studies to explain this clinical condition.

Methods: To evaluate the incidence of AF variation and its relationship with VA, 20 sides of 10 randomly selected and silicone injected cadaveric heads were examined by microsurgical method at the University of Wisconsin Neuroanatomy Laboratory.

Results: Complete AF variation in atlas was detected in 30% of the samples. This variation was unilateral on the right side in two cases and bilateral in one case. The mean dimensions of AF were D1=6 mm and D2=5.5 mm on the right, and D1=7.5 mm and D2=6.5 mm on the left. The mean pre-foraminal, foraminal and post-foraminal diameters of VA were 4 mm, 2.5 mm and 3 mm, respectively, on the right, and 6 mm, 4 mm and 5 mm, respectively, on the left. In all cases, the suboccipital nerve was accompanying VA in the AF.

Conclusion: Being aware that this variation may have a high incidence may help to determine surgical strategy before craniocervical junction surgery and prevent life-threatening arterial injuries. In addition, although the dimensions of the AF is adequate for the passage of VA, presence of arterial compression due to other structures passing through the foramen may explain the reason for the relief of most cases with foramen decompression.

Keywords: Arcuate foramen, atlas, cadaver study, osseous anomaly, vertebral artery, vertebrobasilar insufficiency

ÖZ

Amaç: Arkuat foramen (AF) atlasın posterior arkındaki vertebral arter (VA) oluğunda (sulkus arteriae vertebralis) bulunan, prevalansı bölgesel ve etnik faktörler nedeni ile değişebilen osseöz bir varyasyondur. AF'nin içindeki yapılara bası oluşturarak vertebrobaziler yetmezlik bulgularına neden olduğu düşünülse de bu kliniği açıklayacak yeterli sayıda kadavra çalışması yoktur.

Yöntemler: AF varyasyonun insidansını ve içinden geçen VA ile olan ilişkisini değerlendirmek için renkli silikon enjekte edilmiş ve rastgele olarak seçilmiş 10 kadavranın 20 tarafı Wisconsin Üniversitesi Nöroanatomi Laboratuvarı'nda mikroşirürjikal yöntem ile incelendi.

Bulgular: Örneklerin %30'unda atlasta komplet tipte AF varyasyonu saptandı. Bu varyasyon iki olguda sağda tek taraflı iken bir olguda bilateraldi. AF'nin ortalama boyutları sağda D1=6 mm, D2=5,5 mm, solda D1=7,5 mm, D2=6,5 mm, VA'nın ortalama çapı ise foramen öncesi, foramen içi ve foramen sonrası sırası ile sağda 4 mm, 2,5 mm ve 3 mm, solda 6 mm, 4 mm ve 5 mm idi. Olguların hepsinde suboksipital sinir AF içerisinde VA'ya eşlik ediyordu.

Sonuç: Bu varyasyonun yüksek insidansının olabileceğinin bilinmesi kraniyoservikal bileşke ameliyatlarından önce ameliyat stratejisinin belirlenmesini ve hayati tehlike yaratabilecek arter yaralanmalarının engellenmesini sağlayabilir. Ayrıca, AF boyutlarının VA'nın rahatlıkla geçişine uygun olmasına karşın foramen içinden geçen diğer yapılar nedeni ile arteryel bası oluşturduğunun görülmesi foramen dekompresyonu ile olguların çoğunun rahatlama nedenini de açıklayabilir.

Anahtar Kelimeler: Arkuat foramen, atlas, kadavra çalışması, osseöz anomali, vertebral arter, vertebrobaziler yetmezlik

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Introduction

Arcuate foramen (AF) is an osseous variation on the vertebral artery groove (sulcus arteriae vertebralis) at the posterior arch of the atlas. The vertebral venous plexus, perivascular sympathetic plexus and suboccipital nerve pass along with the vertebral artery (VA) and it is defined by more than one name in the literature (1,2) (Appendix 1). This foramen, which is normally found in the first cervical vertebrae of primates and other lower vertebrates, has been reported in complete or incomplete types in humans, and its prevalence ranges from 5% to 68% (1-18).

Cadaver studies are an important method in elucidating the ethiopathogenesis of diseases and determining the treatment. It is thought that AF causes Barre Lieou syndrome, which also includes vertebrobasilar insufficiency (VBI) findings, by compressing the structures within AF, therefore foramen decompression is performed in its treatment (19,20). However, only one study was found in the literature in English (18).

In this study, we investigated the incidence of AF and the effect of this foramen on VA in colored silicon injected cadavers.

Methods

Between August 2018 and February 2019, 20 sides of 10 randomly selected cadavers (50-80 years, 8 males, 2 females) who were injected color silicone in University of Wisconsin Neuroanatomy Laboratory were incised with a reverse U-shaped incision applied behind the ear in prone position. Muscles in the craniovertebral junction were dissected, and occipital region and upper cervical vertebrae up to C3 were revealed. OPMI Neuro/NC 4 surgical microscope was used for dissection. AF dimensions (D1=horizontal length of AF, D2=vertical length of AF), and pre-foraminal (a), intra-foraminal (b) and post-foraminal (c) VA diameters were measured in all cases (Figure 1A, 1B). Measurements were made with digital caliper. Descriptive statistical methods were used in the study. Data were saved to Microsoft Excel and mean values were calculated.

Since our study was conducted on cadavers, ethics committee approval was not obtained and the privacy of the cases was preserved in the pictures.

Appendix 1. Various nomenclatures used to identify arcuate foramen

Arcuate foramen
Ponticulus posticus
Kimmerle's anomaly/variant/deformity
Atlas bridging
Posterior ponticle of the atlas
Foramen atlantoideum posterius/vertebrale
Foramen retroarticular superior
Foramen sagittale
Canalis arteria vertebralis
Pons posticus
Posterior atlantoid foramen
Posterior glenoid process
Posterior glenoid spiculum
Retroarticular canal
Retroarticular VA ring
Retroarticular vertebral ring
Retrocondylar bony foramen
Retrocondylar VA ring

VA: vertebral artery

Results

AF variation was found in three of 10 cadavers examined and this variation was complete in all cases (Figure 2). All three patients were male, and AF was unilateral on the right side in two patients and bilateral in one patient (Tables 1, 2). The mean pre-foraminal, intra-foraminal and

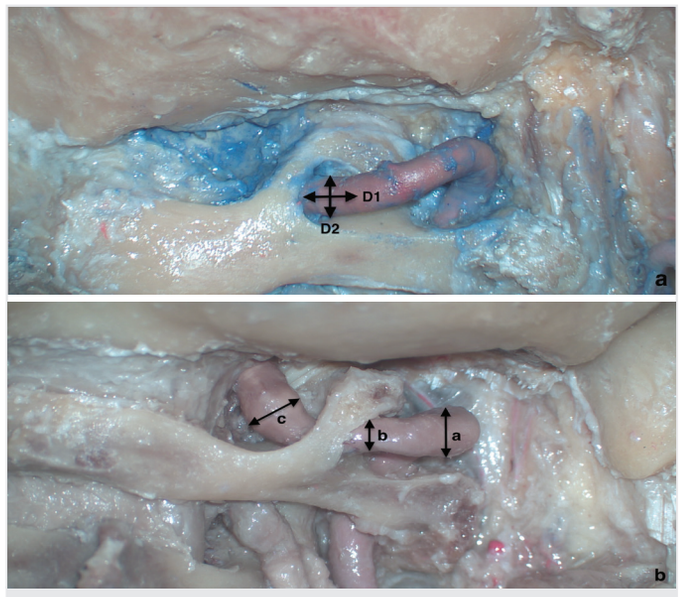

Figure 1. A) Arcuate foramen dimensions, D1=Horizontal length, D2=Vertical length. B) a: pre-foraminal, b: foraminal, c: post-foraminal parts of the sulcal vertebral artery

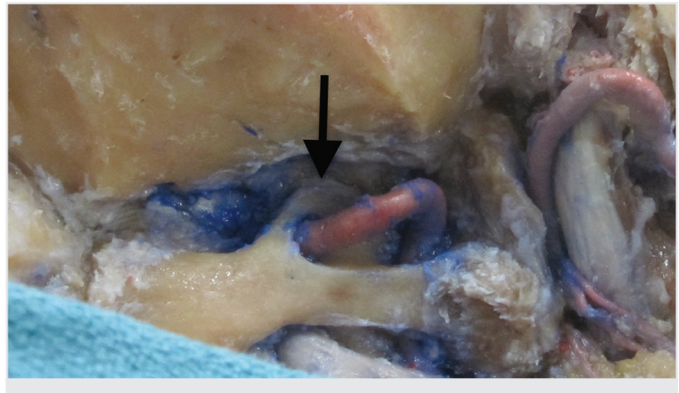

Figure 2. Complete arcuate foramen variation in the right atlas (arrow)

Table 1. Demographic characteristics of arcuate foramen

	Case number	AF number
Male	3	4
Female	0	0

AF: arcuate foramen

post-foraminal V3 diameters were 4 mm, 2.5 mm, 3 mm on the right, respectively, and 6 mm, 4 mm, 5 mm on the left, respectively. The mean dimensions of AF were D1=6 mm and D2=5.5 mm on the right, and D1=7.5 mm and D2=6.5 mm on the left (Tables 3, 4). Left AF dimensions were approximately 1-1.5 mm wider than the right. Although AF dimensions were wider than the pre-foraminal VA, it was noted that the diameter of the V3 was narrowed at the AF level and widened again starting from the AF exit (Figure 3). In all cases, the VA was accompanied by suboccipital nerve inside the AF (Figure 4).

Discussion

In our study, we found that there was 30% AF variation in the atlas, which is six times the incidence of AF in cadavers reported by Tubbs et al. (18). In addition, this variation was four times higher in males than in females, although there were studies reporting no statistically significant difference between the genders (Tables 1, 2) (7). Again, unlike Elliott and Tanweer's (7) meta-analyzes, AF was complete in all cases. This may be due to ethnic differences of the cases or the fact that most of the other studies were performed on dry atlas or by radiological examination. As a matter of fact, it has been reported that there are various types of AF variation, that its prevalence varies according to regional and ethnic groups, and that it is seen most frequently in the Middle East and North America, at least in Indians, and can be overlooked in radiological examination (1,2,8,13,17,21). In our study, the high incidence of AF may be related to the fact that we conducted this study in North America.

Table 2. Characteristics of arcuate foramen

Case number	3
Bilateral	1
Unilateral	2
Only on the right	2
Only on the right	(-)
Complete	4
Incomplete	(-)

Table 3. Mean length and height of the arcuate foramen in cadavers

Dimensions	**Mean**
Length	
Right	6 mm
Left	7.5 mm
Height	
Right	5.5 mm
Left	6.5 mm

Table 4. Mean diameter of V3 in the sulcal piece of vertebral artery in cadavers

Diameter	Pre-foraminal	Foraminal	Post-foraminal
Right	4 mm	2.5 mm	3 mm
Left	6 mm	4 mm	5 mm

It has been reported that the only advantage of this variation is the low risk of fracture, and it has also been reported that it usually leads to dissection by stretching the VA, vertebrobasilar ischemia during strong interventions in the cervical spine, complications in cases where C1-C2 stabilization is required, and Barre Lieou syndrome mostly by causing neurovascular compression (1,5,7,14,15,18,19,22-27).

Anatomical studies in stained cadavers are important not only because of demonstrating the variation itself, but also the relationship between neighboring vascular and neural structures. In this way, it can be easier to understand the etiology of the pathology due to variation and to find solutions against this pathology.

In the literature, the portion of VA between C2 and foramen magnum is called the third segment (V3) and left VA is reported to be generally wider than the right (3,28). In our cases, the left VA was wider than the right (Table 4). In addition, although the dimensions of AF on both sides were larger than the pre-foraminal diameter of VA, V3 compression was observed at the foramen level (Table 3). Tubbs et al. (18) also reported compression of VA, however, Afsharpour et al. (29) reported that there was no compression of VA at the level of AF. This different result in the second study may be related to the fact that the AF variation in the cases is bilateral (lateral and dorsal) on both sides (29).

Not only V3, but also vertebral venous plexus, perivascular sympathetic plexus and suboccipital nerve pass through the AF located on the

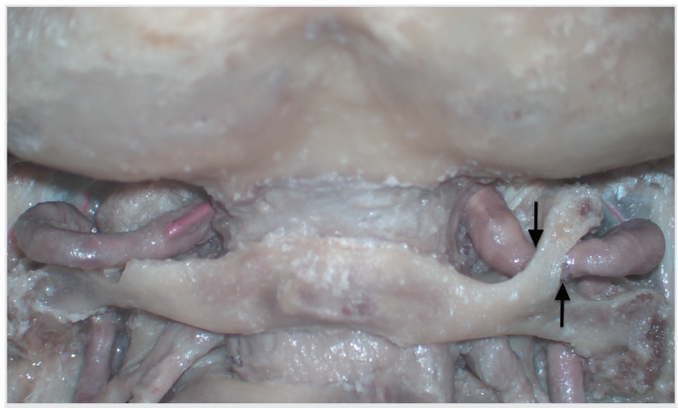

Figure 3. Unilateral arcuate foramen, vertebral artery narrowing at the foramen level (arrow)

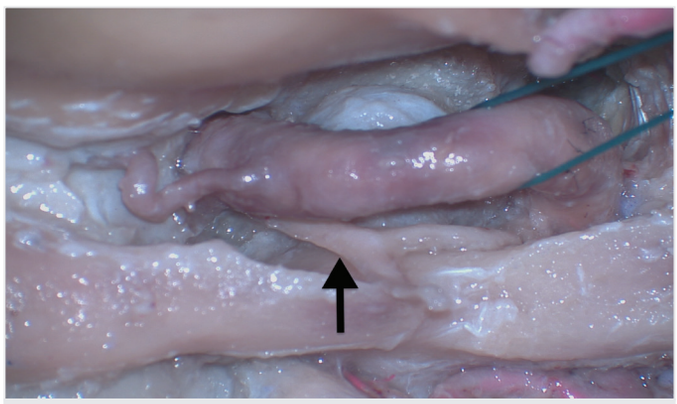

Figure 4. Suboccipital nerve in the arterial groove of the atlas (arrow)

sulcal part of the atlas (1,2). The fact that AF contains all these other neurovascular structures causes pressure on VA within the foramen. As a matter of fact, AF decompression is applied in these cases considering that VBI Clinic in Barre Lieou syndrome is formed by this mechanism (19,20). However, although clinical improvement was achieved in most of the cases with foramen decompression, 13.33% of young patients without cervical arthrosis also reported not to respond completely to treatment (19).

In order to fully understand the incidence of AF variation and the ethiopathogenesis of Barre Lieou syndrome, more detailed studies on cadavers of different ethnic backgrounds in different geographical regions are required. In the first stage of cadaver studies, it is difficult to obtain a large series of cases. The publication of these studies may lead to the acquisition of large series over time.

Conclusion

In our study, we encountered 30% AF variation in cadavers. The high incidence of AF variation in the interventions to the craniovertebral junction should be remembered and a detailed examination of this region should be performed before the intervention. Thus, by determining the treatment strategy, the possibility of life-threatening VA injury can be reduced. In our study, we also found that AF dimensions are suitable for the passage of VA easily, but that the suboccipital nerve passes through this foramen and may cause arterial compression. Although this finding suggests that foramen decompression is required in the treatment of Barre Lieou syndrome, further cadaver studies are needed to elucidate the ethiopathogenesis of patients who do not respond to this treatment.

Ethics Committee Approval: Since our study was conducted on cadavers, ethics committee approval was not obtained and the privacy of the cases was preserved in the pictures.

Informed Consent: Informed verbal and written informed consent was obtained from the teachers.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - N.K.; Concept - N.K., M.B.; Design - N.K., U.Ç., B.Ö., M.B.; Data Collection and/or Processing - N.K., U.Ç., B.Ö.; Analysis and/or Interpretation - N.K., U.Ç., B.Ö., M.B.; Literature Search - N.K., U.Ç., B.Ö.; Writing Manuscript - N.K., M.B.

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Validity and Reliability of the Turkish Version of "Nijmegen-Gender Awareness in Medicine scale"

"Nijmegen-tıpta Cinsiyet Farkındalığı ölçeği" Türkçe Geçerlik ve Güvenirlik Çalışması

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ABSTRACT

Introduction: Gender is a concept that expresses how the society sees, perceives, thinks individuals and how they should behave as a men and women. Gender-based norms and values, while strengthening the differences between men and women, also bring social inequalities. One of the areas that cause inequality is health. The aim of this methodological and descriptive study is to analyze the validity and reliability of the Turkish version of "Nijmegen gender awareness in medicine scale".

Methods: The study was carried out with 150 medical students. The data of the study were collected in April 2016.

Results: As a result of the reliability analysis of the Turkish version of the scale, two items were excluded from the original scale (26 item). It was determined that three items (items 8, 10, and 11) were placed in another subdimension (factor 3) but as these items were not structurally compatible with the other items that they were factored with these items were also removed from the scale. In order to test the reliability of the scale consisting of 21 items split-half reliability method was used. The model was found to be compatible.

The validity of the scale was assessed by factor analysis. Kaiser-Meyer-Olkin and Bartlett tests were performed to determine the adequacy of the sample size. The fit indices obtained from the model generated by confirmatory factor analysis confirmed the three-dimensional structure of the scale.

Conclusion: It was determined that the Turkish version of the scale was valid and reliable.

Keywords: Gender, medicine, education, undergraduate, student

ÖZ

Amaç: Toplumsal cinsiyet, toplumun bireyleri nasıl gördüğü, algıladığı, düşündüğü kadın ve erkek olarak nasıl davranmaları gerektiğini ifade eden kavramdır. Cinsiyete dayalı normlar ve değerler, kadınlar ve erkekler arasındaki farklılıkları güçlendirirken sosyal eşitsizlikleri de beraberinde getirir. Eşitsizliğe neden olan alanlardan biri de sağlıktır. Bu metodolojik ve tanımlayıcı çalışmanın amacı "Nijmegen-tıpta cinsiyet farkındalığı ölçeği" Türkçe geçerlik ve güvenirlik analizlerinin yapılmasıdır.

Yöntemler: Çalışma 150 tıp öğrencisi ile gerçekleştirilmiştir. Çalışmanın verileri 2016 Nisan ayında toplanmıştır.

Bulgular: Ölçeğin Türkçe versiyonunun güvenirlik analizi sonucunda, orijinal ölçeğin (26 madde) iki maddesi çıkarılmıştır. Üç madde (madde 8, 10 ve 11) başka bir alt boyutta (faktör 3) yerleşmiştir, ancak bu öğeler faktörün diğer maddeleriyle yapısal olarak uyumlu olmadığı için ölçekten çıkarılmıştır. Yirmi-bir maddeden oluşan ölçeğin güvenirliğini test etmek için yarıya bölme güvenilirlik yöntemi kullanılmıştır. Modelin uyumlu olduğu bulunmuştur.

Ölçeğin geçerliliği faktör analizi ile değerlendirilmiştir. Örneklem büyüklüğünün yeterliliğini belirlemek için Kaiser-meyer-olkin ve Bartlett testleri yapılmıştır. Doğrulayıcı faktör analizi ile oluşturulan modelden elde edilen uyum indeksleri, ölçeğin üç boyutlu yapısını doğrulamıştır.

Sonuç: Ölçeğin Türkçe versiyonunun geçerli ve güvenilir olduğu belirlenmiştir.

Anahtar Kelimeler: Cinsiyet, tıp, eğitim, lisans, öğrenci

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Introduction

While biological sex expresses the biological and physiological characteristics of women and men, gender expresses the roles, behaviors and activities socially constructed by society (1). Gender is a concept that expresses how the society sees, perceives, thinks individuals, and how they should behave as men and women (2). The content of this concept is determined by the norms set by the society and these norms are learned in the process of socialization by men and women. Gender-based norms and values also bring about social inequalities while strengthening the differences between men and women (1). One of the areas that cause inequality is health. There is an invisible and inseparable bond between health and gender. Gender awareness of physicians is aimed at improving the health of women and men, and at the same time it contributes to the rights and equality in health (3,4).

The integration of gender issues from the undergraduate level to the whole medical education process (in terms of knowledge, attitude and skill) during continuous professional development is defended by all medical disciplines (5,6). Gender awareness of physicians means that physicians know and understand the concept of gender and incorporate the concept of gender as a basic determinant of health and illness into their daily practice (7). Gender-sensitive medical education is possible by integrating gender and gender-related processes, reactions and treatments into the education curriculum. Although the importance of biological sex and gender is recognized in health area, it takes time to integrate these issues into the medical education curriculum. In recent years, an increasing number of researches on the integration of these subjects into medical education have been reported in countries such as Netherlands, Sweden, Australia and the United States (5,8). Canada is also a country working on this issue. In Netherlands, a national project was initiated in 2002 to include issues related to gender-linked health problems into the medical education (9,10). In our country, with the gender equality attitude document, higher education institutions and the higher education committee are committed to acting in a sensitive manner to gender equality in all components (11).

The purpose of this study was to investigate the Turkish validity and reliability of a scale developed to measure the gender awareness of medical faculty students.

Methods

Type of Study

This research was a methodological and descriptive study designed to test the validity and reliability of the Turkish version of the "Nijmegen-gender awareness in medicine scale (N-GAMS)".

Nijmegen-gender awareness in medicine scale

	Turkish version	English version
Item	**Toplumsal cinsiyet duyarlılığı**	**Gender sensitivity**
1	Hekimler, kadın ve erkeğin sadece biyolojik farklılıklarını dikkate almalıdır. R	Physicians should only address biological differences between men and women. R
2	Cinsiyete özgü olmayan sağlık sorunlarında hastanın cinsiyeti hekim için önemsizdir. R	In non-sex-specific health disorders, the sex/gender of the patient is irrelevant. R
3	Hekimler, kadın ve erkeğin şikâyetlerini mümkün olduğunca biyomedikal yönle sınırlandırmalıdır. R	A physician should confine as much as possible to biomedical aspects of health complaints of men and women. R
4	Erkek ve kadın hekimler arasındaki fark, üzerinde durulmayacak kadar önemsizdir. R	Differences between male and female physicians are too small to be relevant. R
5	Erkek ve kadınlar aynı olmadığından, hekimler herkesi farklı şekilde tedavi etmelidir.*	Especially because men and women are different, physicians should treat everybody the same. R
6	Toplumsal cinsiyet farklarını dikkate alan hekim önemsiz konularla uğraşıyor demektir. R	Physicians who address gender differences are not dealing with the important issues. R
7	Hasta hekim iletişiminde hekim için hastanın erkek ya da kadın olması fark etmez. R	In communicating with patients, it does not matter to a physician whether the patients are men or women. R
	-	In communicating with patients, it does not matter whether the physician is a man or a woman. R
9	Erkek ve kadın hastalar arasındaki fark hekimlerce dikkate alınamayacak kadar önemsizdir. R	Differences between male and female patients are so small that physicians can hardly take them into account. R
	Hastaya yönelik toplumsal cinsiyet algısı	Gender role ideology towards patients
	-	Male patients better understand physicians' measures than female patients.
	-	Female patients compared to male patients have unreasonable expectations of physicians.
12	Muayene odasında konuşulması gerekmeyen problemleri, kadınlar erkelerden daha sıklıkla hekimleri ile tartışmak isterler.	Women more frequently than men want to discuss problems with physicians that do not belong in the consultation room.
13	Kadınlar, hekimlerden çok daha fazla duygusal destek beklerler.	Women expect too much emotional support from physicians.
14	Erkek hastalar kadın hastalardan daha az talepkardır.	Male patients are less demanding than female patients.
15	Kadınlar gerçek ihtiyaçlarından daha fazla sağlık hizmeti tüketicisidirler.	Women are larger consumers of health care than is actually needed.

Nijmegen-gender awareness in medicine scale		
	Turkish version	**English version**
Item	**Toplumsal cinsiyet duyarlılığı**	**Gender sensitivity**
16	Erkekler kendilerine zarar vermediğini düşündükleri sağlık sorunları için hekime gitmezler.	Men do not go to a physician for harmless health problems.
17	Kadınlar sağlıkları hakkında daha fazla sızlandıkları için tıbben açıklanamayan belirtiler daha çok gelişir.	Medically unexplained symptoms develop in women because they lament too much about their health.
18	Kadın hastalar erkek hastalardan daha fazla ilgiye ihtiyaç duydukları için sağlıklarından daha çok şikâyet ederler.	Female patients complain about their health because they need more attention than male patients.
19	Erkekler doğrudan iletişim kurdukları için sağlık şikayetlerinin nedenlerini bulmak erkeklerde daha kolaydır.	It is easier to find causes of health complaints in men because men communicate in a direct way.
	Hekime yönelik toplumsal cinsiyet algısı	Gender role ideology towards doctors
8	Hasta hekim iletişimde hekimin erkek ya da kadın olması fark etmez.** R	-
10	Hekimlerin değerlendirmelerini, erkek hastalar kadın hastalardan daha iyi anlarlar. **	-
11	Kadın hastaların erkek hastalara göre hekimlerden mantık dışı beklentileri vardır.**	-
20	Erkek hekimler kadın hekimlerle karşılaştırıldığında tıbbın teknik yönlerine daha fazla vurgu yaparlar.	Male physicians put too much emphasis on technical aspects of medicine compared to female physicians.
21	Kadın hekimler erkek hekimlere göre muayenelerini daha çok uzatırlar.	Female physicians extend their consultations too much compared to male physicians.
22	Erkek hekimler kadın hekimlerden daha verimlidir.	Male physicians are more efficient than female physicians.
23	Kadın hekimler erkek hekimlerden daha empatiktir. *	Female physicians are more empathic than male physicians.
24	Kadın hekimler bir hastanın hastalığı nasıl deneyimlediğini gereksiz yere dikkate alırlar.	Female physicians needlessly take into account how a patient experiences disease.
25	Kadın hekimler hastalarıyla oldukça duygusal bağ içindedirler.	Female physicians are too emotionally involved with their patients.
26	Erkek hekimler muayenelerinde kadın hekimlere göre daha acelecidirler.	Compared to female physicians, male physicians are too hurried in their consultations.

*Items removed in factor analysis due to low factor loading.
** Excluded item (items which were not structurally compatible with the other items that they were factored with)
Items scored in reverse - R

Sample

It is emphasized that enough samples should be taken to apply factor analysis in scale studies. It is stated that the correlation coefficients calculated with small sample are less reliable. Tavşancıl suggested that the sample size should be at least five times, or even ten times the number of items (12). Since there are 26 items in this scale, it was estimated that at least 130 students should be reached for this study. Third-year students who have not yet received clinical training but who have received preclinical medical training are considered eligible for determining awareness in the study and the research was carried out on this group. In the 2016-2017 academic years, 165 third-year students (n=348) studying at Erciyes University Faculty of Medicine were included in the study. Fifteen of these students were not included in the survey because the scale questions were incomplete and analyses were made on 150 students.

The data of the study were collected in April 2016. The purpose of the study was explained to the students, and the questionnaires were distributed and collected. The survey took about 10 minutes.

Data Collection Tools

Two forms were used to collect the data:

- Socio-demographic information form: This form consists of seven questions asking the socio-demographic characteristics of the students (age, sex, marital status, educational status of parents, working status of parents).

- N-GAMS (Nijmegen gender awareness in medicine scale):

In 2008, the scale was developed by Verdonk et al. (7) and it was revised in 2012 (13). The scale was developed to measure the gender attitudes and values of medical students. It was aimed to make a basic assessment

of gender sensitive perspective inclusion to the education curriculum and to make an evaluative measurement after integration. It consists of 26 items and three sub-dimensions [Gender Sensitivity (GS), Gender Role Ideology Towards Patients (GRI-P), GRI Doctors (D)]. The scale is in five-point Likert (1=totally disagree, 5=totally agree). There are nine items on the scale (from 1 to 9) that determine GS, ten items (from 10 to 19) that determine GRI-P, seven items (from 20 to 26) that determine GRI-D. All items that determine GS are scored inversely. While the GS sub-dimension scale focuses on attitudes of students towards gender issues in patient care (students' ability to perceive gender differences, problems and health inequalities in health care), GRI-P measures students' thoughts on gender roles about patients. GRI-D measures students' thoughts on gender roles about doctors. Increasing scores of GS subscale means that the GS of the student increases. Higher scores in the other two sub-dimensions show that gender stereotypes are more accepted. Reliability coefficients in the original study were found to be 0.76, 0.89 and 0.89, respectively, for the subscales (13).

Procedure

For the linguistic equivalence of the scale, translation into Turkish was made according to the forward and backward procedure. Firstly, the scale was translated into Turkish individually by three professors working at the university who dominate the issue of gender and medicine education at language level and expert in their areas. Then, these people discussed the translation text. Necessary corrections were made in terms of meaning and language. Finally, a common text was created. After that, the text was translated back into English by two lecturers from the English department to confirm that whether each item lost its meaning. The faculty members, who translated into Turkish and English, then made the necessary corrections by debating on the scale together. The pilot application of the questionnaire was carried out with a total of ten residents and 45 randomly selected interns working in family medicine department and public health department. Criticisms about the clarity of the language of the scale were taken from residents and intern physicians. After the pilot application, these criticisms were reassessed among the research lecturers and the questionnaire was rearranged. In order to obtain expert opinion on the completed scale, a final version of the form of the questionnaire to be applied to students was sent to the two lecturers working in medical education at different universities and their opinions were taken.

Ethical Approach

Before starting the research, an e-mail was written to Petra Verdonk and necessary permission was obtained in order to translate the scale into Turkish. Another permission was obtained from the Dean of Erciyes University Faculty of Medicine and the Ethics Committee of Erciyes University for the study to be conducted in medical faculty students (decision no: 2016/368, date: 24.06.2016). Informed consent form was obtained from participants.

Statistical Analysis

Data were evaluated using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York, USA) and IBM SPSS AMOS 24.0 statistical package program. As descriptive statistics, number of units (n), percentage (%), and mean ± standard deviation (mean ± SD) values were given. Normality of the numerical variables were evaluated by Shapiro-Wilk normality test and Q-Q graphs.

The internal consistency between the items in the evaluation of scale validity Cronbach alpha coefficient, unit number adequacy in the sample Kaiser-Meyer-Olkin (KMO) test, factoring Barlett test, and determination of factor structure was assessed by analysis of the main components. The varimax method was used to determine the factors to be included in the final inventory. Confirmatory factor analysis (CFA) was conducted. The reliability of the scale was evaluated by means of intra-group correlation coefficients and split-half reliability. With 95% confidence interval, $p<0.05$ value was considered statistically significant. In the validity study, item analysis and discriminant validity studies were performed, and internal consistency and test re-test reliability coefficients were calculated for the reliability studies.

Results

The data of 150 students were analyzed. The distribution of socio-demographic characteristics of the students is shown in Table 1.

Table 1. Distribution of sociodemographic characteristics of students

Characteristics		
Age (mean ± standard deviation)	**21.7±2.3 years**	
	n	**%**
Sex (n=144)		
Male	79	53.7
Female	68	46.3
Mother's educational status (n=146)		
Illiterate	6	4.1
Literate	7	4.8
Primary school graduate	36	24.7
Secondary school graduate	16	11.0
High school graduate	42	28.8
Undergraduate graduate	39	26.6
Father's educational status (n=147)		
Illiterate	3	2.0
Literate	1	0.7
Primary school graduate	25	17.0
Secondary school graduate	13	8.8
High school graduate	38	25.9
Undergraduate graduate	67	45.6
Mother's working status (n=146)		
Housewife	105	71.9
Retired	9	6.2
Working	32	21.9
Father's working status (n=145)		
Unemployed	3	2.1
Retired	46	31.7
Working	96	66.2

Reliability Analysis of the scale

Reliability and item analysis were performed to evaluate the fiction, content, structure, and phenomenon questioning competence of the scale. In order to measure gender awareness in medical students that we want to measure with scale, item total test correlation coefficients were examined to determine the measurement power of each item and to bring the scale to a more reliable state. The item total test correlation coefficient should be no minus marked and greater than + 0.25 (14). Therefore, two items (item 5 and 23) that did not fulfill this requirement were removed from the scale. It was determined that three items (items 8, 10, and 11) were placed in another subdimension (factor 3), but as these items were not structurally compatible with the other items that they were factored with, these items were also removed from the scale. In order to test the reliability of the scale consisting of 21 items, split-half reliability method was used [part 1 cronbach alpha coefficient: 0.788, part 2 cronbach alpha coefficient: 0.871, total cronbach alpha coefficient 0.883 (corrected cronbach alpha coefficient; 0.889)]. The Hotelling T2 test was performed to test the model fit, the model was found to be compatible (Hotelling T2 288, 677; $p<0.001$). Evaluation of the score is as same as the original scale. Increasing score of the GS subscale means that the GS of the student increases. The high scores in the other two sub-dimensions show that gender stereotypes are more accepted.

Validity Analysis of the scale

The validity of the scale was assessed by factor analysis. Before conducting factor analysis, KMO and Bartlett tests were performed to determine the adequacy of the sample size. For the factor analysis of 21 items, the KMO value was calculated as 0.857 and the Bartlett test result was found as (1450.3; SD: 210; $p<0.001$). Table 2 shows the descriptive factor analysis of the scale.

When Table 2 is examined, it is seen that the factor load values of the items change between 0.749 and 0.593 for factor 1 and that the items 1,2,3,4,6,7,9 are in the first factor; Factor 2 is between 0.839 and 0.579, and items 12,13,14,15,16,17,18,19 are in the second factor; for factor 3 the values range from 0.767 to 0.494 and items 20,21,22,24,25,26 are found in the third factor.

The Turkish version of the "Nijmegen gender awareness in medicine scale" was gathered into three factors, as in the original scale.

The first nine items in the original scale (1-9; GS) determine GS. In the adapted scale, two items appear to be removed from the scale. The

Table 2. Descriptive factor analysis of the "Nijmegen gender awareness in medicine scale"

	Factor 1 (Gender sensitivity)	Factor 2 (Gender role ideology toward patients)	Factor 3 (Gender role ideology toward doctors)
Item 1	0.610	-	-
Item 2	0.729	-	-
Item 3	0.593	-	-
Item 4	0.749	-	-
Item 6	0.679	-	-
Item 7	0.596	-	-
Item 9	0.765	-	-
Item 12	-	0.661	-
Item 13	-	0.637	-
Item 14	-	0.716	-
Item 15	-	0.696	-
Item 16	-	0.702	-
Item 17	-	0.787	-
Item 18	-	0.839	-
Item 19	-	0.579	-
Item 20	-	-	0.494
Item 21	-	-	0.595
Item 22	-	-	0.593
Item 24	-	-	0.633
Item 25	-	-	0.767
Item 26	-	-	0.754
SELF-VALUE %	33.146	47.157	54.296
EXPLAİNED VARİANCE %	23.806	16.236	14.254
Total Explained Variance %	23.806	40.042	54.296
Cronbach Alpha Values of Sub-Dimensions (Standard Cronbach Alpha Based on items)	0.809 (0.811)	0.883 (0.884)	0.829 (0.833)

next ten items on the original scale (10-19; GRI-P) measure students' thoughts on gender roles about patients. It appears eight items (12-19) were included in this sub-dimension. The last seven items of the original scale (20-26, GRI-D) define the ideology of gender roles for physicians. This sub-dimension measures students' thoughts on gender roles about doctors. In the adapted scale, six items were included in this sub-dimension.

The ratio of the chi-square statistics to the degree of freedom (χ^2/df) obtained from the conducted analysis was 1.95 (χ^2=362.826 df=186); root mean square approach error was 0.080; The Tucker-Lewis index value was 0.85 and the comparative fit index value was 0.87. The model formed by CFA is presented in Figure 1. The three-dimensional structure of the scale is verified with this model. These results show that the scale reached enough fit values.

Discussion

The aim of this research was to analyze the validity and reliability of the Turkish version of "Nijmegen-gender awareness in medicine scale". For the linguistic equivalence study, which is extremely important in the scale adaptation, backward and forward translation of "Nijmegen-gender awareness in medicine scale" was performed. The members of the faculty who translated it from English into Turkish and from Turkish into English discussed on the scale and completed the translation stage by giving the final state to the scale. All item correlation analyses were performed to ensure scale reliability. Two items (items 5 and 23) with an overall correlation coefficient of less than 0.25 were removed from the scale. Three items (items 8, 10, and 11) were removed from the scale because the items that they were factoring with did not provide meaningful consistency. Factor distributions of the 21 items showed the same distribution as the original scale.

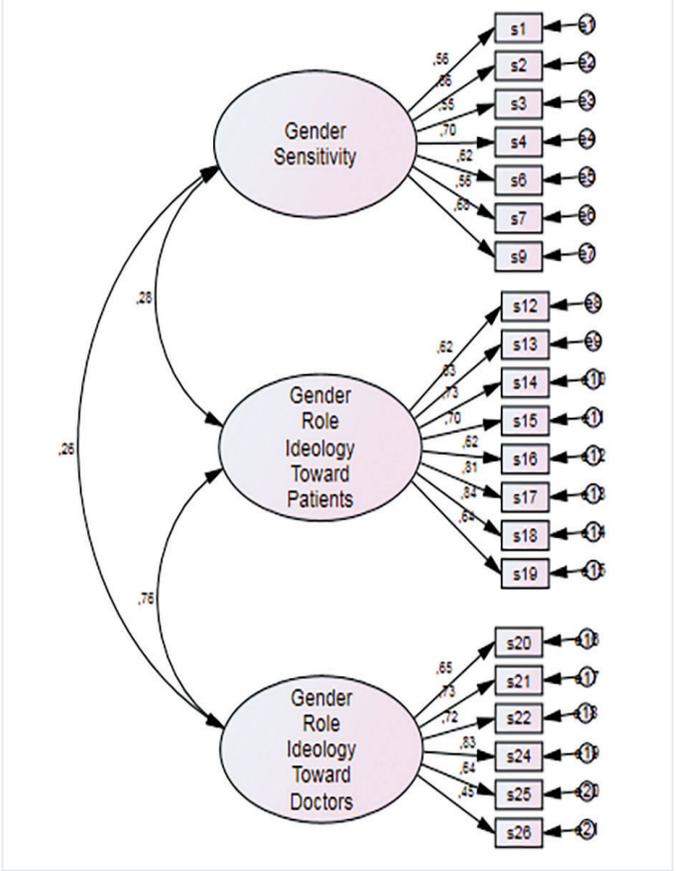

Figure 1. Confirmatory Factor Analysis of "Nijmegen gender awareness in medicine scale"

As a result of AFA (explanatory factor analysis), a three-factor structure that accounts for 54.3% of the total variance was obtained. In addition, when the compliance index limits for DFA are taken into consideration, it is seen that the model has a sufficient level of adaptation and that the Turkish version of the original factor structure conforms to the factor structure.

Conclusion

From this study, it was determined that the Turkish version of the scale was valid and reliable.

Ethics Committee Approval: Another permission was obtained from the Dean of Erciyes University Faculty of Medicine and the ethics committee of Erciyes University for the study to be conducted in medical faculty students (decision no: 2016/368, date: 24.06.2016).

Informed Consent: Informed consent form was obtained from participants.

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The Relationship between Coronary Thrombus Burden and Monocyte to High-Density Lipoprotein Cholesterol Ratio in Patients with Acute Non-ST Elevation Myocardial Infarction

Non-ST Eleve Miyokard Infarklarda Koroner Trombüs Yükü ile Monosit Yüksek Dansiteli Lipoprotein Kolesterol Oranı İlişkisi

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ABSTRACT

Introduction: Non-ST-segment elevation myocardial infarction (NSTEMI) is a condition that constitutes a large part of acute coronary syndromes and has a high mortality rate with diffuse vascular disease. The aim of this study was to examine the association between monocyte to high-density lipoprotein cholesterol ratio (MHR) and thrombus burden, which is indicative of inflammation and cardiovascular endpoints in patients with NSTEMI.

Methods: We retrospectively evaluated 205 consecutive patients who underwent coronary angiography for NSTEMI in our tertiary center. Complete blood count and biochemical analysis were performed using blood samples. Angiographic thrombus burden was classified as previously described by thrombolysis in the myocardial infarction (TIMI) study group.

Results: Patients with high thrombus burden had higher monocyte count, MHR and platelet count compared to the group with low thrombus burden. TIMI and Syntax scores were also higher in the high thrombus burden group. Multiple logistic regression analysis revealed that TIMI and MHR values were independently related to high thrombus burden. [Odds ratio (OR): 1.678 (1.120-2.515) p=0.012) and OR: 1.432 (1.102-1.861), p=0.007) respectively.]

Conclusion: In our study, we found that MHR was closely related to thrombus burden in patients with NSTEMI. With further studies, MHR may be a helpful parameter for risk scoring informing long-term morbidity and mortality.

Keywords: Monocyte to high-density lipoprotein cholesterol ratio, HDL-C, MHR, myocardial infarction

ÖZ

Amaç: Non-ST elevasyonlu miyokard infarktüsü (NSTEMI) akut koroner sendromların geniş bir kısmını oluşturan ve yaygın damar hastalığıyla yüksek mortaliteye sahip bir durumdur. Enflamasyonun aterosklerozun gelişiminden başlayan etkisi plak rüptürü sonucu trombüs oluşumuna kadar sürmektedir. Yüksek trombüs yükü ile kötü sonlanım noktaları arasında yakın ilişki vardır. Amacımız NSTEMI hastalarında enflamasyonun ve kardiyovasküler sonlanım noktalarının göstergesi olan monosit yüksek dansiteli lipoprotein oranı (MHR) ile trombüs yükü arasındaki ilişkiyi incelemektir.

Yöntemler: Tersiyer merkezimizde NSTEMI tanısı ile koroner anjiyografi yapılmış 205 ardışık hastayı retrospektif olarak değerlendirdik. Kan örneklerinden tam kan sayımı ve biyokimyasal analizler yapıldı. Anjiyografik trombüs yükü, miyokard enfarktüsü (TIMI) çalışma grubunda tromboliz ile daha önce tanımlandığı gibi sınıflandırıldı.

Bulgular: Yüksek trombüs yükü olan hastalarda düşük gruba göre daha yüksek monosit sayısı, MHR ve platelet sayısı mevcuttu. Ayrıca TIMI ve Syntax skorları da yüksek trombüs yükü olan grupta daha yüksekti. Çoklu lojistik regresyon analizi MR ve TIMI değerlerinin bağımsız olarak yüksek trombüs yükü ile ilişkili olduğunu ortaya çıkardı. [Odds ratio (OR): 1,678 (1,120-2,515) p=0,012) ve OR: 1,432 (1,102-1,861), p=0,007) sırasıyla].

Sonuç: Çalışmamızda MHR'nin NSTEMI hastalarında trombüs yükü ile yakından ilişkili olduğunu tespit ettik. Yapılacak ek çalışmalar ile MHR uzun dönem morbidite ve mortalite hakkında bilgi veren risk skorlamalarına yardımcı bir parametre olabilir.

Anahtar Kelimeler: Yüksek dasiteli lipoprotein kolesterol oranı, HDL-C, MHR, miyokard enfarktüsü

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Introduction

Acute coronary syndrome (ACS) is defined as unstable coronary artery diseases (CADs), including unstable angina pectoris and acute myocardial infarction (AMI) that occurs in response to plaque rupture and vascular inflammation that results in thrombosis (1). Compared with ST-segment elevation AMI (STEMI), non-(N)STEMI patients tend to be older and have more comorbidity with varied CAD severity (2,3). The role of inflammation is essential in the progression and destabilization of atherosclerosis, and eventually in the initiation of the ACS by leading to plaque erosion and rupture (4,5). Intracoronary thrombosis is closely related to no-reflow, distal embolization and ultimately low procedurally success with thrombus size (6). In accordance with this, there was a close correlation between high thrombus burden and 1-year mortality rate and stent thrombosis (7).

Monocyte to high-density lipoprotein cholesterol ratio (MHR) is a prognostic marker that is associated with cardiovascular outcomes in numerous cardiovascular diseases (8,9). Monocytes play a role in the pathophysiology of CAD by transforming into macrophils as they take part in the inflammatory process (10). The function of HDL is to remove the cholesterol in the peripheral tissue and inhibit the monocytes.

There are no studies examining the relationship between thrombus burden and MHR in patients with NSTEMI. Being aware of this relationship may help us estimate the risk of cardiovascular events and obtain information about prognosis and possible additional therapies.

Methods

Two hundred and five consecutive patients who underwent coronary angiography in our tertiary center for the diagnosis of NSTEMI were retrospectively enrolled and the study was undertaken in compliance with the principles of the Declaration of Helsinki. The medical records of consecutive patients hospitalized between January 2015 and December 2017 at Haseki Training and Research Hospital were reviewed.

Patients, who were diagnosed with NSTEMI and had coronary angiography with or without percutaneous coronary intervention (PCI), were enrolled in our study. Using hospital records, baseline clinical and demographic characteristics of patients including diabetes mellitus, hypertension (HT), CAD, family history of CAD, dyslipidemia, smoking, chronic obstructive pulmonary disease and history of CAD or CAD equivalent, such as peripheral arterial disease, were obtained. The medical records of 321 patients were retrospectively reviewed and analyzed. Finally, 205 patients were included in the study. Patients with a history of CAD, malignancy, active infection, connective tissue disorder, end-stage renal disease or receiving hemodialysis, and patients with no significant CAD or with other causes of coronary pain, such as major myocardial bridging or diffuse coronary spasm during angiography and any missing information were excluded from the study.

The diagnosis of NSTEMI uses the American College of Cardiology/American Heart Association guidelines as a basis, and it is diagnosed in a patient with typical chest pain or an equivalent symptom, high troponin and without a ST-segment elevation in ECG. All patients in the emergency department were given 300 mg oral aspirin, 70 U/kg unfractionated heparin and a loading dose 600 mg clopidogrel intravenously, and radial or femoral routes were used to perform coronary angiographies where two different plane images were used to display individual coronary arteries. Two experienced and independent interventional cardiologists (blinded to the data) analyzed digital angiograms. Angiographic thrombus burden was classified as previously defined by thrombolysis in myocardial infarction (TIMI) study group. The grades according to this classification are as follows: grade 0: no evidence of thrombus, grade 1: suspected thrombus (reduced contrast density, haziness, irregular lesion contour, or a smooth convex "meniscus" at the site of occlusion), grade 2: definite thrombus with greatest dimensions ≤ 1/2 vessel diameter, grade 3: definite thrombus with greatest linear dimension >1/2 but <2 vessel diameters, grade 4: definite thrombus with greatest linear dimension ≥2 vessel diameters, and grade 5: total thrombotic occlusion. The patients were grouped into two categories as low thrombus burden (grades 0-3) and high thrombus burden (grades 4 and 5) (11).

Blood samples taken by antecubital vein puncture on admission to emergency room were used for biochemical analysis and complete blood count. An automated blood cell counter (Beckman Coulter analyzer, Brea, CA, USA) was used to determine blood count parameters of hemoglobin, neutrophils, monocytes, white blood cells, platelets and lymphocytes. The targeted biochemical parameters were creatine, low-density lipoprotein cholesterol, glucose, total cholesterol and triglycerides.

Statistical Analysis

Statistical Package for the Social Sciences version 24.0 (SPSS, Chicago, Illinois) was used for statistical analysis. Continuous variables were given as mean ± standard deviation (normal distribution) and median (interquartile range) (non-normal distribution). Categorical variables were provided as percentages. Chi-square (χ^2) test was used to compare categorical variables between groups. Kolmogorov-Smirnov test was used to determine the distribution of variables and Student's t-test or Mann-Whitney U tests were used to compare the continuous variables between the groups in relation to normal distribution. In order to determine independent predictors for high thrombus burden, variables that were found to be associated with a p level of <0.1 by univariate analysis were included in the multivariate logistic regression analysis. Receiver operating characteristic curve analysis was performed to determine the optimal cut-off value for MHR in relation to high thrombus burden. P<0.05 was considered statistically significant at 95% confidence interval.

Results

A total of 205 patients were included in the study. One hundred and seven patients (52.1%) were male and the mean age was 56.8±12 years.

Patients with high thrombus burden had higher monocyte count, MHR and platelet count compared to the group with low thrombus burden. TIMI and Syntax scores were also higher in the high thrombus burden group.

Univariate regression analysis showed that TIMI, platelet and MHR at p<0.1 were found to be significant. Multiple logistic regression analysis

revealed that TIMI and MHR values were independently related to high thrombus burden [Odds ratio (OR): 1.678 (1.120-2.515) p=0.012) and OR: 1.432 (1.102-1.861), p=0.007) respectively] (Table 2).

Analysis of the receiver-operating characteristic found an optimal MHR cut-off value to be 1.75 with a sensitivity of 71.4% and specificity of 64% (AUC: 0.61; 95% CI: 0.51-0.70) in predicting a high thrombus burden score (Figure 1).

Discussion

The study found that MHR was closely related to thrombus burden in patients with NSTEMI.

The main pathophysiology of ACS is the onset of the formation of the thrombus and rupture of the atherosclerotic plaque. In spite of a successful PCI, the amount of thrombus formed has a close relationship between the distal coronary perfusion and the drop in EF (11,12). There was a close relationship with major adverse cardiac events in patients with an elevated thrombus burden (13-15).

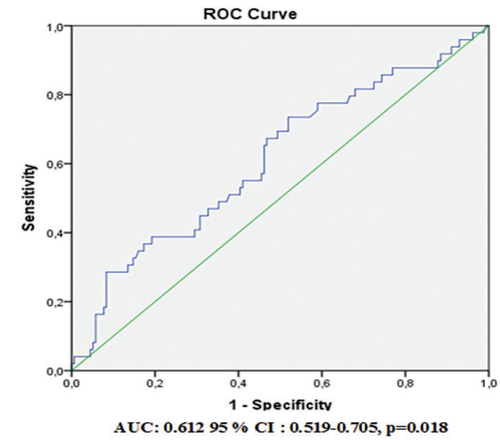

Figure 1. ROC curve of the MHR in predicting the high thrombus burden

ROC: receiver operating characteristic, MHR: monocyte to high-density lipoprotein cholesterol ratio

Table 1. Demographic, clinical and laboratory parameters of study cohort

	Low thrombus burden, (n=155)	High thrombus burden, (n=50)	p
Age, years	56.9±10.9	56.6±12.4	0.84
Male, n (%)	125 (80.6)	40 (80)	0.85
BMI, kg/m^2	26.6±3.0	26.8±3.0	0.69
HT, n (%)	82 (52.3)	25 (52)	0.85
DM, n (%)	43 (27.7)	14 (28)	0.97
HL, n (%)	22 (14.3)	10 (20.4)	0.3
Smoking	92 (59.4)	28 (56)	0.7
Glucose, mg/dL	139.4±58.6	155.6±75.7	0.12
GFR, mL/min/1.73 m^2	89.4±21.7	89.4±24.8	0.99
TC, mg/dL	207.6±45.8	203.1±64.7	0.58
TG, mg/dL	216.4±159.1	186.2±104	0.21
HDL, mg/dL	39.8±9.7	39.6±9.5	0.92
LDL, mg/dL	127.7±42.1	131.8.2±41.2	0.54
Monocyte, (10^3/µL)	0.64±0.3	0.83±0.36	<0.001
MHR, (X100)	1.61±0.81	1.96±0.82	0.006
Neutrophil, (10^3/µL)	9.2±3.5	7.5±2.6	0.72
Lymphocyte, (10^3/µL)	3.5±1.2	2.8±1.8	0.70
Platelet, (10^3/µL)	231.7±72.2	256.3±75.3	0.04
Grace score	95.2±25.6	101.8±26.7	0.12
TIMI score	3.7±1.4	4.2±1.2	0.01
Syntax score 1	13.1±9.1	23.9±9.2	<001

BMI: body mass index, HT: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, GFR: glomerular filtration rate, TC: total cholesterol, TG: triglycerides, HDL: high density lipoprotein, LDL: low density lipoprotein, MHR: monocyte to high-density lipoprotein cholesterol ratio, TIMI: thrombolysis in the myocardial infarction

Table 2. Independent predictors of high thrombus burden

Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
MHR	1.746 (1.185-2.572)	0.02	1.701 (1.088-2.657)	0.02
Platelet	1.004 (1.000-1.008)	0.05	1.004 (0.999-1.009)	0.09
TIMI	1.372 (1.070-1.760)	0.01	1.420 (1.098-1.836)	0.007

OR: odds ratio, CI: confidence interval, MHR: monocyte to high-density lipoprotein cholesterol ratio, TIMI: thrombolysis in the myocardial infarction

The roles of monocyte activation and mature macrophage forms are vital in the development and exacerbation of the atherosclerotic process, which is a lipid directed inflammatory disease (16). Blood monocytes enter the intimal/sub-intimal layers of the vessel wall, then differentiate into foam cells via up-taking oxidized LDL and other lipids through scavenger receptors. Patients diagnosed with hypercholesterolemia have been found to have accelerated monocyte migratory properties (17). Secretion of matrix metalloproteinases, pro-inflammatory cytokines, and tissue factors into the vessel wall occurs. Plaque rupture is caused digestion of the internal elastic lamina by metalloproteinases and the tissue factor that is released and contacts with circulating blood and causes the formation of thrombus (18). Anti-inflammatory and anti-thrombotic effects on human monocytes are exhibited by HDL-C, which counteracts activation and migration. Reddy et al. (19) showed how lower levels of HDL cholesterol, theoretically related to the inadequate limitation of inflammatory response, had a relationship with increased in-hospital patient deaths preceding AMI. MHR is now considered to be a vascular inflammatory marker and a reliable predictor for atherosclerosis formation, progression and cardiovascular outcomes. Furthermore, its value in acute STMI has been studied in previous clinical investigations. Karataş et al. (9) showed that admission MHR values were independently correlated with inpatient major adverse cardiovascular outcomes and death following a primary PCI. Similarly Çiçek et al. (20) recently showed that in-hospital mortality rates, late mortality, re-infarction, target vessel revascularization, major adverse cardiovascular events, and stroke were higher in the group with a greater MHR in comparison to the other MHR groups. They subsequently concluded that admission MHR was significantly and independently related with long-term and short-term mortality in STEMI. Furthermore, Cetin et al. (21) has verified that MHR is an innovative marker of inflammation and that it appears to be an independent predictor of stent thrombosis for STEMI patients. Finally, Balta et al. (22) found a relationship between MHR and no-reflow phenomenon in STEMI patients.

Study Limitations

The most important primary limitations of this study were the small number of patients and the research being conducted in a single center. Additional limitations were the mean age of the study population being fairly young, all of the study data being accumulated at a single point in time, and thus may not be representative of variations over time.

Conclusion

If we can better understand the relationship between basic biochemical tests and the thrombus burden closely related to the prognosis in NSTEMI patients with obtained MHR value, data about the risk of short- and long-term morbidity and mortality, which may be valid in compiling risk scores, can be obtained.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Prevalence and Clinical Importance of Coronary Artery Ectasia: Tertiary Center Experience

Ektazik Koroner Arter Prevalansı ve Klinik Önemi: Tersiyer Merkez Deneyimi

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ABSTRACT

Introduction: The incidence, prognostic significance, clinical features and risk factors of coronary artery ectasia (CAE) in patients undergoing coronary angiography were investigated.

Methods: A total of 10.320 coronary angiographies performed between June 2015 and August 2018 in our clinic were analyzed retrospectively.CAE, defined as the enlargement of a coronary artery to 1.5 times or more than that of the local or commonly adjacent normal coronary artery segment and classified according to Markis classification. CAE was divided into two groups as mild and severe according to the degree of ectasia.

Results: Of 189 patients (1.8%) with coronary ectasia, 143 were male (76%). One hundred and seven patients (57%) were smokers, 96 (51%) were dyslipidemic, 106 (56%) had hypertension and 43 (22%) had diabetes mellitus. In 92%, the symptoms were chest pain and dyspnea. Of 102 patients (54%) presenting with acute coronary syndrome, 43 (23%) were diagnosed as ST-segment elevation myocardial infarction, while 59 (31%) were diagnosed as non-ST segment elevation myocardial infarction or unstable angina pectoris. The right coronary artery was the most affected vessel from ectasia (54.5%, n=103). Type 3 ectasia was the most common (34.9%, n=66), while type 2 ectasia was the least common (10.6%). Hundred and twenty-nine (68.3%) of the patients had mild ectasia, while 60 (31.7%) had severe ectasia. During the three-year follow-up, a total of 16 (8.4%) patients died, three of which were in-hospital and eight were cardiac-related.

Conclusion: Although it is not common in the community, it is important to detect CAE, which is an important cause of mortality and morbidity, and to follow up the patients closely.

Keywords: Coronary artery ectasia, coronary angiography, coronary artery disease

ÖZ

Amaç: Koroner anjiyografi yapılan hastalardaki koroner arter ektazisi (KAE) sıklığı, prognostik önemi, klinik özellikleri ve risk faktörleri araştırıldı.

Yöntemler: Kliniğimizde Haziran 2015-Ağustos 2018 tarihleri arasında yapılan 10.320 adet koroner anjiyografi retrospektif olarak analiz edildi. KAE, koroner arterin bölgesel ya da yaygın olarak komşu normal koroner arter segmentinin 1,5 katı veya daha fazlası olacak şekilde genişlemesi olarak tanımlandı ve Markis sınıflamasına göre sınıflandırıldı. Ektazik koroner arterler ektazi derecesine göre hafif ve ağır olmak üzere iki gruba ayrıldı.

Bulgular: Yüz seksen dokuz (%1,8) koroner ektaziye sahip hastanın 143'ü erkek (%76) idi. Hastaların 107'si (%57) sigara içerken, 96'sı (%51) dislipidemik, 106'sı (%56) hipertansiyon, 43'ü (%22) diabetes mellitus tanılıydı. Hastaların %92'sinde semptom göğüs ağrısı ve nefes darlığıydı. Akut koroner sendrom ile başvuran 102 (%54) hastanın 43'ü (%23) ST-segment elevasyonlu miyokart enfarktüsü iken, 59'u (%31) ST-segment elevasyonu olmayan miyokart enfarktüsü ya da unstabil angına pektoris tanılıydı. Sağ koroner arter ektaziden en çok etkilenen damardı (%54,5 n=103). En fazla tip 3 ektazi (%34,9, n=66) görülürken, en az tip 2 ektazi (%10,6, n=20) görüldü. Hastaların 129'unda (%68,3) hafif düzeyde ektazi izlenirken, 60'ında (%31,7) ağır düzeyde ektazi saptandı. Üç yıllık takip süresince 3'ü hastane içi, 8'i kardiyak nedenli olmak üzere toplam 16 (%8,4) hastada ölüm gerçekleşti.

Sonuç: Toplumda sık görülmese de önemli bir mortalite ve morbidite nedeni olan KAE hastalığının tespiti ve hastaların yakın takibi önem arz etmektedir.

Anahtar Kelimeler: Koroner arter ektazisi, koroner anjiyografi, koroner arter hastalığı

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Introduction

Coronary artery ectasia (CAE) is defined as the enlargement of a coronary artery to 1.5 times or more than that of the local or commonly adjacent normal coronary artery segment (1). Enlargements up to 1.5 times of the coronary artery are described as ectasia, whereas enlargements over two-fold are called aneurysms (2). CAE is seen in the population with a frequency ranging between 0.3-4.9% (3). CAE is frequently associated with coronary artery disease (CAD), but can also be isolated. Isolated CAE is rare among patients who underwent coronary angiography with a frequency of 0.1-0.79% (4,5).

CAE may be congenital or acquired. Most of the etiology includes atherosclerosis (50%) (6), congenital syndromes such as Kawasaki syndrome (20-30%) (7), Ehlers-Danlos syndrome (8), Marfan syndrome and Takayasu disease (9), and connective tissue diseases (10-20%) such as inflammatory or scleroderma, polyarteritis nodosa, systemic lupus erythematosus (10). Studies have shown that ectasia leads to slow flow in the coronary arteries, thrombus formation and vasospasm, and perfusion defects in myocardium may be observed due to slow flow and possible microembolies (11,12). CAE is mostly associated with CAD. The most common symptom is chest pain. Although there is no significant stenosis in the coronary arteries, acute coronary syndrome (ACS) may occur. This has been shown to be caused by dissection and thrombus in the ectasia region (13). Recurrent microembolies due to thrombus can cause impaired coronary perfusion, ventricular arrhythmias and sudden cardiac death (5).

In this study, the incidence of CAE, distribution according to coronary arteries, clinical characteristics and risk factors, and prognostic significance of CAE in patients undergoing coronary angiography in our clinic were investigated.

Methods

A total of 10.320 coronary angiographies performed between June 2015 and August 2018 in our clinic were analyzed retrospectively. CAE was defined as dilatation of coronary artery lumen exceeding the largest diameter of an adjacent normal vessel more than 1.5 fold in accordance with the angiographic description of Hartnell et al. (1). Regional or diffuse enlargement without significant coronary artery stenosis was accepted as isolated ectasia. The presence of more than 50% stenosis of the coronary artery was considered to be significant occlusion and CAD. The study was approved by the Ethics Committee of İstanbul Şişli Hamidiye Etfal Training and Research Hospital, (decision no: 2380, date: 30.04.2019). Because of the retrospective nature of the study, informed consent was not obtained from the patients.

CAE was classified according to the classification of Markis et al. (7). According to this classification, diffuse ectasia of two or three vessels was type 1, diffuse ectasia in one vessel and localized disease in another was type 2, diffuse ectasia in one vessel only was type 3, and localized and segmental involvement was type 4. CAE was divided into two groups according to the degree of ectasia. According to the classification of Markis et al. (7), type 1 and type 2 were defined as severe ectasia and type 3 and type 4 as mild ectasia.

Statistical Analysis

SPSS version 20 for Windows (SPSS, Inc. Chicago, IL, USA) was used to evaluate the data. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as percentage.

Results

A total of 10.320 coronary angiography images over 3 years were analyzed and 189 (1.8%) patients with CAE were identified. Of the patients with ectasia, 143 (76%) were male. While 107 (57%) of the patients were smokers, 106 (56%) were diagnosed as hypertension and 43 (22%) were diagnosed as diabetes mellitus (DM). The number of dyslipidemic patients was 96 (51%). Ninety-two percent of the patients presented with chest pain and dyspnea, while the others presented with atypical complaints (Table 1).

Of 102 (54%) patients presenting with ACS, 43 (23%) had ST-segment elevation myocardial infarction, while 59 (31%) had non-ST-segment elevation myocardial infarction or unstable angina pectoris (Table 1). Regarding patients presenting with ACS, 23 patients had CAD without significant stenosis, 35 had single vessel disease, 23 had two-vessel disease, and 21 patients had three-vessel disease. Sixty-eight patients (36%) had isolated ectasia without significant coronary stenosis.

Ectasia was seen in 106 patients (56.1%) in one coronary artery, in 44 (23.3%) in two coronary arteries, in 30 (15.9%) in three coronary arteries and in nine (4.8%) in four vessels including the main coronary artery. The right coronary artery (RCA) was the vessel most affected by ectasia (54.5%, n=103). Of the ectasia, 54% (n=102) were in the circumflex (Cx) artery, 42.9% (n=81) in the left anterior descending (LAD) artery, and 16.9% (n=32) in the left main coronary artery (LMCA) (Table 2).

Table 1. Basal clinical and laboratory characteristics of patients

Clinical features	Ectasia (n=189)
Age (years)	61±12
Male gender	143 (76%)
Smoking	107 (57%)
Hypertension	106 (56%)
Diabetes mellitus	43 (22%)
EF (%)	52±10
Acute coronary syndrome	102(54%)
STEMI	43(23%)
NSTEMI/USAP	59(31%)
Hemoglobin (g/dL)	13.8±2.1
Platelet (10^9/L)	228±59
Total cholesterol (mg/)	193±57
HDL-k (mg/dL)	40±9
LDL-k (mg/dL)	123±54
Triglyceride (mg/dL)	161±96
Creatinine (mg/dL)	1.1±0.9

EF: ejection fraction, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, USAP: unstable angina pectoris, HDL: high-density lipoprotein, LDL: low-density lipoprotein

Table 2. Characteristics of ectatic coronary arteries in patients

	n	%
Isolated ectasia	68	36
Classification of Markis et al. (7)		
Type 1	40	21.2
Type 2	20	10.6
Type 3	66	34.9
Type 4	63	33.3
Ectasia location		
LMCA (Left main coronary artery)	32	16.9
LAD (Left anterior descending artery)	81	42.9
Cx (Circumflex artery)	102	54
RCA (Right coronary artery)	103	54.5
Degree of ectasia		
Severe (Type 1+Type 2)	60	31.7
Mild (Type 3+Type 4)	129	68.3

LMCA: left main coronary artery, LAD: left anterior descending, Cx: circumflex, RCA: right coronary artery

Regarding Markis et al. (7) classification, the most common ectasia was type 3 (34.9%, n=66), followed by type 4 (33.3%, n=63), type 1 (21.2%, n=40) and type 2 (10.6%, n=20). While 129 patients (68.3%) had mild ectasia, 60 patients (31.7%) had severe ectasia (Table 2). During the three-year follow-up period, a total of 16 patients (8.4%) died, including three in-hospital deaths. Eight out of hospital deaths were cardiac-related deaths.

Discussion

The incidence of CAE detected in coronary angiography performed on suspicion of CAD varies between 0.3-4.9% (3). While this rate was found to be 4.2% in the study conducted by Yilmaz et al. (14), it was found to be 2.8% in the study performed by Sultana et al. (15). The prevalence of CAE was found to be 1.8% in our study. The prevalence of isolated CAE was found to be 1.08% in a series of 3.815 patients by Akyürek et al. (16). In another series, this rate was reported as 3% (9), and Hartnell et al. (1) reported the prevalence of isolated CAE as 17%. In our study, the prevalence of isolated CAE without significant coronary artery stenosis was 36%.

In addition to the studies that reported similar rates of CAE in females and males (17), it was found to be more frequent in males in some studies (1). In our study, 76% of CAE patients were male. In a study, CAD was reported to be 87.1% in patients with ectasia (18). In our study, this rate was 64%. It is known that CAE is most commonly seen in RCA and at least in LMCA (19). In a study based on registry data, the most common involvement was observed in RCA (20). Sultana et al. (15) reported that ectasia was most common in RCA, followed by Cx and LAD, respectively. Similarly, in our patient group, ectasia was most commonly seen in RCA (54.5%), followed by Cx, LAD and LMCA, respectively.

In the study of Demopoulos et al. (17), type 3 ectasia was the most common, while others were found with similar frequency. Yilmaz et al. (14) reported that type 4 ectasia was the most common, whereas type 1 ectasia was the least common. In addition, Markis et al. (7) reported that the most common type was type 1, followed by type 2, 3 and 4, respectively. In our study, the most common type was type 3 with a rate of 34.9%, followed by type 4 (33.3%), type 1 (21.2%) and type 2 (10.6%).

Markis et al. (7) found that hypertension was more common in patients with ectasia and suggested that hypertension could play a role in the pathogenesis of CAE by accelerating the destruction of the media layer. Sultana et al. (15) found hypertension in 55%, DM in 26% and dyslipidemia in 58% of the patients. Similarly, in our study, hypertension was found in 56%, DM in 22%, and dyslipidemia in 51%.

Atherosclerosis plays a major role in the etiology of CAE. Cholesterol crystals, calcification and fibrosis, intima and media destruction, lipid accumulation were detected in pathological examination of CAE and these histological changes were found to be the same as atherosclerotic process. Ectasia occurs as a result of the atherosclerotic process causing widespread destruction of the muscular structure in the media layer and thinning of the vessel wall (1). In our study, obstructive CAD was detected in 64% of the patients and 54% of the patients presented with ACS.

Although the mechanism of ischemia is not clear in patients with isolated CAE, it has been suggested that slow flow in the ectatic vessel, thrombus caused by slow flow and microembolies discharging into the distal coronary bed disrupt perfusion (21). In a study conducted in our country, it was shown that microvascular perfusion is impaired in patients with ectatic coronary disease (22). In another study, it was found that flow velocity in ectatic coronary arteries decreased (23). In our study, 92% of the patients presented with chest pain and dyspnea, while 22 (12%) of the patients who presented with ACS did not have obstructive CAD.

The prognosis of patients with CAE is controversial. While the annual mortality was found to be 15% in the study of Markis et al. (7), Hartnell et al. (1) found annual mortality rate as 4.6% in medical follow-up and 2.4% in surgical groups. In another study, the annual mortality rate was found to be 1.5% in medical follow-up, 2.1% in percutaneous coronary intervention, and 2.9% in coronary bypass surgery (14). In our study, a total of 16 patients (8.4%) died, including three in-hospital deaths, during the three-year follow-up period, while the annual mortality rate was similar to that of many studies.

Conclusion

There is no consensus on the treatment of CAE, which is an important cause of mortality and morbidity, although it is not common in the community. Even if they do not have obstructive CAD, close monitoring of patients with CAE is important. Large-scale prospective studies are needed to determine the choice of treatment and better prognostic evaluation.

Ethics Committee Approval: The study was approved by the Ethics Committee of İstanbul Şişli Hamidiye Etfal Training and Research Hospital, (decision no: 2380, date: 30.04.2019).

Informed Consent: informed consent was not obtained from the patients.

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Neonatal Morbidity in Macrosomic Infants

Makrozomik Bebeklerde Neonatal Morbidite

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ABSTRACT

Introduction: Macrosomy is defined as birth weight being over 4000 grams. Neonatal complications are common in macrosomic infants. In this study, we aimed to compare macrosomic infants with normal weighed infants in terms of neonatal morbidities.

Methods: Macrosomic infants born between 01.01.2015 and 31.08.2015 were included in the study. The study group consisted of 100 infants (group 1) with a birth weight above 4000 grams and the control group consisted of 100 infants (group 2) weighing between 2500-4000 grams. Antenatal, natal and postnatal data of macrosomic and normal weighed infants were recorded. Statistical analysis was performed using SPSS 22.0 for Windows.

Results: Maternal age, macrosomic sibling history, prenatal body mass index (BMI), weight gain during pregnancy were found to be significantly higher in the macrosomic group (p=0.047, p=0.001, p=0.003, and p=0.007, respectively). Gestational week and male gender ratio of infants were higher in the macrosomic group. In the macrosomic group, 1-minute Apgar score was significantly lower, but there was no significant difference in 5-minute Apgar score. The rate of positive pressure ventilation was higher in the macrosomic group (p=0.04). The incidence of clavicle fracture, caput succadeneum and ecchymosis was higher in the macrosomic group (p=0.004, p=0.005 and p=0.022, respectively), but there was no significant difference in plexus brachialis paralysis and cephal hematoma. While hypoglycemia and pathological weight loss were significantly higher in the macrosomic group (p=0.03, p=0.038, respectively), there was no difference between the groups in terms of other variables.

Conclusion: Maternal age, history of macrosomic birth, high prenatal BMI, excess weight gain during pregnancy and gestational diabetes in the mother constitute risk for macrosomic birth. Birth trauma, hypoglycemia and pathological weight loss are common in these infants. For this reason, it is very important to carry out the physical examination of macrosomic infants carefully after birth and to closely monitor them with blood sugar and weight control.

Keywords: Macrosomia, newborn, morbidity

ÖZ

Amaç: Makrozomi; doğum ağırlığının 4000 gramın üzerinde olması şeklinde tanımlanır. Makrozomik bebeklerde neonatal komplikasyonlarla sık karşılaşılmaktadır. Bu çalışmada makrozomik bebeklerle normal tartılı bebekleri neonatal morbiditeler açısından karşılaştırmayı amaçladık.

Yöntemler: Çalışmaya 01.01.2015 ve 31.08.2015 tarihleri arasında doğan makrozomik bebekler dahil edildi. Çalışma grubu, doğum ağırlığı 4000 gramın üstü 100 bebekten (grup 1), kontrol grubu ise ağırlığı 2500-4000 g arasında normal tartılı 100 bebekten (grup 2) oluşuyordu. Makrozomik ve normal tartılı bebeklerin antenatal, natal ve postnatal bilgileri kaydedildi. İstatistiksel değerlendirme Windows SPSS 22.0 programı ile yapıldı.

Bulgular: Makrozomik grupta anne yaşı, makrozomik kardeş öyküsü, gebelik öncesi yüksek vücut kitle indeksi (VKİ), gebelikteki kilo alımı istatistiksel olarak anlamlı yüksek (p=0,047, p=0,001, p=0,003 ve p=0,007) saptandı. Bebeklerin gestasyon haftası ve erkek cinsiyet oranı makrozomik grupta daha yüksekti. Makrozomik grupta 1. dakika Apgar değeri anlamlı olarak daha düşükken, 5. dakika Apgar değerinde anlamlı farklılık saptanmadı. Pozitif basınçlı ventilasyon uygulama oranı makrozomik grupta daha yüksekti (p=0,04). Klavikula kırığı, kaput suksadenum ve ekimoz görülme oranı makrozomik grupta daha yüksek (p=0,004, p=0,005 ve p=0,022) iken pleksus brakialis paralizisi ve sefal hematom açısından anlamlı fark bulunmadı. Hipoglisemi ve patolojik tartı kaybı makrozomik grupta anlamlı oranda yüksek (p=0,03, p=0,038) iken diğer değişkenler açısından gruplar arasında fark yoktu.

Sonuç: Anne yaşı, makrozomik doğum öyküsü, gebelik öncesi yüksek VKİ, gebelikte fazla kilo alımı ve annede gestasyonel diyabet makrozomik doğum için risk oluşturur. Bu bebeklerde doğum travması, hipoglisemi ve patolojik tartı kaybı sıktır. Bu nedenle makrozomik bebeklerin doğum sonrası fizik muayenelerinin dikkatli yapılması, kan şekeri ve tartı kontrolü ile yakın izlenmeleri çok önemlidir.

Anahtar Kelimeler: Makrozomi, yenidoğan, morbidite

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Introduction

Birth weight is one of the most important factors affecting neonatal morbidity and mortality. Fetal macrosomia or large for gestational age is defined as birth weight above 90th percentile for gestational age or more than 4000 grams (1,2). However, there is no consensus on the limit of birth weight. In various studies, infants with birth weight above 4000 g, 4200 g and 4500 g have been identified as macrosomic. However, more commonly used and accepted form (infants more than 4000 grams) was used in our study (3,4). Many risk factors have been identified in macrosomy and usually several factors coexist. These risks include male gender, postmaturity, history of macrosomia in the previous sibling, presence of obesity or diabetes in the mother, and macrosomia-related syndromes such as Beckwith-Wiedemann syndrome (2).

Fetal macrosomia is associated with an increased risk of complications for the mother and fetus or newborn (3,4). Perinatal risks associated with macrosomia include birth trauma, shoulder dystocia, brachial plexus injuries, perinatal asphyxia, and death (3-6). Neonatal risks associated with macrosomia can be listed as hypoglycemia, hematologic disorders and electrolyte disorders (3,4). Increased caesarean section, large perineal tears and severe hemorrhage are among the maternal complications (7,8). Perinatal mortality is twice as high in neonates with birth weight above 4500 grams compared to neonates between 2500-3500 grams. The most common cause for this is birth traumas. The most common birth trauma in macrosomic infants is shoulder dystosis, which may result in fractures of the clavicle and humerus leading to brachial plexus paralysis (2). Much more serious problems, perinatal asphyxia and death may occur due to difficult labor.

In this study, we aimed to compare neonatal morbidities in macrosomic infants and normal weighed infants with a birth weight of 2500-4000 g.

Methods

One hundred macrosomic infants and 100 controls that were born in our hospital were included in the study. The study group consisted of 100 macrosomic cases with a birth weight of more than 4000 grams, and the control group consisted of 100 subjects with a normal weight weighing between 2500-4000 grams. Term infants older than 37 weeks + 6/7 days without missing data in mother and infant files were included in the study. Preterm infants under 37 weeks + 6/7 days of age, infants from multiple pregnancies and infants with intrauterine growth and development restriction were not included in the study. Ethics Committee approval was obtained for the study from İstanbul Haseki Training and Research Hospital Medical Research Ethics Committee (decision no: 255, date: 04.11.2015). An informed consent form was prepared and families were informed, and informed consent was obtained for participation in the study.

Maternal ages, gravidity and parity, prenatal body mass index (BMI), weight gain during pregnancy, presence of gestational diabetes mellitus (GDM) or gestational hypertension (GHT), mode of delivery, and history of macrosomic sibling were recorded. Birth weight of newborns, physical examination findings, presence of perinatal asphyxia, Apgar scores, presence of condition requiring intervention after birth, cord or 1st hour blood gas analysis, problems such as birth trauma, presence of respiratory distress, hypoglycemia, hypocalcemia, hyperbilirubinemia and polycythemia, and pathological weight loss were also recorded.

Infants weighing over 4000 grams were considered macrosomic. Hypoglycemia was defined as venous glucose level <40 mg/dL. Capillary venous hematocrit level above 65% was defined as polycythemia and calcium level below 8 mg/dL (1.1 mmol/L) as hypocalcemia in term infants. The limit of hyperbilirubinemia was evaluated according to the American Academy of Pediatrics 2004 guidelines. Weight losses of more than 10% during neonatal examination were accepted as pathological weight losses.

Statistical Analysis

Statistical Package for Social Sciences (SPSS for Windows 22.0) was used for statistical analysis. Mean, standard deviation, median, minimum, maximum, number and percentage values were used in descriptive statistics of the data. The distribution of variables was measured by Kolmogorov-Smirnov test. Mann-Whitney U test was used to analyze the quantitative data. Chi-square test was used for the analysis of qualitative data and Fischer's test was used when the chi-square test conditions were not met. Significance was evaluated at $p<0.05$.

Table 1. Comparison of macrosomic infants and control group in terms of neonatal and maternal characteristics

	Macrosomic group	Control group	p
Gestational age, weeks	39.8±1.1	39.0±1.0	0.001
Mode of delivery (n), NVD-C/S	43/57	43/57	-
Gender (n) (female/male)	30/70	51/49	0.002
Maternal age (years) (mean ± SD)	29.6±5.5	28.2±5.9	0.047
Gravidity (median)	3	3	0.326
Parity (median)	2	2	0.645
BMI (mean ± SD)	27.0±5.6	24.5±3.9	0.003
Weight gain during pregnancy (kg) (mean ± SD)	13.9±5.8	11.6±4.8	0.007
GDM	16	7	0.046
GHT	1	2	0.561
History of macrosomic sibling	28	10	0.001

NVD: normal vaginal delivery, C/S: cesarean section, SD: standard deviation, BMI: body mass index, GDM: gestational diabetes mellitus, GHT: gestational hypertension

Results

The study group consisted of 100 macrosomic infants and the control group consisted of 100 infants born at normal weight. The mean gestational week (GW) in the macrosomic group was 39.8±1.1 weeks, whereas the mean GW in the control group was 39.0±1.0 weeks (Table 1). GWs of macrosomic infants were found to be significantly higher (p=0.001). When the mode of delivery was examined, it was found that 43% (n=43) of macrosomic infants were born with normal vaginal delivery. There was no difference between the two groups in terms of mode of delivery. In the macrosomic infant group, male gender was found to be significantly predominant (p=0.002).

The mean age of the mothers was 29.6±5.5 years in the macrosomic infant group and 28.2±5.9 years in the control group. The maternal age of macrosomic infants was significantly higher (p=0.047). Mean BMI was 27.0±5.6 in mothers of macrosomic infants and 24.5±3.9 in mothers of control group. The difference between the two groups was statistically significant (p=0.003). The mean weight gain of mothers of macrosomic infants during pregnancy was 13.9±5.8 kg. However, this value was 11.6±4.8 kg in the control group. Mothers of macrosomic infants gained significantly more weight during pregnancy (p=0.007). There was no difference between the mothers of the two groups in terms of gravidity and parity (p=0.326 and p=0.645, respectively). While gestational GDM was detected in 16 mothers in the macrosomic group, GDM was detected in only seven mothers in the control group. The difference between the two groups was statistically significant (p=0.046). There was no difference between the two groups in terms of GHT (p=0.561). History of macrosomic sibling was detected in 28 infants in the macrosomic group and in 10 infants in the control group. The history of having macrosomic siblings was significantly higher in the macrosomic group (p=0.001).

While there was no difference between the blood gas pH values of the macrosomic group and the control group (p=0.071), a significant difference was found in terms of base excess, carbon dioxide levels and bicarbonate values (p=0.046, p=0.128, p=0.028, respectively) (Table 2). While 1-minute Apgar scores were significantly lower in the macrosomic group (p=0.001), 5-minute Apgar scores were similar in both groups (p=0.381).

No asphyxia cases were detected in the macrosomic group and control group (Table 3). The incidence of postnatal positive pressure ventilation (PPV) in macrosomic infants was significantly higher (p=0.001). While clavicle fracture was significantly higher in the macrosomic infant group (p=0.004), there was no difference in plexus paralysis (p=0.497). In the macrosomic infants, the caput succadeneum and ecchymosis were significantly higher (p=0.005 and p=0.022, respectively). Hypoglycemia and weight loss were significantly higher in macrosomic infants (p=0.030 and p=0.038, respectively), whereas there was no difference in terms of transient tachypnea of newborn, jaundice, hypocalcemia, polycythemia and hospitalization rates.

Table 2. Comparison of cord blood gas values and Apgar scores

	Macrosomic group	Control group	p
Cord pH	7.2±0.2	7.3±0.1	0.071
pCO_2 (mmHg)	47.4±10.2	50.4±8.8	0.018
HCO_3 (mmol/L)	22.3±2.5	23.1±2.4	0.028
BE (mmol/L)	-1.5±2.7	-0.6±2.8	0.046
1-minute Apgar score (median)	7	8	0.001
5-minute Apgar score (median)	9	9	0.381

Table 3. Comparison of macrosomic infants with control group in terms of neonatal morbidities

	Macrosomic group (n)	Control group (n)	p
Asphyxia	0	0	-
Need for PPV	4	0	0.001
Fracture of the clavicle	8	0	0.004
Plexus paralysis	2	0	0.497
Cephal hematoma	3	7	0.194
Caput succadeneum	16	4	0.005
Ecchymosis	13	4	0.022
TTN	19	15	0.451
Hypoglycemia	9	2	0.030
Hypocalcemia	2	0	0.497
Polycythemia	4	2	0.407
Weight loss	15	6	0.038
Hospitalization	35	30	0.450

PPV: positive pressure ventilation, TTN: transient tachypnea of newborn

Discussion

In our study, we found that the age of mothers of macrosomic infants was high (p=0.047). Similar to our results, Akın et al. (9) and Wollschlaeger et al. (10) also reported that mothers who give birth to macrosomic infants had a higher age. Adesina and Olayemi (11) reported that there was no difference between macrosomic infants and the control group in terms of maternal age. In our country, Oral et al. (12) reported that maternal age above 35 years was an important risk factor for macrosomic delivery.

Prenatal BMI is an important factor affecting fetal growth (13). In our study, we found that BMI and weight gain of mothers who delivered macrosomic infants were significantly higher, which supported this view. Alberico et al. (14) showed that the risk of macrosomic birth of obese mothers was 1.7 times higher. It was reported that the main factor that increased the risk of macrosomic birth in obese mothers was weight gain during pregnancy (15). Similar to the results in our study, Li et al. (16) reported that prenatal BMI and weight gain during pregnancy were important and modifiable risk factors for macrosomia.

Akın et al. (9) reported that gender was male in 66% of macrosomic infants. According to the results of a multicenter study, a significant relationship was found between male gender and macrosomia (10). In the examination of macrosomic infants, Jazayeri (4) stated that the male gender was higher in infants weighing more than 4500 gr. Similar to the results of Wollschlaeger et al. (10) and Tomic et al. (17), we found that the number of male infants was higher among macrosomic infants (10,17).

Contrary to previous studies, we could not find a significant difference between the macrosomic group and the control group in terms of mode of delivery. Akın et al. (9) reported a C-section (C/S) rate of 37.3% in macrosomic deliveries. In the same study, they stated that low birth trauma and asphyxia rates in their study could be explained by high C / S rates. In Istanbul, Oral et al. (12) found this rate as 28.8%. In a study examining macrosomic births in 23 developing countries, it was found that macrosomia caused an increased risk of C/S (16).

In the study of Mohammadbeigi et al. (18) comparing macrosomic infants with normal weighed infants, no difference was found in terms of blood pressure, gestational age and Apgar scores. Another study demonstrating that Apgar scores of macrosomic infants did not differ from normal weighed infants was reported by Talay et al. (19). In our study, 1-minute Apgar score was found to be lower in macrosomic infants; however, no difference was found in terms of 5-minute Apgar score. In another study, it was reported that there was no difference in terms of 5-minute Apgar score, but that comparison of macrosomic infants weighing 4000-4449 g and >4500 g revealed a significant difference (20). In our study, we found that the frequency of PPV applications in macrosomic infants was significantly higher. In the study of Yıldırım et al. (21) they reported that macrosomic infants born from diabetic mothers needed more ventilation support in the delivery room than other macrosomic babies. In another study, the need for neonatal resuscitation was significantly higher in infants of obese mothers compared to non-obese mothers (22).

The risk of birth trauma and asphyxia increases in macrosomic infants. In the study of Akın et al. (9), no difference was found in terms of early neonatal mortality and asphyxia. We also did not find any significant difference between macrosomic and control groups in terms of intubation and asphyxia. In the study performed by Demirören et al. (23), perinatal asphyxia findings were found in approximately 1/3 of the macrosomic cases, and it was stated that delivery by C/S might be preferred for infants thought to be macrosomic.

In a study investigating fetal macrosomia risk factors, it was stated that GDM, history of macrosomic sibling and maternal preeclampsia increased the risk of macrosomia by 11.9, 3.8 and 3.3 fold, respectively (18). Maternal impaired glucose intolerance, multiparity, history of macrosomic delivery, excess weight gain during pregnancy and male fetus were defined as risk factors for macrosomia. It has been shown that the incidence of macrosomia in pregnant women with two or more of these risks reaches 32% (23). In our study, high rate of macrosomic sibling history in the macrosomic group supported the literature data.

In our study, the incidence of clavicle fracture, caput succadeneum and ecchymosis was increased in macrosomic infants, but no difference was found in terms of plexus brachialis paralysis and cephal hematoma. Linder et al. (24) found that the rate of birth trauma was higher in the macrosomic group. In the study by Al-Wazzan and Sarsam (25), there was a significant difference in Erb paralysis in the macrosomic group, but no difference was found in terms of clavicle fracture. In the study of Akın et al. (9), there was a significant difference in clavicle fracture, but there was no difference in brachial plexus paralysis and cephal hematoma; however, a significant difference was found in the macrosomic group when evaluated by taking into account the whole birth traumas.

Bandika et al. (26) have shown that the frequency of hypoglycemia and hypocalcemia is increased in infants over 4250 grams. In the same study, the risk of hypoglycemia was found to be 21% in large for gestational age infants, but it was shown that the risk of hypoglycemia increased as the birth weight increased. Also, Mohammadbeigi et al. (18) showed that neonatal hypoglycemia was increased 4.7 fold in newborns over 4000 grams. In accordance with the literature, hypoglycemia was found to be significantly higher in the macrosomic group in our study. In the study of Linder et al. (24), hypoglycemia was observed in symmetrical macrosomic infants with a similar frequency as normal weighed infants, but closer blood glucose monitoring was required in asymmetric macrosomic infants).

In studies comparing macrosomic and normal weighed infants, pathological weight loss after birth was not evaluated much. In our study, we found that the pathological weight loss was higher in the macrosomic group compared to normal weighed infants. In a study comparing macrosomic infants with and without diabetic mothers, Yıldırım et al. (21) showed that pathological weight loss was higher in the non-diabetic group (42% vs 27%). Therefore, close monitoring of macrosomic infants in terms of postpartum weight loss is important.

Conclusion

High maternal age, history of macrosomic delivery, high BMI before pregnancy, excess weight gain during pregnancy and maternal GDM pose a risk for macrosomic birth. Birth trauma, hypoglycemia and pathological weight loss are common in macrosomic infants. Therefore,

it is important to perform careful physical examinations of macrosomic babies in the postnatal period and to closely monitor them with blood sugar and weight control.

Ethics Committee Approval: Committee approval was obtained for the study from İstanbul Haseki Training and Research Hospital Medical Research Ethics Committee (decision no: 255, date: 04.11.2015).

Informed Consent: An informed consent form was prepared and families were informed, and informed consent was obtained for participation in the study.

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Comparison of Sublingual and Nasal Applications of Dexmedetomidine Premedication in Pediatric Patients

Çocuk Hastalar için Sublingual ve Nazal Deksmedetomidinin Premedikasyonun Karşılaştırılması

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ABSTRACT

Introduction: Alpha-2 adrenergic agonists are used for premedication in the pediatric population to reduce separation anxiety and achieve smooth induction. The clinical effects of clonidine are similar in both oral and nasal routes. However, oral dexmedetomidine is not preferred because of its poor bioavailability. The objective of this study was to retrospectively evaluate the effects of nasal and sublingual dexmedetomidine premedication in children.

Methods: Sixty-seven patients aged between 2-6 years who underwent elective surgery and received sublingual 2-μg kg^{-1} or intranasal 2-μg kg^{-1} dexmedetomidine premedication one hour before induction of anesthesia were retrospectively evaluated. Heart rate, peripheral oxygen saturation and anxiety scores of patients were compared in 10-minute intervals starting before premedication and up to the operating room. Drug acceptance, parental separation and facemask acceptance were also compared.

Results: There was no significant difference between the two groups in terms of demographic characteristics. There was no significant difference in terms of hemodynamic data, including heart rate, respiratory rate and SpO2. After sixty minutes of premedication, anxiolysis, mask acceptance and parental separation were comparable in two groups. The median sedation level of intranasal group was significantly higher than sublingual group 60 minutes after drug administration [3 (3-3) vs 3 (1-3), respectively p=0.006]. However, the number of children with satisfactory sedation levels was similar in both groups one hour after premedication (Sublingual group=97% vs Intranasal group=100%).

Conclusion: The clinical effects of intranasal and sublingual dexmedetomidine were similar. Level of sedation by sublingual route was less than intranasal route, because a significant proportion of the drug was ingested by children. It may be preferred for premedication in preschool children by intranasal route or at higher doses by sublingual route.

Keywords: Premedication, children, dexmedetomidine, sublingual, nasal

ÖZ

Amaç: Alfa-2 adrenerjik agonistler, pediyatrik popülasyonda premedikasyon için ayırma anksiyetesini azaltmak ve kalıcı indüksiyonu sağlamak için kullanılır. Klonidinin klinik etkileri oral ve nazal yolla benzerdir. Ancak, oral deksmedetomidin, zayıf biyoyararlanımı nedeniyle tercih edilmez. Bu çalışmanın amacı çocuklarda nazal ve sublingual deksmedetomidinin premedikasyon etkilerini retrospektif olarak değerlendirmektir.

Yöntemler: İki-altı yaş arasında elektif cerrahi uygulanan ve anestezi indüksiyonundan 1 saat önce premedikasyon amacıyla sublingual yolla 2 μg/kg^{-1} veya nazal yolla 2 μg/kg^{-1} deksmedetomidin uygulanan 67 hasta retrospektif olarak incelendi. Hastaların kalp atım hızı, periferik oksijen satürasyonu, anksiyete skorları, premedikasyon öncesi ve ameliyathaneye kadar 10 dakikalık aralıklarla karşılaştırıldı. İlaç kabulü, ebeveyn ayrımı ve yüz maskesi kabulü de karşılaştırıldı.

Bulgular: Her iki grup arasında hastaların demografik özelliklerinde anlamlı bir fark yoktu. Her iki gruptada hemodinamik veriler arasında kalp hızı, solunum hızı ve SpO_2 açısından anlamlı fark yoktu. Altmış dakikalık premedikasyon anksiyolizinden sonra, maske kabulü ve ebeveyn ayrımı iki grupta karşılaştırılabilirdi. Grup N'nin ortanca sedasyon seviyesi, ilaç verilmesinden 60 dakika sonra grup S'den anlamlı olarak yüksekti [3 (3-3) ve 3 (1-3), sırasıyla p=0,006]. Bununla birlikte, tatmin edici düzeyde sedasyon seviyesi olan çocuk sayısı, premedikasyondan 1 saat sonra her iki grupta da benzerdi (grup S=%97 ve grup N=%100).

Sonuç: Deksmedetomidinin klinik etkileri intranazal ve sublingual yolla benzerdi. Sublingual yolla sedasyon seviyesi, çocuklar tarafından yutulmasından dolayı intranazal yoldan daha düşüktü. Okul öncesi çocuklarda intranazal yolla veya daha yüksek dozlarda sublingual yolla premedikasyon tercih edilebilir.

Anahtar Kelimeler: Premedikasyon, çocuklar, deksmedetomidin, sublingual, nazal

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Introduction

A satisfactory premedication provides a comfortable induction of general anesthesia with minimal hemodynamic changes and reduces emotional trauma in children before surgery. Because of children showing a psychological response to a needle, a non-invasive route has to be preferred for procedural sedation and anesthetic premedication. Oral or rectal administration of druges for sedation is not suitable because of difficult titration and because they may prolong the onset of sedation. Intranasal and sublingual administration may be preferred as they are painless, easy to use and less first pass metabolism.

Alpha-2 adrenergic agonists provide sedation with comfortable parental separation and alter conditions for induction of general anesthesia while conserving airway reflexes. Dexmedetomidine (DEX) is a more selective α2-agonist drug with shorter half-life. It shows sedative, analgesic, anxiolytic, and anesthetic effects by reducing arterial blood pressure and heart rate. DEX is tasteless, odorless and painless drug (1-3). DEX premedication provides sufficient premedication for general and regional anesthesia through buccal and intranasal route (4-6). A dose of 2-µg kg DEX is systematically taken by the oral mucosa and its buccal bioavailability is as high as 82% (73-92%) in adults (7). The absolute bioavailability of DEX was 65% (35-93%) following intranasal administration in adults (8). To the best of our knowledge, there is no study considering nasal and sublingual administration of DEX for premedication in children.

This study aimed to retrospectively evaluate sedative, respiratory and hemodynamic effects of sublingual and nasal DEX premedication in children.

Methods

The institutional Medical Ethic Committee of Şişli Hamidiye Etfal Research and Training Hospital approval was received (SEEAH, 980,17.04.2018). Oral and written consents were obtained from the parents of the participants, the files of 67 children aged 2-6 years who underwent minor elective surgical procedures such as circumcision, inguinal hernia and tonsillectomy/adenoidectomy between October 2017 and April 2011 were retrospectively reviewed. Exclusion criteria were as follows: Mental retardation, autism, using analgesics and anticonvulsants during the peroperative period, and cerebral palsy.

Patients who received 2 µg kg^{-1} DEX (Precedex®, 100 µg/mL, Abbott Laboratories, North Chicago, IL, USA) premedication one hour prior to induction of anesthesia through sublingual route were identified as group S (n=33) and intranasal route as group N (n=34). The response of the child to drug administration was recorded using two-point scale (1= Poor, crying, 2= Good, not crying). Heart rate (HR), respiratory rate (RR) and peripheral oxygen saturation ($Sp0_2$) were recorded at 10-minute intervals before (baseline) and after premedication. Level of sedation was recorded according to a three-point scale (1= Awake, 2= Drowsy, 3= Asleep). A 4-point scale was applied for preoperative anxiety (1= Crying, very anxious, 2= Anxious, not crying, 3= Calm, but not cooperative, 4= Calm, cooperative or sleep). Sedation score 2 or 3 and anxiety score 3 or 4 were considered as satisfactory response. Preoperative sedation and anxiety scores were recorded at 10-minute intervals until shifting to the operating room. Parental separation scores were assessed using three-point scale (1= Poor, anxious and combative, 2= Good, anxious but easily reassured, 3= Excellent, sleepy and calm). Parents were not allowed to accompany the child during induction of anesthesia. Mask acceptance was evaluated by a 4-point scale: 1= Poor (combative, crying), 2= Fear (moderate fear of the mask), 3= Good (cooperative with reassurance, 4= Excellent (calm, cooperative or sleep). The parents were admitted 5-10 minute after the children arrived to post anesthesia care unit and parents were interviewed regarding their satisfaction related to premedication before patients discharge from post-anesthesia care unit (1= Not satisfied, 2= Good, satisfied, 3= Excellent). All evaluation scores were adopted from published studies investigating premedication in children (9-11).

The adverse effects including respiratory depression (RR<12/min), desaturation (SpO_2 <90% for 15 seconds) and bradycardia (HR<60 beat/min) were recorded from anesthesia forms.

Statistical Analysis

The data are presented as mean values with standard deviations, medians with range, or as a proportion with a 95% confidence interval. Student's t-test was used to compare normally distributed continuous variables between the two groups and the nonparametric Mann-Whitney U test was used for the sedation scores, anxiety scores, parental separation and mask acceptance scores. Categorical data were analyzed by chi-square test or Fisher's exact test. A p value <0.05 was considered to be statistically significant. A power analysis indicated that a simple size of 28 was sufficient to detect a significant statistical difference with α=0.05 and power of 80% in satisfactory sedation scores at parental separation between the two groups. We decided to study 67 patients to account for possible dropouts.

Results

Sixty-seven preschool-age children were included in this study, namely 34 children in group N and 33 children in group S. Demographic data were similar in both groups (Table 1).

There were no significant differences between the two groups in terms of HR and RR before and 60 minutes after premedication. SPO_2 was comparable in both groups at all time points. No respiratory depression and bradycardia were observed in both groups (Table 2).

Drug acceptance by nasal and sublingual routes was comparable. Mean onset time for sedation was statistically shorter in group N, but mean onset time for anxiolysis was similar between the two groups (Table 3).

Anxiolysis and mask acceptance after 60 minutes of premedication were similar in both groups. The sedation and parental separation scores of group N were significantly better than group S 60 minutes after drug administration (Table 4).

Number of patients with sufficient sedation scores for parental separation, mask tolerance at induction of anesthesia and at 60 minutes after premedication were comparable in both groups (Table 5). Although satisfactory sedation scores at the 60^{th} minutes after receiving DEX were similar in both groups, sedation scores of the patients in

group N were significantly higher than that of group S (p<0.001). The reaction of children to parental seperation 60 minutes after receiving premedication was found to be excellent in 15 children (44%) in group N compared to six children (18%) in group S. The induction of general anesthesia was good or excellent in 22 children (65%) in group N compared to 19 children (57%) in group S. Number of patients with unsatisfactory parental seperation in group S was statistically higher than that in group N. Six children (%17) resisted intranasal medication and three children (9%) resisted sublingual medication.

Table 1. Demographic data

	Group S (n=33)	Group N (n=34)	p
Age (year)	4±1.57	3.5±1.59	0.17
Weight (kg)	16.51±3.93	15.05±3.44	0.53
Gender (M/F)	25/8	27/7	0.46

M: male, F: female

Discussion

In this retrospective study, we evaluated sedative, hemodynamic and respiratory effects of sublingual or intranasal DEX admininistration for premedication in preschool children. Two μg kg^{-1} intranasal and sublingual DEX had comparable effects without affecting hemodynamic and respiratory parameters.

Preoperative sedation reduces separation anxiety and provide mask acceptance in the pediatric population. Because of psychological response to a needle, non-invasive approaches should be preferred for sedation in children. Intranasal and sublingual application of sedative drugs is painless, easy to use and bypasses first past metabolism-improving bioavailability over oral and rectal doses.

DEX is a selective α2-agonist drug with a short duration of activity. It was shown that the onset of sedation occurred at 45 minutes in healthy volunteers (12) and at 25 minutes in children (13) following intranasal

Table 2. Respiratory rate (RR), heart rate (HR), peripheral oxgen saturation (SpO_2) of groups

	Group S (n=33)		Group N (n=34)		p
	Baseline	60th minute	Baseline	60th minute	
HR (beat/min)	114.78±12.38	100.75±10.22	113.26±12.4	98.67±11.19	0.06
RR (rate/min)	23.60±2.34	21.15±1.93	23.88±4.63	19.11±3.13	0.051
SpO_2	99.42±0.57	98.64±0.12	99.23±0.58	98.96±0.44	0.12

Table 3. Mean onset time for sedation and anxiolysis

	Group S (n=33)	Group N (n=34)	p
Mean onset time for sedation (minutes)	24.24±12.5	18.23±11.13	0.0417
Mean onset time for anxiolysis (minutes)	29.69±11.03	25.0±6.15	0.1140

Table 4. Sedation, anxiety, parental separation, mask acceptance scores 1 hour after premedication

	Group S (n=33)	Group N (n=34)	p
Sedation	3 (1-3)	3 (3-3)**	0.0086
Anxiety	4 (1-4)	4 (3-4)	0.1363
Parental separation	2 (1-3)	2 (2-3)*	0.0321
Mask acceptance	3 (1-4)	3 (1-4)	0.7354

Data are presented as median (interquartile range), **p<0.001, *p<0.05

Table 5. Anxiety and sedation scores at 60th minute, sedation score at parental separation, mask tolerance at induction and parent satisfaction

	Group S (n=33) n (%)	Group N (n=34) n (%)	p
Satisfactory sedation score at parental separation	32 (97%)	34 (100%)	0.4925
Satisfactory parental separation	26 (78%)	30 (88%)	0.3405
Satisfactory anxiety score	30 (%90)	34 (100%)	0.1139
Satisfactory mask tolerance at induction	19 (57%)	22 (65%)	0.6205
Unsatisfactory parent	14 (43%)	6 (18%)*	0.0154
Sedation score			
Asleep	20 (61%)**	34 (100%)	0.0001
Drowsy	12 (36%) **	0 (0%)	0.0001
Awake	1 (3%)	0 (0%)	0.426

*p<0.05, **p<0.001

DEX application. The absolute bioavailability of intranasal DEX was found to be 65% (35-93%) and onset was more rapid after intravenous administration in healthy volunteers (8). Anttila et al. (7) reported that buccal DEX showed clinical sedative effects that correlated well with plasma level and that buccal bioavailability was as high as 82%.

In our study, 100% of children in group N had satisfactory sedation scores for parental separation compared 97% of children in group S. Sedation and parental separation scores were better in group N at 60th minute. Although buccal bioavailability is higher than intranasal bioavailability in healthy adults, our data were different in children. This may be due to drugs being swallowed by children involuntarily.

Yuen et al. (12) showed that approximately 75% and 92% of subjects attained a sedation level of modified Observer Assessment of Alertness/ Sedation scale of 3 or below after intranasal 1 and 1,5 μg kg^{-1} DEX, respectively, and that it produced sedation in 45-60 minutes (peak= 90-105 minutes). They also found that intranasal administration of 1 μg kg^{-1} of DEX produced satisfactory sedation in 62% of children at the time of cannulation. The median time for onset of sedation was 25 (25-30) minutes and the median duration of sedation was 85 (55-100) minutes.

Schmidt et al. (6) compared preanesthetic effects of transmucosal DEX 1 μg kg^{-1}, oral midazolam 0.5 mg kg^{-1} and oral clonidine 4 μg kg^{-1} on postoperative pain and anxiety in children, and there was no difference between the groups in terms of sedation and response to separation scores, but pain scores, mean arterial pressure and HR were lower in DEX and clonidine groups than midazolam group.

Karaaslan et al. (5) demonstrated that buccal and intramuscular DEX (2.5 μg kg^{-1}) provided equal levels of sedation in adults during spinal anesthesia. Sakurai et al. (4) applied DEX buccaly and found higher sedation scores, and suggested that 3-4 μg/kg of buccal DEX might be less than the optimal dosage of preanesthetics.

Talon et al. (14) compared intranasal 2 μg kg^{-1} DEX to oral cherry flavored midazolam syrup 0.5 mg kg for sedation in children, and DEX was found to be more effective and fast-acting, reliable, safe and relatively less traumatic.

Yuen et al. (15) compared two different doses of intranasal DEX (0.5 or 1 μg kg^{-1}) to oral midazolam (0.5 mg kg^{-1}). These authors found that both doses of DEX were superior to oral midazolam for sedation, and more adequate sedation at induction was achieved in patients receiving 1 μg kg^{-1} dose.

Lami and Pereira (16) showed that 20 hospitalized patients aged 4 months-19 years with ASA physical status II-III received 2-3 μg kg^{-1} DEX through the oral mucosa for elective computerized tomograpy. Twelve patients reached adequate sedation level after 10-45 minutes. Eight patients needed DEX supplementation by the same route or additional anesthesia techniques.

Zub (17) conducted a retrospective study to investigate the efficacy of buccal DEX as a procedural and anesthetic premedication. Thirteen children received buccal DEX at 1.0-4. Mg kg^{-1} and effective sedation was achieved in 11 of 13.

Yuen et al. (18) documented that 2 μg kg^{-1} of intranasal DEX sedated satisfactorily 66% of patients at time of anesthetic induction. We found that mask tolerance in induction was 65% in patients in group N and 57% in patients in group S.

Cimen et al. (19) compared intranasal or buccal 1 μg kg^{-1} DEX for premedication in children and found that intranasal application was more effective.

Petroz et al. (20) compared a single intravenous dose of DEX (2, 4 and 6 μg kg h^{-1}) in children and found that there was no association between DEX dose and depth of sedation in children. Roy et al. (21) showed that 2 μg.kg^{-1} intranasal DEX provided efficient sedation in children.

DEX may cause hemodynamic side effects such as hypotension and bradycardia, especially associated with dose infusion given over <10 min (6,20,22,23). DEX provided adequate sedation at 1 μg kg^{-1} loading and 0.5-0.7 infusion doses without affecting hemodynamics (24). Sakurai et al. (4) suggested that transmucosal buckle DEX (3-4 μg kg^{-1}) provided sufficient and innocuous preoperative sedation of children. There were no cases with bradycardia (HR less than 60). In our study, HR did not decrease significantly after both administration routes.

Conclusion

This study demonstrated that nasal and sublingual DEX (2 μg kg^{-1}) had similar effects as a preanesthetic medication in preschool children.

Ethics Committee Approval: The institutional Medical Ethic Committee of Şişli Hamidiye Etfal Research and Training Hospital approval was received (SEEAH, 980,17.04.2018).

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MTHFR *C677T* and *A1298C* Gene Polymorphisms in Human Kidney Cancer Tissues

İnsan Böbrek Kanseri Dokularında MTHFR *C677T* ve *A1298C* Gen Polimorfizmleri

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ABSTRACT

Introduction: The potential effect of 5,10-methylenetetrahydrofolate reductase (MTHFR) on DNA methylation, DNA repair and DNA synthesis has made MTHFR a cancer-inducing gene. In this study, we aimed to evaluate *C677T* and *A1298C* gene polymorphisms in kidney cancer.

Methods: During the normal treatment procedure, 100 tumor and 100 surrounding healthy kidney tissue samples were obtained from patients after surgery. DNA was isolated from the tissues by DNA Isolation kit. Polymerase chain reaction and restriction fragment length polymorphism methods were used. Genotype and allele distributions were analyzed using SPSS 22 and $p<0.05$ was considered statistically significant.

Results: No significant difference was found between the genotypes and alleles of MTHFR C677T and A1298C polymorphisms in tumor and control groups ($p>0.05$). MTHFR C677T CC genotype (51%) was found to be higher in kidney cancer tissues than CT genotype (34%). Odds ratio of MTHFR C677T CC genotype was found 1.8 compared to CT genotype ($p<0.05$).

Conclusion: Our findings indicate that MTHFR C677T polymorphism may be effective in normal genotype in kidney cancer tissues.

Keywords: MTHFR, kidney cancer, polymorphism, *C677T*, *A1298C*

ÖZ

Amaç: 5,10-metilenetetrahidrofolat redüktaz'ın (MTHFR) DNA metilasyonu, DNA onarımı ve DNA sentezi üzerindeki potansiyel etkisi MTHFR'yi kanseri indükleyen bir gen yapmıştır. Çalışmamızda böbrek kanserinde *C677T* ve *A1298C* gen polimorfizmlerini değerlendirmeyi amaçladık.

Yöntemler: Normal tedavi prosedürü sırasında cerrahi operasyon sonrası hastalardan 100 tümör ve 100 sağlıklı çevre böbrek dokusu örneği alındı. DNA izolasyon kiti ile dokulardan DNA izole edildi. Polimeraz zincir reaksiyonu ve restriksiyon fragman uzunluğu polimorfizmi yöntemi uygulandı. Genotip ve allel dağılımları SPSS 22 ile analiz edildi ve $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Tümör ve kontrol gruplarında MTHFR C677T ve A1298C polimorfizmlerinin genotipleri ve allelleri arasında anlamlı fark bulunmadı ($p>0,05$). Böbrek kanserli dokularda MTHFR C677T CC genotipinin (%51) CT genotipine (%34) oranla daha fazla olduğu bulundu. MTHFR C677T CC genotipinin CT genotipine oranla elde edilen tahmini rölatif riski 1,8 olarak belirlendi ($p<0,05$).

Sonuç: Elde ettiğimiz bulgular böbrek kanserli dokularda MTHFR C677T polimorfizminin normal genotipte etkili olabileceğini göstermektedir.

Anahtar Kelimeler: MTHFR, böbrek kanseri, polimorfizm, *C677T*, *A1298C*

Introductıon

While kidney cancer is the third most common cancer among urogenital cancers, it ranks seventeen among the most common cancers (1). Although kidney cancer patients usually have good outcomes after surgical intervention, less than 20% of individuals with advanced disease have a 2-year survival. Kidney cancer is seen twice in men than in women (2). Kidney cancer is not a single type of cancer and it has genetically and histologically different types responding to therapy differently due to mutations in various genes (3).

5,10-methylenetetrahydrofolate reductase (MTHFR) is the key enzyme in folate metabolism. MTHFR catalyzes the reduction of MTHF to 5-methyl THF using 5,10 FAD as a cofactor that acts as a regulator of folate coenzymes for purine, pyrimidine and methionine synthesis (4). Five-methyl THF provides the methyl group for the synthesis of methionine (5)

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and homocysteine is the carbon donor in methionine remethylation (6). Because of its role in DNA methylation, DNA repair and DNA synthesis, MTHFR may be categorized as a cancer-inducing gene (7).

The effects of gene variants C677T and A1298C of MTHFR, the most important enzyme involved in homocysteine metabolism and regeneration, has been associated with many diseases such as cancer, coronary heart disease, myocardial infarction, diabetes and renal diseases (8-12). In the fourth exon encoding MTHFR, the homozygous C677T mutation at the folate-binding site (MTHFR TT) reduced the enzyme activity to 35% and lead to predisposition to folate deficiency and associated with hyperhomocysteinemia (13,14). It has been observed that enzyme activity with MTHFR A1298C polymorphism in seventh exon is reduced to 60% of normal value (15).

We aimed to evaluate the effects of *MTHFR* gene on kidney cancer formation due to its effects on folate and homocysteine mechanisms.

Materıals and Methods

One hundred patients with kidney cancer, who were admitted to the Urology Department of İstanbul Okmeydanı Training and Research Hospital, were included in the study. Kidney cancer tissues constituted the "tumor group" and surrounding healthy kidney tissues from the same subjects constituted the "control group". The study was approved by the Ethics Committee of İstanbul University Faculty of Medicine, (decision no: 2016/600, date: 13/05/2016) and informed consent were taken. Tissue samples were stored at -80 °C after treated with liquid nitrogen. DNA was obtained from kidney cancer tissues and surrounding healthy kidney tissues by using DNA isolation kit (DNeasy Blood & Tissue Kit, Qiagen, Cat No. 69504) according to the manufacturer's instructions. DNA samples were stored at -20 °C until analysis by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.

Genotyping

The oligonucleotide primers for amplifying the polymorphism regions of MTHFR C677T and A1298C were: 5'-TGAAGGAGAAGGTGTCTGCGGGA-3' (forward), 5'-AGGACGGTGCGGTGAGAGTG-3' (reverse) and 5'-ATGTGGGGGGAGGAGCTGAC-3' (forward), 5'-GTCTCCCAACTTACCCTTCTCCC-3', respectively.

PCRs were performed in a total volume of 25 µL with 1 µl of 100-200 ng DNA, 1 µl of forward and reverse primers, 1.5 µl of dNTPs, 2.5 µl of buffer, 0.25 µl of DNA polymerase (GeneMark GMbiolab Co., Ltd. Taichung, Taiwan) and 18.75 µl of dH_2O. The PCR mixture was incubated for 5 minutes at 95 °C, followed by 35 cycles of 45 seconds at 94 °C, 45 seconds at 59 °C and 45 seconds at 72 °C and a final step at 72 °C for 7 minutes for MTHFR C677T. For MTHFR A1298C; PCR mixture was incubated for 8 minutes at 95 °C, followed by 40 cycles of 1 minute at 94 °C, 1 minute at 63 °C and 1 minute at 72 °C and a final step at 72 °C for 7 minutes.

The PCR products for MTHFR C677T sites were digested by HinfI (Jena Bioscience, Cat. No. EN-117S) restriction enzyme. The RFLPs were performed in 20 µl reaction volume with 5 µl of PCR product, 2 µl of Buffer, 0.4 µl of restriction enzyme and 12.6 µl of distilled water. The 198 base pair (bp) PCR product was digested with HinfI 10 minutes at 37 °C and 20 minutes at 65 °C. The fragments were separated on a 3% agarose gel stained with ethidium bromide. After digestion, CC homozygotes showed 1 band of 198 bp, while TT homozygotes and CT heterozygotes showed 2 bands (175 and 23 bp) and 3 bands (198, 175 and 23 bp), respectively.

The PCR products for MTHFR A1298C sites were digested by MboII (Jena Bioscience, Cat. No. EN-E2284-01) restriction enzyme. The RFLPs were performed in 20 µl reaction volume with 5 µl of PCR product, 2 µl of Buffer, 0.4 µl of restriction enzyme and 12.6 µl of distilled water. The 240 bp PCR product was digested with MboII 10 minutes at 37 °C and 20 minutes at 65 °C. The fragments were separated on a 3% agarose gel stained with ethidium bromide. After digestion, CC homozygotes showed 1 band of 240 bp, while 2 bands (215 and 25 bp) with AA homozygotes and 3 bands (240, 215 and 25 bp) with AC heterozygotes were observed under ultraviolet light.

Statistical Analysis

Statistical analyses were performed using SPSS 22 statistical software (IBM Corp., Armonk, NY, USA). Pearson chi-square test was used for evaluating the differences between the two groups. Spearman's rho test was performed to analyze the correlation between clinical parameters, genotypes, and alleles in the two groups. A p value of less than 0.05 was considered statistically significant.

Results

One hundred patients with kidney cancer, including 71 men and 29 women, were included in the study. The clinical parameters of only 50 patients were identified in Table 1, as the remaining 50 patients did not have clinical parameters. According to the Fuhrman grading system, 11 of the samples were grade 1, 47 were grade 2, 34 were grade 3 and eight were grade 4. The mean age was 59.21±11.79 years (range: 31-86) and mean tumor diameter was 5.97±2.57 (range: 2.3-14) (These data were not shown in the table).

Table 1. Clinical and demographic characteristics of fifty patients

Group		Height, (cm)	Weight (kg)	Age (year)	BMI (kg/m²)	WC (cm)	TC (mg/dL)	TG (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	Lymp (mg/dL)	Neut (mg/dL)
Male	Mean	171.08	80.5	59.6	27.49	104.24	195.95	162.29	42.92	125.16	1.64	5.17
n=38	SD	5.21	9.67	9.91	3.8	6.2	36.25	35.17	3.14	27.28	0.19	0.95
Female	Mean	163.17	73.75	57.58	28.7	95.33	200.58	139.17	49.5	121.33	1.66	4.69
n=12	SD	4.23	6.62	10.67	3.1	7.97	38.44	24.79	5.56	32.91	0.13	0.61

SD: standard deviation, BMI: body mass index, WC: waist Circumstance, TC: total Cholesterol, TG: triglyceride, HDL: high density lipoprotein, LDL: low density lipoprotein, Lymp: lymphocyte, Neut: neutrophil

Table 2. The frequency of genotypes and alleles for MTHFR C677T and risk estimation

MTHFR C677T	Group				Distribution relationship		Risk estimation	
	Tumor		Control		Total n (%)	p	OR (95% CI)	p
Allele	n	%	n	%				
C	136	68	126	63	262 (65.5%)	0.29	Reference	Reference
T	64	32	74	37	138 (34.5%)		1.248 (0.826-1.886)	0.293
Genotype	n	%	n	%	Total n (%)	p	OR (95% CI)	p
CC	51	51	39	39	90 (45%)	0.127	Reference	Reference
TT	15	15	13	13	28 (14%)		1.133 (0.484-2.656)	0.773
CT	34	34	48	48	82 (41%)		1.846 (1.007-3.383)	0.046*

OR: odds ratio, CI: confidence interval, *: p<0.05

Table 3. The frequency of genotypes and alleles for MTHFR A1298C and risk estimation

MTHFR A1298C	Group				Distribution relationship		Risk estimation	
	Tumor		Control		Total n (%)	p	OR (%95CI)	p
Allele	n	%	n	%				
A	123	61.5	119	59.5	242 (60.5%)	0.682	Reference	Reference
C	77	38.5	81	40.5	158 (39.5%)		1.087 (0.728-1.624)	0.682
Genotype	n	%	n	%	Total n (%)	p	OR (%95CI)	p
AA	38	38	34	34	72 (36%)	0.825	Reference	Reference
CC	15	15	15	15	30 (15%)		1.118 (0.477-2.621)	0.798
AC	47	47	51	51	98 (49%)		1.085 (0.479-2.459)	0.845

OR: odds ratio, CI: confidence interval

The Hardy-Weinberg equilibrium analysis showed that both polymorphisms were in equilibrium (p>0.05). No significant difference was found between the genotypes and alleles of MTHFR C677T and A1298C polymorphisms in tumor and control groups (p>0.05) (Table 2 and 3).

The genotype and allele distributions of MTHFR C677T in tumor and control groups are defined in Table 2. There was no significant difference between tumor and surrounding healthy tissues in terms of MTHFR C677T genotypes and alleles. Tumors with homozygous normal CC genotype had higher frequency (51%) than the control tissues (39%) (p>0.05). The frequency rate of the mutant T allele was also slightly higher in the surrounding healthy tissues (37%) than tumors (32%) (p>0.05). Compared to CT genotype, odds ratio (OR) of MTHFR C677T CC genotype was found as 1.8 (OR: 1.846 (1.007-3.383), p=0.046). Thus, wild type genotype is higher in kidney cancer due to possible effects on DNA.

The genotype, allele distributions and risk estimation of MTHFR A1298C in tumor and control groups are shown in Table 3. The polymorphism of MTHFR A1298C mutant CC genotype was similar in the control (15%) and tumor (15%) tissues (p>0.05). The frequency of A alleles was not statically different between the tumor (61.5%) and control (59.5%) groups (p>0.05). There was no effect of MTHFR A1298C polymorphism on the risk of kidney cancer formation (p>0.05).

There was no correlation between MTHFR C677T, A1298C, tumor diameter and Fuhrman grade for 100 tumors (p>0.05). Furthermore, no correlation was found between MTHFR polymorphisms and clinical parameters of 50 patients and these results were not given in the table.

Discussion

We aimed to analyze the possible effects of MTHFR C677T and A1298C polymorphisms on kidney cancer. We found that these polymorphisms had no effect on kidney cancer. However, there was no correlation between MTHFR polymorphisms and clinical parameters (p>0.05).

MTHFR enzyme consists of 656 amino acids and is encoded by the *MTHFR* gene (16). This enzyme converts 5,10 MTHFR irreversibly into 5-methyl THF (16,17). 5-methyl THF provides a methyl group for DNA methylation and methionine synthesis (17). MTHFR polymorphisms have been associated with renal diseases (18,19). Since MTHFR polymorphisms are also associated with chemotherapy response, they may be indicative of the identification of individualized treatment protocols (20). There have been few studies in the literature describing the relationship between kidney cancer and MTHFR polymorphisms. One of these studies was conducted by Sakano et al. (21) in Japanese population. They found that MTHFR C677T and A1298C polymorphisms might be predictive factors in the clear cell renal cell carcinoma with a gender-specific manner and associated with aggressiveness or prognosis.

The C677T polymorphism results in a change from cytosine to thymine, the 677th nucleotide in exon 4, which affects the N-terminal catalytic domain of the MTHFR protein, resulting in decreased MTHFR activity (22). Different results were obtained for C677T polymorphism in various cancer types. Cetintas and colleagues found MTHFR C677T polymorphism TT genotype as a potential biomarker for cancer in the Turkish population via meta-analysis. However, none of these cancer cases were kidney cancer (23). MTHFR C677T polymorphisms were found

to be associated with increased clear cell renal cell carcinoma risk in men (24). MTHFR T allele was identified as a risk factor for the development of ovarian carcinoma (25), but not in breast tumors (26). MTHFR C677T TT genotype was also found to reduce risk of colorectal cancer in the Japanese population. It has been suggested that MTHFR TT genotype has a protective role of folate by ensuring a sufficient thymidylate pool for DNA synthesis (27). Another study showed that MTHFR CC genotype was associated with a higher prevalence of p16 hypermethylation and might contribute to the pathogenesis of multiple myeloma (28). Cancer protective associations of MTHFR C677T TT genotype were identified in the red cell folate by changing a metabolic phenotype (29). In a meta-analysis, *C677T* of the *MTHFR* gene was found to be a low-penetrance susceptibility gene for prostate cancer via protective effects (30). The protective effects of T allele were found also in gastric cancer, colorectal cancer (31) and lung squamous cell carcinoma (32). In our study, C677T mutant TT genotype and T allele were not statically different between tumor and control tissues ($p>0.05$). The OR of the MTHFR C677T polymorphism CC genotype was 1.8 compared to CT genotype (OR: 1.846 (1.007-3.383), $p=0.046$). In our study, we could not observe the protective effects of T allele or TT genotype, but cancer tissues were mostly found in normal genotype (CC, 51%) than heterozygous or mutant genotype (CT, 34% or TT, 15%). Given that the MTHFR C677T TT genotype reduces enzyme activity to almost 1/3 (13,14), the MTHFR C677T CC genotype may be present or mutated as a wild type in cancerous tissues for cancer-inducing effects such as p16 hypermethylation (28).

MTHFR activity is reduced as a result of the change from Adenine (A) → Cytosine (C) nucleotide 1298 in the 7th exon of the *MTHFR* gene (22). The higher risk of breast cancer and/or ovarian cancer with MTHFR A1298C polymorphism was detected in a study by Liu et al. (33). Dixit et al. (34) found an association between A1298C polymorphism and increased risk of gallbladder cancer. They also found correlation between this variation, grade and histopathology. The A1298C AA genotype was significantly higher in patients with oral squamous cancer than in controls. Ferlazzo et al. (35) also found hypermethylation of cancer-related genes such as p16 and O^6-methylguanine-DNA MGMT and suggested that these genes might be affected by MTHFR polymorphisms in oral squamous cancer. Wang et al. (36) suggested A1298C AC+CC genotypes might be a risk factor for the development of breast cancer in Chinese population via meta-analysis. The A1298C CC genotype was found to be lower in prostate cancer tissues than control tissues (37-38). The CC genotype was found to slightly reduce prostate cancer risk in Europeans, whereas increase prostate cancer risk in Asians. In a study by Skibola et al. (39), the frequency of CC genotypes was higher in the controls than in patients with acute lymphoid leukemia (39). However, no association was found between the MTHFR A1298C polymorphism and stomach cancer in another study. Similarly to the results in stomach cancer by Kim et al. (40), we did not find any association between the alleles and genotypes of MTHFR A1298C polymorphism and kidney cancer. The mutant CC genotype and C allele were not different between the groups (p0.05). There was no significant relationship between MTHFR A1298C polymorphism and kidney cancer (p0.05).

Conclusion

We evaluated MTHFR polymorphisms due to their possible contribution to kidney cancer formation. It was found that wild type genotype of MTHFR C677T polymorphism was higher in kidney cancer tissues. However, our results should be verified with larger study groups.

Ethics Committee Approval: Ethics committee approval was obtained for the study (İstanbul University Training and Research Hospital Ethics Committee (decision no: 2016/600, date: 13/05/2016).

Informed Consent: Informed verbal and written informed consent was obtained from the teachers.

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Reliability of 2D Magnetic Resonance Imaging Texture Analysis in Cerebral Gliomas: Influence of Slice Selection Bias on Reproducibility of Radiomic Features

Serebral Gliomlardaki İki Boyutlu Manyetik Rezonans Görüntüleme Yapısal Analizinin Güvenilirliği: Kesit Seçiminin Radyomik Özelliklerin Yeniden Üretilebilirliğine Etkisi

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ABSTRACT

Introduction: In this study, we aimed to investigate the reproducibility of two-dimensional (2D) texture features between adjacent magnetic resonance imaging (MRI) slices in patients with cerebral gliomas.

Methods: For this retrospective methodological study, T2-weighted MRI and semi-automatic segmentation data of 25 patients with lower-grade gliomas were obtained from a public database. Only two regions of interests were used in this study: (i), the largest slice and (ii) one of the adjacent slices. Using PyRadiomics, an open source software to extract radiomic features from medical images, a total of 1116 texture features from six different feature classes were extracted from original, Laplacian of Gaussian-filtered, and wavelet-transformed images. Intra-class correlation coefficient (ICC) values with and without 95% confidence interval (CI) were used for reliability analysis. The ICC threshold for excellent reproducibility was 0.9.

Results: In the reliability analysis without considering the 95% CI for the ICC values, 28% of the texture features had excellent reproducibility. On the other hand, considering the 95% CI, only 10% of the texture features had excellent reproducibility. Neither a feature class (range of excellent reproducibility rates without 95% CI, 21.2%-34.4%; with 95% CI, 2.1%-18.3%) nor an image type (range of excellent reproducibility rates without 95% CI, 22.3%-41.9%; with 95% CI, 9.1%-14%) had considerable reliability in two adjacent MRI slices.

Conclusion: 2D MRI texture analysis of gliomas using T2-weighted sequence is substantially sensitive to slice selection bias, which may lead to non-reproducible results in radiomic works.

Keywords: Glioma, MRI, texture analysis, radiomics, reliability

ÖZ

Amaç: Bu çalışmadaki amacımız serebral gliomlardaki iki boyutlu (2D) manyetik rezonans görüntüleme (MRG) yapısal analizinde kesit seçiminin radyomik özelliklerin yeniden üretilebilirliğine etkisini ardışık kesitler kullanarak araştırmak.

Yöntemler: Bu metodolojik çalışmaya halka açık bir veri bankasından düşük dereceli gliomu bulunan 25 hastanın T2 ağırlıklı MRG görüntüleri ve semi-otomatik segmentasyon verileri dahil edildi. Sadece iki ilgili bölge veya segmentasyon alanı kullanıldı: (i), en büyük kesitten elde edilen ve (ii), hemen komşuluğundaki kesitten elde edilen. Radyomik özellikler açık kaynak kodlu PyRadiomics yazılımı kullanılarak elde edildi. 6 farklı özellik sınıfından 3 farklı görüntü tipi kullanılarak toplamda 1116 yapısal özellik elde edildi. Güvenilirlik analizi %95 güven aralığı (GA) kullanılarak ve kullanılmadan sınıf içi katsayısı (SİK) ile yapıldı. Mükemmel yeniden üretilebilirlik için SİK eşik değeri 0,9 idi.

Bulgular: %95 GA kullanılmadan yapılan güvenilirlik analizinde, yapısal özelliklerin %28'i mükemmel yeniden üretilebilirliğe sahipti. Bunun yanında, %95 GA kullanılarak yapılan güvenilirlik analizinde ise, yapısal özelliklerin sadece %10'u mükemmel yeniden üretilebilirliğe sahipti. Ardışık MRG kesitlerinde ne bir özellik sınıfı (aralık, %95 GA kullanılmadan %21,2-%34,4; kullanılarak, %2,1-%18,3) ne de bir görüntü tipi (aralık, %95 GA kullanılmadan, %22,3-%41,9; kullanılarak, %9,1-%14) önemli düzeyde yeniden üretilebilirliğe sahipti.

Sonuç: Serebral gliomlardaki 2D T2 ağırlıklı MRG yapısal analizi kesit seçimine duyarlıdır. Bu durum dikkate alınmadığında radyomik çalışmalarda yeniden üretilebilirlik sorunlarına neden olabilir.

Anahtar Kelimeler: Gliom, MRG, yapısal analiz, radyomik, güvenilirlik

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Introduction

The most common primary malignant cerebral tumors in adults are gliomas (1). Considering certain prognostic and therapeutic implications, gliomas can be divided into low-grade [World Health Organization (WHO)], grade I and grade II) and high-grade (WHO grade III and grade IV) based on histopathological and clinical criteria (2). Furthermore, WHO grade II and grade III diffuse gliomas are grouped as lower-grade gliomas, forming a heterogeneous group of tumors that have a wide range of malignancy characteristics (3). High-grade gliomas have very poor survival, while low-grade gliomas are associated with a longer life expectancy. Correct histopathological and genomic diagnosis of gliomas is crucial for appropriate treatment of all gliomas. Although biopsy is the gold standard for this purpose, this has been widely challenged by non-invasive conventional and advanced imaging techniques (4).

Texture analysis has been used for quantifying distribution and patterns of pixels or voxels in traditional or advanced medical images (5,6). In contrast to conventional qualitative and subjective clinical assessment, which might lead to significant variability depending on the experience of radiologists, image texture analysis offers an objective and more accurate non-invasive diagnosis that may influence patient management by more personalized management. Recently, texture analysis has been used in predicting histopathological tumor types, prognostic clinicopathological features, genomic characteristics and survival (7). However, the major problem of this field is the reproducibility of texture feature parameters, resulting in a challenge for creating powerful and stable predictive models to be used in clinical practice (8,9).

Although three-dimensional segmentation is the most representative for tumor texture, several studies have been published using a single image slice in the texture analysis of gliomas (10-13). However, this technique is prone to slice selection bias. To the best of our knowledge, the reproducibility of texture features between image slices has not been studied so far. In this study, we hypothesized that texture feature parameters obtained from different and even adjacent slices might not be correlated with each other and have a dependency to the selected slice. Therefore, in this study, we investigated the reproducibility of two-dimensional (2D) texture features between adjacent magnetic resonance imaging (MRI) slices in patients with lower-grade gliomas.

Methods

Database Characteristics

No ethical approval was obtained for this retrospective methodological study because all patients included in this study were publicly and freely available for scientific purposes in the cancer imaging archive (TCIA) (14). The imaging and segmentation data of the patients used in this study were obtained from the collection named "LGG-1p19qDeletion" in TCIA (14-16).

One hundred and fifty-nine patients in the collection were reviewed for identifying patients with a uniform image acquisition protocol and no signs of previous surgery or biopsy, which would influence texture feature parameters. Following the initial evaluation of the collection, a randomly selected subset of 25 patients with MRI and tumor segmentation data was included in this reproducibility study.

MRI Acquisition Parameters

Only T2-weighted spin-echo MRI images were included in the study. The images were obtained using a 1.5 Tesla MRI unit. Acquisition parameters were uniform, except for time to echo and repetition time. The representative acquisition parameters were as follows: time to echo, 98; repetition time, 4000; slice thickness, 3 mm; pixel spacing, 0.937x0.937 mm^2; echo train length, 16; and acquisition matrix, 256x256.

Texture Feature Extraction

Before feature extraction, the low-frequency signals that would corrupt MRI images were corrected in all images using N4 bias field correction algorithm (17). Then, gray-level intensity values were normalized and discretized (18,19). Normalization procedure was performed using the ±3 sigma technique based on the following mathematical formula:

$$f(x) = \frac{s(x - \mu(x))}{\sigma(x)}$$

where f (x) is normalized gray-level intensity, x is original gray-level intensity, μ (x) is mean gray-level intensity value, σ (x) is the standard deviation of gray-level intensity, and s is the scaling factor, which was 100 in this study.

The discretization was based on the following mathematical formula:

$$X_{b,i} = \lfloor \frac{X_{gl,i}}{W} \rfloor - \lfloor \frac{\min(X_{gl,i})}{W} \rfloor + 1$$

where, $X_{b,i}$ is gray-level intensity following discretization; $X_{gl,i}$ is gray-level intensity prior to discretization; W is the bin-width value, which was five in this study.

The segmentation datasets were obtained from TCIA (14-16), which was used in the study of Akkus et al. (15). The segmentations had been done with semi-automatic fashion and based on normal brain atlas, the posterior probability of the voxels, and geodesic active contour (20-22). Original segmentation data included three image slices. Nonetheless, we only used the largest slice and one of the adjacent slices in the radiomic analysis. Segmentation style and usage in this study are presented in Figure 1.

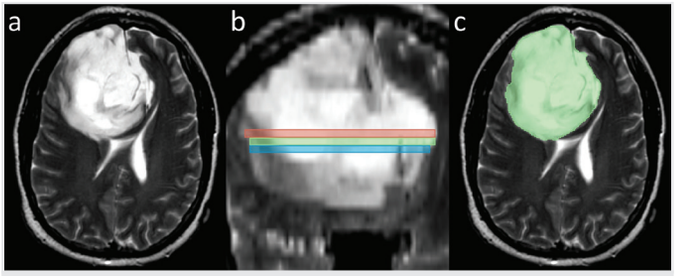

Figure 1. Segmentation style in a 47-year-old male with a grade III diffuse glioma. (a) T2-weighted axial slice shows the right-sided frontal tumor with extension to the left side. (b) Reconstructed coronal T2-weighted MRI image presents the segmentation data decomposed to three consecutive slices. Two axial slices including middle (green-colored segmentation) and upper (red-colored segmentation) or lower (blue-colored segmentation) ones were included in this study. (c) Axial T2-weighted image shows one of the two selected segmentations

MRI: magnetic resonance imaging

Texture features were extracted from the two adjacent MRI slices using PyRadiomics software (PyRadiomics version 2.0.1; Numpy version 1.13.1; SimpleITK version 1.1.0.dev370; PyWavelet version 0.5.2; Python version 2.7.13) (23). Using the original image, the extracted texture feature groups were as follows: (i), 18 first-order features; (ii), 14 gray-level dependence matrix (GLDM) features; (iii), 24 gray-level co-occurrence matrix (GLCM) features; (iv), 16 gray-level run length matrix (GLRLM) features; (v), 16 gray-level size zone matrix (GLSZM) features; and (vi), 5 neighboring gray-tone difference matrix (NGTDM) features. In addition to the original image, we also used Laplacian of Gaussian (LoG)-filtered and wavelet-transformed images in extracting texture features. The LoG filter was used for image filtration with values of 2 mm, 4 mm, and 6 mm; where, 2 mm, 4 mm, and 6 mm represent fine, medium, and coarse patterns, respectively. Wavelet-based texture features were created using eight different frequency band combinations. The total number of the features extracted was 1116 [93 from the original image; 279 (93x3) from LoG-filtered images; and 744 (93x8) from wavelet-transformed images] per lesion. Detailed definitions and mathematical formulas for these features have been described in the website of PyRadiomics in detail, https://pyradiomics.readthedocs.io/en/latest/.

Statistical Analysis

The statistical analysis was performed using SPSS version 20 (SPSS Inc.). The degree of correlation and agreement of quantitative texture features between MRI slices were assessed using intra-class correlation coefficient (ICC) (24). For the ICC analysis, we used a two-way model, single-rating, and absolute agreement. The strength of reproducibility was defined as follows: (i), ICC<0.9, not excellent reproducibility; and (ii), ICC≥0.9, excellent reproducibility (24). The reproducibility was assessed using the ICC values with and without considering 95% confidence interval (CI).

Results

Overall Reproducibility

In the analysis performed without considering 95% CI for the ICC values, approximately one-fourth of the texture features were excellently reproducible (Figure 2a). On the other hand, considering the 95% CI, only one-tenth of the texture features were excellently reproducible (Figure 2b).

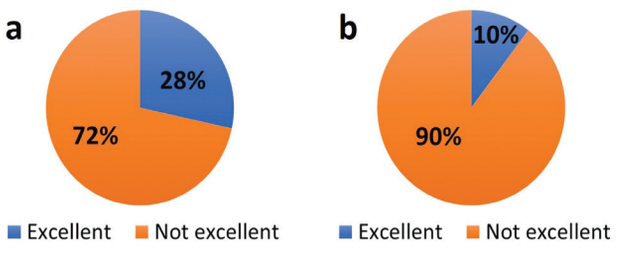

Figure 2. Pie charts show the overall reproducibility rates of 2D texture features between adjacent MRI slices without (a) and with (b) considering 95% confidence interval

MRI: magnetic resonance imaging

Reproducibility Based on Image Types

In the analysis without considering the 95% CI for the ICC values, approximately less than half of the texture features extracted from the original and LoG-filtered image types were excellently reproducible. Nonetheless, for the wavelet-transformed images, approximately one-fourth of the features were excellently reproducible (Figure 3a).

In the analysis with considering the 95% CI for the ICC values, approximately only one-tenth of the texture features extracted from the original, LoG-filtered, and wavelet-transformed image types were excellently reproducible (Figure 3b).

Reproducibility Based on Feature Classes

In the analysis without considering the 95% CI for the ICC values, the feature classes with the highest and lowest rates for excellent reproducibility were GLRLM and GLCM, respectively. For the first-order and GLCM feature classes, approximately one-fourth of the texture features were excellently reproducible. Meanwhile, for the other feature classes (GLDM, GLRLM, GLSZM, NGTDM), approximately one-third of the features were excellently reproducible (Figure 4a).

In the analysis with considering the 95% CI for the ICC values, the feature classes with the highest and lowest rates for excellent reproducibility were NGTDM and GLCM, respectively. For the first-order and GLCM features, only less than one-tenth of the texture features were excellently reproducible. Meanwhile, for the other groups (GLDM, GLRLM, GLSZM, NGTDM), approximately less than one-fifth of the texture features were excellently reproducible (Figure 4b).

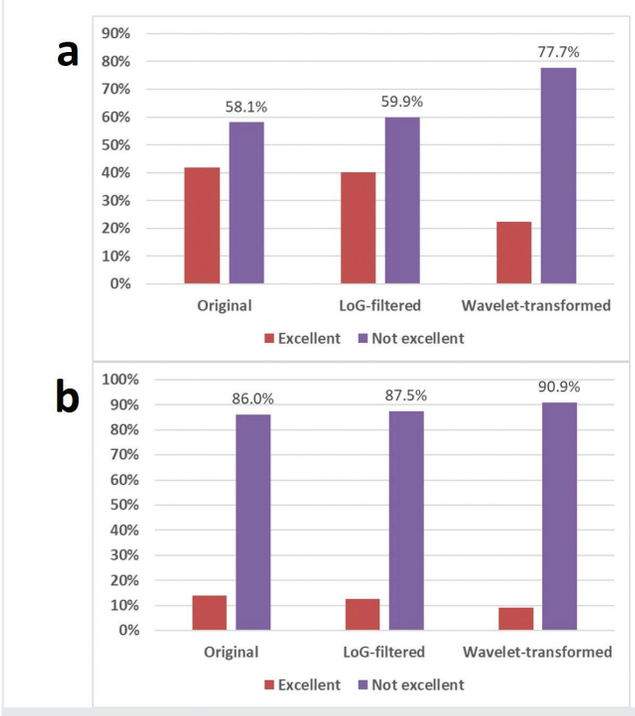

Figure 3. Bar charts present the reproducibility rates of 2D texture features between adjacent MRI slices based on image types without (a) and with (b) considering 95% confidence interval

MRI: magnetic resonance imaging, LoG: laplacian of gaussian

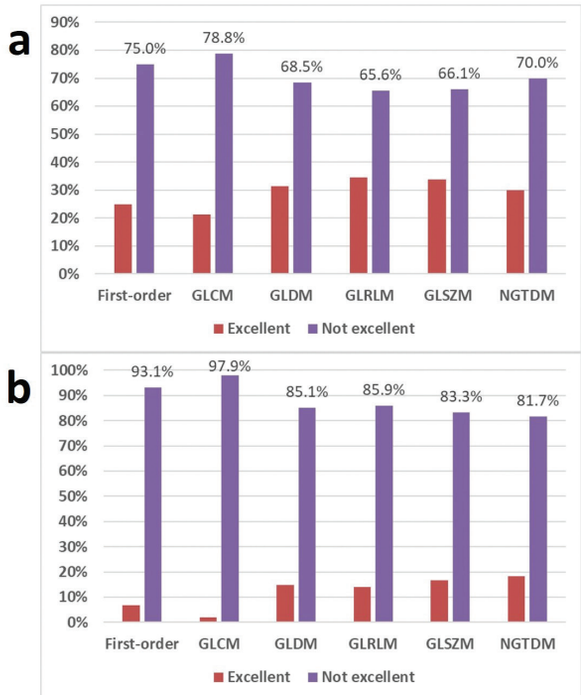

Figure 4. Bar charts present the reproducibility rates of 2D texture features between adjacent MRI slices based on feature classes without (a) and with (b) considering 95% confidence interval.

GLCM: gray-level co-occurrence matrix features, GLDM: gray-level dependence matrix features, GLRLM: gray-level run length matrix features, GLSZM: gray-level size zone matrix features, NGTDM: neighboring gray-tone difference matrix features

Discussion

In this study, we investigated the reproducibility of 2D texture-based radiomic feature parameter values between two adjacent conventional T2-weighted MRI slices in lower-grade (WHO grade II and III) glioma patients. The vast majority of high-dimensional texture features were not excellently correlated between adjacent T2-weighted MRI slices. Neither a feature class nor an image type had considerable reliability in two adjacent MRI slices.

To obtain reliable values in a quantitative method, the parameter values obtained must be resistant to various factors such as segmentation variability, acquisition differences or use of different scanners from different vendors. Although much work has been done using 2D MRI texture analysis in cerebral gliomas (10-13), there is a scarcity of papers regarding the reliability of the technique. Only few papers draw our attention to the in vivo stability of the texture feature parameters. The most significant of those is a methodological study dealing with volume bias, slice bias, and region of interest bias in glioblastomas (9). Although it has been conducted with a very limited number of features, in their seminal work, the authors suggested that increasing fractal tumor volume and even a minimal change of a region of interest area significantly influence the texture feature parameters, providing evidence regarding susceptible nature of the texture analysis. However, the stability of parameters across different slices has not been studied so far. Therefore, a direct comparison of this study with others is not possible.

We think that our study has very significant pre-clinical and clinical implications. In general, a texture-based high-dimensional radiomic workflow includes a few crucial steps as follows: (i), preprocessing of the images; (ii), segmentation of the tumors or lesions; (iii), radiomic feature extraction; (iv), dimension reduction to avoid redundant features, which is optional; and (v), statistical model development using conventional or advanced methods (25). The segmentation step is known to be the most critical and challenging one in radiomic works (6). Therefore, our focus in this work was on the segmentation step with a different perspective, that is, slice selection bias. The most important implication of our work was that 2D MRI texture analysis would lead to non-reproducible feature parameter values due to the high susceptibility of the texture analysis to the slice of interest or slice selection bias. Therefore, the 2D MRI texture analysis using a single slice must be used cautiously in radiomic workflows. If this technique is used in gliomas, a reliability analysis regarding the slice selection bias should be included in the radiomic workflow to exclude the features with poor reproducibility.

A few limitations to this methodological study need to be acknowledged. First, the nature of the study was retrospective, which was disadvantageous due to dependency on limited data. Second, although the image acquisition protocol is fairly uniform, we had to perform a few preprocessing steps to minimize small differences like bias field, the number of gray levels, and relative gray-level intensity range (18,19). It is worth to emphasize that the texture analysis has a dependency on these preprocessing steps to obtain comparable parameters (18,19). For this reason, all of the MRI images in our study underwent N4 bias field correction, gray-level normalization, and gray-level discretization (17-19). We did not consider pixel rescaling because it was homogeneous in all patients. Third, we included only T2-weighted MRI images, because they are widely used in radiomic works (26,27). This study can be expanded using other sequences in future studies. Fourth, we only included lower-grade tumors (WHO grade II and III) to represent gliomas. Nonetheless, whether our findings might be extrapolated to other gliomas should be further studied. Fifth, a Bland-Altman analysis could have been included as a statistical method to reveal the degree of agreement between the slices. Instead, we used the ICC in this study, which can serve as a single strong metric not only for the degree of correlation but also for the agreement between quantitative measurements (24).

Conclusion

2D MRI texture analysis of gliomas was substantially susceptible to selected slices, which may lead to non-reproducible results in radiomic works. The vast majority of high-dimensional texture features were not excellently correlated between adjacent T2-weighted MRI slices. Neither a feature class nor an image type had considerable reliability in two adjacent MRI slices. Therefore, a reliability analysis with considering different slices must be incorporated into every scientific research using this technique. Otherwise, the unstable feature parameters might cause non-reproducible outcomes in terms of selected texture features and statistical predictive models.

Ethics Committee Approval: Not required due to use of public data.

Informed Consent: Not required due to use of public data.

Peer-review: Internally peer-reviewed.

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The Role of Magnetic Resonance Imaging in the Differential Diagnosis of Giant Rectal and Perirectal Masses

Dev Rektal ve Perirektal Kitlelerin Ayırıcı Tanısında Manyetik Rezonans Görüntülemenin Rolü

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ABSTRACT

Introduction: Our purpose was to depict some specific qualitative and quantitative magnetic resonance imaging (MRI) and diffusion weighted imaging (DWI) findings in differential diagnosis of huge tumors of rectum and perirectal region.

Methods: A total of 81 patients who had ≥5 cm huge tumors of rectum and perirectal region [36 (44%) women and 45 (56%) men] with a mean age of 54±15 (standard deviation) were enrolled in this retrospective study. Pre-operative MRI with DWI examinations of patients were reviewed by an experienced radiologist. Qualitative (signal intensity, contrast enhancement pattern, the existence of lymphadenopathy and metastasis) and quantitative imaging findings were statistically analyzed according to histopathological results.

Results: Of 81 huge tumors of rectum and perirectal region, 60 were malignant and 21 were benign. Among (n=60) malignant tumors, there were 48 rectal adenocancers, two prostate adenocancers, three leiomyosarcomas, three ovarian cancers and four rectal gastrointestinal stromal tumors (GISTs). All rectal GISTs (n=4) showed peripheral heterogeneous arterial enhancement and had hypointense peripheral components whereas central components were more heterogeneous and iso-/hyper-intense on T2-weighted sequences. Most of rectal adenocancers (41/48, 85%) showed significant enhancement. Lymphadenopathy, invasion and far metastasis were only observed in malignant tumors. Mean "apparent diffusion coefficient" (ADC) ratios of malignant tumors (0.56±0.10) were significantly lower than those of benign tumors (0.95±0.21) ($p<0.05$).

Conclusion: Specific MRI findings combining with ADC ratio estimation can be helpful for differential diagnosis of bulky rectal and perirectal tumor, and appropriate management of patient.

Keywords: Gastrointestinal stromal tumor, magnetic resonance imaging, rectal cancer, diffusion weighted imaging

ÖZ

Amaç: Dev rektal ve perirektal bölge kitlelerinin ayırıcı tanısında önemli olabilecek bazı spesifik kalitatif ve kantitatif manyetik rezonans görüntüleme (MRG) ve difüzyon ağırlıklı görüntüleme (DAG) bulgularını tanımlamayı amaçladık.

Yöntemler: Bu retrospektif çalışmada, pre-operatif MRG ve DAG tetkikinde rektal ve perirektal bölgede ≥5 cm kitlesi olan toplam 81 hasta [36 (%44) kadın ve 45 (%56) erkek] yer aldı. Ortalama yaş 54±15 (standart sapma) idi. Pre-operatif MRG ve DAG tetkikleri abdominal görüntüleme konusunda tecrübeli bir radyolog tarafından tekrar değerlendirildi. Kalitatif (sinyal intensiteleri, kontrastlanma paterni, lenfadenopati ve metastaz varlığı) ve kantitatif görüntüleme bulguları ile histopatolojik sonuçlar arasındaki ilişki istatistiksel olarak incelendi.

Bulgular: Çalışmamızda yer alan toplam 81 hastada, 60 malign ve 21 benign dev rektal ve perirektal kitle mevcuttu. Malign kitleler (n=60) içinde, 48 rektal adenokanser, iki prostat adenokanser, üç leiomyosarkom, üç over kanseri ve dört rektal gastrointestinal stromal tümör (GİST) mevcuttu. Tüm rektal GİST'lerde (n=4) arteryal fazda başlayan periferik heterojen kontrastlanma izlendi ve T2- ağırlıklı sekanslarda santral kesimleri heterojen, izo-hiperintens seçilirken periferik kesimlerinde hipointens sinyal özellikleri saptandı. Rektal adenokanserlerinin çoğunda (41/48, %85) yoğun kontrastlanma mevcuttu. Lenfadenopati, komşu organ invazyonu ve uzak metastaz sadece malign kitlelerde izlendi. Ortalama "apparent diffusion coefficient" (ADC) oranları, malign kitlelerde (0,56±0,10) benign kitlelere (0,95±0,21) göre anlamlı derecede düşüktü ($p<0,05$).

Sonuç: Spesifik MRG özellikleri ve ADC oran ölçümlerinin birlikte değerlendirilmesi, dev rektal ve perirektal kitlelerin ayırıcı tanısında önemli bir role sahiptir ve hasta tedavisini planlamada yol göstericidir.

Anahtar Kelimeler: Gastrointestinal stromal tümör, manyetik rezonans görüntüleme, rektal kanser, difüzyon ağırlıklı görüntüleme

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Introduction

Giant tumors located in the rectal and perirectal regions cause compression and distortion in normal anatomic structures, so it may be difficult to determine the origin of the tumor and decide the correct diagnosis and treatment (1-6). Masses such as rectal adenocarcinoma, sarcoma, neuroendocrine tumor, leiomyoma, ovarian mass, rectal gastrointestinal stromal tumor (GIST), prostate adenocarcinoma, lymphoma, neurogenic tumor and congenital cyst should be considered in the differential diagnosis of giant rectal and perirectal tumors (6). Although rectoscopy-guided biopsy is the most important method for diagnosis, it is insufficient to evaluate intramural and extramural extension of the mass (1,5). Pre-operative imaging is necessary to determine the location of the mass (submucosal/intramural/extramural) and its extension, to evaluate the need for surgical approach to the patient and to decide the surgical technique to be applied (1-7). Computed tomography (CT) and magnetic resonance imaging (MRI) are used in the diagnosis and evaluation of rectal and perirectal tumors (1-7). MRI is more appropriate because it does not contain radiation and has high soft tissue resolution (1-5). Diffusion-weighted imaging (DWI) may also provide important findings in use with MRI (8-10).

To the best of our knowledge, there is no detailed study in the literature regarding MRI and DWI characteristics that may help in the differential diagnosis of giant rectal and perirectal tumors. Therefore, we aimed to identify some specific qualitative and quantitative MRI and DWI findings that may be important in the differential diagnosis of giant rectal and perirectal masses.

Methods

Written consent was obtained from the patients and approval was obtained from the ethics committee in accordance with the Helsinki Declaration Criteria before the initiation of study (University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee of Clinical Studies, decision no: 235, date: 23/01/2019). Lower abdominal MRI reports performed in a single center between January 2014 and January 2019 were reviewed for rectal and perirectal masses using hospital information system. MRI examinations of patients with ≥5 cm rectal and perirectal masses were detected retrospectively. Patients without histopathological diagnosis (n=15) and patients with incomplete or inadequate MRI examination for evaluation (n=7) were excluded. Eighty-one patients (36 female, 44% and 45 male, 56%) with ≥5 cm mass in the rectal and perirectal region and pre-operative MRI and DWI were included in our study. The mean age was 54±15 years.

Contrast-enhanced lower abdominal MRI examinations were performed using a 1.5 Tesla MRI (Magnetom Avanto®, Siemens Healthineers, Erlangen, Germany). The contrast-enhanced lower abdominal MRI parameters were: sagittal T2-weighted turbo spin-echo (TSE) BLADE (TR/TE: 5000/112 ms, FOV: 350, matrix: 256×256, section thickness, 7 mm), coronal fat-suppressed T2-weighted TSE BLADE (TR/TE: 4000/84 ms, FOV: 320, matrix, 256×320, section thickness, 5 mm), axial T2-weighted fast spin-echo sequence (TR/TE: 3700/88 ms, FOV: 320, matrix: 182×320, section thickness, 5 mm), pre-contrast and post-contrast axial T1-weighted 3D VIBE (TR/TE: 4.5/2.1 ms, FOV: 380, matrix: 195×320, deflection angle, 15 °C section thickness, 5 mm), diffusion weighted single shot echo planar imaging with b values 0 and 1000 s/mm^2 (FOV: 430, TR/TE: 5200/58, matrix: 115×192, section thickness: 5 mm, NEX: 3).

Pre-operative MRI and DWI examinations were re-evaluated by a radiologist (F.K.) experienced in abdominal imaging who was blinded to the histopathological information of the patients. Longest diameter (mm) of the masses, contour characteristics (regular/irregular), signal intensity characteristics (hypo-, iso-, hyper-intense) in T1- and T2-weighted sequences, contrast patterns (mild/intense, homogeneous/heterogeneous), tumor content (hemorrhagic signal, cystic component), invasion, lymphadenopathy and metastasis were noted. In addition, the apparent diffusion coefficient (ADC) values and ratios of the masses were calculated. For ADC calculation, circular region of interest (ROI) measurements ranging from approximately 100 to 200 mm^2 were used. It was ensured that no lumens and extra-mass structures entered into the ROI. ROI measurements were performed in three different locations in the mass and gluteus maximus muscle in the same section. The ratio of the ADC value of the mass to the ADC value of the muscle (ADC ratio) was calculated for the standardization with the obtained mean ROI measurements.

Statistical Analysis

All patients had histopathological results. The relationship between qualitative (signal intensities, contrast enhancement pattern, presence of lymphadenopathy and metastasis) and quantitative imaging findings and histopathological results were statistically analyzed. The suitability of the parameters to normal distribution was evaluated by Shapiro-Wilk test. The Mann-Whitney U test was used for the comparison of the quantitative data and the chi-square test was used for the comparison of the qualitative data. Significance was evaluated at $p<0.05$.

Results

In our study, 81 giant rectal and perirectal masses, 60 of which were malignant and 21 were benign, were detected. The mean longest diameter was 86±32 mm (range: 50-208 mm) in malignant masses and 66±15 mm (range: 50-110 mm) in benign masses. Malignant masses (n=60) included 48 rectal adenocarcinomas, two prostate adenocarcinomas, three leiomyosarcomas, three ovarian cancers, and four rectal GISTs. Benign mass group (n=21) consisted of two ovarian fibromas, five mature teratomas, five leiomyomas, three perirectal abscesses, two ovarian cystadenomas and four endometriomas. Most of the malignant

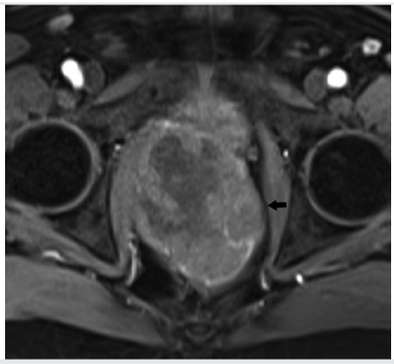

Figure 1: Rectal GIST (arrow) with regular contours and heterogeneous peripheral contrast enhancement in arterial phase.

masses (47/60, 78%) had irregular contours. All benign masses (20/21, 95%) except one perirectal abscess had regular contours. All rectal GISTs (n=4) had regular peripheral contours and mild heterogeneous contrast enhancement beginning in the arterial phase (Figure 1). Unlike other malignant tumors (n=56), heterogeneous, iso-hyperintensity was observed in central sections in T2-weighted sequences of all rectal GISTs (n=4), whereas hypointense signal characteristics were detected in peripheral sections (Figure 2 a,b). Peripheral marked diffusion restriction was present in rectal GISTs (Figure 2 c,d). Most rectal adenocarcinomas (41/48, 85%) had intense enhancement. Lymphadenopathy (43/60, 71%), adjacent organ invasion (28/60, 46%) and distant metastasis (16/60, 26%) were observed only in malignant masses. Significant statistical difference was found between the benign and malignant groups in terms of signal intensities in T1- and T2-weighted sequences ($p<0.05$). Table 1 shows the distribution of benign and malignant masses according to qualitative MRI characteristics.

The mean ADC values and ratios were significantly lower in malignant masses than benign masses ($p<0.05$). Table 2 summarizes the quantitative DWI findings of benign and malignant masses. In giant rectal adenocarcinomas (n=48), the mean ADC value was $0.87\pm0.16\times10^{-3}$ mm^2/s and the ADC ratio was 0.57±0.10 (Figure 3 a,b,c). The mean ADC value of mucinous rectal adenocarcinomas (4/48) was $0.98\pm0.25\times10^{-3}$ mm^2/s. In non-mucinous rectal adenocarcinomas (44/48), the mean ADC value was found to be low with $0.86\pm0.15\times10^{-3}$ mm^2/s and was close to the ADC value of mucinous rectal adenocarcinomas. Rectal GISTs, leiomyosarcomas, prostate cancers, and ovarian cancers yielded low ADC values ($0.83\pm0.07\times10^{-3}$ mm^2/s, $0.60\pm0.08\times10^{-3}$ mm^2/s, 0, $52\pm0.16\times10^{-3}$ mm^2/s, and $0.77\pm0.15\times10^{-3}$ mm^2/s, respectively) and ADC ratios were obtained in (0.53±0.06, 0.45±0.05, 0.41±0.09, and 0.54±0.05, respectively) (Figure 4 a,b,c).

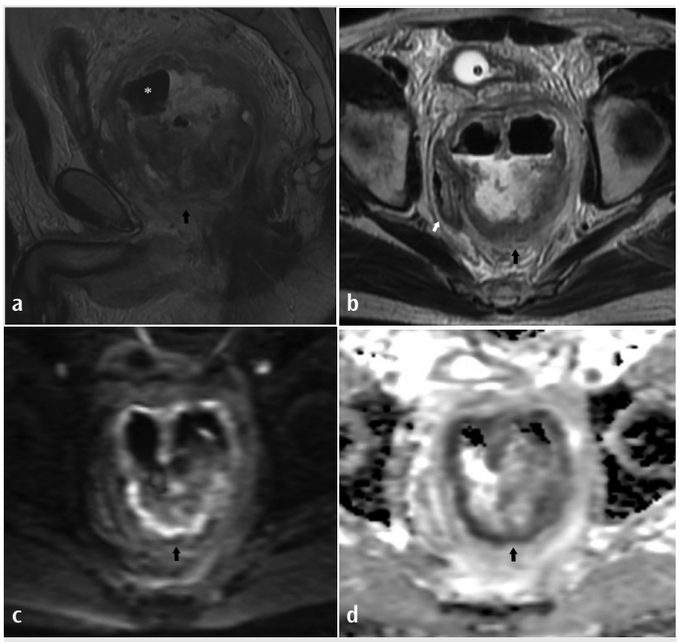

Figure 2a: Air (*) inside the ulcerated rectal GIST (black arrow) which shows peripheral hypo-intensity and heterogeneous central hyper-intensity on sagittal T2-weighted sequence.

Figure 2b: Rectal GIST (black arrow) originated from left anterolateral wall of rectum (white arrow) and showed regular contours, heterogeneous central hyper-intensity and peripheral hypo-intensity on axial T2-weighted sequence.

Figure 2c: Peripheral hyper-intensity (black arrow) and diffusion restriction in rectal GIST on DWI.

Figure 2d: Peripheral hypo-intensity (black arrow) and diffusion restriction in rectal GIST on ADC map.

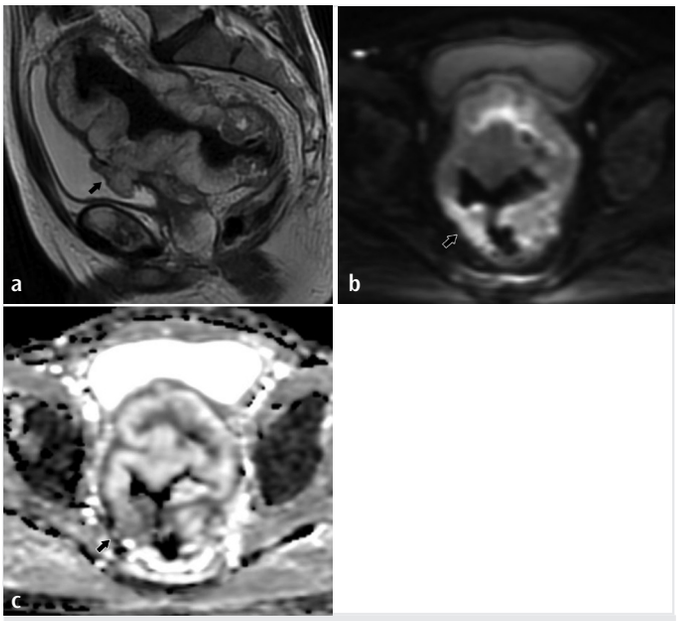

Figure 3a: Giant rectal adenocarcinoma with bladder invasion (black arrow) and hyper-intensity on sagittal T2-weighted sequence.

Figure 3b: Giant rectal adenocarcinoma with peripheral hyper-intense focal areas (black arrow) on DWI.

Figure 3c: Diffusion restriction of giant rectal adenocarcinoma with peripheral hypo-intense focal areas (black arrow) on ADC map.

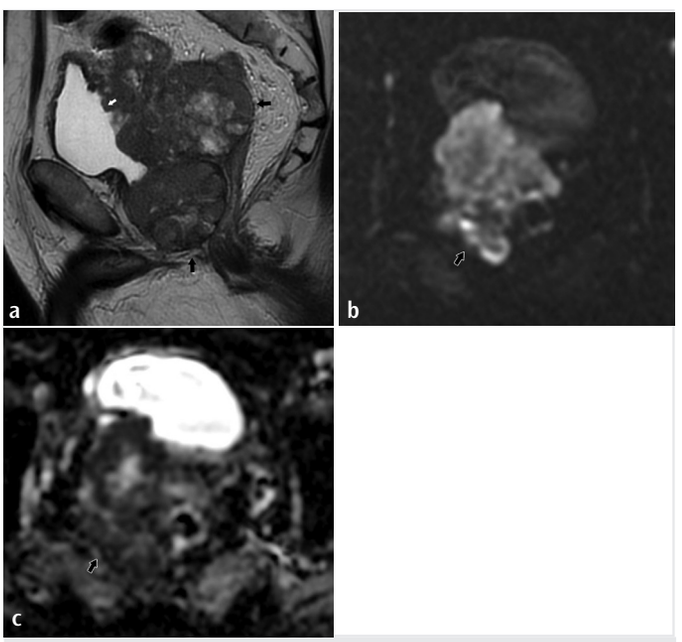

Figure 4a: Giant prostate adenocarcinoma (black arrow) with invasion of rectum (black arrow) and bladder (white arrow) on sagittal T2-weighted sequence.

Figure 4b: Giant prostate adenocarcinoma (black arrow) with irregular contours and hyper-intensity on DWI.

Figure 4c: Diffusion restriction of giant prostate adenocarcinoma (black arrow) with hypo-intensity on ADC map.

Table 1. Distribution of benign and malignant giant rectal and perirectal masses according to qualitative magnetic resonance imaging

MRI features	Benign masses (n=21)						Malignant masses (n=60)				
	Ovarian cystadenoma (n=2)	Leiomyoma (n=5)	Mature teratoma (n=5)	Endometrioma (n=4)	Perirectal abscess (n=3)	Over fibroma (n=2)	Rectal cancer (n=48)	Leiomyosarcoma (n=3)	Rectal GIST (n=4)	Over cancer (n=3)	Prostate cancer (n=2)
Regular contour	2	5	5	4	2	2	6	1	4	2	-
Irregular contour	-	-	-	-	1	-	42	2	-	1	2
T1A iso-hypointense	2	5	3	1	3	2	48	2	3	3	2
T2A hypointense	-	5	3	4	-	2	2	1	-	1	-
T2A hyperintense	2	-	2	-	3	-	46	2	4	2	2
T2A peripheral hypointense, central hyperintense	-	-	-	-	-	-	-	-	4	-	-
Intense enhancement	2	5	5	-	-	-	41	3	-	1	2
Peripheral heterogeneous enhancement	-	-	-	-	3	2	7	-	4	2	-
Cystic component	2	3	5	4	3	-	5	1	2	3	2
Lymphadenopathy	-	-	-	-	-	-	40	1	1	1	-
Adjacent organ invasion	-	-	-	-	-	-	23	2	-	1	2
Distant metastasis	-	-	-	-	-	-	12	1	-	3	-

GIST: gastrointestinal stromal tumor, MRI: magnetic resonance imaging

Discussion

Differential diagnosis of giant rectal and perirectal tumors can be difficult in pre-operative imaging and sometimes even in histopathological evaluation. Therefore, taking into account some specific findings, evaluating pre-operative MRI and DWI findings in detail may help in making the correct diagnosis and deciding the appropriate treatment method (2,4,11-13). DWI is a an imaging modality showing the movement of water in the tissue (8-10). The ADC map is generated from DWI and allows us to detect and measure diffusion restriction. Increased cellularity leads to diffusion restriction (8-10). Diffusion restriction is hyperintense on DWI and hypointense on ADC map (8-10). In addition, ADC value provides us the quantification of diffusion and can be helpful in the differential diagnosis of benign and malignant tumors (8-10).

There are many studies in the literature regarding the efficacy of MRI and DWI in the diagnosis and post-treatment evaluation of rectal cancer. In a study by Li et al. (11), when compared with conventional MRI (71.42%), combined use of MRI (92.85%) and DWI (b value: 1000 s/mm^2) in patients with rectal adenocarcinoma (n= 84) was observed to significantly increase diagnostic accuracy. In another study, Gu et al. (14) evaluated DWI (b value: 1000 s/mm^2) and positron emission tomography (PET) CT findings in 33 patients with rectal adenocarcinoma. A significant negative correlation was found between ADC that shows increased tumor cell number and standard uptake value that shows metabolic activity, and a positive correlation was detected between total diffusion index and total lesion glycolysis (14). Çolakoğlu and Erden (15) evaluated the findings of DWI (b value: 1000 s/mm^2) in mucinous (n=18) and non-mucinous (n=44) rectal adenocarcinomas. Diffusion properties and ADC values of mucinous and non-mucinous adenocarcinomas were found to be different (15). In mucinous adenocarcinomas ($1.631\pm0.375\times10^{-3}$ mm^2/s), higher ADC values were obtained compared to non-mucinous adenocarcinomas ($0.921\pm0.157\times10^{-3}$ mm^2/s), and a threshold value of 1.27×10^{-3} mm^2/s was calculated with high sensitivity (94.4%) and specificity (94.4%) (15). In a similar study, Nasu et al. (16) investigated the DWI (b value: 1500 s/mm^2) and ADC characteristics of mucinous (n=15) and tubular (n=66) rectal adenocarcinomas. A higher ADC value was detected in mucinous adenocarcinomas ($1.49\pm0.34\times10^{-3}$ mm^2/s) than tubular adenocarcinomas ($0.80\pm0.15\times10^{-3}$ mm^2/s) (16). In our study, the number of mucinous rectal adenocarcinomas (n=4) was low and the mean ADC value was close to non-mucinous rectal adenocarcinomas (n=44). In another study, Bassaneze et al. (17) calculated the mean ADC value before chemotherapy as $1.01\pm0.05\times10^{-3}$ mm^2/s in locally advanced rectal adenocarcinomas (n=33). In our study, low ADC values ($0.87\pm0.16\times10^{-3}$ mm^2/s) were obtained in giant rectal adenocarcinomas (n=48). In addition, the ADC ratio was calculated in our study and not only rectal adenocarcinomas, but also other rectal and perirectal masses ≥5 cm in size were evaluated.

Table 2. Quantitative DWI[a] findings and statistical results in benign and malignant giant rectal and perirectal masses

	Benign masses	Malignant masses	p*
Mean ADC[b] value, ($\times10^{-3}$ mm^2/s)	1.49±0.39	0.84±0.17	<0.00001
Mean ADC ratio[c]	0.95±0.21	0.56±0.10	<0.00001

*Mann-Whitney U test was used and p< 0.05 was considered statistically significant.
[a]DWI: diffusion-weighted imaging, [b]ADC: apparent diffusion coefficient, [c]ADC ratio: ratio of ADC of mass to ADC of muscle

The degree of DWI is associated with the b value (9,10). At high b, a strong diffusion effect and diffusion restriction are achieved, and the noise signal ratio is reduced (9,10). Therefore, using the appropriate b value is important for image quality and accurate evaluation (9,10). Chen et al. (18) used 10 different b values ranging from 0 to 2000 s/mm^2 in the evaluation of rectal cancers by DWI. The most suitable b value combination was found to be 0 and 1000 s/mm^2 (18). In our study, b values of 0 and 1000 s/mm^2 were used.

In another study, the role of MRI in the differential diagnosis of postoperative rectal cancer recurrence (n=17) and benign lesion (n=8) was investigated (19). It was reported that malignant and benign lesions could be distinguished with high sensitivity (100%), specificity (91.7%) and accuracy (96.6%) rates with a threshold ADC value of 1.21×10^{-3} mm^2/s (19). In the dynamic contrast test, the time-intensity curve has also been reported to have a high accuracy rate (92%) in distinguishing between malignant and benign masses (19). No significant difference was found between the malignant (2.84±1.52) and benign (2.58±0.80) groups in terms of signal intensity changes in T2-weighted sequences (p>0.05) (19). In contrast, in our study, a significant difference was found between the benign and malignant groups in terms of T1- and T2- weighted signal intensities.

In 14 patients with <5 cm four rectal GISTs and >5 cm 10 rectal GISTs, Jiang et al. (20) observed that six of the GISTs were irregularly contoured and 11 showed heterogeneous enhancement on MRI and CT (20). Kim et al. (4) defined the MRI characteristics of rectal GISTs as eccentric mural masses with regular contour, calcification, necrosis or ulceration, that has hypointensity in T1-weighted sequences, iso-hyperintense signaling in T2-weighted sequences and intensely heterogeneous contrast enhancement. In our study, which included fewer rectal GISTs, all rectal GISTs had contours and signal characteristics were similar. However, the enhancement characteristics were heterogeneous but milder. It was thought that GISTs ≥5 cm in our study may be the cause of peripheral heterogeneous mild enhancement. In addition, the hypointense appearance of peripheral sections of rectal GISTs and heterogeneous hyperintense appearance of central sections of T2-weighted sequences was one of the striking findings of our study. However, in our study, low ADC values and ratios were also obtained in rectal GISTs.

There are some limitations of our study. One of them is the retrospective nature of the study with a small number of benign masses. The other is that qualitative and quantitative MRI findings were evaluated by a single radiologist.

Conclusion

The evaluation of specific MRI characteristics and ADC ratio measurements have an important role in the differential diagnosis of giant rectal and perirectal masses, and guide the planning of patient treatment.

Ethics Committee Approval: University of Health Sciences, Ümraniye Training and Research Hospital Ethics Committee of Clinical Studies, (decision no: 235, date: 23/01/2019).

Informed Consent: Written consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - F.K., Ö.D.; Concept - F.K., Ö.D.; Design - F.K., Ö.D.; Data Collection and/ or Processing - F.K., Ö.D.; Analysis and/or Interpretation - F.K., Ö.D.; Literature Search - F.K., Ö.D.; Writing Manuscript - F.K., Ö.D.

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Delayed Surgical Resection After Long-course Neoadjuvant Chemoradiotherapy in Rectal Cancer: Single Center Experience

Rektum Kanserinde Uzun Süreli Neoadjuvan Kemoradyoterapi Sonrası Gecikmiş Cerrahi Rezeksiyon: Tek Merkez Deneyimi

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ABSTRACT

Introduction: The aim of this study was to evaluate whether delayed rectal cancer surgery after long-course neoadjuvant concomitant chemoradiotherapy was effective on pathological complete response (pCR), disease-free survival (DFS), and overall survival (OS).

Methods: A total of 112 patients with rectal carcinoma diagnosed at the Radiation Oncology Clinic between 2011 and 2017 were retrospectively analyzed. We compared the outcomes of patients who were operated on greater than >9 weeks (delayed surgery) and less than <8 weeks (early surgery) after completion of neoadjuvant chemoradiotherapy.

Results: When we compared the delayed and early surgery groups, pCR rate was higher in the Delayed surgery group (18.2% vs. 5.2%, p=0.032). Tumor regression was found to be close to statistical significance in the delayed surgery group (p=0.050). The decrease in postoperative T stage was found to be statistically significant in the delayed surgery group (p=0.007). When the study was completed, the patient group who underwent delayed surgery had a longer life and this was statistically significant (p=0.044). The OS rate (p=0.004) and DFS rate (p=0.003) was statistically significant in the delayed surgery group.

Conclusion: Delaying surgery after neoadjuvant chemoradiotherapy increases the pCR rate, DFS and OS.

Keywords: Rectal cancer, delayed surgery, neoadjuvant long-course radiotherapy, chemotherapy

ÖZ

Amaç: Bu çalışmanın amacı uzun süreli neoadjuvan kemoradyoterapiden sonra gecikmiş rektal kanser cerrahisinin patolojik tam yanıt (pCR), hastalıksız sağkalım (DFS), genel sağkalım (OS) için etkili olup olmadığını değerlendirmektir.

Yöntemler: Retrospektif olarak, 2011-2017 yılları arasında Radyasyon Onkolojisi Kliniğine rektum karsinomu tanısı alan toplam 112 hastadan veri alındı. Neoadjuvan kemoradyoterapinin tamamlanmasından sonra >9 (9-12 hafta) haftadan uzun sürede ameliyat edilen ve <8 (6-8 hafta) haftadan kısa sürede ameliyat edilen hastaların sonuçlarını karşılaştırarak verilerimizi inceledik.

Bulgular: >9 hafta ve <8 hafta tedavi aralığını kıyasladığımızda, hastalarda pCR oranları >9 hafta sonra %5,2 vs %18,2 (p=0,032) daha yüksekti. Ameliyat sonrası >9 hafta içinde tümör regresyonu istatistiksel olarak anlamlılığa çok yakın bulundu (p=0,050). Ameliyat sonrası >9 hafta içinde postoperatif T evresinde azalma istatistiksel olarak anlamlı bulundu (p=0,007). Çalışma tamamlandığında, gecikmiş cerrahi uygulanan hasta grubu daha uzun ömürlü ve bu istatistiksel olarak anlamlı (p=0,044) idi. Gecikmiş cerrahi gurubunda genel OS (p=0,004) ve hastalıksız DFS (p=0,003) istatistiksel olarak anlamlı bulundu.

Sonuç: Neoadjuvan kemoradyoterapi sonrası gecikmiş cerrahi patolojik tam yanıt oranı, hastalıksız sağkalım ve genel sağkalımı artırır.

Anahtar Kelimeler: Rektum kanseri, gecikmiş cerrahi, neoadjuvan uzun süreli radyoterapi, kemoterapi

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Introduction

Rectal cancer makes up approximately one-fourth of large bowel cancers. Locally advanced rectal tumors are commonly treated with preoperative neoadjuvant concomitant chemoradiotherapy (nCCRT) and followed by total mesorectal excision (TME) (1). nCCRT is employed for locally advanced rectal cancer to downstage size of a tumor and facilitate subsequent R0 resection or sphincter-preserving surgery (SPS) (2,3). Since the results of the Lyons R90-01 study have been published, a 6 to 8-week interval from the completion of nCCRT to surgery has become standard practice (4). The effect of complete pathological complete response (pCR) on disease-free survival (DFS) and overall survival (OS) has not been clearly defined (5,6). In some clinical trials, 50-60% of patients are downsized after nCCRT with 8-20% of patients showing a pCR (7-9).

Our study aimed to analyze the effect of time interval from completion of nCCRT to surgery on oncologic parameters such as pCR, tumor downstaging, distant metastases, local recurrence, DFS and OS.

Methods

We evaluated 112 patients with locally advanced rectal cancer between 2011 and 2017 at İstanbul Training and Research Hospital. Patients were divided into two groups according to the interval after nCCRT to surgery: <8 week (group 1) and >9 week (group 2). The data were analyzed retrospectively.

The nCCRT and surgery range were initially 6-8 weeks. Since 2015, due to the increasing number of publications on the extension of this period, this period has been extended up to 9-12 weeks, thus ensuring organ protection in some patients. Although the onset times of our patients were different, we aimed to compare these two groups retrospectively. Eleven patients in group 2 had delayed surgery due to patient's preference and logistic reasons (9-12 weeks and they were in first group years patients). Three of these 11 patients had a complete pCR and only one patient died. Therefore, our follow-up period was almost the same between the two groups.

All patients included in our study were aged ≥18 years, had pathological diagnosis of rectal carcinoma by endoscopic biopsy, had tumors with T3/4 stage or N0/+ as demonstrated in pelvic magnetic resonance imaging (MRI). The tumor location of the patients before nCCRT was evaluated endoscopically. The first 5 cm was accepted as lower rectum and 5-10 cm was regarded as the middle rectum. All patients underwent blood tests, digital rectal examination, colonoscopy and biopsy, computed thorax tomography or 18-fluorodeoxyglucose positron emission tomography/computed tomography (18-FDG PET/CT), and pelvic MRI staging before nCCRT. Preoperative blood tests, colonoscopy and pelvic MRI were performed again. All patients received long-course radiotherapy and underwent TME after nCCRT. Patients were controlled every three months in the first two years and then every six months. The treatment interval was calculated from the end of the CRT to the date of surgery. OS was calculated from the date of diagnosis to the date of death or last follow-up, and DFS as the time to local recurrence or distant metastases.

Ethical Approval

All performed procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol of this retrospective study was approved by the İstanbul Training and Research Hospital Local Ethics Committee in our hospital (approval number: 1655, date: 18.01.2019).

Pathological Response Assessment

After surgery, samples were analyzed histopathologically by an experienced gastrointestinal system pathologist. Tumor regression grading (TRG) was assessed according to the Modified Ryan Classification. The TRGs were as follows: TRG0 was a pCR, no visible tumor cells; TRG1 was very few or small groups of tumor cells, TRG2 was a residual tumor in fibrotic tissue, TRG3 was residual tumor without any signs of destroyed tumor cells (10).

Radiotherapy/Chemotherapy Definitions

Bladder, femoral heads, small bowels and pelvic bones were contoured as critical organs. The gross tumor volume (GTV) was defined based on 18-FDG PET/CT and MRI images of the tumoral lesion in the rectum and the fixed lymph nodes. The clinical target volume (CTV) included mesorectum, presacral space, internal iliac lymph nodes and GTV. The planning target volume was CTV plus a 1 cm margin above the sacral promontory. 3D conformal RT (3DCRT) was applied with box technique. 6-18 MV photon energy was used. Preoperative long-course radiation therapy of 45 Gy/25 fractions was delivered to the pelvis, followed by a 5.4 Gy/3 fractions boost to a primary tumor using Varian DHX Linear accelerator machine. The median radiation dose applied was 45-50.4 Gy. During radiation therapy, all patients were examined weekly to examine toxicity. Chemotherapy was given concurrently with radiotherapy and the regimen continued with 5-fluorouracil (180 mg/m^2 per day for 7 d/w) intravenous infusion or orally 5-FU derived capecitabine (850 mg/m^2 twice a day) for five days of radiotherapy (11). Patients were referred to the medical oncology clinic for adjuvant treatment with postoperative pathological results.

Statistical Analysis

Statistical analysis for group comparisons was performed using Pearson's x^2 test, Mann-Whitney U test depending on the nature of the data. A p value less than 0.05 was considered statistically significant. Survival curves were constructed using Kaplan-Meier analyses. All statistical tests were performed using IBM SPSS version 18.0 (IBM Co., Armonk, NY, USA).

Results

Of the patients, 36 were female and 76 of them were male. The median age was 61 years and the tumors were most often located in the distal rectum. The follow-up period in group 1 was 54.6 months and was 67.2 months in group 2. Histopathology was mucinous adenocarcinoma in eight patients (14%) in group 1 and six patients (10.9%) in group 2. All other patients had adenocarcinoma. The general characteristics of all patients are shown in Table 1.

The localization was middle rectum in 30 patients (52.6%) in group 1 and in 25 patients (45.5%) in group 2. The tumor was located in the distal rectum in 27 patients (47.4%) in group 1 and in 30 patients (54.5%) in group 2. There was no statistically significant difference between the groups (p=0.448). Preoperative tumor grade, preoperative T/N stage, chemotherapy protocol, the type of surgery, the presence of lymphovascular invasion/perineural invasion were not statistically significant between the two groups. Postoperative N stage regression was not statistically significant (p=0.519).

Local recurrence was observed in four patients (3.5%) in group 1 and in one patient (0.9%) in group 2 (p=0.326). Distant metastasis was present

Table 1. General characteristics of all patients

		Minimum-maximum	Median	Median ± SD (n %)
Age		27.0-86.0	61.0	60.5±12.1
Gender	Female			36 (32.1%)
	Male			76 (67.9%)
Surgery time (week)		6.0-12.0	8.0	8.8±2.2
Follow-up (month)		6.0-60.0	19.5	26.5±16.6
Preoperative CEA		0.1-123.0	2.8	8.5±18.1
Preoperative CA19-9		0.6-417.0	8.9	22.7±52.6
Surgery	LAR			69 (61.6%)
	Miles			43 (38.4%)
	Middle			55 (49.1%)
Localization	Lower			57 (50.9%)
Preoperative stage	T3			87 (77.7%)
	T4			25 (22.3%)
Histology	Adenocarcinoma			98 (87.5%)
	Mucinous			14 (12.5%)
LVI	(-)			68 (69.4%)
	(+)			30 (30.6%)
PNI	(-)			70 (71.4%)
	(+)			28 (28.6%)
Tumor regression	Grade 0			13 (11.6%)
	Grade 1			27 (24.1%)
	Grade 2			55 (49.1%)
	Grade 3			17 (15.2%)
Complete response	Present			13 (11.6%)
	Absent			99 (88.4%)
Chemotherapy	5-FU intravenous			28 (25.0%)
	Capesitabine			84 (75.0%)
Locally recurrence (month)		9.0-60.0	12.0	22.0±21.4
Distant metastases (month)		4.0-38.0	12.0	12.9±7.4
Distant metastases	Absent			93 (83.0%)
	Present			19 (17.0%)
	Lung			11 (9.8%)
	Liver			6 (5.3%)
	Brain			1 (0.9%)
	Bone			1 (0.9%)
	Local recurrence			5 (4.4%)
	Exitus			23 (20.5%)
	Alive			89 (79.5%)

SD: standard deviation, LAR: lower anterior resection, LVI: lymphovascular invasion, PNI: perineural invasion, CEA: corcinoembryonic antigen

Table 2. Comparison of group 1 and group 2

	6-8 week Patient number (%)	9-12 week Patient number (%)	p
Gender			
Female (n=36, 32%)	17 (29.8)	19 (34.5)	0.593[a]
Male (n=76, 78%)	40 (70.2)	36 (65.5)	
Age			
Median (minimum-maximum-SD)	62 (27-86) 62.11±12.60	58 (31-80) 58.85±11.40	0.156[b]
Localization			
Middle (55)	30 (52.6)	25 (45.5)	0.448[a]
Distal (57)	27 (47.4)	30 (54.5)	
Histology			
Adenocarcinoma (98)	49 (86.0)	49 (89.1)	0.617[a]
Mucinous carcinoma (14)	8 (14.0)	6 (10.9)	
Preoperative stage			
T3N+ (85)	48 (84.2)	37 (67.3)	
T4N+ (22)	7 (12.3)	15 (27.3)	0.105[a]
T3/4N0 (5)	2 (3.5)	3 (5.5)	
Chemotherapy protocol			
5-FU intravenously (26)	14 (24.6)	12 (21.8)	0.731[a]
Capesitabine orally (86)	43 (75.4)	43 (78.2)	
Operation type			
LAR (69)	33 (57.9)	36 (65.5)	0.411[a]
Miles (43)	24 (42.1)	19 (34.5)	
Lymphovascular invasion			
Absent (69)	40 (70.2)	29 (52.7)	
Present (30)	14 (24.6)	16 (29.1)	0.060[a]
pCR (13)	3 (5.3)	10 (18.2)	
Perineural invasion			
Absent (70)	37 (64.9)	33 (61.8)	
Present (28)	17 (29.8)	11 (20)	0.076[a]
pCR (13)	3 (5.3)	10 (18.2)	
Postoperative T stage			
T0 (16)	5 (8.8)	11 (20)	
T1 (7)	7 (12.3)	-	
T2 (30)	20 (35.1)	10 (18.2)	0.007[a]
T3 (48)	21 (36.8)	27 (49.1)	
T4 (11)	4 (7)	7 (12.7)	
Postoperative N stage			
N0 (70)	36 (63.2)	34 (61.8)	
N1 (36)	18 (31.6)	18 (32.7)	0.989[a]
N2 (6)	3 (5.3)	3 (5.5)	
TRG			
TRG0 (complete response, 13)	3 (5.3)	10 (18.2)	
TRG1 (27)	11 (19.3)	16 (29.1)	0.050[a]
TRG2 (55)	34 (59.6)	21 (38.2)	
TRG3 (17)	9 (15.8)	8 (14.5)	
Response			
Partial response (99)	54 (94.7)	45 (81.8)	0.033[a]
Complete response (13)	3 (5.3)	10 (18.2)	

Table 2 contiuned

	6-8 week Patient number (%)	9-12 week Patient number (%)	p
Last situation Exitus (23) Alive (89)	 16 (28.1) 41 (71.9)	 7 (12.7) 48 (87.3)	0.044[a]
Distant metastases Absent (89) Present (19)	 43 (80.7) 11 (19.3)	 46 (85.5) 8 (14.5)	0.503[a]
Local recurrence Absent (108) Present (4)	 54 (94.7) 3 (5.3)	 54 (98.2) 1 (1.8)	0.326[a]
Overall survival Median (month)	54.62 (44.41±64.83) %95 CI	67.24 (55.73±78.75) %95 CI	0.004[c]
Disease free survival Median (month)	49.14 (38.62±59.65) %95 CI	61.19 (50.71±71.67) %95 CI	0.003[c]
Nausea Absent (97) Present (15)	 49 (86) 8 (14)	 48 (87.3) 7 (12.7)	0.839[a]
Diarrhea Absent (47) Present (65)	 25 (43.9) 32 (56.1)	 22 (40) 33 (60)	0.679[a]
Cystitis Absent (106) Present (6)	 54 (94.7) 3 (5.3)	 52 (94.5) 3 (5.5)	0.964[a]
Proctitis Absent (68) Present (44)	 36 (63.2) 21 (36.8)	 32 (5.2) 23 (41.8)	0.590[a]
Fatigue Absent (104) Present (8)	 52 (91.2) 5 (8.8)	 52 (94.5) 3 (5.5)	0.496[a]

[a]: chi-square, [b]: T-test [c]: Mann-Whitney U test, SD: standard deviation, pCR: pathological complete response, TRG: tumor regression grade, CI: confidence interval

in 11 patients (19.3%) in group 1 and in eight patients (14.5%) in group 2 (p=0.503). Distant metastasis and local recurrence were more common in group 1, but it did not reach statistical significance. Sixteen patients (28.1%) died in group 1 and seven patients (12.7%) died in group 2 (p=0.044).

The rate of SPS was 33.3% (n=9) in group 1 and 43.3% (n=13) in group 2. The decrease in postoperative T stage was higher in group 2 (p=0.007). TRGs were found to be almost significant between the two groups (p=0.050). pCR was significantly higher in group 2 (p=0.032). DFS during follow-up was 80.7% in group 1 and 85.5% in group 2 (p=0.003) (Figure 1). OS was 71.9% in group 1 and 87.3% in group 2 (p=0.004) (Figure 2). Comparison of general characteristics of group 1 and group 2 are shown Table 2.

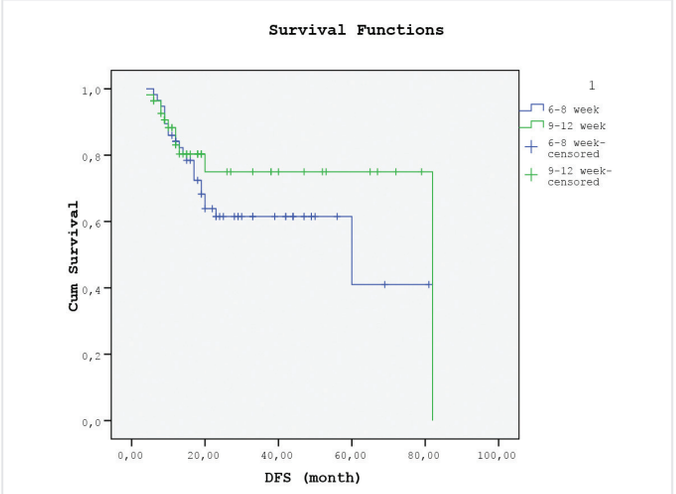

Figure 1. Disease-free survival time in both groups

Side Effects

Diarrhea was the most common side effect and was observed in 65 patients (58%) (p=0.679). Proctitis was observed in 44 patients (39.2%)

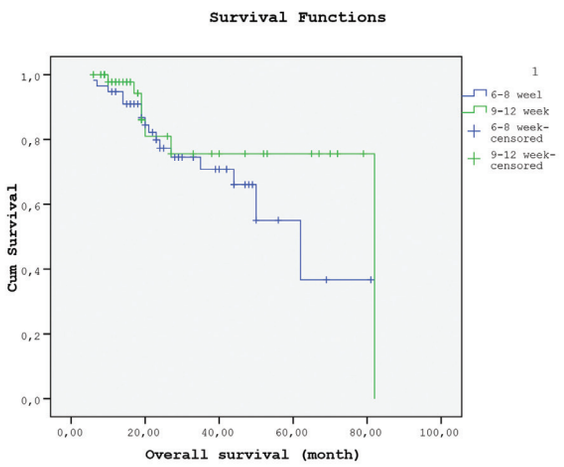

Figure 2. Overall survival time in both groups

patients (p=0.590). Nausea was observed in 15 patients (13.3%) (p=0.839), cystitis was reported in six patients (5.3%) (p=0.964) and fatigue was observed in eight patients (7.1%) (p=0.496). Side effects were similar in both groups and difference was not statistically significant.

Discussion

Rectal cancer makes up approximately one-fourth of colon cancers. Treatment includes radiation therapy, chemotherapy and surgery. nCCRT is generally used in patients with clinical locally advanced rectal cancers. In the literature, long-term results of nCCRT and patients who achieved a pCR after curative surgery have been reported (12,13). The Lyon R90-01 trial showed that a longer interval of 6 to 8 weeks between preoperative irradiation and surgery, compared with two weeks, increased tumor down-staging (26% versus 10%), but did not affect 5-year survival rates (14).

Mihmanlı et al. (15) showed that a longer interval before surgery was associated with high pCR rates, lymph nodal downstaging, decreased rate of TRG poor response and improved DFS and OS. In our study, pCR rates were significantly higher in group 2 (p=0.033), with a rate of 18.2%. Also, in our study, TRG response rate was found to be near significant (p=0.050) and DFS was found to be significant (p=0.003). The decrease in T stage was statistically significant in group 2 compared to the total number of patients (p=0.007). In our study, we observed statistical significance between the two groups in terms of OS and DFS. However, local recurrence and distant metastasis were not statistically significant in both groups. The regression in TRG was near significant between the two groups (p=0.050). In subgroup analysis, we found that local recurrence and distant metastasis were observed in patients with no regression in TRG. Long surgery time increases the number of patients who can respond fully pathologically. We believe that the pathology and molecular pattern of the tumor causes TRG to remain without regression. The number of patients in this group was almost equal in both groups. We believe that the excess in the group positively affects DFS and OS, which the decline in TRG will increase as the number of patients undergoing delayed surgery increases, and that this will reduce local recurrence and distant metastasis and contribute positively to OS and DFS.

Increased chance of SPS with nCCRT has been reported. Randomized trials have shown that nCCRT increases the chance of achieving SPS by approximately 60% (3,4,16). In our study, there were 27 patients (47.4%) in the lower rectum in group 1 and 30 patients (54.5%) in group 2. SPS was performed in 10 patients (37%) in group 1 and 14 patients (46.6%) in group 2. In conclusion, in the absence of nCCRT, SPS could be performed in 42.1% of patients who were planned to undergo APR. This shows lower rates than the literature. We think that the reason for this is that T and N stages of our lower rectum tumors were higher than the others.

In a study by Tulchinsky et al. (16), patients who were operated seven weeks after surgery showed a statistically significant increase in the complete response rate compared to those who were operated seven weeks before surgery. They also showed better DFS rates in patients who were operated seven weeks after CRT. However, contribution to OS has not to be shown. In our study, pCR rates, DFS and also OS were found to be significantly higher in group 2 (p=0.033, p=0.003, p=0.004, respectively).

De Campos-Lobato et al. (17) reported that more than 8 weeks interval between completion of CRT and surgical procedure was associated with significant improvement in pCR rate (30.8% vs. 16.5%, respectively, p=0.03). In the same study, they reported decreased 3-year local recurrence rate (1.2% vs. 10.5%, respectively, p=0.04). In our study, no statistically significant difference was found between two groups in terms of local recurrence (p=0.326).

Patel et al. (18) have shown that patients with <4 cm tumors were less likely to have pCR. In our study, the tumor was found to be T4 stage in three patients (23%) and T3 stage in ten patients (77%), and the mean tumor diameter was 5.4 cm in pCR patients.

In rectal cancer, the response to nCCRT is different among patients. While there is a partial response in approximately 40% of patients, pCR is achieved after surgery in 8-20% of patients. Some of the tumors (~20%) exhibit resistance to nCCRT, demonstrating either progression or only minimal regression or stable disease (19-22). In our study, similar to the literature, 11 patients (19.3%) in group 1 and nine patients (16.4%) in group 2 did not downstage (p=0.685).

In pathological specimens, tumor differentiation, mucinous tumor histology and macroscopic ulceration are related to the low response rate to nCCRT (23-27). In our study, pCR was not observed in any patient with mucinous histology. One (7.1%) of 14 patients had local recurrence and three patients (21.4%) had lung metastasis with mucinous histology. In these patients, two (14.2%) had a tumor downstaging, three (21.4%) remained at the same stage, and nine (64.2%) did not downstage. No pCR was observed in mucinous carcinomas.

We did not evaluate surgical complications in our study because we focused on predicting the effects of prolonged surgical intervals on pCR, DFS and OS.

Conclusion

nCCRT and curative surgery remain the standard treatment for patients with locally advanced rectal cancer. Delaying surgery by 9 to 12 weeks after the end of nCCRT increases pCR rate. Moreover, it reduces the T

stage of the tumor and decreases the TRG. Our findings seem to support the benefit of a longer time interval between chemoradiotherapy and surgery in rectal cancer in terms of pCR. There was no local recurrence or distant metastasis or death in any patient with a pCR. These results suggest that longer preoperative intervals support ongoing tumor necrosis and regression. Based on this, we think that OS and DFS reach statistical significance.

Ethics Committee Approval: The protocol of this retrospective study was approved by the İstanbul Training and Research Hospital Local Ethics Committee in our hospital (approval number: 1655, date: 18.01.2019).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - A.H.Y.; Concept - Ö.M., N.D.; Design - Ö.M., B.İ., H.B.; Data Collection and/or Processing E.A., A.H.Y.; Analysis and/or Interpretation - N.D., A.H.Y.; Literature Search - B.İ., E.A.; Writing Manuscript - Ö.M.

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Baseline SUV Range for Liver and Blood Pool in Patients Undergoing F-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

F-18 FDG PET/BT Çekilen Hastalarda Karaciğer ve Kan Havuzu için Bazal SUV Aralığı

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ABSTRACT

Introduction: The aim of the study was to define the baseline SUV_{max} range in the liver and blood pool of patients undergoing fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) imaging.

Methods: Five hundred and thirty-one patients (264 females, 267 males; mean age: 59.6±13.4 years) who were admitted to our department for PET/CT imaging before treatment were included in the study. Patient preparation, acquisition parameters and reconstruction protocols were standardized for all patients prior to PET/CT imaging. The mean serum glucose levels and mean age of the patients were calculated. These patients were divided into 10 groups as esophagus, stomach, colon, rectum, larynx, lung, breast, endometrium, ovarian cancers and lymphoma. 2D region of interests were plotted to calculate the mean SUV values in the right lobe of the liver and the aortic arch for the blood pool.

Results: Normal Gaussian distributions of mean SUV changes for liver and blood pool were obtained. Mean SUV_{max} and SUV_{mean} values for liver were 2.73±0.22 and 2.34±0.16, respectively, and 1.80±0.2 and 1.57±0.14 for blood pool, respectively.

Conclusion: It was concluded that the obtained SUV ranges may provide ease of application in the clinic in evaluating qualitative tumor response and comparing tumor/background ratios in cancer patients.

Keywords: PET/CT, SUV measurement, tumor background ratio

ÖZ

Giriş: Çalışmanın amacı, florodeoksiglukoz-pozitron emisyon tomografi/bilgisayarlı tomografi görüntüleme (FDG-PET/BT) yapılan hastaların karaciğer ve kan havuzundaki bazal SUV_{maks} aralığının tanımlanmasıdır.

Yöntemler: Bölümümüze tedavi öncesi PET/BT görüntüleme için gelen 531 hasta (264 kadın, 267 erkek; yaş ortalaması 59,6±13,4 yıl) çalışmaya dahil edildi. Tüm hastalar için PET/BT görüntüleme öncesi hasta hazırlığı, aküzisyon parametreleri ve rekonstrüksiyon protokolleri standardize edildi. Hastaların ortalama serum glukoz seviyeleri ve yaş ortalamaları hesaplandı. Bu hastalar özofagus, mide, kolon, rektum, larinks, akciğer, meme, lenfoma, endometrium ve over kanserleri olmak üzere 10 gruba ayrıldı. Karaciğerin sağ lobuna ve kan havuzu için aort kavisine ortalama SUV değerlerinin hesaplanabilmesi için 2 boyutlu ilgi alanı bölgeleri çizildi.

Bulgular: Hastaların gruplar arası karaciğer ve kan havuzu için ortalama SUV değişimlerinin normal Gaussian dağılımları elde edildi. Ortalama SUV_{maks} ve SUV_{ort} değerleri karaciğer için sırasıyla 2,73±0,22, 2,34±0,16; kan havuzu için 1,80±0,2, 1,57±0,14 olarak hesaplandı.

Sonuç: Elde edilen SUV aralıklarının kanserli olgularda kalitatif tümör cevabı değerlendirmede ve tümör/background oranlarını kıyaslamada klinikte uygulama kolaylığı sağlayabileceği kanaatine varıldı.

Anahtar Kelimeler: PET/BT, SUV ölçümü, tümör background oranı

Introductıon

F-18 fluorodeoxyglucose positron emission tomography/computed tomography (F-18 FDG PET/CT) is increasingly used in tumor diagnosis, staging, treatment response evaluation, and radiotherapy planning. Combined PET/CT devices provide both metabolic information from F-18 FDG PET and anatomical information from CT in a single imaging (1).

The most important difference of PET/CT from radiological imaging methods such as direct radiographs and CT, which provides structural information about various diseases, is that it provides functional information. In functional imaging, it is possible to monitor tissue perfusion, glucose metabolism and receptor activities by using appropriate methods and imaging agents (2).

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FDG studies constitute the majority of PET applications in the world. FDG, just like D-glucose, passes through the cell membrane and phosphorylated to the FDG-6-phosphate by the enzyme hexokinase. However, after this step, it cannot be catabolized and accumulates in the cell. Tissues with increased glucose utilization and metabolism appear as hypermetabolic foci in PET images with higher concentrations than normal tissues, and tissues with reduced glucose metabolism appear as hypometabolic foci in PET images with lower concentrations than normal tissues.

FDG, which is transported into the cell via the glucose transporter proteins from the circulation, shows a biodistribution quite similar to glucose in the body. The brain holds very intense FDG due to the use of high amounts of glucose in the gray cortex. FDG uptake in the heart changes in relation to the patient's fasting. FDG uptake is more pronounced as glucose use increases in satiety, and it decreases in long-term hunger. The liver maintains a lower density and homogeneous FDG. Gastric and intestinal involvement varies according to the patient. Bone and muscles maintain high FDG in case of activation.

One of the most important features of PET is the ability to digitize the results. The most commonly used term is the standardized uptake value (SUV). It is particularly suitable for monitoring response to treatment. It is a semiquantitative parameter. If the dose is evenly distributed throughout the body, the SUV should be approximately 1 everywhere. The SUV is therefore a relative uptake measurement, a unitless value and reflects the ratio. SUV may vary with factors such as patient imaging time, partial volume effects, reconstruction parameters, and attenuation correction methods. The SUV is obtained by dividing the mean activity (mCi/mL) in a region of interest (ROI) to the injected dose (mCi/kg) (2,3).

Foci with non-physiological and increased FDG uptake compared to background activity are evaluated in the interpretation of images. SUV> 2.5 may indicate that the lesion is hypermetabolic. These hypermetabolic foci do not always mean that there is a tumoral lesion (3). Generally, lesions with higher involvement than blood pool (BP) suggest malignancy. Semiquantitative calculation of tumor metabolism is based on the ratio of F18-FDG uptake to lesion involvement in reference sites such as BP, mediastinum, liver and cerebellum. These are the most commonly used tissues (3-5).

The aim of this study was to define the F-18 FDG uptake range for BP and liver from these reference regions before treatment of patients with different diagnoses.

Methods

A total of 531 patients (264 females and 267 males) who were admitted Nuclear medicine department for PET/CT imaging before treatment were included in the study. Ethics committee approval was not received because our study was a retrospective study. Written consent was obtained from all patients. Patients were divided into 10 groups according to the diagnosis. Patient groups and number of patients are given in Table 1. Age (years), weight (kg), height (cm) and serum glucose levels (mg/dL) of all patients were recorded. Body mass index (BMI) values were calculated (Table 2). Fasting blood glucose levels were measured before F-18 FDG injection following a 5-hour fasting and 4.2 MBq/kg F-18 FDG injection was performed in patients with a glucose level below 200 mg/dL. After the injection, the patients were taken to special waiting rooms to rest. After an average of 60 minutes, the patient was positioned in the supine position with the arms up from the vertex to the proximal thigh, and low-dose CT (120 kVp and 80 mAs) and PET (Philips True Flight Select model) images were obtained. CT data were used for attenuation correction. Patient preparation, acquisition protocols and reconstruction parameters were standardized prior to PET/CT imaging for all patients. OSEM reconstruction algorithm was used with reconstruction parameters of 3 iterations and 33 subsets for

Table 1. Number of patients by diagnosis

Group	Diagnosis	Patient number
1	Esophagus cancer	50
2	Stomach cancer	51
3	Colon cancer	49
4	Rectum cancer	54
5	Larynx cancer	55
6	Over cancer	50
7	Endometrium cancer	56
8	Lung cancer	57
9	Breast cancer	56
10	Lymphoma	53

Table 2. Age, fasting blood glucose, injection dose and body mass index according to patient groups

Group	Age (years)	Fasting blood glucose (mg/dL)	Activity (MBq)	Body mass index
1	61±13.4	96±20.3	233±33	23±5.3
2	60.1±13.1	96.0±17.2	244.2±22.2	24.2±5.3
3	61.9±12.1	105±27.1	246.1±23.7	26.2±4.8
4	62.5±13.8	103.3±18.9	241.6±25.2	27.1±5.5
5	64.9±10.2	97.1±20.3	242.7±28.5	25.3±5.8
6	64.2±9.6	101.5±25.6	235.7±22.9	29.8±6.3
7	52.9±11.3	99±16.1	250.5±35.9	32.1±6.3
8	61.2±12.1	101.2±24.5	262.7±38.2	26.8±5.8
9	57.1±13.6	101.5±20	252.7±31.8	31±6.8
10	50±16.9	99±22	247.9±36.3	27.1±5.6

MBq: megabecquerel

all patients. The lesion and high activity ROIs were removed from the axial fusion images obtained after imaging and 2D ROIs were plotted to calculate the average SUV in the right lobe of the liver (Figure 1) and aortic arch for BP (Figures 1 and 2). SUV_{max} and SUV_{mean} in the area related to the plotted ROIs were calculated and recorded.

Statistical Analysis

The data obtained were recorded into SPSS 15.0 data analysis program, and normal Gaussian distributions of mean SUV changes between the groups for BP and liver were obtained.

Results

SUV changes for BP and liver between groups were calculated and shown in Table 3. According to the results, mean SUV_{max} and SUV_{mean} of all patients were 2.74±0.43 and 2.34±0.41 for liver, respectively, and 1.82±0.37 and 1.58±0.33 for BP, respectively. The SUVs obtained separately for each group are shown in Table 3 and the graphs are shown in detail in Figure 3. Using SPSS 15.0, ANOVA test was performed to determine statistical difference between mean SUVs for liver and BP between the groups. Significant differences were found between the groups according to statistical results. The highest SUV was found in patients with endometrial carcinoma (SUV_{max}: 3.2±0.33 and SUV_{mean}: 2.7±0.33 for liver; SUV_{max}: 2.22±0.39 and SUV_{mean}: 1.86±0.34 for BP). Liver SUV_{max}/BP SUV_{max} ratios of all groups were determined and this ratio was calculated as an average of 1.5 (Table 3). Table 4 shows the p values expressing inter-group significance.

Discussion

PET/CT is a highly useful hybrid modality for imaging, tumor diagnosis, staging, and evaluation of treatment response. Its most important advantage is its ability to provide quantitative results that provide the clinician with the most benefit in reporting. The most commonly used quantitative parameter is the SUV. It is frequently used especially in the evaluation of response to treatment. For these reasons, it is clinically useful to know the SUV variation range in F-18 FDG PET/CT imaging. In this study, a range was created for SUV_{max} and mean values of the two areas (liver and BP), which are considered as reference.

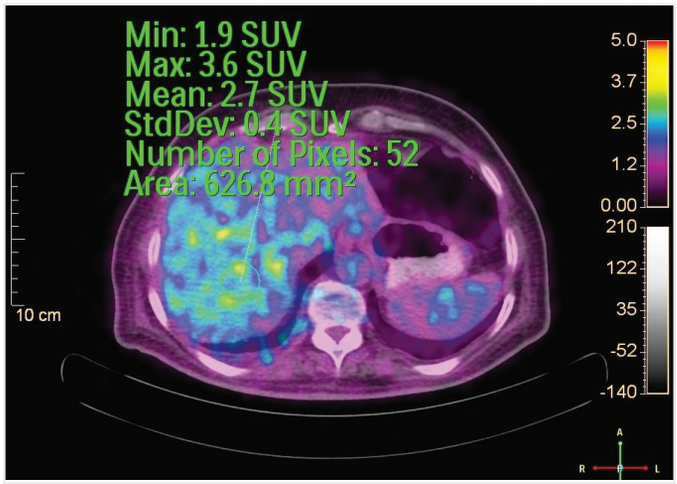

Figure 1. 2D ROI plotted on right lobe of liver

Min: minimum, max: maximum, SUV: standard uptake value, StdDev: standard deviation, ROI: region of interest

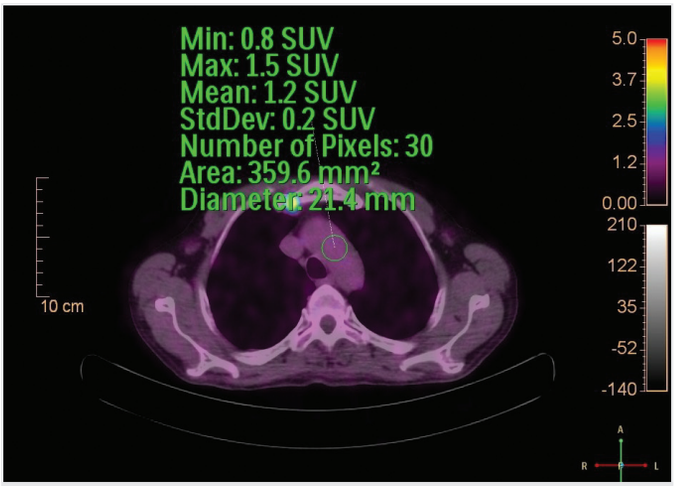

Figure 2. 2D ROI plotted on aortic arch

Min: minimum, max: maximum, SUV: standard uptake value, StdDev: standard deviation, ROI: region of interest

Table 3. Standard uptake value changes for liver and blood pool

Diagnosis	Liver SUV_{max}	Liver SUV_{mean}	BP SUV_{max}	BP SUV_{mean}	Liver/BP SUV_{max}
Esophagus cancer	2.55±0.3	2.30±0.37	1.70±0.27	1.54±0.24	1.50
Stomach cancer	2.7±0.3	2.27±0.33	1.69±0.27	1.48±0.26	1.59
Colon cancer	2.62±0.35	2.26±0.30	1.65±0.27	1.44±0.23	1.58
Rectum cancer	2.67±0.41	2.36±0.33	1.77±0.26	1.56±0.29	1.50
Larynx cancer	2.89±0.48	2.43±0.46	1.97±0.39	1.66±0.37	1.47
Over cancer	2.8±0.47	2.43±0.5	1.84±0.35	1.67±0.40	1.52
Endometrium cancer	3.2±0.33	2.7±0.33	2.22±0.39	1.86±0.34	1.44
Lung cancer	2.6±0.37	2.2±0.31	1.77±0.3	1.48±0.28	1.47
Breast cancer	2.82±0.39	2.43±0.36	1.94±0.30	1.67±0.30	1.45
Lymphoma	2.45±0.4	2.0±0.40	1.58±0.34	1.38±0.32	1.55
Mean	2.74±0.43	2.34±0.41	1.82±0.37	1.58±0.33	1.50

SUV: standard uptake value, BP: blood pool

Table 4. Intergroup p values

Malignancy	Esophagus	Stomach	Colon	Rectum	Larynx	Over	Endometrium	Lung	Breast	Lymphoma
Esophagus	-	0.6	0.07	0.8	0.00	0.04	0.00	0.9	0.01	0.95
Stomach	0.6	-	0.9	1	0.2	0.9	0.00	0.99	0.84	0.03
Colon	0.99	0.98	-	0.99	0.011	0.33	0.00	1	0.16	0.49
Rectum	0.84	1	0.99	-	0.09	0.8	0.00	1	0.5	0.09
Larynx	0.00	0.26	0.01	0.09	-	0.97	0.00	0.01	0.9	0.00
Over	0.04	0.9	0.3	0.8	0.9	-	0.00	0.38	1	0.00
Endometrium	0.00	0.00	0.00	0.00	0.00	0.00	-	0.00	0.00	0.00
Lung	0.99	0.99	1	1	0.012	0.38	0.00	-	0.18	0.33
Breast	0.01	0.8	0.16	0.57	0.99	1	0.00	0.18	-	0.00
Lymphoma	0.95	0.03	0.49	0.09	0.00	0.00	0.00	0.33	0.00	-

P<0.05 was considered significant

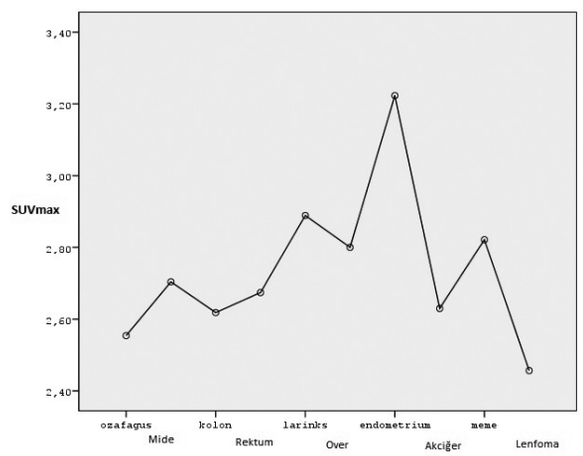

Figure 3. Mean SUV_{max} measurements of ROIs plotted on the right lobe of liver according to diagnosis

SUV: standard uptake value, ROI: region of interest

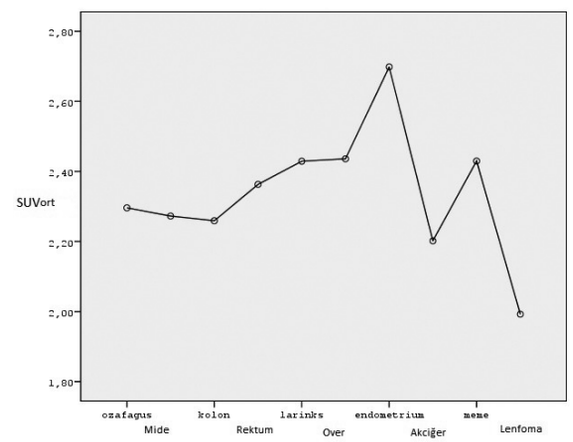

Figure 4. Mean SUV_{mean} measurements of ROIs plotted on the right lobe of liver according to diagnosis

SUV: standard uptake value, ROI: region of interest

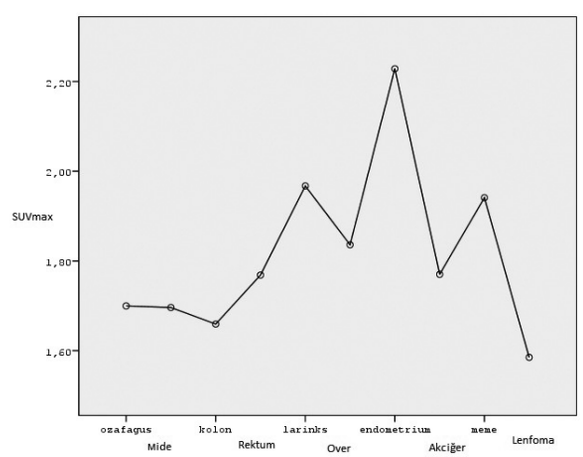

Figure 5. Mean SUV_{max} measurements of ROIs plotted on aortic arch according to diagnosis

SUV: standard uptake value, ROI: region of interest

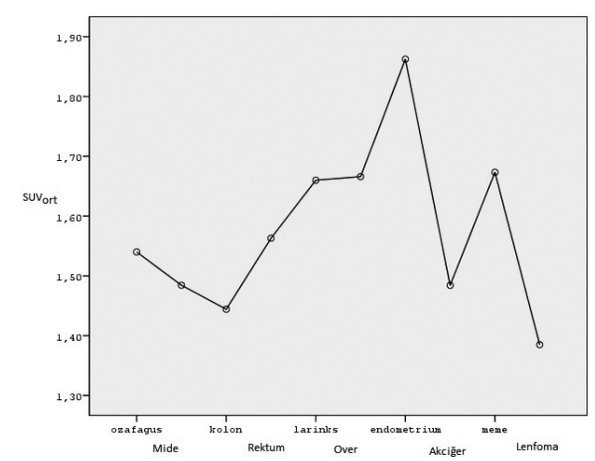

Figure 6. Mean SUV_{mean} measurements of ROIs plotted on aortic arch according to diagnosis

SUV: standard uptake value, ROI: region of interest

The SUV varies depending on many factors. Imaging time, patient's BMI, reconstruction parameters and resolution of the device are among these (2,3,6-8). Numerous studies have been conducted on the effects of imaging time on SUV (9). In a study by Boellaard et al. (10) in 2004, they showed that many technical factors such as image reconstruction parameters and ROI might have a significant effect on SUV results. Another study evaluated SUV variability and the effect of various SUV measurements on treatment response in the event of repeated imaging (11). In a multicenter study conducted by Westerterp et al. (12), they evaluated FDG-PET studies by focusing on the inter-center methodological variability and showed the need for standardization of FDG-PET between centers. Some physiological factors affecting SUV include plasma glucose level during FDG-PET scan, FDG plasma clearance, scan period and patient movement. Since FDG uptake is time dependent, the time interval between FDG administration and PET scan will also affect the SUV. Therefore, it increases with the prolongation of the time to imaging after FDG injection. In our study, patients were randomized in order to prevent the difference that would occur due to the time elapsed after the injection (2).

The SUV is a numerical parameter that helps visualization in the diagnosis of oncologic patients and especially in evaluating response to treatment. In our study, we determined the normal range of SUV according to patient diagnoses. For this purpose, we evaluated two reference areas. In the study conducted in 531 patients, the mean SUV_{max} was 2.7±0.2 for liver and 1.8±0.2 for BP. When the patients were grouped according to their diagnosis, statistically significant differences were found between the SUV_{max} and SUV_{mean}. There was a linear correlation between liver SUV changes and BP SUV changes. SUV ratios of reference areas were 1.50±0.05 in all patients. According to their diagnosis, the SUV_{max} and SUV_{mean} range of the patients were determined. Liver and BP SUV changes of patients with endometrial carcinoma were significantly different between all other groups (p=0.00). However, the ratio did not change since the rate of BP SUV changes was also high.

When SUV changes were examined, a statistical variation was found for liver and BP in patients with different diagnoses. This variation constitutes a physiological limit. This baseline range was defined in the study. In a similar study by Boktor et al. (13), a variation range was also defined. In this study, SUV changes with recurrent PET/CT scans were evaluated.

Knowing baseline SUV variations of patients prior to treatment makes an important contribution in determining pathological F-18 FDG involvement areas and in evaluating tumor response.

Conclusion

SUV measurements are currently the most appropriate method for the quantitative assessment of changes in metabolic activity. However, it is important to understand the limitations of these measurements and to minimize the effects of variables that can be controlled. It was concluded that the obtained SUV ranges might provide ease of application in the clinic in the evaluation of quantitative tumor response and comparison of tumor/background ratios in cancer patients.

Ethics Committee Approval: Retrospective study.

Informed Consent: Written consent was obtained from the patients themselves.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - Y.P., D.G.; Concept - Y.P.; Design - Y.P.; Data Collection and/ or Processing - Y.P., D.G.; Analysis and/or Interpretation - Y.P., D.G., G.G., E.S.; Literature Search - Y.P.; Writing Manuscript - Y.P., G.M., G.G., E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Effect of Transarterial Y-90 Microsphere Treatment on Biochemical Parameters in Liver Tumors

Karaciğer Tümörlerinde Transarteriyel Y-90 Mikroküre Tedavisinin Biyokimyasal Parametreler Üzerine Etkisi

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ABSTRACT

Introduction: The aim of this study was to evaluate the effect of yttrium-90 (Y-90) microsphere transarterial radioembolization (TARE) treatment on early and late biochemical parameters and to determine the appropriate and effective follow-up schedule in the patients and to determine the biochemical parameters to be considered.

Methods: A total of 106 patients with histopathologically verified primary or metastatic unresectable liver tumors that were treated with TARE at a single institution between 2016-2018 were retrospectively scanned from database. Of these patients, 27 patients (18 male and 9 female patients; mean age: 61.5±10.5 years, range: 40-77 years) were included in the study. It was investigated whether there was a significant difference between the biochemical parameters just before the treatment, on the 10th day and 3 months after the treatment.

Results: Statistically significant difference was observed only between pre-treatment albumin (albumin 1) and 10th day albumin (albumin 2), and between pre-treatment albumin (albumin 1) and 3rd month albumin (albumin 3) levels ($p<0.05$). There was no statistically significant difference between other biochemical parameters ($p>0.05$).

Conclusion: Albumin value was the most sensitive biochemical parameter in TARE treatment with Y-90 microsphere. It is of great importance that albumin value is frequently followed carefully in these patients.

Keywords: Y-90 microsphere, radio-embolization, side effect, liver

ÖZ

Amaç: Yitriyum-90 (Y-90) mikroküre ile transarteriyel radyoembolizasyon (TARE) tedavisinin erken ve geç biyokimyasal parametreler üzerine etkisinin araştırılarak tedavi edilen hastalarda uygun ve etkili takip planının yapılması ve özellikle dikkat edilmesi gereken biyokimyasal parametrelerin belirlenmesi amaçlanmıştır.

Yöntemler: Yerel veri tabanınından tek merkezde 2016-2018 yılları arasında primer veya metastatik inoperabl karaciğer tümörü histopatolojik olarak kanıtlanmış toplam 106 hastaya TARE tedavisi uygulandığı saptandı. Bu hastaların 27 tanesinin (18 erkek, 9 kadın; ortalama yaş: 61,5±10,5 yıl, aralık: 40-77 yıl) tedavi öncesi, erken ve geç tedavi sonrası tüm biyokimyasal parametrelerine ulaşılarak çalışmaya dahil edildi. Tedaviden hemen önce, tedavi sonrası 10. gün ve 3. ay biyokimyasal parametreler arasında anlamlı farklılık olup olmadığı araştırıldı.

Bulgular: İstatistiksel anlamlı farklılık sadece tedavi öncesi albümin (albümin 1) ile tedavi sonrası 10. gün takip albümin (albümin 2) değerleri ile tedavi öncesi albümin (albümin 1) ile tedavi sonrası 3. ay takip albümin (albümin 3) değerleri arasında saptandı ($p<0,05$). Bakılan diğer biyokimyasal parametreler arasında ise istatistiksel herhangi bir anlamlı fark saptanamadı ($p>0,05$).

Sonuç: Y-90 mikroküre ile TARE tedavisinde en hassas biyokimyasal parametrenin albümin değeri olduğu saptanmıştır. Tedavi uygulanan hastalarda albümin değeri takiplerinin sıklıkla ve dikkatle takibi büyük önem taşımaktadır.

Anahtar Kelimeler: Y-90 mikrosfer, radio-embolizasyon, yan etki, karaciğer

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Introduction

Liver cancer, including primary hepatocellular carcinoma and intrahepatic cholangiocarcinoma (comprising 10-15% of cases) as well as other rare types, is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death worldwide in 2018, with about 841.000 new cases and 782.000 deaths annually (1). In addition, liver is a frequent site of metastasis for many common malignancies such as breast and colon (2-4). The prognosis of unresectable liver cancer is poor (5). Treatment options include chemotherapy, transarterial chemoembolization, regional radiotherapy, radiofrequency ablation, transarterial radioembolization (TARE) and transplantation (5).

In recent years, TARE with yttrium-90 (Y-90) microspheres has become a safe treatment option for unresectable primary and metastatic liver malignancies (6-9). It may also be preferred as a bridge prior to resection, radiofrequency ablation and liver transplantation (7). TARE may be helpful in the management of advanced liver malignancies (10-13). Its palliative role through tumor necrosis and delaying progression has also been shown (6).

TARE is an internal, local, highly selective radiation therapy that has minor embolization effects (14). This treatment modality has less side effects and complications when compared to other local and systemic therapies of liver malignancies with the help of different arterial access to tumor tissue (6,14). In order to decide TARE treatment, complete blood count and biochemical tests including liver and renal function (albumin, total bilirubin, aspartate amino transferase, alanine amino transferase, blood urea nitrogen and creatinine) should be analyzed. Biochemical tests, clinical status of patients and possible side effects should be checked regularly after treatment (14). The most frequent side effects of the treatment occur immediately after treatment and they usually do not need further treatment. On the other hand, rare serious side effects and complications can be observed mostly 3 months following TARE (15,16).

The aim of this study was to evaluate the early and late effects of TARE treatment on biochemical parameters and to determine the appropriate follow-up schedule.

Methods

Patient Population and Data Collection

The study protocol was approved by the İstanbul Training and Research Hospital Local Ethics Committee as a retrospective study (decision no: 1584, date: 21.12.2018). A total of 106 patients with histopathologically verified primary or metastatic unresectable liver tumors that were treated with TARE at a single institution for 2 years were identified from our database. Medical records of the patients were scanned to collect clinicopathological and biochemical results. Patients with previous TARE treatment, patients with previous abnormal biochemical tests and patients with a follow-up of less than 6 months were excluded from the study. Twenty-seven patients (18 male, 9 female; mean age: 61.5±10.5 years, range: 40-77 years) with available pre-treatment and 3 months follow-up biochemical tests were included in the current study. The study population included 10 patients with primary hepatic malignancy (hepatocellular carcinoma) and 17 patients with hepatic metastasis (12 colorectal cancers, two neuroendocrine tumors, one ovarian carcinoma, one breast cancer and one malignant melanoma).

Neutrophil count (normal range: 34-71.1 x10^9/L), C-reactive protein (CRP) (normal range: 0-5 mg/L), aspartate aminotransferase (AST) (normal range: 0-35 IU/L), alanine aminotransferase (ALT) (normal range: 0-35 IU/L), albumin (normal range: 3.5-5.2 g/dL), total bilirubin (normal range: 0.3-1.2 mg/dL), direct bilirubin (normal range: 0-0.2 mg/dL), tumor markers such as alpha-fetoprotein (normal range: 0-9 µg/L), carcinoembryonic antigen (normal range: 0-3 U/mL), Ca-15-3 (normal range: 0-31.3 U/mL) and Ca-125 (normal range: 0-35 U/mL) were measured before the day of treatment. On the 10th day of follow-up, neutrophil count, CRP, AST, ALT, albumin, total and direct bilirubin levels were noted. At the 3rd month of the treatment, all parameters evaluated during pretreatment tests were re-recorded.İstanbul Training and Research Hospital, Clinical Research Ethics Committee (decision no: 1584, date: 21.12.2018).

Technical Information

Before treatment, baseline F-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) imaging (Figure 1) and magnetic resonance imaging were performed. Also, all patients underwent liver angiography with technetium-99m (Tc-99m)-labeled micro-aggregated albumin (MAA) scintigraphy to determine aberrant vasculature and also to calculate the percentage of pulmonary shunting (17). The total volume of the liver and the tumor area were determined using Tc-99m MAA single PET/CT scan (4). Whole liver dose, tumor dose and healthy injected liver dose were all calculated by using the medical internal radiation dose formula (8,18). For both Tc-99m MAA scintigraphy and also for TARE treatment, the femoral artery route was preferred to reach the right and/or left hepatic artery. The patients were discharged home on the following day of the treatment and were seen every 10 days for one month and then regularly every month to monitor side

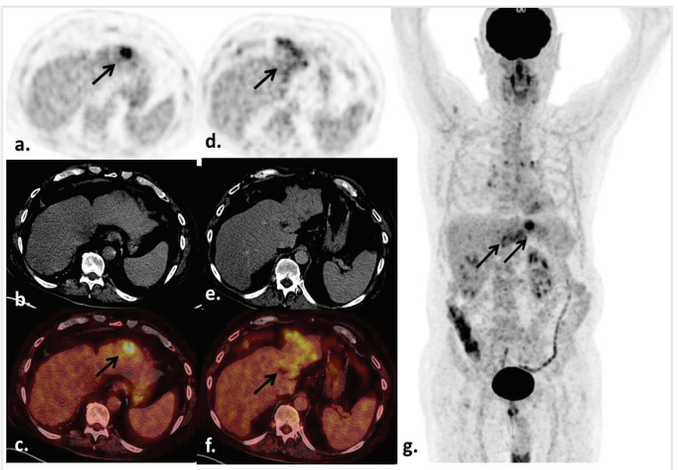

Figure 1. Pretreatment F-18 FDG PET/CT images of a 57-year-old male patient with hepatocellular carcinoma showed high FDG uptake in the left lobe of the liver extending along the portal vein without any distant metastasis: Axial PET (a), CT (b), fusion (c) and MIP images (d) (arrows)

FDG: fluorodeoxyglucose, PET: positron emission tomography, CT: computed tomography, MIP: maximum intensity projection

effects, complications, disease burden, and also for further treatment requirements (4).

Statistical Analysis

All statistical analyses were performed using SPSS software (Version 20.0; SPSS Inc., New York, NY) with a value of $p<0.05$ considered to be statistically significant. Paired t-test was used to compare pretreatment and 10th day early post-treatment and also 3rd month post-treatment biochemical parameters.

Results

Between August 2016 and September 2018, 106 TARE procedures were performed in our institution. A total of 27 TARE procedures in 27 patients, who met the inclusion criteria, were included in the current study. Table 1 lists the descriptive analysis of the biochemical tests just before the treatment, on the 10th day of follow-up and at 3 months of the follow up.

The patient population was heterogeneous with different previous treatment histories including chemotherapy. The majority of patients received treatment to the right lobe (n=22; 81.5%) and 18.5% received treatment only to the left lobe (n=5). The most common side effect following treatment was post-embolization syndrome with fatigue, nausea, low-grade fever, and right upper quadrant pain. No grade 2 or 3 adverse events were detected during follow-up visits in the study population. None of the patients were treated with a total bilirubin level greater than 2 mg/dL or albumin level <3 g/dL.

Statistical significance was observed only between pre-treatment albumin (albumin 1) and 10th day albumin (albumin 2), and between pre-treatment albumin (albumin 1) and 3rd month albumin (albumin 3) levels ($p<0.05$). There was no statistically significant difference between the other biochemical parameters ($p>0.05$) (Table 2).

Table 1. Descriptive analysis of biochemical parameters before and early or late after treatment

Variable	Mean ± SD	Range
Pre-treatment parameters		
Neutrophil-1 (n=27)	4.6±2.1	1.2-10.5
CRP-1 (n=27)	4.1±4.9	0.2-14.2
ALT-1 (n=27)	32.5±26.9	11-124
AST-1 (n=27)	44.5±32.2	14-166
Albumin-1 (n=27)	4.0±0.5	3.3-5.9
Total bilirubin-1 (n=27)	0.9±0.45	0.35-1.89
Direct bilirubin-1 (n=27)	0.2±0. 2	0.05-1.01
AFP-1 (n=10)	7315.9±17225.5	1.3-54000
CEA-1 (n=12)	26.2±23.6	3.6-72.4
Ca-15-3.1 (n=1)	76.2	-
Ca-125.1 (n=2)	44.3±22.8	26.0-59.0
Post-treatment (Early) Parameters (10th day)		
Neutrophil-2	4.3±1.7	1.7-8.7
CRP-2	9.7±12.9	0.7-49.2
ALT-2	41.5±29.2	9-116
AST-2	58.1±33.1	17-141
Albumin-2	3.7±0.5	2.3-4.4
Total bilirubin-2	1.4±2.7	0.4-14.4
Direct bilirubin-2	0.5±1.5	0.03-7.6
Post-treatment (late) parameters (3rd month)		
Neutrophil-3	5.04±3.1	2.5-16.3
CRP-3	10.8±17.9	0.5-67.2
ALT-3	39.0±33.9	11-171
AST-3	55.0±55.8	28.0-300.0
Albumin-3	3.5±0.6	2.5-4.8
Total bilirubin-3	1.8±3.2	0.5-17.05
Direct bilirubin-3	0.7±1.8	0.04-9.35
AFP-3	16938.9±44706.9	2.06-142760.0
CEA-3	25.7±38.6	1.4-96.1
Ca-15-3.3	118.1	-
Ca-125.1 (n=2)	111.5±117.2	28.6-194.4

SD: standard deviation, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, AFP: alpha-fetoprotein, CEA: carcinoembryonic antigen

Discussion

Our institutional experience of TARE with Y-90 microsphere has shown that it is a relatively safe local treatment option for unresectable intrahepatic malignancies in the scope of biochemical parameters, although albumin levels changed significantly early after the treatment and in the late follow up.

TARE can selectively provide very high radiation exposure to tumor tissue with fewer side effects. Previous studies have shown that this therapy is an effective and safe option for unresectable liver malignancies such

Table 2. Statistical analysis of biochemical parameters before treatment, early or late after treatment

Biochemical parameters	p
ALT-1/ALT-2	0.174
ALT-1/ALT-3	0.402
AST-1/AST-2	0.059
AST-1/AST-3	0.145
Neutrophil-1/Neutrophil-2	0.528
Neutrophil-1/Neutrophil-3	0.540
CRP-1/CRP-2	0.081
CRP-1/CRP-3	0.122
Total Bilirubin-1/Total bilirubin-2	0.299
Total Bilirubin-1/Total bilirubin-3	0.162
Direct Bilirubin-1/Direct bilirubin-2	0.278
Direct Bilirubin-1/Direct bilirubin-3	0.170
Albumin-1/Albumin-2	0.001
Albumin-1/Albumin-3	0.001
AFP-1/AFP-3	0.320
CEA-1/CEA-3	0.875

p value<0.05=statistically significant

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, AFP: alpha-fetoprotein, CEA: carcinoembryonic antigen

as hepatocellular carcinoma and liver metastases from colorectal and breast cancer, neuroendocrine tumors, melanoma, pancreatic, renal and lung cancer (6,10,14,19).

Y-90 is a high-energy beta emitter that is used to label microspheres. Radiolabeled microspheres cannot get through venous capillaries due to their larger diameter than the end arterial capillary bed. So, Y-90 labeled microspheres are trapped in the tumor bed and high radiation doses can be achieved in the tumor tissue, causing irreversible cell damage in the epithelial, stromal, and endothelial cells of the area (14). Endothelial cells were suggested to be the main and first target of internal radiation therapy. Endothelial cells of tumors are damaged and cell death is observed afterwards (20,21). In addition, malfunction and transient failure of the liver may be observed after treatment, which may lead to insufficient production of some proteins (22). These mechanisms may explain why albumin levels in this study were significantly decreased during very early and late follow-up.

Common side effects of treatment are nausea, vomiting, mild abdominal pain and fever with a reported incidence of 20-70%, and may be associated with systemic reaction to endothelial damage (14,23). Vascular dissection/occlusions, pseudo-aneurysms, liver abscess formation, biliomas, cholecystitis, gastritis, duodenitis, pleural effusions and perihepatic fluid collections are some of the mild to serious complications after TARE (6). Transaminase enzymes may increase transiently in the first 4-6 weeks of treatment and may last up to 2-3 months (14). It has been shown that liver toxicity is up to 96% in terms of transaminase levels in patients treated with the whole liver approach (24). In another phase 2 study, altered bilirubin levels were reported at 3 months in 13.5% of patients (25). In contrast, no clinically apparent hepatic toxicity was observed in another large cohort study (26). In the current study, similar to the results of the last study, we could not demonstrate significant fluctuation of transaminases or bilirubin levels either in the early or late follow-up of patients.

Radiation-induced liver damage was described many years ago in the scope of external beam radiotherapy that is related with centrilobular vein damage (27). In this syndrome, ascites without jaundice, elevated alkaline phosphatase and less frequently increased liver transaminases are observed (28). On the other hand, radioembolization-induced liver damage, which is a typical liver toxicity syndrome specifically associated with radioembolization, has recently been described (29). Severe abdominal pain, ascites, jaundice, bilirubin elevation, variable elevation of gamma gamma glutamyl transferase, and alkaline phosphatase without significant increase in transaminase enzymes and decreasing blood albumin levels usually at the 3rd month of treatment are the components of the syndrome (14,28). This can also promote our study data that albumin is the critical parameter that must be checked regularly. In a recently published study, it was shown that significant decline in overall survival was observed as serum albumin, and hence hepatic synthetic function, even with the majority of patients having a normal total bilirubin. They also concluded that the median overall survival of patients with normal serum albumin was greater and that patients with an albumin below 3 g/dL might not derive a significant clinical benefit from treatment with Y-90 TARE when albumin fell below 3 g/dL (4). Similarly, an albumin level >3 g/dL has been previously reported as a predictor of survival in a group of patients with colorectal histology treated with Y-90 TARE (30).

The primary purpose of this study was to identify the effect of treatment on early and late follow-up biochemical parameters that could be used to predict safety and efficacy.

Study Limitations

Our study population was heterogeneous in terms of demographics and histology, which is one of the main limitations along with retrospective design. Additionally, follow-up duration was not long enough to give information about relationship between survival and biochemical parameters.

Conclusion

Our experience with Y-90 TARE has shown that it is a relatively safe treatment option in the scope of biochemical parameters for properly screened patients with intrahepatic malignancies. Our data suggests that the critical biochemical parameter is albumin, which should be checked regularly before, early and late after treatment.

Ethics Committee Approval: İstanbul Training and Research Hospital, Clinical Research Ethics Committee (decision no: 1584, date: 21.12.2018).

Informed Consent: Informed consent forms were obtained.

Peer-review: Internally peer-reviewed.

Author Contributions: Concept - B.Y., C.G.; Design - B.Y., C.G.; Supervision - B.Y.; Resources - B.Y., C.G.; Materials - B.Y., C.G.; Data Collection and/or Processing - B.Y., C.G.; Analysis and/or Interpretation - B.Y.; Literature Search - B.Y.; Writing Manuscript - B.Y.; Critical Review - B.Y., C.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Elastofibroma Dorsi: Positron Emission Tomography/Computed Tomography Perspective

Elastofibroma Dorsi, Pozitron Emisyon Tomografi/Bilgisayarlı Tomografi Perspektifi

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ABSTRACT

Introduction: Elastofibroma dorsi (ED) is a rare, benign and slowly growing connective tissue tumor that is frequently observed in the subscapular region in elderly people. It can be detected with various imaging modalities, such as computed tomography (CT), magnetic resonance imaging, ultrasonography and positron emission tomography (PET). In this retrospective study, the clinical features of EDs detected in PET/CT examinations performed for malignant or non-malignant causes were evaluated.

Methods: In this retrospective study, PET/CT examinations performed between May 2014 and December 2017 in a single institution for oncological and non-oncological diseases were evaluated retrospectively. Anatomical dimensions of the lesions were evaluated on axial CT sections. The metabolic activities or receptor expression status of the lesions were evaluated according to the SUV_{max} values obtained from the region of interests drawn on the lesions detected in PET scans.

Results: A total of 7300 PET/CT reports were searched for term "ED" and the images of patients with ED were re-evaluated. ED was detected in 174 scans of 131 patients (97 female and 34 male; mean age: 62.13±8.6 years). The prevalence of ED was 1.79%. Bilateral ED was detected in 116 patients (88.5%) and 15 patients (11.5%) had unilateral ED. The mean diameter was 2.6x4.9±1.1x1.9 cm, and mean SUV_{max} value was 2.46±0.74. There were statistically significant differences regarding SUV_{max} values and measured dimensions (p=0.001).

Conclusion: In this study, the prevalence and demographic patterns of ED were demonstrated with F-18 fluorodeoxyglucose and Ga-68 DOTATATE PET-CT. Knowledge of the distribution and uptake patterns of PET agents and their physiological uptake sites will prevent unnecessary procedures and interventions.

Keywords: Elastofibroma dorsi, PET/CT, F-18 FDG, Ga-68 DOTATATE

ÖZ

Amaç: Elastofibroma dorsi (ED), nadir görülen ve yavaş büyüyen bir bağ dokusu tümörü olup, sıklıkla yaşlı hastalarda subskapüler bölgede gözlenmektedir. Bilgisayarlı tomografi (BT), manyetik rezonans görüntüleme, ultrasonografi ve pozitron emisyon tomografi (PET) gibi çeşitli görüntüleme yöntemleri ile tanı konulabilmektedir. Bu retrospektif çalışmada malign veya malign olmayan sebeplerden ötürü uygulanan PET/BT incelemelerinde saptanan ED'lerin klinik özellikleri değerlendirilişti.

Yöntemler: Bu çalışmada Mayıs 2014-Aralık 2017 tarihleri arasında tek bir merkezde onkolojik veya onkolojik olmayan hastalıklar nedeniyle gerçekleştirilen PET/BT incelemeleri retrospektif olarak değerlendirilmiştir. Lezyonların anatomik boyutları BT incelemelerindeki aksiyel kesitler üzerinden değerlendirilmiştir. Lezyonların metabolik aktiviteleri veya reseptör ekspresyon durumları PET incelemesinde saptanan lezyonlar üzerine çizilen ilgi alanlarından elde edilen SUV_{max} değerleri ile hesaplanmıştır.

Bulgular: Toplamda 7300 PET raporu "ED" açısından taranmış ve ED saptanan hastaların görüntüleri tekrar değerlendirilmiştir. Yüz otuz bir hastaya ait 174 incelemede (97 kadın, 34 erkek, ortalama yaş: 62.13±8.6) ED saptandı. Prevelans %1,79 olarak saptandı. Yüz on altı hastada (%88,5) bilateral olarak ED saptanmış iken; sağda daha sık olmak üzere 15 hastada tek taraflı (%11,5) ED saptandı. Ortalama çap 2,6x4,9±1,1x1,9cm; ortalama SUV_{max} değeri ise 2,46±0,74 olarak hesaplandı. SUV_{max} değerleri ile ölçülen boyutlar arasında istatistiksel olarak anlamlı farklılık (p=0,001) saptandı.

Sonuç: Bu çalışmada F-18 florodeoksiglikoz ve Ga-68 DOTATATE PET/BT incelemelerindeki ED'nin prevelansı ve demografik özellikleri belirtilmiştir. Çeşitli PET ajanlarının tutulum özelliklerinin ve dağılım sahalarının bilinmesi, gereksiz tetkiklerin ve girişimlerin önüne geçecektir.

Anahtar Kelimeler: Elastofibroma Dorsi, PET/BT, F-18 FDG, Ga-68 DOTATATE

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Introduction

Elastofibroma dorsi (ED) is a rare, benign and slowly growing connective tissue tumor that occurs most often in the subscapular area in the elderly, especially in women. It was first described by Jarvi and Saxen (1) in 1961. ED is described as the accumulation of abnormal elastic fibers that cause a pseudo tumor and is generally regarded as a reactive process due to recurrent micro-traumas (2-4). This lesion classically occurs in the subscapular region, deep to serratus anterior and latissimus dorsi muscles. It is mostly bilateral in up to 80% of cases. When unilateral, it is reported more frequently on the right side than the left (4). Less common locations of ED are ischial tuberosity, olecranon or elsewhere along the thoracic wall (5-8). No treatment is required unless the patient is symptomatic. If symptomatic, the lesion can be surgically excised.

Although the prevalence of ED has been reported up to 17% in some autopsy series (3), incidental detection rate of these lesions was reported less than this number in chest CT (2%) and positron emission tomography/computed tomography (PET/CT) (1.7%) studies (9-12). Poorly defined, soft tissue density lesion with internal fat striations at CT in the subscapular region is considered diagnostic for ED in most cases. Similar to CT, magnetic resonance imaging (MRI) findings may demonstrate a fibro fatty lesion with the fibrous tissue appearing isointense with skeletal muscle on T1- and T2-weighted imaging. Various studies and case reports can be found in the literature defining the role of PET/CT (10,11,13-16).

The aim of this study is to investigate the prevalence and uptake patterns of different PET radiopharmaceuticals in Turkish population.

Methods

Patients and Methods

In this retrospective study, the reports of 7300 PET/CT examinations performed in a single institution and reported by a single nuclear medicine specialist between May 2014 and December 2017 were retrospectively searched for the term “ED”. PET/CT images of patients in the search result were re-evaluated.

Positron Emission Tomography/Computed Tomography İmaging

All PET scans were performed for oncological and non-oncological purposes. Oncological PET scans were performed with F-18 Fluorodeoxyglucose (FDG), Ga-68 DOTATATE [a peptide with somatostatin receptor (SSTR) affinity] or Ga-68 prostate specific membrane antigen (PSMA). Non-oncological PET scans included benign diseases like sarcoidosis, fewer of unknown origin or cardiac viability evaluation etc.

All patients were scanned using the same PET/CT device (Siemens Biograph mCT 20 ultra HD, Hoffmann Estates, Illinois, USA) according to the national or international guidelines. For oncological and non-oncological PET/CT scans other than cardiac viability, PET/CT scans were performed 45-60 minutes after the IV injection of 3.7-5.2 MBq/kg F-18 FDG or 1.8-2.2 MBq/kg Ga-68 DOTATATE. After acquisition of a scout image, CT imaging for PET/CT was performed using a multi-detector scanner with 20 slices, at 80-140 kV, 20-266 mAs, 0.8 pitch and 512x512 matrix [personalized settings determined by automatic exposure control system; automatically defined by the software used by manufacturer (CareDose 4D) depending on the patient and region assessed]. CT imaging was performed between vertex and upper-thigh in craniocaudal direction with 3 mm of slice thickness and 0.5 seconds of rotation time. Then, PET imaging was performed in the same range through craniocaudal direction at 8 to 9 bed positions, 1.5 minutes for each PET bed. Ultra HD images were acquired using Time of flight (TOF) + True X algorithm for Siemens mCT 20 ultra HD London Symphony Orchestra PET-CT at iteration 2 and subset 16 values for reconstruction. For cardiac viability PET/CT scan, 25-50 mg of oral glucose loading and supplemental insulin administration was performed after 6 hours of fasting. Then, 3.7-5.2 MBq/kg F-18 FDG was injected intravenously. A non-enhanced low-dose CT was acquired for attenuation correction. The subsequent PET scan was acquired in the 3D cardiac GATED mode from the level of the heart (1 bed position, 10 min per bed position) without repositioning the patient on the table. Patients were allowed to breathe normally during all PET and CT acquisitions. PET images were reconstructed using CT data for attenuation correction. All images were evaluated with Multiseries Viewer Software (Syngo via, Siemens Healthineers).

None of the patients had surgical intervention for ED. The anatomical diameters of ED were measured from right to left and anterior to posterior on axial CT image with the longest diameter of the lesion. For visual analyses, radiopharmaceutical uptake of the lesions was divided into 3 subgroups, group 1 (no or lower uptake than the mediastinal intravascular uptake), group 2 (uptake equal or minimally higher than the mediastinal intravascular uptake) and group 3 (uptake marked higher than mediastinal intravascular uptake). Quantitative evaluation of SUV_{max} values was performed by gathering by the region of interest (ROI) drawn around the ED on PET scans and SUV_{max} was calculated according to the following formula: maximum activity inside the ROI (MBq/gr)/injected radiopharmaceutical dosage (MBq/kg body mass). SUV_{max} values gathered from F18 FDG PET scans were taken into consideration due to different uptake mechanism of Ga-68 bound peptides. The demographics of patients and characteristics of ED are given in Table 1.

Table 1. Demographics of patients with elastofibroma dorsi

Patients/Scans (n)	**131/174**
Oncological F-18 FDG PET	164
Non-oncological F-18 FDG PET	6
F-18 FDG PET for viability	3
Ga-68 DOTATATE PET	1
Age (years)	62.13±8.6
Gender (F/M)	97 F/34 M
Bilateral (n %)	116/88.5%
Unilateral (n %)	15/11.5%
Right (n %)	12 (9.3%)
Left (n %)	3 (2.2%)
SUV_{max} (mean ± SD)	2.46±0.74 (1.18-4.97)
Diameters (cm) (RLxAP) (mean ± SD)	2.6x4.9±1.1x1.9 cm

FDG: fluorodeoxyglucose, PET: positron emission tomography, F: female, M: male, SD: standart deviation, RL: right to left, AP: anterior to posterior

Statistical Analysis

All data were expressed as mean ± standard deviation. Pearson correlation coefficient test was used to analyze SUV_{max}, visual assessment and lesion size values and to compare differences between the groups. All statistical analyses were performed using the statistical package for the social sciences software (SPSS, version 15.0; SPSS Inc.) for Windows. A p value of less than 0.05 was considered statistically significant. If there was no statistically significant difference, p value was not given in the text.

Results

We have evaluated 7300 PET reports of 6803 patients and detected ED in 174 PET/CT scans of 131 patients. Forty-three these were single or multiple follow-up scans. Follow-up scans were performed for treatment response evaluation and/or restaging. Ninety-seven of these 131 patients were female (74%) and 34 were male (26%). The mean age was 62.13±8.6 years. One hundred and sixty-five of the scans were performed for oncological purposes (94.8%), while nine of them (5.2%; three cardiac viability assessment and six other benign diseases) were performed for other purposes.

Prevalence of ED was 1.92%. One hundred and sixteen patients (88.5%) had bilateral and 15 patients (11.5%) had unilateral ED, more dominant on the right side (12 on right; three on left). The mean diameters were 4.9x2.4±1.1x1.9 cm, and mean SUV_{max} value for FDG PET was 2.46±0.74. There was a weak positive correlation between SUV_{max} values and diameters (p=0.05). The SUV_{max} value (SUV_{max}: 4.21) for single Ga-68 DOTATATE scans was not taken into account, as its uptake mechanism is different from FDG and shows SSTRs instead of metabolism. On visual assessment, radiopharmaceutical uptake of ED was similar to or minimally higher than the mediastinal intravascular uptake in most of the cases (168 out of 174). In six scans, uptakes were higher than the mediastinal intravascular uptake; but uptake was lower than the mediastinal intravascular uptake in none of the scans.

In the follow-up scan group, there was no statistically difference in terms of size and SUV_{max} value changes between initial and follow-up scans. The characteristic of patients and descriptive numbers are summarized in Table 1.

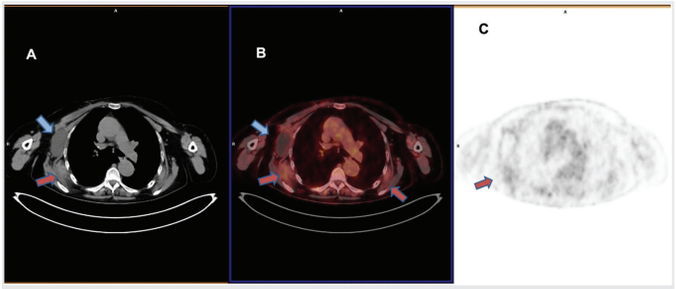

Figure 1. Axial slices of computed tomography (CT) (A), F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT fusion (B) and F-18 FDG PET (C) images of a 64-year-old woman who was operated from right breast and axilla three weeks before PET/CT examination. Bilateral elastofibroma dorsi (EDs) (brown arrows) are noted; slightly larger on the right side. The largest one is measuring 2.8x3.9 cm and SUV_{max} was 3.12. Postoperative seroma (blue arrow) is noted just anterior of the right ED, due to recent axillar lymphadenectomy

Discussion

ED is a benign, soft tissue mass lesion located mostly at subscapulary region and it was first described in 1961 (1). It is characterized by the proliferation of elastin fibers in a stroma of collagen and adipose connective tissue. Although it may be diagnosed with various imaging modalities such as CT, MRI or even ultrasonography, diagnosis can be challenging in some cases with PET/CT in case of history of previous thoracic surgery, lymphomas, sarcomas etc.

Although the prevalence of ED was reported to differ between autopsy series (17%) (3) and imaging modalities (1.6 to 2% for CT and 1.7% for PET-CT) (9-11), ED detection rate in our study (1.92%) is similar with the reported CT and PET/CT literature. It is well known that ED is more seen in elderly people (fifth and seventh decades of life) and females, and we found similar results in our study found (mean age: 62.13±8.6 years and 74% female dominance) (4,9-12).

Although it has been reported that ED can be seen in various locations, other than subscapular region (1%) (5-7), we have observed ED only at subscapular region in our series. Various numbers have been reported in the literature regarding the location and bilaterality of ED (58%-85.5%) (9-13). Similar to the literature, we detected bilateral localization of ED in 88.5% of patients (Figure 2). Similar to the reported numbers, we have found a right-sided dominance in unilateral cases (80% vs 20%) (9,10). Slightly larger ED was noted on the right side in case of bilateralism; however, no statistically significant difference was observed. Various studies have reported the mean diameters of ED in a range between 2.0x1.2 cm to 14x13 cm with a huge variability, and our results (2.6x4.9±1.1x1.9 cm) are consistent with most of the studies in the literature (4,8-15).

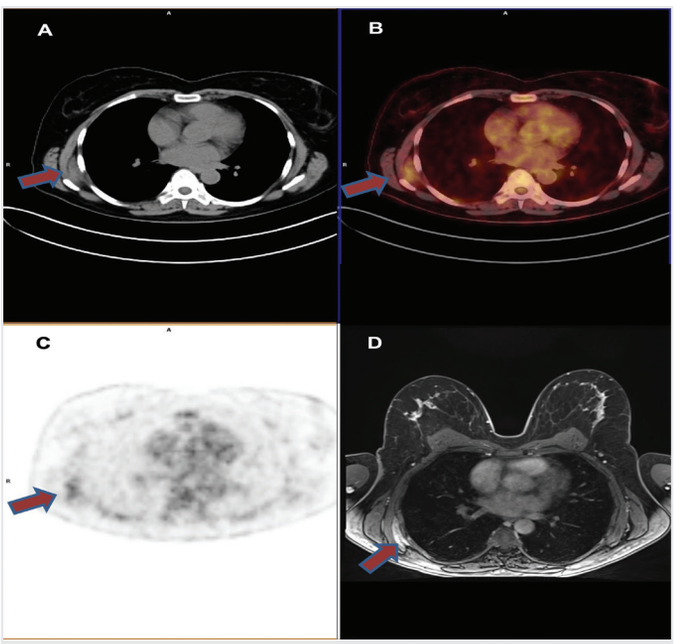

Figure 2. Axial slices of computed tomography (A), fusion (B), F-18 fluorodeoxyglucose (FDG) positron emission tomography (C) and T1-weighted magnetic resonance image (MRI) after contrast agent administration (D) in a 51-year-old woman with right sided breast carcinoma. Right sided, unilateral soft tissue lesion (arrows) measuring 2.4x3.2 mm and shows increased FDG uptake (SUV_{max}: 3.31) is noted. Well-differentiated unilateral soft tissue lesion with enhancement is noted on MRI

In the literature, several studies have declared the strong and weak aspects of PET/CT imaging for ED, especially for F-18 FDG (10,11,13,14). However, they all agree that PET/CT is not the tool for the diagnosis of ED. Instead of being a diagnostic tool for ED, interpretation of PET/CT findings is important to avoid misdiagnosis and unnecessary interventions.

Different studies have reported various results for measured mean SUV_{max} values for F-18 FGD PET. Erhamamci et al. (10) reported SUV_{max} as 2.31±0.61 (range: 1.0 to 4.3), Blumenkrantz et al. (11) as 2.1 (range: 1.4-3.2), and Onishi et al. (14) as 2.0±0.63 (range: 0-5.1) (13). In our study, we found similar results with the literature (SUV_{max} 2.46±0.74; range: 1.18-4.97). There are some studies and case reports reporting higher SUV_{max} values, such as SUV_{max} equal to 3.2 (up to 4.7) (11,13,15), which might be tricky if the interpreter just gives moderately high SUV_{max} value, instead of a more specific diagnosis. The exact mechanism of FDG uptake in ED is unknown, but anticipated as a combination of high vascularity and increased metabolic activity within the mass (14,17).

Various studies showed uptake of different radiopharmaceuticals in ED, other than F-18 FDG; such as I-131, F-18 PSMA and Ga-68 DOTATATE, which is a SSTR agonist (18-21). In our study, all procedures, except one, were performed with F-18 FDG. Only one patient's ED was demonstrated with Ga-68 DOTATATE (Figure 3). Ga-68 DOTATATE is a radiolabeled SSTR analogue showing high affinity to SSTR type 2, but it can bind with varying affinity to the other SSTRs. Somatostatin is an endogenous cyclic tetradecapeptide hormone. Primarily inhibitory in nature, this small peptide has anti-secretory and anti-proliferative effects and functions as a neurotransmitter. SST binds to five subtypes of G-protein-coupled transmembrane receptors (SSTR 1-5). SSTRs are widely expressed in normal tissues as well as malignant and inflammatory situations. Various studies have searched the immunohistochemical staining status of ED, and expression of vimentin, factor XIIIa and CD34 were detected with negative for smooth muscle actin, S-100, desmin, and p53 (22,23). To our knowledge, there is no study histopathologically investigating SSTR expression in ED. According to our knowledge, following the case report by Ishiyama et al. (21), this is the second case showing STTR expression with Ga-68 DOTATATE PET/CT in ED.

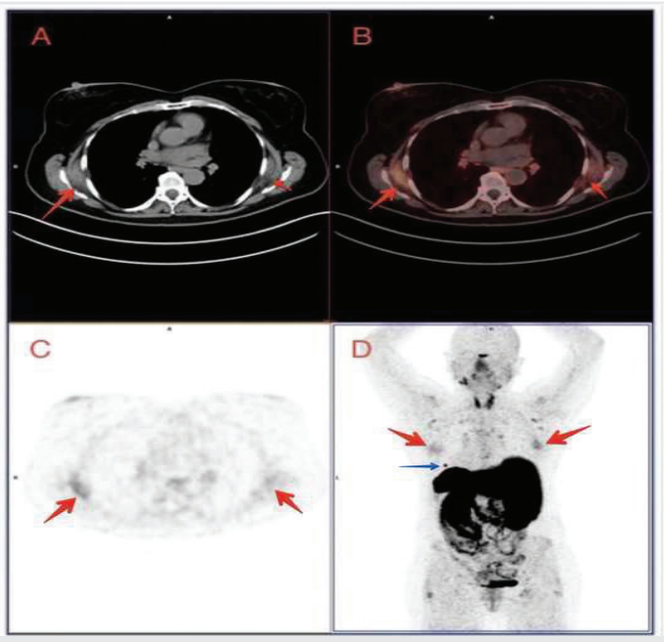

Figure 3. Axial slices of computed tomography (CT) (A), fusion (B), positron emission tomography (PET) (C) and posterior projection of MIP (D) images of a 59-year-old woman with Ga-68 DOTATATE PET/CT examination who was operated for rectal neuroendocrine neoplasia. Ga-68 DOTATATE PET/CT revealed poorly circumscribed, soft-tissue lesions with minimally fat strands (A) and showing increased STTR expression (B and C), correspondent with elastofibroma dorsi. Right-sided ED is slightly larger than the left one and measures 28x42 mm and SUV_{max} value was 4.21. Also, focal Ga-68 DOTATATE uptake corresponding with accessory spleen (blue arrow) is noted on MIP image

The detection rate of benign lesions increases with increasing exponential use of PET/CT in daily practice. Although the characteristics of ED are well described for CT and FDG PET/CT, the mechanism of low to mild FDG uptake is unclear. Various speculations can be made such as increased vascularity, reactive and inflammatory processes. However, according to our knowledge, no confirmative studies were conducted. In most of the ED cases, tissue sampling for diagnosis is not necessary; however, in some challenging cases, various imaging modalities or even surgical resection might be needed, especially in thoracic malignancies with previous surgical intervention.

Study Limitations

Our retrospective study has limitations such as lack of histological confirmation, but lesions remained similar on follow-up images or had fully benign appearance. Contrast-enhancement was not observed in CT scans and no routine and detailed clinical questionnaire were given for ED diagnosis.

Conclusion

Although PET/CT imaging is not the recommended tool for the diagnosis of ED; knowing the typical features and recognition of uptake patterns of PET radiopharmaceuticals are important for the nuclear medicine specialists and also for the refereeing clinicians, especially for the oncological patients with unilateral lesions or lesions with asymmetrical intense radiopharmaceutical uptake.

Ethics Committee Approval: Retrospective study.

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

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Pyogenic Granuloma: Retrospective Analysis of Eleven Cases with Literature Data

Piyojenik Granülom: On-bir Olgunun Literatür Verileri Eşliğinde Retrospektif Analizi

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ABSTRACT

Introduction: The aim of the present study was to determine the demographic characteristics of patients undergoing surgery for pyogenic granuloma (PG) in our clinic and to discuss them with the literature data.

Methods: The patients who were reported as PG after pathology results were analyzed in terms of age, gender, tumor localization, tumor size, etiologic factors, time of occurrence and recurrence.

Results: The ages of 11 patients diagnosed with PG ranged from 14 to 62 years with a mean age of 42.36 years. Eight patients were between 30-60 years old. Five patients were female (45.45%) and six were male (54.55%). Oral cavity localization (tongue in three patients, hard palate in one patient, and both tongue and buccal mucosa in one patient) was observed in five patients. Nose localization (septum in two patients, inferior concha in one patient, and middle concha in one patient) was observed in four patients and two patients had skin localization (scalp in one patient and back of auricle in one patient). Onset of symptoms varied between 2 and 21 weeks (mean: 10.36 weeks). Tumor size varied between 5 and 25 mm (mean: 11.33 mm). There were seven pedunculated lesions and four nodular lesions among all specimens.

Conclusion: PG is a diagnosis that should be kept in mind in the differential diagnosis of rapidly growing, hemorrhagic oral cavity and unilateral nasal masses. Total excision of the lesion with intact mucosal margins is required to prevent recurrence.

Keywords: Pyogenic granuloma, lobular capillary hemangioma, oral cavity, nasal obstruction, epistaxis

ÖZ

Amaç: Bu çalışmanın amacı kliniğimizde piyojenik granülom nedeniyle opere edilen hastaların demografik özelliklerini belirlemek ve literatür verileri eşliğinde tartışmaktır.

Yöntemler: Patoloji sonucu piyojenik granülom olarak rapor edilen hastalar yaş, cinsiyet, tümör lokalizasyonu, tümör boyutu, etiyolojik faktörler, ortaya çıkma zamanı ve nüks açısından incelendi.

Bulgular: Piyojenik granülom tanısı alan 11 hastanın yaşları 14 ile 62 arasında değişmekteydi ve ortalama yaş 42,36 idi. Sekiz hastanın yaşı 30-60 arasındaydı. Hastaların 5'i kadın (%45,45) ve 6'sı erkekti (%54,55). Beş hastada (%45,45) oral kavite (3 dil, 1 sert damak ve 1 hastada hem dil hem de yanak mukozası), 4 hastada (%36,36) burun (2 septum, 1 alt konka ve 1 orta konka) ve 2 hastada (%18,18) deri (1 skalp ve 1 aurikula arkası) yerleşimi gözlendi. Semptomların görülme zamanı 2-21 hafta (ortalama: 10,36) arasında değişmekteydi. Tümör boyutu 5-25 mm (ortalama: 11,33 mm) arasında değişmekteydi. Tüm piyesler içerisinde 7 pedinküllü ve 4 nodüler lezyon mevcuttu.

Sonuç: Piyojenik granülom özellikle kanamalı hızlı büyüyen oral kavite lezyonlarının ve tek taraflı burun kitlelerinin ayırıcı tanısında akılda tutulması gereken bir tanıdır. Rekürrensi önlemek amacıyla lezyonun sağlam mukozal sınırlar ile total eksizyonu gerekmektedir.

Anahtar Kelimeler: Piyojenik granülom, lobüler kapiller hemanjiom, oral kavite, burun tıkanıklığı, burun kanaması

Introduction

Pyogenic granuloma (PG) is a benign vascular lesion with no known cause. It is usually observed on skin and mucous membranes. It generally presents as a red, frequently bleeding, pedunculated or nodular painless lesion and rarely mimics a malign mass due to rapid growth (1,2). Trauma, chronic irritation and hormonal changes are accused in the etiology (3). PG can also be observed in other parts of the body, most frequently in head and neck region. It can be seen frequently in the oral cavity and more rarely in the nasal cavity and larynx in head and neck region (1,4,5).

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The aim of the present study was to determine the demographic characteristics of the patients undergoing surgery for PG in our clinic and to discuss them with literature data.

Methods

This retrospectively designed study was approved by İstanbul Training and Research Hospital Local Ethics Committee (decision no: 1040, date: 21.07.2017). The files of patients who underwent surgery under local and general anesthesia between 2013 and 2016 in clinic of otorhinolaryngology were retrospectively reviewed and patients who were reported as PG after pathology result were included in the study. Informed consent was obtained from all patients included in the study. The patients were examined in terms of age, gender, tumor localization, tumor size, etiologic factors, time of occurrence and recurrence.

Statistical Analysis

Statistical analysis program was not used to evaluate the study data. Continuous variable were expressed as mean and categorical variables as percentage.

Results

A total of 11 patients who were operated at the otorhinolaryngology clinic were diagnosed with PG. The age of the patients ranged from 14 to 62 years with a mean age of 42.36 years. All demographic characteristics of patients are shown in Table 1, 2.

No etiology was determined in nine patients (81%). PG was determined to develop on hard palate in one patient after hot meal and in tongue and buccal mucosa at the same side in the other patient due to irritation associated with decay tooth. There was no history of nasal trauma, surgical intervention or tampon application in any patients. All female patients had at least one history of delivery and had no history of oral contraceptive use and gynecologic malignity. There were no pregnant patients.

Paranasal sinus computed tomography (CT) and magnetic resonance imaging (MRI) were performed in two patients with unilateral nasal obstruction and epistaxis. PG was reported to be hypointense on T1-weighted images (WI), and hyperintense on T2-WI with contrast enhancement (Figure 1) in MRI, and polyploidy soft tissue mass with smooth surface, without bone destruction in CT (Figure 2). In all

Table 1. Distribution of age and localization in terms of gender

		Male	Female	Total
Age, years	<20	2	0	2
	30-50	1	4	5
	50<	3	1	4
Localization	Oral cavity	4	1	5
	Nose	1	3	4
	Skin	1	1	2

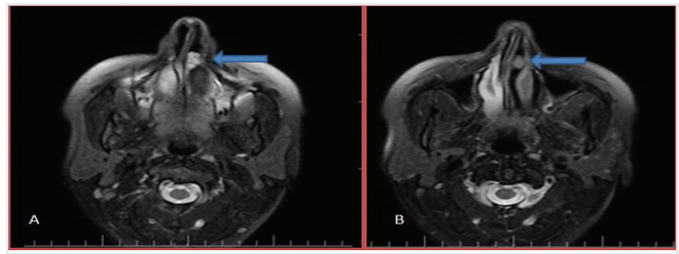

Figure 1. Axial T1 (A) and T2 (B) magnetic resonance images

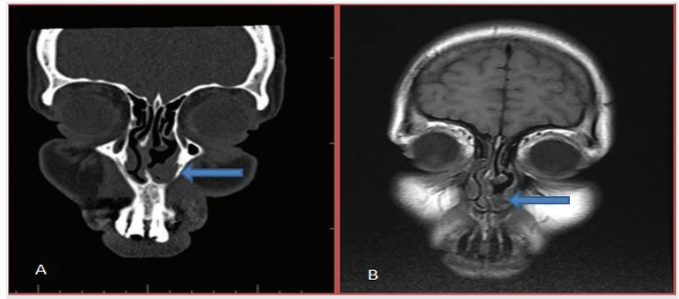

Figure 2. Coronal computed tomography (A) and T1-weighted magnetic resonance (B) images

Table 2. Table of all data

Case	Age	Gender	Size (mm)	Time (Week)	Peduncle	Symptom	Etiology	Localization
1	36	F	10	16	Yes	Mass	Unknown	Scalp
2	45	F	15	5	No	Hemorrhage obstruction	Unknown	Left inferior turbinate
3	52	F	6+8	8	Yes	Mass	Dental irritation	Tongue + right buccal mucosa
4	36	F	25	21	Yes	Hemorrhage obstruction	Unknown	Right middle turbinate
5	49	F	17	5	No	Hemorrhage	Unknown	Left septum
6	42	M	15	2	No	Hemorrhage obstruction	Unknown	Left septum
7	19	M	7	15	No	Mass	Unknown	Tongue
8	14	M	8	8	Yes	Mass	Unknown	Tongue
9	62	M	12	9	Yes	Mass hemorrhage	Unknown	Tongue
10	59	M	5	17	Yes	Mass	Unknown	Back of right auricle
11	52	M	8	8	Yes	Mass hemorrhage	Hot	Hard palate

F: female, M: male, mm: millimeter

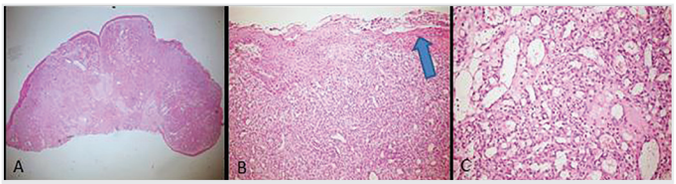

Figure 3. Postoperative histopathological examination (B: arrow shows ulceration of squamous epithelium)

patients, PG was excised totally as a solid mucosal margin around the mass. Postoperative recurrence was not observed after a mean follow-up period of 27 months (range: 12-48 months).

Histopathological examination (Figure 3) revealed a lobular polyploidy lesion at small magnification (A). At greater magnification (B), granulation tissue consisting of numerous vascular structures, hyalinized connective tissue and inflammatory cells was observed under squamous epithelium showing ulceration (arrow in right upper corner) and reactive changes. At a greater magnification (C), sporadically swollen endothelial cells with open lumens and thin wall in various sizes and forms, with some having a dilated appearance as well as numerous vascular structures and infiltration of mixed inflammatory cells in partially edematous hyalinized stroma were observed.

Discussion

PG is a rapidly growing, vascular and benign inflammatory lesion involving the skin and mucous membranes (1,2). The lesion was defined by Hullihen in 1844 for the first time and named as Granuloma Pyogenicum by Hertzell in 1904 (3). It was suggested that this denomination was wrong upon the fact that no bacterial infectious agent was determined in series of subsequently reported cases and granuloma was not identified in histopathological examinations. It is recommended to use the term lobular capillary hemangioma by Mills et al. (6), in 1980. Nevertheless, the term "PG" is used very commonly in the literature.

Even though the cause of PG is unknown, increased hormonal activity is the most implicated factor because it is frequently seen in pregnant women, and this lesion was also named as pregnancy tumor by some authors (7). The use of oral contraceptive and some gynecologic malignancies have been suggested to likely play a role in the etiology by changing the hormonal balance in the body, as well. Chronic irritation, nasal trauma and surgical procedures, disordered oral hygiene, habit of biting lips, and intranasal tampon application are also factors to be accused in etiology (8-12). Although there are cases of PG developing after blunt laryngeal trauma and insect sting in the literature, no distinct etiological cause has been determined in several studies (13,14). In the present study, etiological cause could not be determined in nine patients (81%) except for one female patient with lesion on buccal mucosa and lateral side of tongue as a result of chronic irritation associated with tooth decay and one male patient with lesion developing on hard palate after hot meal.

Even though PG is observed in neonatal age and childhood, it is identified mostly in the third decade and more frequently in women (15,16). While it is more frequent in men, particularly in childhood, the incidence is higher in women during adulthood (17). In the present study, while there were two male patients under the age of 20 years, the female-male ratio for age interval of 30-50 years was found to be 4/1. This ratio suggests that levels of estrogen and progesterone in the body may play a role in the etiology.

PG most frequently involves the skin and mucous membranes in the body. In a case series of 82 patients published by Akamatsu et al. (4), PG was most frequently localized in the head-neck region at a rate of 56%, in the upper extremities at a rate of 22%, in the torso at a rate of 16%, and in the lower extremities at a rate of 6%. It was observed that the most common localization was oral cavity and nasal mucosa in cases with PG localized in the head and neck region (4).

PG is diagnosed by excisional biopsy. In histopathological examination, it appears as an atrophic granulation tissue covered with fibrous tissue or increased granulation tissue covered with hyperplastic epithelial tissue. The presence of fibroblasts increased with vascular gaps covered by numerous endothelial and clustered endothelial cells constituted characteristic microscopic appearance of PG. It is described in three stages depending on the prognosis of the lesion. At the cellular stage, small lumen formations are observed within the compact cellular stroma. While increased vascular lobules filled with erythrocytes are observed at capillary stage, fibrosis is observed to develop in and around lobules at late stage (18).

PG was found at a rate of 3.2% among all of the biopsies taken from oral cavity (11). In other series, PG was identified at the rates of 21% and 50.35% in all oral cavity biopsies taken from tumor-like soft tissues (10,12). While gingiva is mostly involved at a rate of 83-93.95% in oral cavity, tongue, lip, palate, and buccal mucosa are involved less (10-12). The reason behind why gingival involvement was not observed in the present study was thought to be associated with the fact that these patients applied to dentistry instead of otorhinolaryngology. Six lesions were found in the oral cavity of five patients including four tongue localizations, one hard palate localization, and one buccal mucosa localization.

In a case series with 38 patients with nasal cavity localization, PG was most frequently associated with septum at a rate of 71%, nasal base at 13%, inferior turbinate at 13%, and middle turbinate at 3% (8). Right and left localization was found to be at a similar rate (8). In the present study, two lesions were associated with septum and one lesion was associated with inferior turbinate had left (75%) localization; whereas, one lesion was associated with middle turbinate had right (25%) localization. However, this rate was considered to be insignificant due to low number of patients.

PG may have various symptoms depending on localization and size. While the most frequent symptom is mass and hemorrhage for lesions localized in oral cavity, episodic epistaxis (95%) and nasal obstruction (35%) at affected side are the most frequent symptoms for nasal lesions (11,19). Rhinorrhea, facial pain, hyposmia and headache are less common symptoms (19).

In patients with PG localized in the oral cavity, differential diagnosis should be established with fibrous hyperplasia, peripheral giant cell

granuloma, fibroma and hemangioma (12). In nasal lesions, differential diagnosis of masses such as inverted papilloma, capillary hemangioma, meningoencephalocele, adenocarcinoma, hemangiopericytoma, esthesioneuroblastoma, angiosarcoma, Kaposi sarcoma, and lymphoma should be made (8,9,19). Differential diagnosis should be made with Kaposi's sarcoma in localized lesions of the skin (20). Radiological imaging may be needed to support the diagnosis and establish differential diagnosis for suspicious lesions (9). Polypoid soft tissue mass with smooth surface and no bone destruction in CT and hypointensity on T1-WI, hyperintensity on T2-WI and proper contrast enhancement in MRI was determined in two cases with intranasal localization.

Although PG often appears to be a single lesion, the so called scattered PG in which more than 100 lesions occur on the same patient has also been reported in the literature (21). It was observed as a single lesion in all patients except for one woman with two simultaneous lesions on the lateral side of tongue and buccal mucosa at the same side based on tooth irritation.

Recurrence of lesion is rare after total excision. While oral cavity lesions are mostly excised under local anesthesia, excision under general anesthesia accompanied with endoscope is recommended for large nasal lesions (22). In the present study, skin and oral cavity lesions were excised under local anesthesia. Nasal lesions were excised with endoscope; septal lesions were excised under local anesthesia, and lesions associated with inferior and middle turbinate were excised under general anesthesia. Recurrence was observed in 0-8% in the nasal cavity and 2-14.88% in the oral cavity at 1-5 years of follow-up (8-10,12). Insufficient excision, failure of eliminating etiological factors and repetitive traumas have been shown as the cause of recurrence and re-recurrence after revision surgery has also been reported (12). Postoperative recurrence was not observed in the present study after a mean follow-up of 27 months (range: 12-48 months).

Conclusion

PG is a rare diagnosis in otorhinolaryngology practice and it should be considered especially in the differential diagnosis of rapidly developing oral cavity and unilateral nasal masses. In order to prevent recurrence, total excision of the lesion with solid mucosal margins is required.

Ethics Committee Approval: This retrospectively designed study was approved by İstanbul Training and Research Hospital Local Ethics Committee (decision no: 1040, date: 21.07.2017).

Informed Consent: Informed consent was obtained from all patients included in the study.

Peer-review: Externally peer-reviewed.

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A Cross-sectional Study Evaluating Childhood Autism Awareness of Residents Otorhinolaryngology Department in İstanbul

İstanbul'da Kulak Burun Boğaz Bölümü Asistanlarının Çocukluk Çağı Otizm Farkındalıklarını Değerlendiren Kesitsel Bir Çalışma

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ABSTRACT

Introduction: Otorhinolaryngology (ENT) physicians may be effective in the early diagnosis of autism spectrum disorder (ASD). The aim of this study was to investigate the awareness of ENT residents in İstanbul about recognizing ASD.

Methods: The type of the study was cross-sectional. The study population consisted of 97 ENT residents, and 83 (85%) of these residents were included in the study. The questionnaire consisted of questions about the sociodemographic data of the participants and Autism Spectrum Disorder Awareness Questionnaire. Autism Spectrum Disorder Awareness Questionnaire contains the findings of ASD reported in the literature. This questionnaire includes observable findings of possible ASD in a child during routine examination of the ENT physician.

Results: In our study, the most known finding of childhood autism was found to be difficulty in making eye contact (97.5%). Regarding work experience, "difficulty in making eye contact" (100%) and "lack of age-appropriate language development" (91.5%) findings were well-known findings among residents with less than four years of experience. On the other hand, "very sensitive vision, hearing and touch senses" (95.8%) and "seem unable to hear even if hearing tests are normal" (91.7%) findings were more prominent among residents with four or more years of experience.

Conclusion: The ASD awareness of the ENT residents participating in our study can be considered as relatively good. The "Autism Spectrum Disorder Awareness Questionnaire" developed by the researchers is planned to be validated with the studies to be carried out later and developed to be used for ENT specialists. Such questionnaires can also be used to raise awareness among ENT residents and specialists.

Keywords: Awareness, childhood autism, otorhinolaryngology, resident, Turkey

ÖZ

Amaç: Kulak burun boğaz (KBB) hekimleri, otizm spektrum bozukluğunun (OSB) erken tanısında etkin olabilir. Bu çalışmanın amacı, İstanbul'daki KBB asistan hekimlerinin OSB'yi tanıma konusundaki farkındalıklarını araştırmaktır.

Yöntemler: Araştırmanın tipi kesitseldir. Çalışma evrenini KBB uzmanlık alanında çalışan ve uzmanlık eğitimi alan 97 asistan oluşturmaktadır ve bu asistanların 83'ü (%85) çalışmaya dahil edilmiştir. Soru formu katılımcıların sosyodemografik bilgilerini sorgulayan sorular ve "Otizm Spektrum Bozukluğu Farkındalık Anketi"nden oluşmaktadır. Otizm Spektrum Bozukluğu Farkındalık Anketi literatürde bildirilen OSB bulgularını içermektedir. Söz konusu anket KBB hekiminin rutin muayenesinde, bir çocukta olası OSB'nin gözleme dayalı olarak fark edilebilecek bulgularını sorgulamaktadır.

Bulgular: Çalışmamızda çocukluk çağı otizminin en bilinen bulgusu, göz teması kurmada zorluk çekme olarak bulunmuştur (%97,5). Hekimlik yapılan süreye göre katılımcıların OSB bulgularını doğru yanıtlama durumları incelendiğinde, dört yıldan az kıdemi olan asistanların iyi bildiği bulgular arasında "göz teması kurmada güçlük çekme" (%100) ve "yaşına uygun dil gelişiminin geride olması" (%91,5), dört yıl ve daha fazla kıdeme sahip asistanlar arasında ise "görme, işitme ve dokunma duyularının çok hassas olması" (%95,8) ve "işitme testleri normal olsa bile duymuyormuş gibi gözükebilme" (%91,7) bulguları öne çıkmaktadır.

Sonuç: Çalışmamıza katılan KBB asistanlarının OSB farkındalığı göreceli olarak iyi düzeyde kabul edilebilir. Araştırmacılar tarafından geliştirilen "Otizm Spektrum Bozukluğu Farkındalık Anketi"nin daha sonra gerçekleştirilecek çalışmalar ile valide edilmesi ve KBB uzmanları için de kullanılabilecek şekilde geliştirilmesi düşünülmektedir. Bu tür anketler, KBB asistanları ve uzmanları arasındaki farkındalığı artırmak için de kullanılabilir.

Anahtar Kelimeler: Farkındalık, çocukluk çağı otizmi, kulak burun boğaz, asistan, Türkiye

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Introduction

Autism spectrum disorder (ASD) is in the group of neuropsychiatric disorders characterized by delay, pause and deviation in social, communicative and cognitive development that started in the first years of life (1). According to the epidemiological statistics published by the United States Center for Disease Control and Prevention and the Autism and Developmental Disabilities Monitoring Network, 1 out of 68 children has ASD diagnosis and its prevalence is increasing rapidly (2). Combining the prevalence of juvenile diabetes mellitus, childhood cancers, and pediatric acquired immunodeficiency syndrome, ASD is more common (3,4). Although the etiology cannot be attributed to a specific cause, it is known that psychosocial factors, neurobiological factors, prenatal and postnatal factors and genetic background may be effective in the emergence of the disease as a phenomenon (5).

Studies have shown that early diagnosis and rapid initiation of appropriate treatment play a key role in the development of communication and social skills (6-10). While diagnosing at an early age is positively associated with developmental outcomes, the effectiveness of interventions may be reduced in older children (7,8). However, it was reported that the time to diagnosis was relatively long when the parent noticed and reported the first symptoms, which led to delayed diagnosis and treatment (8).

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) ASD diagnostic criteria emphasized abnormal reactivity to sensory stimuli, including sounds, and atypical processing of environmental sounds (11). Many children can first be brought to an otorhinolaryngology (ENT) outpatient clinic for assessment of communication and hearing problems. ASD is a lifelong condition that affects all ages of the ENT patient population (12). However, comorbid conditions such as sleep disorders, food allergies, eczema and asthma are slightly higher in patients with ASD (13,14). In addition to hearing problems, parents of children with autism may also consult an ENT physician with these complaints. This offers ENT physicians the opportunity to assist in the early diagnosis of children with autism. Asking parents a simple question about their child may generate a warning to the doctor for the diagnosis of ASD. For example, the question "Do you have any concerns about your child's physical or behavioral development?" might be helpful. The awareness of ASD is extremely important for ENT physicians to be effective in early diagnosis and intervention (12).

The aim of this study was to define the awareness of ENT residents in İstanbul about recognizing ASD by considering the increase in incidence, the importance of early diagnosis and the fact that the first place of application can be ENT outpatient clinics.

Methods

After 6 years of medical training, physicians who are eligible to become a general practitioner optionally prefer an area of expertise following success in "Medical Specialization Examination". In this way, they start to work as a resident in Training and Research Hospitals of the Ministry of Health or Medical Faculty Hospitals. This training is usually four or five years and they become specialists after training (15). The reason why the research universe included residents is that it is an important group both in terms of receiving training in the field of expertise and providing health services. First-time practices and experiences during the residency training will also continue in specialist training.

The type of the research was cross-sectional and the research population consisted of ENT residents working in the Training and Research Hospitals in İstanbul. The aim of the study was to reach the whole universe (97 people). The data collection process took place between February and March 2017. The place of the study was 13 hospitals in which ENT residents were working. Informed consent was obtained from the physicians who agreed to participate in the study and participation was made on a voluntary basis. The questionnaire was applied under observation. Residents who could not be reached at the time of the study (being in the operating room, on leave, etc.) were tried to be reached by hospital visit, phone call and message at most three times; failure to respond was accepted as rejection. In addition, participants who left more than 20% of the questions blank were excluded from the study. Of the 14 people who were not included in the study, four refused to participate, two left the majority of the questions blank and eight could not be reached for various reasons. A total of 83 ENT residents participated in the study. All of the 13 public hospitals in İstanbul, where ENT residents work, were included in our study. Six of these hospitals are located on the European side and seven on the Asian side. The districts where the hospitals were located and the number of assistants included in the study are presented in Table 1.

The questionnaire consists of a 10-item "Individual Questionnaire" and "Autism Spectrum Disorder Awareness Questionnaire" which includes 19 questions measuring the knowledge and awareness about ASD. Within the scope of the Individual Questionnaire, the age, gender, hospital of training, years of experience as a physician and ENT resident, and the presence of someone diagnosed with ASD in their environment were questioned. In addition, the physicians were asked questions about whether a child with ASD had previously applied, and if so, the reasons for the application, and whether the physicians had previously

Table 1. The districts where the hospitals were located and the number of residents included in the study

Hospital code	District/County	The number of residents enrolled in the study
A	Ümraniye	5
B	Pendik	8
C	Ataşehir	4
D	Göztepe	8
E	Üsküdar	7
F	Üsküdar	4
G	Kartal	1
H	Bakırköy	6
I	Şişli	5
J	Şişli	8
K	Bağcılar	9
L	Fatih	9
M	Fatih	9
Total		83

referred for suspected ASD for further examination and diagnosis, and if so, the number of referrals. "Autism Spectrum Disorder Awareness Questionnaire" is a questionnaire containing the findings that can be evaluated during a routine ENT examination of a possible ASD child and suggesting possible ASD, and consists of two parts as "basic questions" and "optional questions". This questionnaire was prepared in the light of the current literature (11,16-23) to observe a possible ASD in a child who applied to an ENT physician for any reason. The basic part questions the findings that are important to be known by physicians, and are more common and easier to recognize and consists of 19 questions. The optional part questions the findings that can be brought to light with the symptoms asked to the family with more examination and consists of 17 questions. The optional part is left to the physician's choice considering the workload of the resident. Seventy-eight participants answered the optional part. The questionnaire was prepared in Likert type and the answer options were "definitive finding", "supportive finding", "Not sure/I do not know", and "Not related to autism". All sentences are definitive or supportive findings in ASD.

Ethics Committee Approval

The authors declared that the study was conducted in accordance with the principles of the "Ethical Principles for Medical Research Involving Human Subjects" of World Medical Association Declaration of Helsinki. Ethics Committee approval was received from Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2016.651, date: 02.12.2016). The authors have no conflict of interest to declare in this study. The authors declared that this study has received no financial support.

Statistical Analysis

In statistical analysis, frequency and percentage were used for tabulation of categorical variables and mean and standard deviation were used for presentation of measurable variables.

Results

This cross - sectional study was conducted in 13 public hospitals in Istanbul by the researchers and a survey was conducted to 83 ENT residents under observation. While 82% of the participants were male, the mean age was 28.24±2.90 years. The number of residents with a child with ASD diagnosis in their environment was four. Forty-two point two percent of the participants stated that they referred at least one child who applied for routine ENT examination with suspicion of ASD for further diagnosis. Table 2 presents the general characteristics of the participants and their exposure to the patient with ASD.

The participants were asked with an open-ended question about why children diagnosed with ASD frequently applied. Forty-two percent (n=35) of the residents reported that they were consulted most commonly with hearing problems and hearing screening, and 12% (n=10) reported delay in speech. Other less commonly reported reasons for application were acute otitis media, sinusitis and nasal obstruction. Another open-ended question was what could be done in the diagnosis/follow-up of ASD in the specialty of ENT. The most common response was "demand for training of physicians about the findings and features of ASD" with 19% (n=16). Other responses were reported as "Which cases will be referred to where", "How hearing and speech therapy can be given to patients", and "Request to extend the examination period to obtain a more detailed anamnesis".

When the responses of the participants to the sentences evaluating their awareness were examined, the most well-known finding was "Difficulty in making eye contact" and 64.6% of the participants stated it as definitive finding, and 32.9% described it as a supportive finding. Thirty-one point three percent of the participants stated "Age-appropriate

Table 2. General characteristics of the participants and their encounter with autism spectrum disorder patients (n=83)

Variable	n	%
Gender		
Female	15	18.1
Male	68	81.9
Age (mean ± SD*)	28.24±2.90	
Work Hospital		
Faculty of medicine hospital	34	41.0
Training and research hospital	49	59.0
Duration of medical experience		
Less than 1 year	6	7.2
1-4 years	53	63.9
4 years and more	24	28.9
Duration of ENT residency		
Less than 1 year	26	32.1
1-4 years	44	54.3
4 years and more	11	13.6
The presence of someone diagnosed with ASD in your environment		
Yes	4	4.8
No	79	95.2
Application status of a child diagnosed with ASD		
Yes	57	68.7
No	26	31.3
Referring the child with another complaint for further investigation on suspicion of ASD		
Yes	35	42.2
No	48	57.8
Number of patients referred with suspicion of ASD		
1	2	10.5
2	5	26.3
3 and more	12	63.2
Referred department		
Child and adolescent psychiatry outpatient clinic	22	75.9
Request further examination	7	24.1
Do you think you need training to guide such a child for further examination/diagnosis?		
Yes	60	80.0
No	15	20.0

*SD: standard deviation, ENT: otorhinolaryngology, ASD: autism spectrum disorder

language development in children with ASD is delayed" as definitive finding and 57.8% as supportive finding. The other well-known finding was that "Children with ASD may have very sensitive vision/hearing and touch sensations (such as closing their ears and not letting being touched when they hear some sounds)", and 83.1% of the respondents described this finding as definitive or helpful. The basic questions regarding the awareness and knowledge residents about ASD are presented in Table 3.

When the responses of the participants to the optional questions about ASD awareness were examined, "Children with ASD have difficulty in social communication" was expressed by all participants as a finding of ASD. Sixty point three percent of physicians reported this finding as definitive finding and 39.7% reported as supportive finding. "Children with ASD have difficulty in establishing a friendship" was one of the other commonly known statements (definitive finding; 51.3%, supportive finding; 46.2%). Another statement with high awareness level was "Children with ASD may show intense interest in certain things/areas" (definitive finding; 48.1%, supportive finding; 42.9%). Optional questions and answers regarding the awareness and knowledge of residents about ASD are presented in Table 4.

Table 5 compares the duration of medical experience and the correct response status of ASD findings. Since all of the questions directed to the participants in this comparison were either the definitive or supportive findings of autism, the answers "definitive finding" and "supportive finding" were combined and coded as "finding". The other two answers "Not sure/I do not know" and "Not related to autism" were combined and coded as "not a finding". The duration of medical experience was divided into two groups as "less than four years" and "four years and more". When the correct responses of the participants to ASD findings in terms of duration of medical experience were examined, "difficulty in making eye contact" (100%) and "lack of age-appropriate language development" (91.5%), and "limited social smiling" (84.7%) findings were well-known findings among residents with less than four years of experience. On the other hand, "very sensitive vision, hearing and touch senses" (95.8%), "difficulty in making eye contact" (91.7%), and "seem unable to hear even if hearing tests are normal" (91.7%) findings were more prominent among residents with four or more years of experience. Table 5 presents the comparison of the duration of medical experience and the correct response status of the participants to the ASD findings.

Discussion

In the literature, awareness of ASD has been evaluated in many groups such as pediatricians, psychiatrists, neurologists, family physicians, pharmacists, educators, psychologists, and speech therapists throughout the society (3,16,17,22,24). One of the early medical contacts of children who have not yet been diagnosed with ASD may be with ENT physicians whom they are brought with suspicion of hearing and communication problems. The knowledge and awareness of ENT physicians about ASD symptoms is critical for early diagnosis (11). In this study, ASD awareness was evaluated in ENT residents, a group both receiving education and offering health services.

Table 3. Basic questions about autism spectrum disorder awareness and knowledge of otorhinolaryngology residents (n=83)

Questions	Number (%)							
	Definitive finding		Supportive finding		Not related to autism		Not sure/I do not know	
Children with ASD do not look at their name	13	(14.6)	55	(67.1)	7	(8.5)	8	(9.8)
Age-appropriate language development is delayed in children with ASD	26	(31.3)	48	(57.8)	5	(6.0)	4	(4.8)
Children with ASD have difficulty making eye contact	53	(64.6)	27	(32.9)	1	(1.2)	1	(1.2)
Children with ASD have difficulty in nonverbal communication	23	(28.4)	34	(42.0)	11	(13.6)	13	(16.0)
Children with ASD have stereotypic and repetitive behaviors	36	(43.9)	26	(31.7)	14	(17.1)	6	(7.3)
Children with ASD may have very sensitive vision/hearing and touch senses (such as closing their ears and not letting being touched when they hear some sounds)	32	(38.6)	37	(44.6)	9	(10.8)	5	(6.0)
Children with ASD have limited social smiling	24	(28.9)	43	(51.8)	9	(10.8)	7	(8.4)
Children with ASD use pronouns upside down (confuse me and you)	5	(6.2)	26	(32.1)	21	(25.9)	29	(35.8)
Children with ASD may appear to be unable to hear even if their hearing tests are normal	20	(24.1)	49	(59.0)	10	(12.0)	4	(4.8)
Children with ASD have difficulty understanding other people's body language	19	(23.2)	46	(56.1)	7	(8.5)	10	(12.2)
Children with ASD have difficulty understanding other people's gestures	20	(24.7)	38	(46.9)	13	(16.0)	10	(12.3)
Children with ASB may clap their hands from time to time	15	(18.3)	38	(46.3)	13	(15.9)	16	(19.5)
Children with ASD sometimes walk at their fingertips/revolve around themselves	10	(12.0)	26	(31.3)	24	(28.9)	23	(27.7)
Children with ASD find it difficult to imitate the people around them	3	(3.7)	29	(35.8)	24	(29.6)	25	(30.9)
Children with ASD say some pattern sentences/words to themselves over and over again	23	(28.0)	38	(46.3)	13	(15.9)	8	(9.8)
Children with ASD have a hard time showing what they want	8	(9.6)	29	(34.9)	20	(24.1)	26	(31.3)
Echolalia/parrot speech can be found in children with ASD	7	(8.4)	31	(37.3)	20	(24.1)	25	(30.1)
Children with ASD have limited use of simple body language such as "make bye-bye"	8	(9.9)	38	(46.9)	17	(21.0)	18	(22.2)
Children with ASD have difficulty in understanding and fulfilling orders	13	(15.7)	48	(57.8)	11	(13.3)	11	(13.3)

ASD: autism spectrum disorder, ENT: otorhinolaryngology

DSM-5 ASD diagnostic criteria emphasized the atypical processing of environmental sounds (25). In addition, the relative indifference towards human voice of children with ASD is known (26). While 23.8% of ENT residents answered as "definitive finding" to "Children with ASD may seem to be unable to hear even if their hearing tests are normal", 59.5% answered as "supportive finding". In our study, this finding can be interpreted as a finding with high awareness.

The American Academy of Pediatrics recommends that a child should be screened for routine development and autism when the child is 18 to 30 months old or at any time, if the caregiver has concerns about the ASD findings (27). Every child with ASD may need to be screened for speech and language development, and every child with these symptoms should be screened for ASD (27). Lack of language development may differ among children with ASD; some may not speak at all, others may have delayed language development (4,28). In our study, 89.1% of the respondents stated "Age-appropriate language development in children with ASD is delayed" as a definitive or supportive finding, so this can be interpreted as being known to a great extent.

In our study, 50% of the participants stated "Most of the children with ASD have superior skills in painting, music, mathematics and computer technologies" as definitive or supportive findings. Approximately 25.6% evaluated this finding as not related to ASD. It is known that 46% of those diagnosed with ASD have an average or above average intellectual functioning (4,29). While approximately half of the participants reported "Most of the children with ASD have strong memories" as definitive or supportive findings, 35.9% stated that they did not know the relationship of this finding with autism or were not sure about the relationship with autism. It is important for health professionals to recognize that children with ASD may have abilities that are indicative of higher intellectual functioning than expected, as it may mask the diagnosis of ASD and lead to a delay in diagnosis.

The most known finding by participants was having difficulty in making eye contact. While 64.6% of the participants stated that it was a definitive finding, 32.9% described it as a supportive finding. Because there is no laboratory test or biological marker to diagnose a child with ASD, it is very important to carefully observe the behavior of children (30). Eye contact may be weak or absent in patients with ASD (12). In an autism awareness study conducted in pharmacists in Istanbul, more than half of pharmacists reported that there was limited or no eye contact as an ASD finding (17). In a study conducted on primary school teachers, approximately half of the participants stated that they thought that children with ASD had difficulty in making eye contact (31).

In our study, having difficulty in establishing a friendship was defined by the participants as a definitive finding of autism by 60.3% and a supportive finding by 39.7%. Almost all of the participants attributed this finding to autism. "Making friends" is an issue that children are challenged, as reported by the parents of children with ASD in Dillenburger et al. (16) study. In another study, it was stated that children with ASD wanted to be friends with others but they did not have the ability to maintain friendship (32).

One of the well-known findings by the participants was that vision/hearing and tactile sensations of children with ASD may be very sensitive, such as closing their ears and not letting being touched when

Table 4. Optional part questions and answers about assistant physicians' awareness and knowledge of autism spectrum disorder (n=78)

Questions	Number (%)							
	Definitive finding		Supportive finding		Not sure/I do not know		Not related to autism	
Children with ASD cannot play imaginary games	3	(3.9)	19	(24.7)	22	(28.6)	33	(42.9)
ASD starts in early childhood	38	(48.7)	27	(34.6)	5	(6.4)	8	(10.3)
Children with ASD have difficulty establishing a relationship with friends	40	(51.3)	36	(46.2)	1	(1.3)	1	(1.3)
Children with ASD have difficulty in social communication	47	(60.3)	31	(39.7)	0	0	0	0
Children with ASD have anger attacks	24	(30.8)	35	(44.9)	7	(9.0)	12	(15.4)
Children with ASD like sameness/resist changes	31	(39.7)	35	(44.9)	7	(9.0)	5	(6.4)
Children with ASD have routines	34	(43.6)	31	(39.7)	9	(11.5)	4	(5.1)
Children with ASD may show intense interest in certain things/areas	37	(48.1)	33	(42.9)	5	(6.5)	2	(2.6)
Children with ASD have difficulties focusing on jobs outside their interests	36	(46.2)	36	(46.2)	4	(5.1)	2	(2.6)
Children with ASD have difficulty finding the object pointed by the finger	9	(11.5)	27	(34.6)	24	(30.8)	18	(23.1)
Children with ASD are sensitive to smell and taste	10	(13.0)	18	(23.4)	35	(45.5)	14	(18.2)
Children with ASD sometimes stare into space	15	(19.2)	31	(39.7)	21	(26.9)	11	(14.1)
Children with ASD will not open their arms and run towards the other person	11	(14.3)	24	(31.2)	25	(32.5)	17	(22.1)
Children with ASD may not want to share an object with others	14	(17.9)	35	(44.9)	16	(20.5)	13	(16.7)
Children with ASD may have different eating habits than their peers	13	(16.7)	35	(44.9)	21	(26.9)	9	(11.5)
Most children with ASD have strong memories	9	(11.5)	27	(34.6)	28	(35.9)	14	(17.9)
Many children with ASD have outstanding skills in painting, music, mathematics and computer technologies	12	(15.4)	27	(34.6)	19	(24.4)	20	(25.6)

ASD: autism spectrum disorder

they hear some sounds. Eighty-three point two percent of the residents stated "sensory sensitivity" as a finding. In addition, while approximately half of the participants reported "Children with ASD do not open their arms and run towards the other person" as a finding, one third stated that they were not sure or did not know. Avoidance from hug or contact is a relatively less known feature among the participants. In 2015, Biyani et al. (12) provided a comprehensive guide to the management of children with ASD for ENT practice. In this study, it was reported that patients with ASD might have delayed fine motor skills, their voice tone might not be compatible with expressed emotions, and they might have difficulty in empathizing. Avoidance from hug or contact was described as a symptom. Other specific features related to ASD are the fact that the thought process is mostly concrete, having difficulty in understanding literary expressions and idioms, and hypersensitivity to loud sounds, bright lights and strong odors (4,12,25,29).

The characteristics of ASD known by the residents according to the duration of medical experience were examined. Almost all of the residents who have been assistants for four years or more have described

Table 5. Comparison of the duration of the medical experience and the correct response status of the autism spectrum disorder findings of the participants

		Duration of medical experience			
		<4 years		≥4 years	
		n	%	n	%
Children with ASD do not look at their name	Not a finding	9	15.5	6	25.0
	Finding	49	84.5	18	75.0
Age-appropriate language development is delayed in children with ASD	Not a finding	5	8.5	4	16.7
	Finding	54	91.5	20	83.3
Children with ASD have difficulty making eye contact	Not a finding	0	0	2	8.3
	Finding	58	100	22	91.7
Children with ASD have difficulty in nonverbal communication	Not a finding	15	25.9	9	39.1
	Finding	43	74.1	14	60.9
Children with ASD have stereotypic and repetitive behaviors	Not a finding	15	25.4	5	21.7
	Finding	44	74.6	18	78.3
Children with ASD may have very sensitive vision/hearing and touch senses (such as closing their ears and not letting to be touched when they hear some sounds)	Not a finding	13	22.0	1	4.2
	Finding	46	78.0	23	95.8
Children with ASD have limited social smiling	Not a finding	9	15.3	7	29.2
	Finding	50	84.7	17	70.8
Children with ASB use pronouns upside down (confuse me and you)	Not a finding	31	53.4	19	82.6
	Finding	27	46.6	4	17.4
Children with ASD may appear to be unable to hear even if their hearing tests are normal	Not a finding	12	20.3	2	8.3
	Finding	47	79.7	22	91.7
Children with ASD have difficulty understanding other people's body language	Not a finding	13	22.4	4	16.7
	Finding	45	77.6	20	83.3
Children with ASD have difficulty understanding other people's gestures	Not a finding	15	26.3	8	33.3
	Finding	42	73.7	16	66.7
Children with ASB may clap their hands from time to time	Not a finding	22	37.3	7	30.4
	Finding	37	62.7	16	69.6
Children with ASD sometimes walk at their fingertips/revolve around themselves	Not a finding	37	62.7	10	41.7
	Finding	22	37.3	14	58.3
Children with ASD find it difficult to imitate the people around them	Not a finding	35	59.3	14	63.6
	Finding	24	40.7	8	36.4
Children with ASD say some pattern sentences/words to themselves over and over again	Not a finding	18	31.0	3	12.5
	Finding	40	69.0	21	87.5
Children with ASD have a hard time showing what they want	Not a finding	32	54.2	14	58.3
	Finding	27	45.8	10	41.7
Echolalia/parrot speech can be found in children with ASD	Not a finding	35	59.3	10	41.7
	Finding	24	40.7	14	58.3
Children with ASD have limited use of simple body language, such as "making bye-bye"	Not a finding	27	47.4	8	33.3
	Finding	30	52.6	16	66.7
Children with ASD have difficulty in understanding and fulfilling orders	Not a finding	14	23.7	8	33.3
	Finding	45	76.3	16	66.7

ASD: autism spectrum disorder

"Vision, hearing and tactile sensations can be very sensitive" as an ASD finding. Sensory sensitivity is a finding that can be easily noticed in the clinic. An ENT physician, who can detect signs such as closing his/her ears and not letting being touched when he/she hears some sounds, can easily suspect ASD and refer the child for further evaluation. Some findings such as seeming unable to hear even if hearing tests are normal are less known among physicians with a shorter duration of medical experience compared to those with more experience. It may be useful to focus on resident training by identifying lesser-known symptoms.

Strengths and Limitations of the Study

As a first step, due diligence should be made before initiatives to raise awareness on ASD. This study is the first known study in the literature to determine the awareness of ASD among ENT residents. In addition, the study was conducted in a large sample of all ENT residents in 13 public hospitals in Istanbul. The questions about the awareness of ASD used in our study question the findings that are important to be known by physicians, and are more common and more easily noticed. All of the questions are findings of ASD and the questionnaire can be instructive in this respect.

In our study, all of the sentences are a possible finding of ASD. The fact that our questionnaire was designed in this way is also intended to be instructive for residents receiving ENT specialist training. A statement that was not a finding was not included in the questionnaire in order to ensure that false statements are not catchy.

In our study, some questions about childhood autism are not included. Although these questions are used in screening tests, choosing more specific questions for ENT examination in terms of OCD awareness may be a limitation. In addition, the results of this study cannot be generalized to all residents in Turkey. This study, using a questionnaire completed by the participant himself/herself under observation, may have caused desirability bias to provide correct answers.

Conclusion

Autism awareness of the participants in our study can be considered as relatively good. Participants represent a group that has not yet become an ENT specialist, receiving training and providing health care. In addition to hearing disorders, comorbid medical disorders including sleep disorders, food allergies, eczema and asthma are more common in patients with ASD; ENT physicians should be careful and rigorous in terms of ASD (13,14). Analogs of this study should be applied to both residents and specialists in other ENT clinics and a situation determination should be made. If awareness of ASD can be integrated into ENT specialist training curriculum or bedside practices in outpatient clinic, especially early diagnosis and intervention can go to very high levels. This can be considered as a requirement considering the rapid increase in the prevalence of ASD.

Adequate knowledge and awareness of childhood autism among ENT residents will enable early detection of children with autism in the community, which will allow for early intellectual, social and behavioral interventions. The questionnaire used in this study is intended to be developed by the researchers as "Autism Awareness Scale in Otorhinolaryngology Physicians". This scale can be used later in other cities in Turkey and can contribute to early diagnosis of ASD in Turkey.

Ethics Committee Approval: Ethics committee approval was received from Marmara University Faculty of Medicine Clinical Research Ethics Committee (approval number: 09.2016.651, date: 02.12.2016).

Informed Consent: Informed consent was obtained from the physicians who agreed to participate in the study and participation was made on a voluntary basis.

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Investigation of Neutrophil-to-lymphocyte Ratio as a Biomarker to Evaluate Systemic Inflammation in Clinical Otosclerosis

Klinik Otosklerozda Sistemik Enflamasyonu Değerlendirmek için Biyobelirteç Olarak Nötrofil Lenfosit Oranının Araştırılması

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ABSTRACT

Introduction: Otosclerosis with yet unexplained etiopathogenesis, especially for inflammatory mechanism, affects otic capsule of ear and causes progressive hearing loss.

We aimed to investigate whether there is systemic inflammation in patients with otosclerosis by measuring neutrophil-to-lymphocyte ratio (NLR) as a biomarker.

Methods: This retrospective study included 98 patients which were divided into 2 groups as clinical otosclerosis and control group. The otosclerosis group consisted of 49 patients who stapes fixation was confirmed during operation based on operative notes and underwent surgery for otosclerosis from January of 2015 to November of 2018. The control group consisted of 49 age and sex-matched subjects who were scheduled for septoplasty or septorhinoplasty, who did not have any otologic complaints, and who had normal otologic examination. In both group of the patients white blood cell count (WBC), neutrophil and lymphocyte counts, and other laboratory data were recorded; and NLR values were calculated from their pre-op complete blood cell count differentials. Age, gender, WBC, neutrophil, lymphocyte, and NLR values were compared between the groups to evaluate any correlations in between.

Results: For the mean NLR, there was not a statistically significant difference between the groups (p=0.143). WBC comparison of the groups showed no statistically significance (p=0.315). For average neutrophil and lymphocyte counts, there were not a statistically significant difference between the groups; (p=0.757) and (p=0.071), respectively.

Conclusion: Although NLR is related to the prognosis and severity of several diseases, we found no association with clinical otosclerosis in this study. The reasons of insignificant results are thought to be that otosclerosis does not cause a systemic inflammation at all or the patients were in the inactive period of the disease.

Keywords: Otosclerosis, systemic inflammation, biomarker, neutrophil-to-lymphocyte ratio

ÖZ

Amaç: Otik kapsülü etkileyerek önemli bir ilerleyici işitme kaybı hastalığı olan otosklerozun etiyopatogenezini açıklayabilecek çeşitli mekanizmalar öne sürülmüş olup sistemik enflamasyon bunlardan birisidir.

Biz bu çalışmamızda otoskleroz hastalarındaki nötrofil/lenfosit oranını (NLO) ölçerek otosklerozun olası etiyolojik faktörlerden birisi olarak kabul edilen sistemik enflamasyonun varlığını araştırmayı amaçladık.

Yöntemler: Bu retrospektif çalışma 98 hastayı içermektedir. Hastalar klinik otosklerozu olanlar ve kontrol hastaları olarak 2 gruba ayrıldı. Otoskleroz grubu, hastanemizde 2015 Ocak-2018 Kasım tarihleri arasında otoskleroz ameliyatı geçirerek stapes fiksasyonu ameliyat notaları incelenerek teyit edilmiş 49 hastadan oluştu. Kontrol grubu, hastanemizde septoplasti veya septorinoplasti operasyonu planlanmış, otolojik şikayeti olmayan ve otolojik muayenesi normal olan, yaş ve cinsiyetleri otoskleroz grubu ile aynı 49 hastadan oluşturuldu. Her iki grupta da ameliyat öncesi yapılan rutin hemogram tetkiklerinden lökosit, nötrofil ve lenfosit sayıları ve diğer laboratuvar verileri kaydedilerek NLO değerleri hesaplandı. Yaş ve cinsiyet; lökosit, nötrofil ve lenfosit sayıları ile NLO değerleri ortalamaları gruplar arasında karşılaştırılarak aradaki ilişki değerlendirildi.

Bulgular: Ortalama NLO için gruplar arasında fark olmakla birlikte bu fark istatistiksel açıdan anlamlı değildi (p=0.143). Ortalama lökosit sayısı açısından gruplar arasında fark olmakla birlikte bu fark da istatistiksel açıdan anlamlı değildi (p=0.315). Aynı şekilde ortalama nötrofil ve özellikle lenfosit sayıları için gruplar arasında fark olmakla birlikte bu farklar istatistiksel açıdan anlamlı değildi; sırasıyla (p=0.757) ve (p=0.071).

Sonuç: NLO'nun enflamatuvar bileşeni olan birçok hastalığın prognozu ve şiddeti ile ilişkisi literatürde gösterilmiş olmasına rağmen, biz bu çalışmada klinik otoskleroz ile istatistiksel açıdan anlamlı bir ilişkisini gözlemlemedik. Biz bu sonuçlara göre, otosklerozun sistemik bir enflamasyona neden olmadığını ya da hastaların otosklerozun histopatolojik olarak inaktif döneminde olduklarını düşünmekteyiz.

Anahtar Kelimeler: Otoskleroz, sistemik inflamasyon, biyobelirteç, nötrofil lenfosit oranı

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Introduction

Otosclerosis is a bone remodeling disorder of the human bony inner ear leading to progressive hearing loss that usually affects both ears with yet unexplained etiopathogenesis. It is a unique human disease with no animal model at all. It does not have any lesion or any systemic clue other than the ear. Genetic predisposition, viral infection, autoimmunity, inflammatory mechanisms, hormonal and metabolic factors have been blamed for the pathogenesis of the disease. Some proinflammatory cytokines have been studied to investigate the inflammatory mechanism of otosclerosis (1).

Systemic inflammation can be measured by using a variety of biochemical and hematological markers. Neutrophil-to-lymphocyte ratio (NLR) has been recognized as a systemic inflammatory marker in recent years. Since high NLR correlates with the severity of the inflammation, it can help predict clinical outcomes for many systemic diseases. NLR has also been studied in various autological disorders such as Bell's palsy (BP), sudden hearing loss, tinnitus, chronic otitis media (COM) (2). In contrast to many inflammatory cytokines, determination of NLR is a very practical and readily available way to detect inflammation without extra cost because it can be easily calculated from a simple complete blood cell count (CBC) (3).

In this study, we aimed to investigate whether there is ongoing systemic inflammation in patients with clinical otosclerosis. By doing so, we hoped to help clarify one of the suspected etiopathogenetic factors of otosclerosis by measuring NLR as an inexpensive, simple and reproducible testing method. To the best of our knowledge, this is the first study in the literature to investigate serum NLR in patients with otosclerosis.

Methods

This study is a retrospective investigation of the data obtained from the digital patient files. This study was performed with the approval of the Clinical Research Ethics Committee of İstanbul Bağcılar Training and Research Hospital (approval number: 2019.01.2.04.119.r1.008). This study included 98 patients, who were divided into two groups as clinical otosclerosis and control group. The otosclerosis group consisted of 49 patients with confirmed stapes fixation during surgery based on operative notes and underwent surgery for otosclerosis (eg. Stapedectomy) between December 2014 and November 2018 at the Department of Otolaryngology at İstanbul Bağcılar Training and Research Hospital. Tympanic membranes of the patients were intact and there was no hyperemia or any other infection sign in the preoperative otoscopic examination. In these patients, white blood cell count (WBC), neutrophil and lymphocyte counts, and other laboratory data were recorded; and NLR values were calculated from pre-op CBC differentials by dividing neutrophil count by lymphocyte count.

The control group consisted of 49 age- and gender-matched subjects who were scheduled for septoplasty or septorhinoplasty in our hospital, who did not have any otologic complaints, and who had a normal otologic examination. They underwent blood count analysis from which the same hematological parameters described above were recorded and calculated from. Age, gender, WBC, neutrophil and lymphocyte counts and NLR values were compared between the groups to evaluate any correlations in between. Patients with history or clinical findings of any acute or chronic infectious, inflammatory or systemic disease that could have an effect on blood counts according to strict literature review were excluded from the study completely.

Statistical Analysis

SPSS (Version 15) program was employed for evaluating the data gathered in the study. Besides using descriptive statistics (mean, standard deviation) in evaluating the data, independent samples t-test was used for comparing the quantitative data, and for comparing the normally distributed parameters between groups. The significance level was set at $p<0.001$ and $p<0.05$.

Results

This study included 98 patients [28 females (28.6%) and 70 males (71.4%)] with a mean age of 37.79±10.84 years. Otosclerosis group consisted of 49 patients with a mean age of 37.85±9.72 years. The control group consisted of 49 patients with a mean age of 37.73±11.96 years. There was no statistically significant difference between the groups in terms of mean ages and genders (p=0.235) (Table 1).

The mean NLR of the otosclerosis and the control group was 1.99±0.78 and 1.76±0.55, respectively. The independent samples t-test showed no statistically significant difference between the groups (p=0.143). The mean WBC level was 7.15±1.87 in the otosclerosis group and 7.43±1.88 in the control group. WBC comparison of the groups showed no statistical significance (p=0.315).

The average neutrophil counts of the otosclerosis and the control groups were 4.16±1.47 and 4.14±1.23, respectively (p=0.757). The mean lymphocyte counts of the otosclerosis and the control groups were 2.22±0.64 and 2.46±0.74, respectively (p=0.071). The independent samples t-test showed that there was no statistically significant difference between the groups (Table 2).

Table 1. Demographic features of the groups

	Patient		Age
	Male	Female	
Otosclerosis group	14 (28.6%)	35 (71.4%)	37.85±9.72
Control group	14 (28.6%)	35 (71.4%)	37.73±11.96
Total	28	70	37.79±10.84
			p=0.235

Table 2. Laboratory data of the groups. The independent sample t-test, p<0.05

	Otosclerosis group	Control group	p
WBC	7.15±1.87	7.43±1.88	0.315
Neutrophil (10^3/μ)	4.16±1.47	4.14±1.23	0.757
Lymphocyte (10^3/μ)	2.22±0.64	2.46±0.74	0.071
Neutrophil to Lymphocyte Ratio	1.99±0.78	1.76±0.55	0.143

WBC: white blood cell

Discussion

Although less than 0.5% of the general population develops clinical otosclerosis, the development of histological otosclerosis without clinical symptoms is much more common, which is reported in about 10 % of large autopsy series (4). Because inflammatory mechanism has also been one of the blamed factors of the disease, an anti-inflammatory therapy may be considered to control early active phases of otosclerosis (1). Approximately 5000 studies have been published based on the pathology and treatment of otosclerosis in the last 5 decades. In the second half of this period, more than 1500 articles have been published, while only about 100 publications provided data on the etiopathogenesis of the disease; so that the etiopathogenesis of otosclerosis yet remains unexplained. Viral, genetic, inflammatory, autoimmune, environmental, hormonal and some other factors have been blamed in both the development and the progression of the disease (1). Some molecules such as transforming growth factor-beta (TGF-β1), tumor necrosis factor-alpha (TNF-α), and bone morphogenetic proteins (BMP) have been studied to reveal the suspected relationship between the inflammatory mechanism and otosclerosis. TGF-β1 is a cytokine involved in the pathogenesis of various inflammatory diseases and associated with otosclerosis in some studies (5). Increased expression of TNF-α, which is a proinflammatory cytokine, has been demonstrated in the otosclerotic bone. It may lead to extensive osteoclast activation and bone resorption (6,7). BMP, which has been suggested to play a role in pathological bone remodeling underlying otosclerosis, is also an inflammatory cytokine (1).

The NLR, combining the deleterious effects of neutrophilia and lymphopenia, is now recognized as a systemic inflammatory marker (8). In contrast to other inflammatory biomarkers such as interleukin-6 (IL-6), IL-1 α, TNF-α, determination of NLR does not incur any additional cost. It can easily be calculated from the neutrophil and lymphocyte counts available from routine CBC differentials (9). In several studies, an association has been found between a high NLR level and the prognosis and severity of disease in several cancers, and in inflammatory diseases such as BP and sudden hearing loss (10-13).

In recent studies, NLR has been identified as a reliable marker for the diagnosis and prediction of many ORL diseases. Özler and Günak (14) showed that mean NLR values were significantly higher in patients with BP than in the control group. They described a positive correlation between NLR values and the grade and prognosis of BP. Kılıçkaya et al. (15) investigated the systemic inflammatory effect of COM with cholesteatoma and showed that NLR had no predictive value with respect to bone erosions and associated complications in patients with cholesteatoma. Eryilmaz and Derin (16) studied the NLR values in pediatric patients and compared with those in COM with and without cholesteatoma. There was no statistically significant difference between the two groups in terms of NLR. However, mean platelet volume was lower in patients with cholesteatoma than controls, which they suggested could act as a predictor for cholesteatoma. When 247 patients with sensory neural hearing loss (SHL) were compared according to the recovery, Ulu et al. (17) reported that NLR levels were higher in patients who did not recover. This may be explained with the higher inflammatory situation in unrecovered patients, and this result may help clinicians caring for SHL patients with higher NLR levels in terms of treatment and prognosis. Kum et al. (10) reported that NLR values were significantly higher in patients with SHL compared to the control group. Similarly, the mean NLR was higher in the unrecovered patients when compared with those who recovered; a significant correlation was observed between NLR values and the severity of hearing loss, indicating inflammation. Atan et al. (18) conducted a study with 77 patients and showed that NLR was high in OME. In another study, NLR was similarly higher in OME patients compared with the control group, and this finding showed the importance of the inflammation in the pathophysiology of OME (4).

In summary, NLR is an easily measured biomarker that correlates with clinical status. It is calculated from CBC and is an inexpensive, easy to obtain, a widely available marker of inflammation that can help in the risk classification of patients with various diseases (19,20). It is as valuable as many other high-cost inflammatory markers (9). For these reasons, we measured NLR, neutrophil, lymphocyte and WBC counts in patients with otosclerosis and compared to values in the control group in both age-matched and gender-matched manner to investigate whether there is a systemic manifestation in the disease process and inflammatory factor in the etiopathogenesis. To the best of our knowledge, the present study is the first to assess the NLR values in patients with otosclerosis. While an increase in NLR is expected in inflammatory diseases, we found no increase in NLR and WBC counts in patients with otosclerosis that may demonstrate that no systemic reaction is produced by the disease. Another reason why the result is not significant might be that the otosclerosis group was not in the active inflammation period of the disease process. The limitation of our study was the lack of a group of patients with active inflammation. However, it is very difficult to catch and create such a group of otosclerosis patients in clinical practice.

Conclusion

Although NLR is related to the prognosis and severity of several diseases, we found no association with clinical otosclerosis in this study. The reasons for insignificant results are thought to be that otosclerosis does not cause a systemic inflammation at all or the patients were in the inactive period of the disease. Further studies will be beneficial to clarify these.

Ethics Committee Approval: This study was performed with the approval of the Clinical Research Ethics Committee of İstanbul Bağcılar Training and Research Hospital (approval number: 2019.01.2.04.119. r1.008).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

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Preliminary Outcomes of Hip Arthroscopy in the Treatment of Femoroacetabular Impingement with Early Stage Osteoarthritis

Femoroasetabular Sıkışma Sendromunun Eşlik Ettiği Erken Evre Kalça Artrozunda Artroskopik Tedavinin Erken Dönem Sonuçları

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ABSTRACT

Introduction: Femoroacetabular impingement (FAI) has been recognized as a risk factor of osteoarthrosis that causes a painful joint and decreased range of motion. Arthroscopic procedures were used for the treatment of FAI with satisfactory outcomes. However, the outcomes of arthroscopic treatment after arthritic findings have been shown to be unsatisfactory. There are only limited studies focusing on the effect of arthroscopic treatment of FAI on the setting of arthrosis. In this study, we aimed to evaluate the early results of arthroscopic treatment in patients with FAI and osteoarthritis (OA).

Methods: We retrospectively identified 17 consecutive patients with FAI and Tönnis grade 1 or 2 OA of the hip who had undergone hip arthroscopy and had a follow-up period of at least one year. The arthroscopic procedures included femoral osteoplasty, acetabular rim trimming, labral repair, labral debridement, microfracture and debridement of the ligamentum teres. The Tönnis grading was used in this study for the assessment and grading of OA. Functional outcomes were measured by Harris Hip score (HHS), Hip Outcome Score (HOS) and Short Form 12.

Results: At the last follow up, the mean HHS and HOS increased from 53.2 and 65.3 to 82.4 and 88.1, respectively. In total, 16 of 17 (94%) patients reported that they were satisfied with the outcome of the surgery. One patient reported that the symptoms relieved for 6 months, but returned. He was offered arthroplasty but he refused.

Conclusion: In the current study, it was observed that arthroscopic treatment could help to relieve patient symptoms in early stage OA with FAI.

Keywords: Hip arthroscopy, femoroacetabular impingement, hip osteoarthritis

ÖZ

Amaç: Femoro-asetabular sıkışma (FAS) sendromu ağrı ve hareket kısıtlılığı ile beraber dejeneratif eklem hastalığının bir nedenidir. Artroskopik yöntemler erken dönemde FAS tedavisinde etkili olarak kullanılmaktadır. Ancak eklemde dejeneratif bulguların ortaya çıkmış olması artroskopik tedavinin başarısını olumsuz olarak etkilemektedir. Literatürde, artroz gelişmiş kalçalarda artoskopik yöntemlerin başarısını araştıran çalışma sayısı kısıtlı olmakla beraber artroskopik tedavinin başarısı konusunda bir fikir birliğine varılamamıştır. Biz bu çalışmamızda kliniğimizde FAS sendromu ile beraber Tönnis evre 1-2 artrozu (OA) olan hastalarda artroskopik tedavinin kısa dönem klinik sonuçlarını araştırmayı amaçladık.

Yöntemler: Kliniğimizde FAS sendromu ile beraber Tönnis evre 1-2 OA'sı olan ve artroskopik olarak tedavi edilmiş 17 hasta retrospektif olarak incelendi. Artroskopik tedavide artroskopik bulgulara göre femoral osteoplasti, asetabular tıraşlama, labral tamir, labral debridman, mikro kırık ve lig teres debridmanı yapıldı. Radyolojik değerlendirmede Tönnis evrelemesi ve OA'nın değrelendirilmesinde kullanıldı. Hastaların fonksiyonel durumları operasyon öncesi ve sonrası Harris Kalça skoru (HKS), Hip Outcome skoru (HOS) ve Short Form 12 ile değerlendirildi.

Bulgular: Son klinik kontrolde HKS ve HOS sırasıyla 53,2 ve 65,3'ten 82,4 ve 88,1'e yükseldi. Toplamda 17 hastanın 16'sı (%94) sonuçtan memnun olduklarını bildirdi. Bir hasta semptomlarının yaklaşık 6 ay kadar gerilediğini ancak tekrar başladığını ifade etti. Bu hastaya artroplasti önerildi ancak hasta kabul etmedi.

Sonuç: Bu çalışma bize artroskopik tedavinin erken orta evre OA'sı gelişmiş FAS sendromlu hastalarda erken dönemde semptomatik ve fonksiyonel iyileşme sağladığını gösterdi.

Anahtar Kelimeler: Kalça artroskopisi, femoroasetabular sıkışma, osteoartrit

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Introduction

Femoroacetabular impingement (FAI) has been recognized as a risk factor for labral tears, chondral delamination and finally osteoarthrosis which lead to pain and decreased range of motion (ROM) on the hip joint (1). Repetitive microtrauma at flexion and internal rotation can cause labral delamination and tears caused by abnormal femoral offset or acetabular over coverage. Satisfactory outcomes with the arthroscopic treatment have been reported if arthroscopic osteoplasty of the impinging lesion and debridement of the injured labrum are performed in the setting of normal femoral and acetabular articular surfaces (2,3). However, only few studies have specifically evaluated patients with FAI and osteoarthritis (OA), and they generally reported favorable results in terms of patient-reported outcome measures (4-7). Daivajna et al. (5) concluded that hip arthroscopy improved outcome scores in 56% of patients with severe OA of the hip (Tönnis grade 2 and 3) for at least two years after surgery. On the other hand, Philippon et al. (8) showed that, in the elderly population, 20% of patients aged 50 years and older required total hip arthroplasty (THA) within three years of hip arthroscopies.

In this study, our hypothesis was that arthroscopic intervention could reveal the symptoms of patients with OA and delay the need for arthroplasty. Therefore, we aimed to report our preliminary results of hip arthroscopy in the treatment of FAI with early stage OA.

Methods

The Institutional Review Board of İstanbul Training and Research Hospital approved this study (decision no: 1523) and consent form was obtained from all patients. We retrospectively identified 17 consecutive patients with FAI and Tönnis grade 1 or 2 OA of the hip who had undergone hip arthroscopy and included them in this study. Inclusion criteria were patients diagnosed with FAI and OA based on physical examination and radiographs who were operated arthroscopically and had at least one-year follow-up. Exclusion criteria were as follows: patients with no signs of impingement (negative impingement sign, negative FABER test, and no radiographic signs of impingement), patients with avascular necrosis or previous hip surgery (open or arthroscopic). The diagnosis of FAI was based on patient history, physical examination and radiological findings consistent with FAI of cam type, pincer type or mixed. The OA is diagnosed based on patient history and clinical examination, and graded on plain radiographs. The Tönnis radiological grading was used in this study for the assessment and grading of OA as this is widely used in practice and is practical in the outpatient clinical situation than other systems that may require the physical measurement of radiographs or other imaging techniques. In Tönnis grading, no signs of OA is defined as “grade 0”; increased sclerosis, slight narrowing of the joint space, no or slight loss of head sphericity or lipping at the joint margins are defined as “grade 1”; small cysts, moderate narrowing of the joint space, moderate loss of head sphericity are defined as “ grade 2” and large cysts, severe narrowing or obliteration of the joint space, severe deformity of the head are defined as “grade 3” (9).

The surgical decision was made based on clinical findings and radiological images. Patients diagnosed with FAI and early/moderate stage OA that did not respond to conservative treatment for six months were scheduled for arthroscopic treatment.

Age at the time of surgery, gender, duration of symptoms and hip ROM were noted. Preoperative and postoperative subjective pain scores were measured by visual analog scale. Preoperative and postoperative functional outcomes were measured by Harris Hip score (HHS), Hip Outcome score (HOS) and Short Form 12 at six weeks, six months, one year and at the last follow up. Surgical findings including chondral pathologies, labral tears and osteophytes were noted.

Surgical Technique

Under general anesthesia and muscle relaxation, traction was applied on fracture table to distract the hip joint properly. All surgeries were performed by the first author. Standard anterolateral portal was established under fluoroscopic guidance and an anterior portal was established under direct visualization. Central compartment was first evaluated. If present, intra-articular free bodies were removed, and chondral or labral pathologies were addressed. The treatments for chondral pathologies were debridement and microfracture (Figures 1,2). Labral tears were either repaired or debrided (Figures 3-5). Repair versus debridement of the labrum was based on the amount of labral tissue, location of the tear, size of the tear, and reparability of the tear. Acetabular over-coverage (pincer) was removed using the burr. Access to the peripheral compartment was achieved through a capsulotomy between anterolateral and anterior portals and a transverse cut. Traction

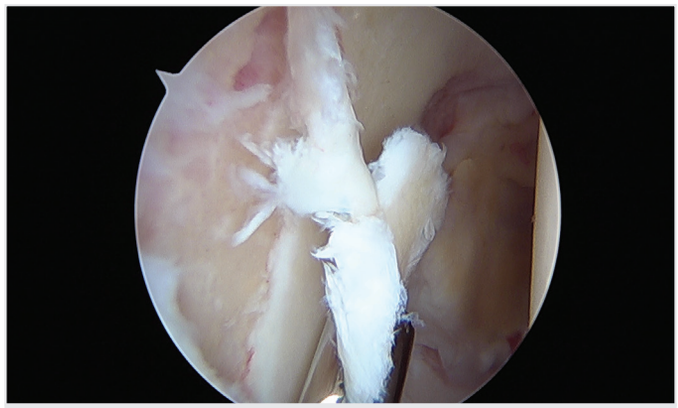

Figure 1. Unstable cartilage remnants are removed

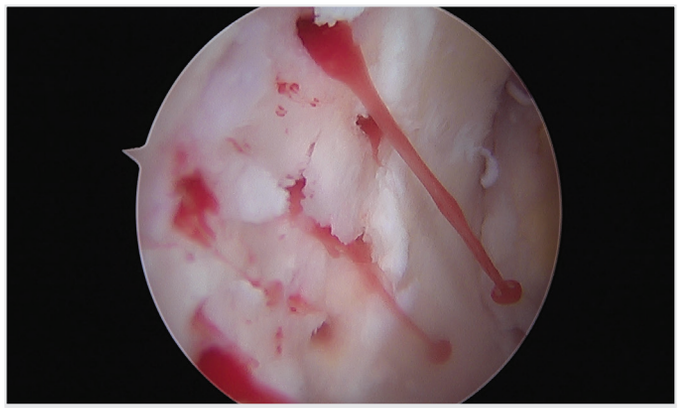

Figure 2. Blood and marrow elements coming from microfracture holes

was then released and a careful cam resection, between far lateral, far medial/caudal and posterior was performed. An intra-operative dynamic assessment of impingement was performed in order to avoid residual impingement. The surgical procedure was individualized and femoral micro-fracturing was performed in cases with localized cartilage loss (Figure 6,7), depending on the intra-operative findings so posterior or lateral osteophytes were resected if present (Figure 8). Arthroscopic findings and treatments were noted including chondral surfaces, labrum, ligamentum teres, capsule, femoral neck, and acetabular rim, as well as other pathologies such as loose bodies and adhesions (Table 1). Patients were evaluated with preoperative and postoperative X-rays (Figure 9-12). Patients without micro-fracturing were generally allowed full weight bearing. In case of micro-fracturing, partial weight bearing was recommended for 6 weeks.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency and percentage values were used in the descriptive statistics of the data. The distribution of the variables was measured by Kolmogorov-Smirnov test. Wilcoxon test was used in the analysis of the dependent quantitative data. McNemar's test was used in the analysis of the dependent qualitative data. Furthermore, the SPSS 22.0 program was used to conduct the analyses.

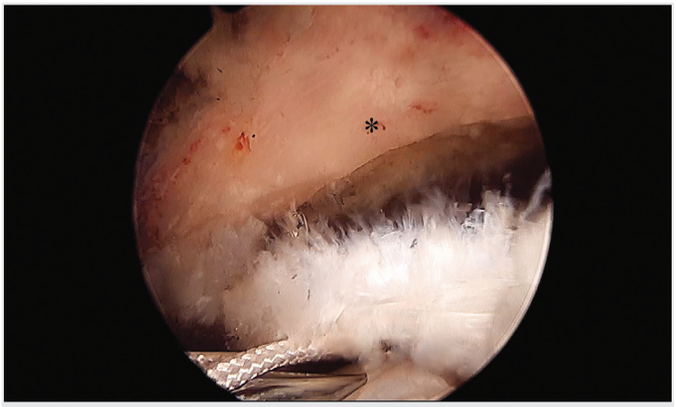

Figure 3. Rim trimming is performed and detached labrum

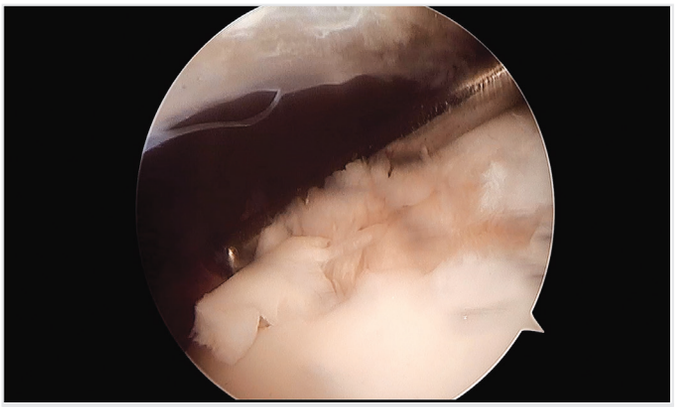

Figure 6. Femoral chondral defect

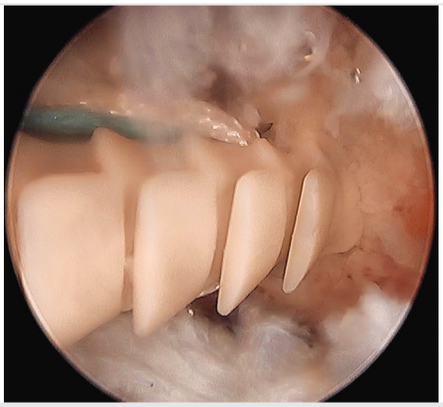

Figure 4. Detached labrum is repaired with knotless suture anchors

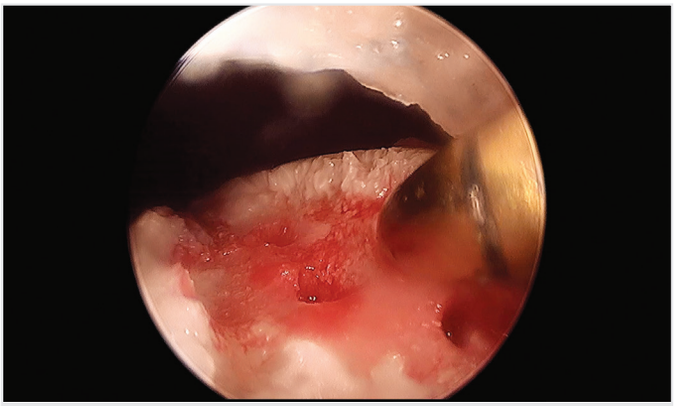

Figure 7. Micro-fracture performed with surgical awls

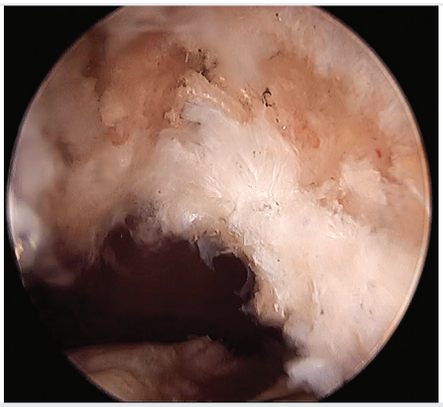

Figure 5. Repaired labrum

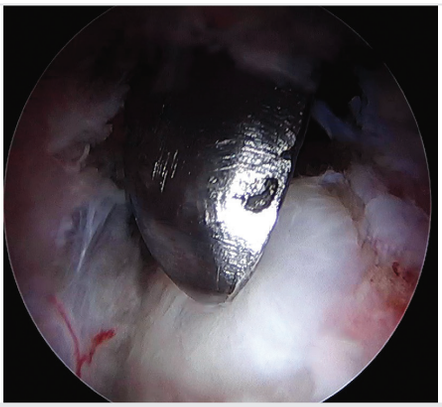

Figure 8. Femoral osteophytes

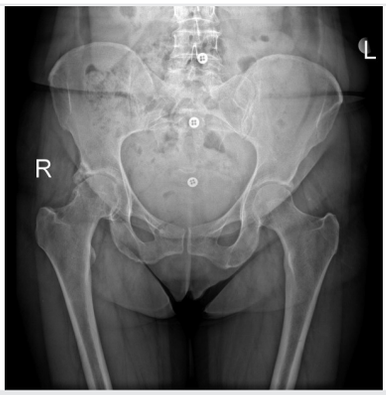

Figure 9. Preoperative X-ray of a patient with pincer type impingement and Tönnis grade 2 arthrosis

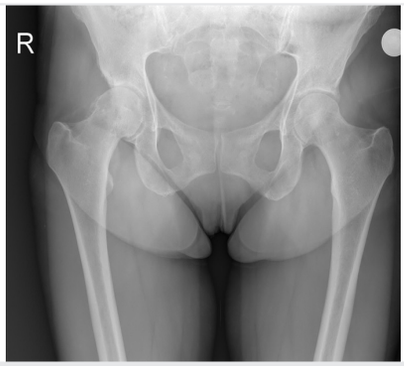

Figure 10. Postoperative X-ray of the same patient with pincer type impingement and Tönnis grade 2 arthrosis

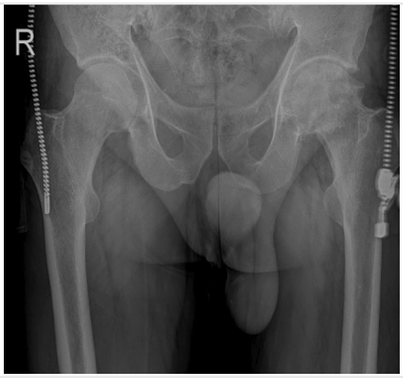

Figure 11. Preoperative X-ray of a patient with cam type impingement and Tönnis grade 2 arthrosis

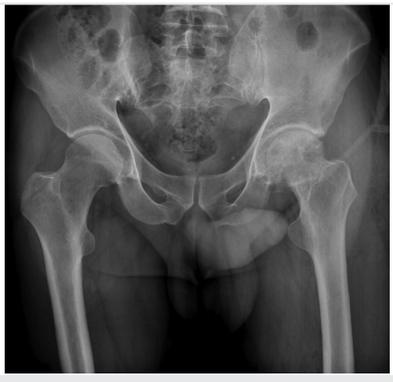

Figure 12. Postoperative X-ray of the same patient with cam type impingement and Tönnis grade 2 arthrosis

Results

The mean age of the patients was 47.2±4.9 years. The mean duration of symptoms reported before surgery was 6.4±2.03 years and mean postoperative follow-up was 14±1.85 months. Eight patients were male and nine were female. According to the preoperative Tönnis classification, 10 hips had grade 1 OA and seven had grade 2 OA.

On radiographic assessment, the mean anterior joint space, the mean lateral joint space and the mean joint space at the fovea were measured as 3.6 mm, 3.7 mm and 3.8 mm, respectively. Only in two patients, the joint space was measured less than 2 mm in one of the spaces.

On clinical examination, mean flexion was 102 °C (range, 90 °C to 140 °C), mean internal rotation was 30 °C (range, 10 °C to 45 °C), and mean external rotation was 33 °C (range: 15 °C to 55 °C) preoperatively. At the last follow-up, mean flexion was 100 °C (range, 90 °C to 140 °C), mean internal rotation was 32 °C (range: 10 °C to 45 °C), and mean external rotation was 35 °C (range, 20 °C to 55 °C).

All cases had labral lesions. The labrum was sutured in two hips and debridement of labral tears were performed in 15 hips. Depending on the intraoperative condition, additional procedures were performed except for resection of impinging bone (Table 1). Grade 4 chondral lesions were localized at the impingement zone (ventral-cranial acetabulum) in 12 cases and at the corresponding femur in three cases. Micro-fracturing was performed in these areas in a total of 13 cases. Of the included procedures (Table 1), 16 patients underwent cam resections and five patients underwent pincer resections.

A comparison of preoperative scores compared with those obtained at the last follow-up revealed improvements for all measured outcomes. At the last follow-up, the mean HHS and HOS increased from 53.2 and 65.3 to 82.4 and 88.1, respectively (Table 2).

Table 1. Arthroscopic procedures performed in included hips

Treatment	Number of procedures
Acetabular micro-fracturing	12
Femoral micro-fracturing	3
Labral repair	2
Labral debridement	15
Cam-osteoplasty	16
Pincer-rim trimming	5
Loose body removal	9
Ligamentum teres debridement	3

Table 2. Preoperative and follow-up scores

	Preoperative mean score	Postoperative mean score	p
Modified Harris Hip score	53	82	<0.001
HOS for activities of daily living	65	88	<0.001
HOS for sports	42	63	<0.001
SF-12 physical component score	33	45	<0.001
VAS	6	3	<0.001

HOS: Hip Outcome score, SF: Short Form, VAS: visual analog scale

Patients were asked at the last follow-up whether they were satisfied with the surgery, and 16 of 17 (94%) patients reported that they were satisfied with the outcome of the surgery. One patient reported that the symptoms relieved for 6 months but returned. He was offered total hip replacement, but he refused. None of the patients had revision arthroscopy. No complications were observed in this small cohort.

Discussion

The most important finding in this study was that arthroscopic treatment of patients with FAI with mild to moderate OA showed significant improvements in all clinical scores at least one year of follow-up. Patients with Tönnis grade 1 or 2 benefited from arthroscopic treatment. In addition, we observed clinical improvement in cases with a joint space of less than 2 mm. However, the number of patients with a narrowed joint space less than 2 mm was too small (n=2) to reach any definitive conclusions.

Hip arthroscopy has been used for a long time to effectively treat femoral and acetabular deformities (cam and pincer, respectively), and repair injuries of the acetabular labrum and adjacent cartilage (10-12). In many studies, hip arthroscopy has been reported to have poor clinical outcomes when performed in patients with advance OA (13). Haviv and O'Donnell reported their experience in 564 hips with OA and they reported that 50% of patients required THA within 1.5 years after arthroscopy (14). In addition, they stated that patient's age (older than 55 years) and advanced OA (Tönnis 3) were associated with poor clinical results. In our study, we only included patients with Tönnis grade 1 and 2 OA. This may be main explanation of our better results. Only one patient needed replacement surgery after a minimum follow-up of 12 months. Therefore, debridement of osteophytes and impinging lesions may decelerate the OA in hip joint.

Philoppon et al. (8) reported their outcomes of arthroscopic treatment of FAI and stated that patients improved in terms of clinical scores, but that they had an increased rates of conversion to THA with any joint space of 2 mm or less (8). In our study, we did not see any clinical difference in patients with joint space less than 2 mm or not. However, only two patients had joint space less than 2 mm. On the other hand, Beaulé et al. (15) showed no correlation between the outcome after open correction for FAI and the intraoperatively documented chondral damage.

Daivajna et al. (5) reported their results in patients with Tönnis grade 2 and 3 OA who had undergone hip arthroscopy and they found that 44% of patients required a total hip replacement after a mean of 18 months after surgery. This worse outcome is probably due to patient selection. They included patients with advanced OA in their study, and it is not a surprising that they had inferior outcomes after surgery. However, they stated that 44% failure implied 56% success and that patients should decide whether 56% chance of symptomatic improvement for a mean of two years was acceptable or not. These patients would go THA even if they had not undergone hip arthroscopy. In addition, hip arthroscopy has very little complication rate and does not compromise possible THA (16).

Arthroscopic debridement has been used for the treatment of the knee OA, it was abandoned after worse outcomes (17). Arthroscopic debridement has been shown to have no clinical benefit compared to conservative or placebo treatment in knee joint (18). Therefore, it has been avoided in the treatment of hip OA. However, biomechanical features of the hip joint are unlike to knee joint (19,20). It is much more congruent compared to knee, and unlike knee osteophytes, is not only the consequence but also the reason of the disease (21,22). Therefore, debridement of osteophytes and impinging lesions may decelerate the OA in the hip joint. On the other hand, there are limited studies investigating the results of hip arthroscopy in OA and patients should be informed for success rates and any possible revision or replacement surgeries (23,24). Literature still lacks long-term controlled studies, and future studies should focus on long-term results in large cohorts.

Study Limitations

There are some limitations to this study. The number of patients included in this study was limited, there was no control group and follow-up period was relatively short. However, early outcomes can give us what to expect in a short time after surgery. In addition, arthroscopic treatment of arthritic hip joint is not a standard treatment and is individualized for each patient. Therefore, it is not always possible to conceive which steps of the surgery affected the outcomes most.

Conclusion

Hip arthroscopy may be effective in the treatment of early stage OA with a low complication rate. Early results after surgery are satisfactory, however; patients should be informed for high conversion rates to THA particularly in advanced cases.

Ethics Committee Approval: The Institutional Review Board of İstanbul Training and Research Hospital approved this study (decision no: 1523).

Informed Consent: Consent form was obtained from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - T.G.; Concept - T.G.; Design - T.G.; Data Collection and/or Processing - T.G.; Analysis and/or Interpretation - T.G., Y.Ö.; Literature Search - T.G., Y.Ö.; Writing Manuscript - T.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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The Effect of Oral Isotretinoin on Bone Healing in Rabbit Rhinoplasty Model: An Experimental Study

Oral İsotretinoinin Tavşan Rinoplasti Modelinde Kemik İyileşmesine Etkisi: Deneysel Çalışma

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ABSTRACT

Introduction: Since the age at which rhinoplasty is frequently performed is also the age at which acne is frequently seen, a person may be a candidate for both this surgery and isotretinoin therapy. In this study, we aimed to investigate the effect of oral isotretinoin on bone healing in rabbit rhinoplasty model.

Methods: Twelve one-year-old New Zealand white rabbits (3-4 g, all male) were included in the study. The animals were divided into two groups as experimental (n=6) and control group (n=6). One mg/kg oral isotretinoin and olive oil mixture was given each day orally to the experimental group starting from the surgery day. Lateral nasal osteotomy was performed starting from the distal end of the nasal bone. The rabbits were sacrificed 4 weeks later and the nasal bone specimens were sent for histopathological examination to evaluate bone healing between the groups. Bone healing was classified according to the grading described by Huddleston.

Results: Grade 1 bone healing was observed in four samples (66.7%) and grade 2 healing was observed in two samples (33.3%) in the study group. In the control group, three samples (50%) had grade 2 bone healing and the other three samples (50%) had grade 3 bone healing. The difference between the groups was statistically significant (p=0.027).

Conclusion: Bone healing was found to be slower in the isotretinoin group than in the untreated group. Although there are studies in the literature reporting that isotretinoin has a positive effect on bone healing, we observed opposite results. Therefore, we think that more experimental and clinical studies are needed to clarify this effect.

Keywords: Isotretinoin, lateral nasal osteotomy, bone healing

ÖZ

Amaç: Burun estetiğinin sıklıkla yapıldığı yaş, aynı zamanda aknenin de sık görüldüğü yaş olduğundan, bir kişi hem bu ameliyat için hem de izotretinoin tedavisi için aday olabilir. Bu nedenle, çalışmamızda tavşan rinoplasti modelinde oral izotretinoinin kemik iyileşmesi üzerine etkisini araştırmayı amaçlandık.

Yöntemler: On iki adet bir yaşında Yeni Zelanda beyaz tavşanı (3-4 g, tümü erkek) çalışmaya dahil edildi. Hayvanlar deneysel (n=6) ve kontrol grubu olmak üzere iki gruba ayrıldı. Operasyon gününden itibaren deney grubuna her gün oral olarak 1 mg/kg oral izotretinoin ve zeytinyağı karışımı verildi. Nazal kemiğin distal ucundan başlayan lateral nazal osteotomi yapıldı. Tavşanlar 4 hafta sonra sakrifiye edildi ve gruplar arasındaki kemik iyileşmesini değerlendirmek için nazal kemik örnekleri histopatolojik incelemeye gönderildi. Tavşanların kemik iyileşmesi, Huddleston tariflenen kemik iyileşme skoruna göre değerlendirildi.

Bulgular: Çalışma grubundaki 4 örnekte (%66,7) 1.derece kemik iyileşmesi ve 2 örnekte (%33,3) 2. derece kemik iyileşmesi gözlendi. Kontrol grubunda ise 3 örnekte (%50) 2. derece kemik iyileşmesi, diğer 3 örnekte (%50) 3.derece kemik iyileşmesi mevcuttu. Gruplar arasındaki fark istatistiksel olarak anlamlıydı (p=0.027).

Sonuç: İzotretinoin grubundaki kemik iyileşmesi, tedavi edilmemiş gruba göre daha yavaş bulundu. Literatürde izotretinoinin kemik iyileşmesi üzerinde olumlu etkisi olduğunu bildiren çalışmalar olmasına rağmen, biz çalışmamızda bunun karşıt sonuçlarını gözlemledik. Bu nedenle, bu etkiyi açıklığa kavuşturmak için daha fazla deneysel ve klinik çalışmaya ihtiyaç olduğunu düşünüyoruz.

Anahtar Kelimeler: İsotretinoin, lateral nazal osteotomi, kemik iyileşmesi

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Introduction

Rhinoplasty is a very common aesthetic surgery that has become more popular day by day. Lateral osteotomy, which is one of the most challenging stages of this surgery, can cause damage to the mucosa and periosteum enveloping the bone tissue (1). It is important to ensure adequate mobilization and not to damage soft and supporting tissues when performing osteotomy. Excessive damage to these tissues will not only cause postoperative bleeding, desepithelization, prolonged ecchymosis and edema, but may also result in unwanted aesthetic and unpredicted functional outcomes (2).

Isotretinoin (13 cis retinoic acid) is a vitamin A derivative used as a drug in the treatment of severe acne that does not respond to antimicrobial therapy. The daily dose of cystic acne treatment is between 0.5 and 2 mg for six months (3). However, as in hypervitaminosis A, lip dryness, decreased bone density, increased risk of fractures, liver lesions, inhibition of bone growth, increased cholesterol and triglyceride, changes in liver enzymes and alkaline phosphatase may be seen as side effects (4).

When fracture happens, bone tissue has a very precious regeneration and healing ability. Beside some other important cells and mediators, osteoclasts and osteoblasts have very crucial roles in this complicated process by synthesizing and mineralizing the bone matrix. Isotretinoin, which is used extensively in dermatology, is known to adversely affect bone healing by interrupting osteoclasts and osteoblasts during the healing process (5).

Since the age at which rhinoplasty is frequently performed is also the age that acne is frequently seen, so a person can be a candidate for both this surgery and isotretinoin therapy at the same time.

In this study, by using rabbit model, we aimed to investigate the effects of isotretinoin on lateral osteotomy that is usually performed during rhinoplasty. As far as we know, this is the first experimental study on this issue.

Methods

Experimental Groups

This study was performed between May and June 2018 at İstanbul Bağcılar Training and Research Hospital Laboratory of Experimental Animals in İstanbul, Turkey. The experimental protocol was approved by the İstanbul Training and Research Hospital Local Ethics Committee of the Experimental Animals (decision no: 2018-09, date: 26.02.2018). The study was conducted in accordance with the principles of the European Community guidelines on the use of laboratory animals. A total of 12 adult, male New Zealand white rabbits weighing approximately 3-4 kg were maintained under ideal conditions of feeding and management in a room with cycles of 12 hours light and 12 hours dark, with constant temperature and relative humidity (60-70%). The rabbits were divided into two groups (n=6 each) designated as the experimental group as group 1 and the control group as group 2 in order to evaluate the effect of oral isotretinoin on bone healing in the early and late post-operative phases of osteotomy.

Drug Administration

İsotretinoin (Roaccutane©, Roche) is an lipid-soluble drug. Therefore, each capsule (Roacuttane 10 mg) was divided in a dark room and 1 mg dosage of drug was diluted in 10 mL olive oil (0.1 mg/mL). Transfer of drug was made with a black, covered box to avoid light. The mixture was given to group 1 on the day of surgery and following every morning by oral gavage by 1 mL/kg dosage for four weeks until euthanasia. Group 2 was used as control group in which only oral olive oil was given.

Surgical Procedure

The rabbits in all groups were anesthetized with xylazine hydrochloride 10 mg/kg (Rompun, Bayer Drugs, İstanbul, Turkey) and 50 mg/kg ketamine hydrochloride 59 mg/kg (Ketalar, Eczacıbaşi) Drugs, İstanbul, Turkey). Nasal dorsal skins were draped with povidone-iodine solution and shaved. After infiltration with 1% lidocaine and 1:100.000 epinephrine mixture (Jetokaine©), a vertical midline nasal dorsum skin incision with 5 cm diameter was made through the periosteum. Continuous osteotomy was performed starting from the distal end of the nasal bone and extending to the nasal bone radius using a 4 mm osteotome without guide. At the end of the surgery, the incised skin was sutured and closed. All rabbits were euthanized after four weeks by intracardiac pentobarbital injection. The nasal bones of the rabbits were resected from the bilateral frontal process of the maxillary bone and separated from the nasal spindle of the frontal bone. The specimens were fixed with 10% buffered formaldehyde. Hematoxylin-eosin was used for staining. Bone healing was classified according to the grading described by Huddleston et al. (6) Fracture-healing phases in each specimen was quantified with use of a scale that assigns a grade based on the relative percentages of fibrosis, cartilage formation, woven and mature bone development in the callus (6). 4 µm sections were taken. Using a microscope (B×51 Japan), histological grading was performed. The grading was as follows: grade 1-fibrous tissue, grade 2-fibrous tissue with less cartilage formation, grade 3-fibrous tissue and cartilage are in the same amount, grade 4-cartilage tissue only, grade 5-predominantly cartilage and less amount of woven bone, grade 6-equal amount of cartilage and immature bone development, grade 7-more as immature bone and less cartilage, grade 8-totally immature bone, grade 9-predominantly immature bone and less amount of mature bone and grade 10-mature (lamella) bone.

Statistical Analysis

All analyses were conducted using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Correlations between categorical variables were assessed using the Pearson $\chi 2$ test and chi-square test. $P<0.05$ was considered statistically significant.

Results

Grade 1 bone healing was observed in four samples (66.7%) and grade 2 bone healing was observed (Figure 1) in two samples (33.3%) in the study group. In the control group, three samples (50%) had grade 2 bone healing and the remaining three samples (50%) had grade 3 bone healing (Figure 2). The difference between the groups was statistically significant ($p=0.027$) (Table 1).

Table 1. Comparison of bone healing grades between the study (isotretinoin) and the control groups

	Grade 1	Grade 2	Grade 3	
Study group	4 (66.7%)	2 (33.3%)	-	p=0.027
Control group	-	3 (50%)	3(50%)	
Total	4	5	3	

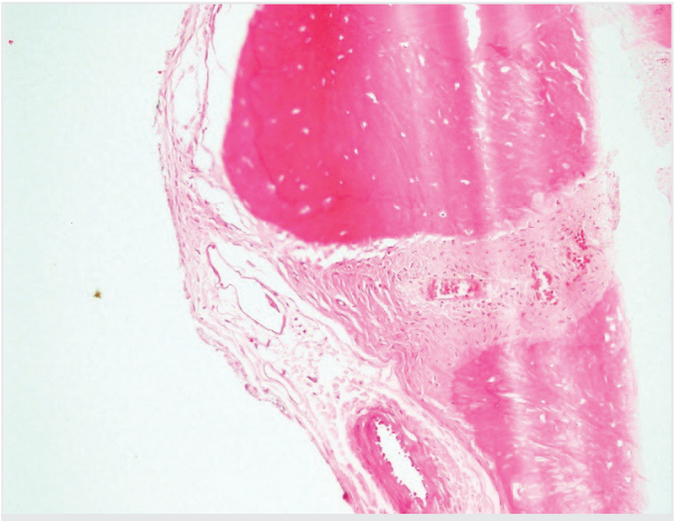

Figure 1. Grade 2 bone healing of the rabbit nasal bone; fibrous tissue is dominant with respect to cartilage tissue (hematoxylin-eosin, x100)

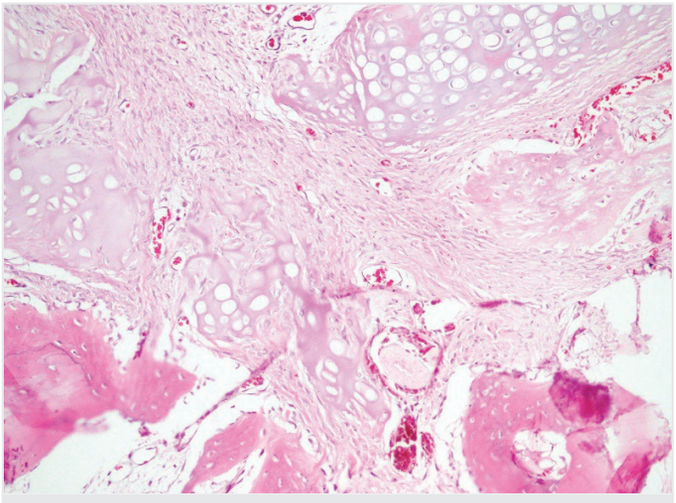

Figure 2. Grade 3 bone healing of the rabbit nasal bone; fibrous tissue formation is almost equal to cartilage tissue formation (hematoxylin-eosin, x100)

Discussion

Kindmark et al. (7) reported that inhibition of the release of markers that provide bone turnover and calcium regulation at the beginning of isotretinoin treatment was inhibited and that this effect was reversible in the first 14 days despite the continuation of treatment (7). While the mechanism of action of isotretinoin is not fully understood, it is believed that this drug affects the cellular differentiation, growth, morphogenesis and apoptosis, controls tumor growth and modifies cellular cohesiveness. Isotretinoin reduces the size and activity of the sebaceous glands and produce a wound-healing-like pattern followed by repair and remodeling of the skin (8,9). Nishio et al. (10) reported decreased inflammatory cells infiltrating large medullary areas, growth factors and fragmented thin bone formation in external retinoic acid given animals; which pointed out that isotretinoin had a negative effect on bone formation. Similar to this, we found that nasal bone healing was adversely affected in rabbits with isotretinoin treatment.

On the contrary, the rate of new bone formation in calvarial defect of the daily retinoic acid-treated group was reported to be higher than in the untreated group in a study performed on rats (11). Similar to this study, Kamm (12) reported that synthetic isotretinoin accelerated bone repair in their animal studies. Bergoli et al. (13) investigated the formation of new bone in the cavity formed after tooth extraction in a study conducted in 32 rats. In this study, new bone formation was reported to be faster in the isotretinoin-treated group on days 7,21,28 and 90. However, Valentic et al. (14) and Frankel et al. (15) reported higher rates of cortical and medullary bone resorption in long bones after giving high doses of vitamin A in rats. Similar to that, we observed grade 1 bone formation in four samples and grade 2 bone formation in two samples in the isotretinoin treated group in our study, which suggests that vitamin A might have a negative effect on bone healing.

The limiting feature of this study was that the number of rabbits was low and bone healing was not observed at different time periods.

Conclusion

Although there are studies reporting that isotretinoin has a positive effect on bone healing in the literature, we observed opposite results. Therefore, we think that more experimental and clinical studies are needed to clarify this effect.

Ethics Committee Approval: The experimental protocol was approved by the İstanbul Training and Research Hospital Local Ethics Committee of the Experimental Animals (decision no: 2018-09, date: 26.02.2018).

Informed Consent: Informed consent was not obtained due to the study is an animal experiment.

Peer-review: Externally peer-reviewed.

Author Contributions: Surgical and Medical Practices - Ş.Ö., H.D.T., F.E.; Concept - Ş.Ö.; Data Collection and/or Processing - Ş.Ö.; Analysis and/or Interpretation - H.D.T., F.E.; Literature Search - H.D.T., F.E.; Writing Manuscript - Ş.Ö., H.D.T.

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Retrospective Evaluation of Corrosive Substance Ingestion: Single Center Experience

Koroziv Madde Alımlarının Retrospektif Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Introduction: Caustic substance ingestion is a serious problem due to high morbidity and mortality. Chemical products used in homes are the source of accidental or deliberate caustic exposures that can be seen in people of different ages. The severity of the lesions produced by the caustic substances in the tissue depends on the type, amount and concentration of the caustic agent taken, as well as the time of contact with the mucosa. In this article, we aimed to evaluate the demographic characteristics, endoscopic results, clinical findings and complications of our patients admitted to our university hospital for corrosive substance ingestion.

Methods: We retrospectively identified adult patients admitted to our hospital between 2013-2019 for corrosive substance ingestion. We examined the endoscopy findings and endoscopy requirement within 24 hours of ingestion in 75 adult patients with acute corrosive substance ingestion.

Results: Forty-three patients (57%) were female and 32 (43%) were male. The mean age of the males was 39.3±14.50 years and the mean age of the females was 34.1±16.91 years. Sixteen corrosive substance ingestions (21.3%) were suicidal and 59 (78.6%) were accidental. Thirty-seven patients (49.3%) were asymptomatic and did not require endoscopy and seven patients (9.3%) were recommended endoscopy but they did not consent. Fifteen patients (20%) had normal endoscopic findings, nine (12%) had Los Angeles (LA) grade A esophagitis, five (6.6%) patients had LA Grade B esophagitis, and one patient (1.3%) had LA grade D esophagitis due to crystal drain opener ingestion. One patient (1.3%) with history of thinner ingestion had esophageal polyp and Schatzki ring. Regarding corrosive substances, 25 patients (33.3%) had bleach ingestion. There was no mortality due to corrosive substance ingestion.

Conclusion: Caustic substance ingestion is often inadvertent and is accompanied by mild symptoms or esophageal damage. Endoscopy may not be performed, especially in asymptomatic people with bleach or softener ingestion. In suicidal ingestions,

ÖZ

Amaç: Kostik madde içilmesi yüksek morbidite ve mortalite nedeniyle ciddi bir sorun teşkil etmektedir. Evlerde kullanılan kimyasal ürünler, farklı yaşlardaki kişilerde görülebilen kaza veya kasıtlı olarak kostik maruz kalmaların kaynağıdır. Kostik maddelerin dokuda ürettiği lezyonların ciddiyeti, alınan kostik maddenin türüne, miktarına ve konsantrasyonuna, ayrıca mukoza ile temas zamanına bağlıdır. Bu çalışmada, üniversite hastanemize koroziv madde içilmesi nedeniyle başvuran hastalarımızın demografik özelliklerini, endoskopik sonuçlarını, klinik bulgularını ve komplikasyonlarını değerlendirmeyi amaçladık.

Yöntemler: Hastanemize koroziv madde alımı nedeniyle 2013-2019 yılları arasında başvuran yetişkin hastaları geriye dönük olarak hastane veri kayıt sisteminden tespit ettik. Akut korozif madde alımlı 75 erişkin hastanın, alımdan sonraki 24 saat içinde endoskopi gereksinimi ve endoskopi yapılmış olanların endoskopi bulgularını inceledik.

Bulgular: Hastaların 43'ü (%57) kadın, 32'si (%43) erkekti. Erkeklerin yaş ortalaması 39,3±14,50, kadınların yaş ortalaması ise 34,1±16,91 yıl idi. On altısında (%21,3) koroziv madde alımı intihar amaçlı olup, 59'unda (%78,6) yanlışlıkla alım şeklindeydi. Otuz yedi (%49,3) hasta asemptomatik olup endoskopi gerektirmedi, 7 (%9,3) hastaya endoskopi önerilmesine rağmen hastalar endoskopiyi kabul etmedi. On beş (%20) hastada endoskopi normal, 9 (%12) hastada özofajit Los Angeles (LA) grade A, 5 (%6,6) hastada özofajit LA grade B, 1 (%1,3) hasta kristal lavabo açıcısı içmiş olup özofajit LA grade D mevcuttu. Bir (%1,3) hasta da tiner içmiş olup özofageal polip, Schatzki halkası şeklinde raporlanmıştı. Alınan maddelere baktığımızda 25 (%33,3) hastada çamaşır suyu içimi mevcuttu. Koroziv madde içimine bağlı mortalite yoktu.

Sonuç: Kostik madde içimleri sıklıkla yanlışlıkla olup, hafif semptomlar veya özofageal hasar ile geçmektedir. Özellikle çamaşır suyu veya yumuşatıcı içen asemptomatik kişilerde endoskopi yapılmayabilir. İntihar amaçlı alımlarda hastalar

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serious injuries may occur because patients ingest too much, and endoscopy is indicated for suicidal ingestion. Endoscopy should be used only to evaluate esophageal and gastric injury and to determine prognosis. A careful psychiatric evaluation should be performed for suicidal ingestion.

Keywords: Caustic intoxication, corrosive substance ingestion, esophagitis

çok fazla içtikleri için ciddi yaralanmalar olabilmektedir ve bu durumlarda endoskopi işlemi endikedir. Endoskopi sadece özofagus ve mide yaralanmasını değerlendirmek ve prognoz tayini için kullanılmalıdır. İntihar amaçlı alımlarda dikkatli bir psikiyatrik değerlendirme yapılmalıdır.

Anahtar Kelimeler: Kostik intoksikasyonu, koroziv madde alımı, özofajit

Introduction

Caustic substance ingestion is a serious problem due to high morbidity and mortality. Chemical cleaning products used in households are the most common cause of caustic exposure. Accidental or intentional caustic exposure may occur at different ages (1). Diluted acids or alkalis generally cause limited mucosal damage. In contrast, concentrated caustic agents with pH <2 or >12 can cause severe esophageal damage as well as a wide range of gastrointestinal injuries (2-5). Most patients with mild injuries recover without serious consequences. However, numerous corrosive intoxications can cause serious chemical injuries and death (4,6,7). It may cause complications such as pneumonia, respiratory failure, bleeding, perforation, stenosis and fistula (8,9). Mortality is most commonly caused by tracheal necrosis and perforation of the esophagus or stomach, followed by mediastinitis or peritonitis (6,10,11). The severity of the lesions caused by the caustic substances depends on the type, amount and concentration of the caustic agent taken, as well as the duration of contact with the mucosa.

In this article, we aimed to evaluate the demographic characteristics, endoscopic results, clinical findings and complications of patients admitted to our university hospital with corrosive substance ingestion.

Methods

We retrospectively identified adult patients admitted to the Mersin University Faculty of Medicine Hospital between 2013-2019 for corrosive substance ingestion. We retrospectively reviewed the medical reports of patients with acute corrosive ingestion who were evaluated endoscopically within 24 hours after ingestion and who did not require endoscopy. We classified these patients according to gender and age, type of corrosive substance detected and endoscopy results. Ethics committee approval was obtained from Mersin University Faculty of Medicine Clinical Research Ethics Committee (decision no: 104, date: 06/03/2019). Informed consent was obtained from the patients during the endoscopy and the study was completed by retrospective file scanning.

Statistical Analysis

SPSS 21.0 for Windows program was used to calculate the statistical analysis. Descriptive statistical methods were used to evaluate the study data.

Results

A total of 75 adults were admitted to our hospital with acute corrosive substance ingestion. Forty-three patients (57%) were female and 32 (43%) were male. The mean age of the men was 39.3±14.50 years and the mean age of the women was 34.1±16.91 years. In 16 (21.3%) of our patients, corrosive substance ingestion was suicidal and it was accidental in 59 (78.6%). Regarding gender distribution in suicidal ingestion, seven patients (43.7%) were male and 9 (56.2%) were female.

There was a small amount of accidental ingestion in 37 patients (49.3%) and the patients were also asymptomatic, so endoscopy was not required. Seven patients (9.3%) with mild symptoms were recommended endoscopy but they did not consent. Fifteen patients (20%) had normal endoscopic findinsgs. Nine (12%) had Los Angeles (LA) grade A esophagitis, five (6.6%) patients had LA grade B esophagitis, and one patient (1.3%) had LA grade D esophagitis due to crystal drain opener ingestion. One patient (1.3%) with history of thinner ingestion had esophageal polyp and Schatzki ring.

Regarding ingested corrosive substance, twenty-five patients (33.3%) had a history of bleach ingestion and only four patients (16%) had LA grade A esophagitis, while the others were either asymptomatic or had normal endoscopic findings. The corrosive substance could not be reached in 24 patients (32%) and only reported as corrosive substances, and two (8.3%) had LA grade A esophagitis, the others were either asymptomatic or had normal endoscopic findings. We think that those who had anamnesis as “corrosive substance ingestion” also ingested bleach. Details of other corrosive exposures are presented in Table 1. According to the anamnesis, the amount in suicidal ingestions was higher than the amounts in accidental ingestions.

None of the patients had organ perforation, organ failure or mortality.

Discussion

Oral ingestion of corrosive substances may cause perforation, necrosis and death in the acute phase. In the long term, it may cause stenosis in the esophagus and development of carcinoma. Despite various educational and legal efforts to reduce the occurrence of caustic injury, it remains a major medical problem worldwide. The most serious intoxications are mostly related to ingestion of a large amount of caustic product and suicide attempts where damage is usually extensive (9-11). In our series, the most common cause of ingestion was accidental (78.66%), unlike suicidal (21.33%). This indicates that more caution signs should be added on caustic substances.

When the studies involving caustic poisoning cases in our country are reviewed, we see that most of the cases are suicidal and include female patients (12-16). In a study of 108 cases in the Aegean region, Karaoğlu et al. (17) reported that 56.4% of the esophagitis cases due to oral ingestion of corrosive substances were women and 43.6% were male patients. In the same study, it was determined that oral ingestion of corrosive

Table 1. Corrosive substances ingested and endoscopic findings

Corrosive substance ingested	Number (%)	Endoscopic findings
Bleach	25 (33.3%)	LA grade A esophagitis in four (16%), no problem in others.
Corrosive (Unknown)	24 (32%)	LA grade A esophagitis in two (8.33%), no problem in others.
Descaling agent	8 (10.6%)	Three (37.5%) had normal endoscopic findings, two (25%) had LA grade A esophagitis, two (25%) were asymptomatic, one (12.5%) did not give approval.
Hydrochloric acid	6 (8%)	Two (33.33%) had LA grade B esophagitis, two (33.33%) had LA grade A esophagitis, two (33.33%) did not accepte endoscopy and one of them was intubated-extubated, then the patient escaped from the hospital.
Thinner	4 (5.3%)	There was no problem in three (75%), esophageal polyp and Schatzki ring in one (25%).
Softener	2 (2.6%)	Asymptomatic, endoscopy was not needed.
Dishwashing liquid	1 (1.3%)	Asymptomatic, endoscopy was not needed.
Air conditioner cleaner	1 (1.3%)	Normal endoscopic findings.
Peroxide	1 (1.3%)	LA grade B Esophagitis.
Agrochemicals	1 (1.3%)	Asymptomatic, endoscopy was not needed.
Tincture of iodine	1 (1.3%)	Asymptomatic, endoscopy was not needed.
Crystal drain opener	1 (1.3%)	Ulcers covering the entire mucosa, LA grade D Esophagitis.

LA: Los Angeles

Table 2. Alkali caustic substances

Caustic substance	Chemical content
Drain Openers	Sodium hydroxide, sodium hypochlorite
Oven cleaners	Sodium hydroxide
Toilet cleaners	Ammonium chloride
Household cleaners	Ammonium hydroxide, ammonium chloride
Bleaching products	Sodium hypochlorite, hydrogen peroxide
Dishwashing liquid	Sodium carbonate, sodium silicate
Watch battery	Sodium hydroxide, potassium hydroxide
Hair straighteners	Calcium hydroxide, lithium hydroxide

Table 3. Acidic caustic substances

Caustic substance	Chemical content
Toilet cleaners	Hydrochloric acid, sulfuric acid, phosphoric acid
Metal cleaners	Hydrochloric acid
Pool cleaners	Hydrochloric acid
Rust inhibitors	Hydrochloric acid, sulfuric acid, hydrofluoric acid
Battery fluids	Sulfuric acid

substance for suicidal purposes was 16.3% in men and 39% in women. Fifty-seven percent of our patients were female and 43% were male. The mean age of men was 39.3 years and the mean age of women was 34.1 years. Regarding gender distribution in suicidal ingestion, 56.2% were women.

Mortality after caustic ingestion is high worldwide and ranges from 5% to 20% (2,4,7,8). In our study, the mortality rate was 0%. Only one of our patients had widespread ulcerated lesions in the esophageal mucosa and stomach as a result of drinking a crystal drain opener, and no complication occurred during the follow-up. In one patient, intubation was required due to laryngeal edema developed after hydrochloric acid ingestion, the patient refused endoscopy after extubation and escaped from the hospital for psychiatric reasons. Our other patients had no serious problems.

Alkaline agents (Table 2) are swallowed without stimulating protective reflexes because they are tasteless and odorless (18). Solids are more difficult to swallow because of their adhesion to mucous membranes (18). Generally, alkaline substances damage the esophagus rather than the stomach, while acid substances (Table 3) can cause severe stomach damage (18). The most important difference between alkali and acid injury is the rapid penetration of alkalis into tissues (18). Especially swallowing bleach (5% sodium hypochlorite) has been reported frequently, but rarely causes serious esophageal injury. In our series, there was a 33% incidence of bleach ingestion, and only four (16%) of the patients who ingested bleach had LA grade A esophagitis, the others were either asymptomatic or had normal endoscopic findings. In 32% of the patients, substance information was not available and reported as corrosive only, and only 8% had LA grade A esophagitis. Therefore, we think that endoscopic evaluation is not necessary especially in asymptomatic patients with bleach ingestion. Our patient with the most damage had grade D esophagitis with drain opener ingestion.

Depending on the nature of the substance, diagnostic endoscopy can be performed in symptomatic patients. Kikendall (19) and Poley et al. (20) stated that it was better to perform endoscopy between 48-72 hours because the damage would be better detected. There are some literatures stated that endoscopy should not be performed after the first 24 hours to avoid iatrogenic rupture (21). In many case series, this time limitation has been found to be safer for complications. It is recommended that endoscopy is performed regardless of the presence of oropharyngeal burns in severely affected pediatric and adult patients with symptoms such as stridor or marked oropharyngeal burn, vomiting, drooling, rejection of eating during accidental ingestion (21-24). Endoscopy is still controversial in patients with a suspected history of ingestion. Some authors advocate endoscopy only in symptomatic patients (25). In our cases, 44 (58.6%) patients were asymptomatic and

did not require endoscopy or did not consent. When we examined the endoscopies performed after approximately one day; endoscopic examinations of 15 patients (20%) were normal and nine patients (12%) had grade A, five patients (6.6%) had grade B, and one patient (1.3%) had grade D esophagitis. One patient (1.3%) had esophageal polyp and Schatzki ring. Therefore, we recommend endoscopy according to the nature of the substance and the ingestion of large amounts of corrosive substances only in symptomatic patients.

Currently, there are some unconfirmed treatment approaches in the prevention and treatment of complications. These include caustic neutralization, corticosteroids, collagen synthesis inhibitors, antibiotics, heparin, early esophageal dilatation and stent placement in the esophagus. Urgent surgery is only effective in the early intervention in cases with perforation. In our patients, there was only one patient who was hospitalized and no patient had perforation. He improved during follow-ups.

Although there is no uniform guidance for nutritional support for patients after caustic injury, and the approach varies from patient to patient, appropriate nutritional support reduces the risk of malnutrition or infection. This may be particularly important in elderly patients (26,27). In our patient with grade D esophagitis, we provided IV nutrition support and oral intake was started during the follow-up. Nutritional support and hydration are very important for the healing of esophageal mucosa.

Conclusion

It was observed that ingestion of caustic material was often accidental, and generally improved with mild course. Depending on the type and amount of corrosive substance, endoscopy may not be performed especially in asymptomatic people who drink bleach or softeners. In suicidal ingestion, serious injuries may occur because patients drink too much, so endoscopy is indicated in patients with suicidal ingestion. Endoscopic evaluation is required in patients with resistant symptoms. Endoscopy should be used only to evaluate esophageal and gastric injury and to determine prognosis. We think that a careful psychiatric evaluation should be performed in suicidal ingestions.

Ethics Committee Approval: Ethics committee approval was obtained from Mersin University Faculty of Medicine Clinical Research Ethics Committee (decision no: 104, date: 06/03/2019).

Informed Consent: Informed consent was obtained from the patients during the endoscopy and the study was completed by retrospective file scanning.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - M.Z.A., O.S.; Data Collection and/or Processing - M.Z.A.; Analysis and/or Interpretation - S.Y., O.S., M.Z.A.; Literature Search - O.S., F.A.; Writing Manuscript - M.Z.A.; Critical Review - M.Z.A, O.S., E.U., F.A., S.Y., O.Ö.

Conflict of Interest: The authors have no conflict of interest to declare.

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Evaluation of the Patients with Abnormal Uterine Bleeding Based on PALM-COEIN Classification

Anormal Uterin Kanama ile Başvuran Kadınların PALM-COEIN Klasifikasyonuna göre Değerlendirilmesi

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ABSTRACT

Introduction: The PALM-COEIN classification, described and recently published by the International Federation of Gynecology and Obstetrics (FIGO), allows epidemiological information in women with abnormal uterine bleeding, as well as thorough assessment and proper management. We aimed to classify patients who applied to our gynecology outpatient clinic with abnormal uterine bleeding according to PALM-COEIN classification.

Methods: Our prospective observational study was conducted with non-pregnant women aged 15-45 years who were admitted to the gynecology outpatient clinic between June 2017 and March 2018. Patients were grouped according to PALM-COEIN classification by anamnesis, transvaginal ultrasonography, laboratory tests, hysteroscopy and pathology results.

Results: The cases were classified into two groups as structural causes (PALM) and non-structural causes (COEIN). There were 199 cases (49.4%) in the PALM group and 204 cases (50.6%) in the COEIN group. In the PALM group, polyp was found as the most common cause of abnormal uterine bleeding in 79 cases (19.6%). The most common cause in COEIN group iatrogenic was with 80 cases (19.9%). There was a statistically significant difference between the two groups regarding age, body mass index and the need for surgery.

Conclusion: The diagnosis and management of abnormal uterine bleeding becomes easier and more objective with the use of PALM-COEIN system.

Keywords: Abnormal uterine bleeding; PALM-COEIN, FIGO classification, terminology

ÖZ

Amaç: Uluslararası Jinekoloji ve Obstetri Federasyonu tarafından tanımlanan ve yakın zamanda kullanıma sunulmuş olan PALM-COEİN sınıflaması, anormal üterin kanaması olan kadınlarda epidemiyolojik bilgi sağlamasının yanısıra hastaların ayrıntılı değerlendirilmesine ve doğru yönetimine olanak sağlamaktadır. Amacımız, anormal üterin kanama ile jinekoloji polikliniğimize başvuran kadınların PALM-COEİN sınıflamasına göre sınıflandırılmasıdır.

Yöntemler: Çalışmamız, Haziran 2017-Mart 2018 tarihleri arasında jinekoloji polikliniklerine anormal üterin kanama şikayetiyle başvuran 15-45 yaş arası gebe olmayan kadınlar arasında prospektif olarak yapıldı. Hastalar anamnez, transvajinal ultrason, laboratuvar tetkikleri, histeroskopi ve patoloji sonuçlarıyla değerlendirilerek PALM-COEİN sınıflandırmasına göre gruplandırıldı.

Bulgular: Olgular yapısal nedenler (PALM) ve yapısal olmayan nedenler (COEİN) diye sınıflandırıldığında oranların sırasıyla %49,4 ve %50,6 olduğu görüldü. PALM grubunda 199 olgu, COEİN grubunda ise 204 olgu bulundu. PALM grubunda 79 olguyla en sık neden AUK-P (%19.6) idi. Toplam 204 olgunun olduğu COEIN grubunda en sık neden 80 olguyla ve %19.9 oranla AUK-I bulundu. İki grup arasında (PALM ve COEİN), abortus, küretaj, ektopik gebelik, sezaryen öyküsü, komorbidite, kanser öyküsü, ailede kanser öyküsü, başvuru yakınması, smear, polikistik over görünümü, adneksiyel patoloji varlığı ve boyutu açısından istatistiksel anlamlı fark bulunmadı.

Sonuç: Anormal üterin kanamanın tanısı ve yönetimi, PALM-COEİN sınıflamasının kullanılmasıyla daha kolay ve objektif hale gelmiştir.

Anahtar Kelimeler: Anormal üterin kanama, PALM-COEİN, FİGO sınıflaması, terminoloji

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Introduction

Abnormal uterine bleeding (AUB) is a common symptom in gynecology practice. Approximately 10-35% of women have experienced AUB at least once in their lifetime (1). In the United States, the prevalence of abnormal uterine bleeding is 53 in 1000 between 18-50 years of age, with a mean menarche age of 12 years and a mean menopause of 51 years (2,3). AUB is an important health problem for women in reproductive age who need to admit to a hospital and it has consequences such as blood loss, reduced sexual and reproductive health, and increased health care use and expenditure (4). It is responsible for 25% of gynecologic operations, 30% of all outpatient applications and 70% of outpatient applications among perimenopausal and postmenopausal patients (5).

The PALM-COEIN classification, that is described and recently published by the International Federation of Gynecology and Obstetrics (FIGO), allows epidemiological information in women with abnormal uterine bleeding, as well as thorough assessment and proper management of patients. This new classification introduces a new terminology system as well as etiology. According to the new terminology, the use of the terms "severe menstrual bleeding" instead of "menorrhagia" and "intermenstrual hemorrhage" instead of "metrorrhagia" has been proposed. The term "dysfunctional uterine bleeding" is not used in the new terminology.

In the PALM-COEIN classification, the PALM group includes polyps, adenomyosis, leiomyoma and malignancy as structural causes, while the COEIN group includes non-structural causes such as coagulopathy, ovarian dysfunction, endometrial, iatrogenic and unclassifiable (6).

In this study, we aimed to classify non-pregnant women aged 15-45 years who were admitted to the gynecology outpatient clinic with the complaint of AUB between June 2017 and March 2018. We also aimed to evaluate the clinical and demographic characteristics of these patients, and to shed light on the diagnosis and treatment algorithm for this condition affecting many women.

Methods

This study was conducted prospectively in non-pregnant women aged 15-45 years who were admitted to the gynecology outpatient clinic between June 2017 and March 2018. University of Health Sciences, Kanuni Sultan Süleyman Training and Research Hospital Local Ethics Committee approved the study (KAEK/2018.4.12). All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all patients, allowing the use of their blinded clinical data for research purposes.

General physical and pelvic examinations were performed after all complaints were received and detailed anamnesis was taken. Age, obstetric history, bleeding pattern, drug use, contraceptive method, and presence of systemic disease, cancer and family history were questioned. In sexually active patients, transvaginal ultrasonography (TV-US) was performed in the dorsal lithotomy position after urination. Sexually inactive patients were evaluated by abdominal ultrasonography. Cervix, cervical canal, uterus, endometrial cavity and ovaries were evaluated, and abnormal findings (e.g. myoma, polyps, adnexal mass, etc.) were recorded. Endometrial thickness measurements were made by measuring the largest anterior-posterior diameter on the long axis. Patients with abnormal masses in the uterine cavity were evaluated by office hysteroscopy. Endometrial biopsy was performed in septic intervention unit of our hospital. Smears, endometrial biopsies and histopathologic examination of the specimens were evaluated in pathology laboratory of our hospital. All patients were requested to have laboratory tests including complete blood count, prothrombin time (PT), activated partial prothrombin time (aPTT), pregnancy test (beta-HCG), free T3 (fT3), free T4 (fT4) and thyroid stimulating hormone (TSH).

Exclusion criteria were as follows: patients with positive pregnancy test, postmenopausal bleeding, acute genital tract infection, and patients who did not want to participate in the study.

The polyps constituted the AUB-P group, whereas malignancy and hyperplasia constituted the AUB-M group. The proliferative endometrium (AUB-O group) and the secretory endometrium (AUB-E group) were diagnosed with endometrial biopsy. Adenomyosis (AUB-A group) and leiomyomas (AUB-L group) were diagnosed by ultrasonography. Anamnesis and laboratory tests were used for diagnosing AUB-C and AUB-I groups. The diagnosis of isthmocele (AUB-N group) was made by ultrasonography and office hysteroscopy.

Endometrial biopsy results were divided into 11 groups as benign endometrial fragments, typical and atypical simple endometrial hyperplasia, typical and atypical complex endometrial hyperplasia, proliferative endometrium, endometrial polyp, chronic endometritis, secretory endometrium, endometrium adenocarcinoma and cervical carcinoma.

Statistical Analysis

In power analysis with G * Power 3.1 program with an effect size of 0.5 and level of significance of 5%, the number of samples required for 80% power was found as 385. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) for Windows version 22.0. $p<0.05$ was considered statistically significant. Risk ratio, odds ratio (OR) and 95% confidence interval were calculated. The difference between mean values and characteristics between the groups were analyzed with independent samples t-test and chi-square test. Means were presented with standard deviation (SD).

Results

A total of 403 women aged 15-45 years with abnormal uterine bleeding were included in this prospective observational study. Demographic and clinical findings of all participants were summarized and presented in Table 1.

According to the PALM-COEIN classification developed by FIGO in 2011, 199 cases (49.4%) with structural causes were included in the PALM group and 204 cases (50.6%) with non- structural causes were included in the COEIN group (Table 2). The most common etiologic cause in the COEIN group was AUB-I with 80 cases (19.9%) and was AUB-P with 79 cases (19.6%) in the PALM group. Patients using selective serotonin reuptake inhibitors (SSRIs), warfarin, and the most preferred intrauterine device

(IUD) in our population, progesterone IUD users were grouped as AUB-I. In this group, von Willebrand disease was present in two cases and immune thrombocytopenic purpura was present in two cases. Fifteen patients with no etiological causes and two isthmocele cases (4.2%) were evaluated in the AUB-N group (Figure 1 showing the distribution of patients based on PALM-COEIN classification).

When we compared the patients in the structural (PALM) and non-structural (COEIN) groups, there was a statistically significant difference between the two groups regarding age and body mass index (BMI) ($p<0.001$). The relationship between parity and etiology was not statistically significant in both structural and non-structural reasons (Table 3). When the cases were evaluated according to the contraceptive methods, it was seen that the use of contraceptive method, especially IUD (70%) and oral contraceptive (78.6%), was higher in the COEIN group (p=0.006).

When the rates of surgery were evaluated during the study period, the rate of surgery in the PALM group was significantly higher than the COEIN group ($p<0.001$) (Table 3).

Table 1. Demographic characteristics of the patients

Characteristics	Mean ± SD or number (%)
Age (years)	39.7±5.3 (range: 15-45)
BMI (kg/m^2)	29.7±4.8 (range: 19-44)
Parity	
0	22 (5.5)
≥1	382 (94.5)
Abortus	
0	276 (68.5)
≥1	127 (31.5)
Curettage	
0	343 (85.1)
≥1	60 (14.9)
Ectopic pregnancy	
0	392 (97.3)
≥1	11 (2.7)
History of cesarean section	
Absent	263 (65.3)
Present	140 (34.7)
Comorbidity	
Absent	302 (74.9)
Present	101 (25.1)
Cancer history	
Absent	397 (98.5)
Present	6 (1.5)
Contraceptive method	
Absent	242 (60)
Bilateral tubal ligation	37 (9.2)
Intrauterine device	60 (14.9)
Intrauterine device with progesterone	45 (11.2)
Condom	3 (0.7)
Oral contraceptive	14 (3.5)
Injectable contraception	1 (0.2)
Minipill	1 (0.2)
Complaint	
Menometrorrhagia	319 (79.2)
Menorrhagia	63 (15.6)
Metrorrhagia	21 (5.2)

SD: standard deviation, BMI: body mass index

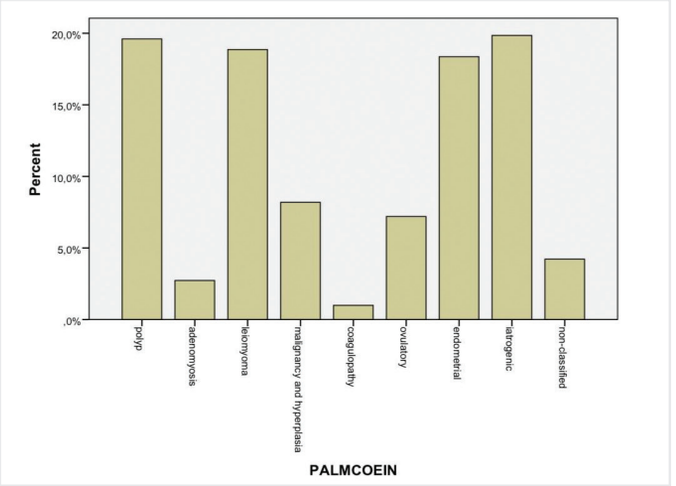

Figure 1. The figure showing the distribution of the patients based on PALM-COEIN classification

Table 2. The distribution of the patients based on PALM-COEIN classification

Group	Number, %	
Polyp	79 (19.6)	PALM (n=199, 49.4%)
Adenomyosis	11 (2.7)	
Leiomyoma	76 (18.9)	
Malignancy and hyperplasia	33 (8.2)	
Coagulopathy	4 (1.0)	COEIN (n=204, 50.6%)
Ovulatory	29 (7.2)	
Endometrial	74 (18.4)	
Iatrogenic	80 (19.9)	
Non-classified	17 (4.2)	

Table 3. Comparison of the patients in the structural and non-structural groups

Characteristics	PALM group	COEIN group	p
Age (years)	40.7±4.4	38.8±5.8	**<0.001**
BMI (kg/m^2)	30.6±4.6	28.9±4.9	**<0.001**
Parity			
0	14 (63.6)	8 (36.4)	Not significant
≥1	185 (48.6)	196 (51.4)	
Surgery			
None	164 (45.3)	198 (54.7)	**<0.001**
Hysterectomy	21 (100)	0	
Myomectomy	5 (83.3)	1 (16.7)	
Operative hysteroscopy	9 (69.2)	4 (30.8)	
Ovarian surgery	0	1 (100)	

PALM: structural group, COEIN: non-structural group, BMI: body mass index

Discussion

AUB is an important public health problem that occurs in 10-35% of women at least once in their lifetime (5). Many studies have been conducted on this situation, which affects social life, sexual health and mental status of women. The use of the objective PALM-COEIN system will provide a faster and more effective planning of diagnosis and treatment, rather than the classical terminology system that is difficult to use and inadequate to determine the etiology, which can vary relatively to the perception of the patient and the clinician. We grouped 403 patients aged 15-45 years who were admitted to Gynecology outpatient clinic with abnormal uterine bleeding between June 2017 and March 2018 according to PALM-COEIN classification.

When our cases were divided into two groups as structural causes (PALM) and non-structural causes (COEIN), the rates were 49.4% and 50.6%, respectively. In a similar study conducted by Mishra and Sultan (7) in 236 cases, the rate of PALM group was 50.2% and the rate of COEIN group was 49.8%, which is similar to our results.

The most frequent cause of all etiologic factors in our study was iatrogenic causes, known as AUB-I in the COEIN group (19.9%). The widespread use of copper IUD as a contraceptive method in our society seems to increase this rate. Copper IUD, first used in the early 1970s, is a highly reliable and safe form of contraception currently used by 15.5% of women in reproductive age and 7.7% of American women using contraception worldwide (8). A total of 60 patients (14.9%) preferred contraception with copper IUD. Andrade and Pizarro Orchard (9) found that the average amount of blood loss per woman per cycle increases from 32 mL to 37-40 ml with copper IUD.

In our study, 45 patients were found to prefer hormone-releasing IUD either for contraception or for management of AUB. Many women experience unexpected vaginal spotting/bleeding during the first 3-6 months of use of this hormone-releasing IUD. Backman et al. (10) conducted a nationwide study of 17.360 women in Finland and found that the most common reason for discontinuing this hormone-releasing IUD was unexpected, irregular uterine bleeding (10). In a study conducted in England, 10% of new users of this IUD discontinued the method at the end of the first year due to irregular bleeding. The rate of discontinuation due to AUB was 16.7% within 5 years (11).

Iatrogenic causes include the use of SSRIs that cause AUB that affects dopamine metabolism. In a case-control study of SSRIs users, the authors found that the use of SSRIs at moderate and high doses increased AUB (12). Another mechanism behind these effects is that SSRIs limit the uptake of blood serotonin with platelets. Since platelets cannot synthesize serotonin, this causes a decrease in serotonin concentration in platelets and decreased serotonin amount in platelets increases the risk of abnormal bleeding (13). Iatrogenic agents also include anticoagulants such as warfarin. Warfarin blocks the gamma-carboxylation of the terminal regions of vitamin K-dependent proteins by preventing the vitamin K from returning to the epoxide state of vitamin K, resulting in a decrease in clotting factors II, VII, IX and X (14).

According to the results of our study, AUB-P was found as the second most common cause (19.6%) at almost the same rate with AUB-I. This rate was found to be 21% in our study, similar to the study conducted by Toz et al. (15) that evaluated the pathological specimens of patients aged 18-55 years who had hysterectomy, myomectomy and polypectomy due to AUB. This rate was 15% in another study including 176 patients aged 41-50 years (16).

In our study, the rate of AUB-L subgroup in the PALM group was 38%. In the study of Arnold and Saravanan (17), this rate was found 40%, similar to our study. Especially submucosal leiomyomas are thought to contribute to the formation of AUB. However, intramural fibroids may cause AUB by altering the muscular contraction of the uterus and pressing the veins in the uterine wall (18).

The AUB-E group includes the secretory endometrium and chronic endometritis. Seventy-four cases (18.4%) were found in the AUB-E group in our population. In the study conducted by Talukdar and Mahela (18) correlating hysterectomy materials, endometrial biopsy and ultrasound, this rate was similar to our study with 19.4%. Singh et al. (19) performed a study in 550 samples and according to their findings; this rate was different from our study with 24%.

The fifth common cause of AUB was AUB-M (malignancy and hyperplasia) in our study. The AUB-M subgroup was arranged according to endometrial biopsy results; including simple endometrial hyperplasia with or without atypia, complex endometrial hyperplasia with or without atypia, endometrial adenocarcinoma and cervical cancer. Although there was no consensus in the studies on this subject, some researchers evaluated the atypia and hyperplasia in the AUB-E group. However, most investigators chose to consider the atypia and hyperplasia in the AUB-M group. In a similar study by Mishra and Sultan (7), all types of hyperplasia were grouped in the AUB-M group and this rate was found to be 10.2% (7). Toz et al. (15) performed a study on the hysterectomy, myomectomy and polypectomy materials of 471 AUB patients aged 18-55 years and this rate was found to be 11% (17).

In our study, two patients were diagnosed with endometrial cancer. The rate of endometrial cancer in all cases was 0.5%. In the literature, this rate varies between 0.2% and 1.4% (15,17).

The sixth most common cause in our study was the AUB-O group with 29 cases and 7.2% rate. This group includes patients with unregulated proliferative endometrium as a result of endometrial biopsy and ultrasonographic polycystic ovary appearance. Mishra and Sultan (7). reported this rate as 9% in their study (7). In the study of Toz et al. (15), this rate was found to be 2.7%. The reason for this difference is thought that their study was based on the surgery specimens. Because the main treatment of ovulatory dysfunction is medical treatment, there may be missing cases (17).

The seventh most common cause of AUB according to our study was AUB-A. In clinical and histopathological studies, the rate of AUB-A was similarly 3.8% (7). In the study of Toz et al. (15), this rate was found to be 38%, which is quite different from our study (17). The reason for this difference is the difficulty in diagnosing adenomyosis by imaging methods and endometrial biopsy, thus the definitive diagnosis is made with histopathological examinations.

The least common cause of AUB was found to be AUB-C group. Von Willebrand disease was present in two cases and immune thrombocytopenic purpura was present in two cases. According to

another study in 200 cases, this rate was 2% (20). This rate was found to be 0% in the studies of Arnold and Saravanan (17) and Mishra and Sultan (7) (16). The reason for this difference is that multidisciplinary approach is needed for definitive diagnosis of coagulopathies.

A total of 17 cases (4.2%) were classified in the AUB-N group. These cases were not considered in any category or no etiologic cause could be detected in this group.

The American Society of Obstetrics and Gynecology (ACOG) asserted that medical treatment is the first-line treatment in acute AUB in women without systemic hematological disorders. Surgical treatment should be performed considering the stability of the patients, the severity of bleeding and underlying disease. It should be preferred in cases where medical treatment is contraindicated and there is no response to medical treatment (21). Medical treatments include hormonal and non-hormonal options, and the most effective ones in reducing AUB are progesterone IUDs, tranexamic acid and long-term oral progesterone (22). Surgical treatment options range from simple procedures to comprehensive surgery. As a matter of fact, in our study, the rate of surgery in the PALM group was found to be significantly higher than the COEIN group.

Conclusion

As a conclusion, the use of the objective PALM-COEIN system enables a faster and more efficient planning of diagnosis and treatment rather than the classical terminology system based on the perception of the patient and clinician, which is relatively difficult to use and difficult to determine the reason of AUB with.

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Diagnostic Value of Hematological Parameters in Pelvic Inflammatory Disease

Pelvik Enflamatuvar Hastalıkta Hematolojik Parametrelerin Tanısal Değeri

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ABSTRACT

Introduction: In this study, we aimed to investigate the diagnostic value of hematologic parameters in pelvic inflammatory disease (PID).

Methods: In this retrospective study, 122 patients diagnosed as PID (patient group) and 150 healthy women (control group) who applied for routine gynecological examination between May 2010 and May 2016 were included. White blood cell (WBC), neutrophil count, lymphocyte count, mean platelet volume (MPV), platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), platelet distribution volume (PDW), plateletcrit (PCT) values of the patient and control groups were compared.

Results: There was no difference in terms of age, platelet, MPV, PCT, PDW values between the patient and control groups ($p>0.05$). NLR and PLR values were significantly higher in the patient group compared to the control group ($p<0.001$). While NLR showed a significant positive correlation with C-reactive protein (CRP) and WBC count, PLR was found to have a positive correlation only with CRP. In the diagnosis of PID, the sensitivity of NLR was similar to the increase in WBC count, but its specificity was higher. The sensitivity (80.3%) and specificity (78.7%) of NLR were close to neutrophil count, which is an important inflammatory marker, and it was the second most valuable marker after neutrophil count in the diagnosis of PID.

Conclusion: It was concluded that NLR, which is one of the complete blood count parameters, has sensitivity and specificity higher than white cell count and close to neutrophil count in PID diagnosis, and is a valuable inflammatory marker in PID diagnosis.

Keywords: Pelvic inflammatory disease, hematologic parameters, inflammatory marker

ÖZ

Amaç: Bu çalışmada hematolojik parametrelerin pelvik enflamatuvar hastalıktaki (PİH) tanısal değerini incelemeyi amaçladık.

Yöntemler: Bu retrospektif çalışmaya Mayıs 2010 ve Mayıs 2016 tarihleri arasında PİH tanısı alan 122 hasta ile kontrol grubu olarak rutin jinekolojik muayene için başvuran 150 sağlıklı kadın dahil edildi. Çalışma ve kontrol gruplarının beyaz küre (WBC), nötrofil, lenfosit, ortalama platelet hacmi (MPV), platelet/lenfosit oranı (PLR), nötrofil/lenfosit oranı (NLR), platelet dağılım hacmi (PDW), plateletkrit (PCT) değerleri karşılaştırıldı.

Bulgular: Çalışma ve kontrol grupları karşılaştırıldığında yaş, platelet, MPV, PCT, PDW değerleri açısından fark saptanmadı ($p>0,05$). NLR ve PLR değerleri kontrol grubuna göre hasta grubunda anlamlı yüksek saptandı ($p<0,001$). NLR, CRP ve WBC sayımı ile pozitif yönde anlamlı korelasyon gösterirken, PLR'nin yalnızca C-reaktif proteini (CRP) ile pozitif yönde anlamlı korelasyon gösterdiği saptandı. PİH tanısında NLR'nin sensitivitesinin WBC artışı ile benzer, spesifitesinin ise daha yüksek olduğu saptandı. NLR'nin sensitivite (%80,3) ve spesifitesinin (%78,7) önemli bir enflamatuvar belirteç olan nötrofil sayımına yakın olduğu ve PİH tanısında hemogram parametreleri arasında nötrofil sayımından sonra en değerli ikinci belirteç olduğu saptandı.

Sonuç: Hemogram parametrelerinden NLR'nin PİH tanısında WBC sayımından daha yüksek ve nötrofil sayımına yakın sensitivite ve spesifiteye sahip olduğu ve PİH tanısında değerli bir enflamatuvar belirteç olduğu sonucuna varılmıştır.

Anahtar Kelimeler: Pelvik enflamatuvar hastalık, hematolojik parametreler, enflamatuvar belirteç

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Introduction

Pelvic inflammatory disease (PID) is a common infection of women of reproductive age. It is an ascending polymicrobial infection caused by microorganisms colonizing in the endocervix and causing inflammation of the upper genital system. Infection extending to the endometrium and fallopian tubes may affect neighboring pelvic tissues and cause clinical conditions such as endometritis, pelvic peritonitis, tubo-ovarian abscess and salpingitis. The PID clinic may vary from mild symptoms and signs to severe lower abdominal pain, and mild clinical findings may cause difficulty in diagnosis (1-3). There are studies where changes in hematological parameters such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV), plateletcrit (PCT) in various malignant and benign diseases such as coronary artery disease, inflammatory diseases, preeclampsia, gynecologic and gastrointestinal cancers have been evaluated as inflammatory markers with prognostic and predictive value (4,5).

In this study, we aimed to evaluate hematological parameters as inflammatory markers in PID.

Methods

In this study, 122 patients admitted to our gynecology and obstetrics clinic between May 2010 and May 2016 and diagnosed as PID were included in the patient group, and 150 patients who did not have active complaints but who applied to our gynecology outpatient clinic for routine gynecological examination were included in the control group. The files of the patients were retrospectively reviewed and patients diagnosed as PID according to the Sexually Transmitted Disease Guidelines (2) of the Center for Disease Control and Prevention were included in the study. Specificity increasing criteria such as presence of tenderness in uterine, adnexal or cervical movements and associated fever >38.3 °C in patients with acute onset pelvic or lower abdominal pain, increased cervical mucopurulent discharge, increased erythrocyte sedimentation rate or C-reactive protein (CRP) levels were used to diagnose PID. Patients with chronic disease, existing additional focus of infection and malignancy were excluded from the study. In addition, patients with use of non-steroidal anti-inflammatory drugs, antibiotics, oral anticoagulants, and oral contraceptives that could affect the parameters evaluated were excluded. Pre-treatment hemoglobin, hematocrit, white blood cell (WBC) count, platelet, MPV, PCT, platelet distribution width (PDW), CRP values of the subjects included in the patient group were recorded and PLR and NLR were calculated. Patient and control groups were compared in terms of parameters.

Ethics committee approval was obtained for the study (İstanbul Training and Research Hospital Ethics Committee (decision no: 914, date: 06.01.2017). Informed verbal and written informed consent was obtained from.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Regarding descriptive statistics, mean, standard deviation, minimum and maximum were used for numerical variables, and numbers and percentages were used for categorical variables. Comparisons of numerical variables were made by using Student's t-test when normal distribution was met and by using Mann-Whitney U test when normal distribution was not met in the comparison of two independent groups. The relationship between numerical variables was examined by Spearman correlation analysis since no parametric test condition was provided. Statistical significance level was accepted as $p<0.05$.

Results

Demographic characteristics and hematological parameters of the groups are shown in Table 1. There was no significant difference between the groups in terms of mean maternal age (p=0.700), while the mean parity was significantly lower in the patient group (p<0.001).

Table 1. Comparison of demographic characteristics and complete blood count parameters of patient and control groups

	Patient group (n=122)			Control group (n=150)			
	Mean ± SD	Min-Max	Median	Mean ± SD	Min-Max	Median	p
Age	36.4±9.1	18-80	36.5	36.9±4.4	19-45	37.5	0.700
Parity	2.0±1.4	0-7	2	2.7±1.5	0-7	3	**<0.001**
Hemoglobin	11.7±1.8	7.5-15	12	12.7±1.5	7.9-15.9	12.9	**<0.001**
Hematocrit	35.9±4.8	23.4-45.4	36.2	38.2±4.1	25.3-50.2	38.7	**<0.001**
WBC	12.9±5.4	4.9-28	11.74	7.6±2.2	3.6-14.7	7.3	**<0.001**
PLT	305.4±110.8	62-728	281	281.3±71.6	2.7-478	279	0.345
MPV	8.97±1.33	5.8-13.4	9.1	9.28±1.42	2.3-12.4	9.3	0.066
PCT	0.32±0.39	0.1-3.63	0.26	0.27±0.09	0.1-1.1	0.3	0.799
Neutrophil	9.9±5.3	2.4-25.5	8.195	4.7±1.8	1.9-12	4.3	**<0.001**
Lymphocyte	1.9±0.8	0.3-4.4	1.8	2.3±0.7	0.5-4.3	2.3	**<0.001**
PLR	199.4±123.4	35.4-762.8	167.8	131.9±51.2	1.8-371.2	120.4	**<0.001**
NLR	6.99±6.29	1.19-38.07	4.46	2.25±1.84	0.78-20.98	1.92	**<0.001**
PDW	25.5±17.4	10.3-73.4	16.2	24.1±16.2	11-64.1	16.2	0.326
CRP	13.6±19.2	0.1-96.1	7.8	-	-	-	-

SD: standard deviation, Min: minimum, Max: maximum, WBC: white cell count, PLT: platelet, MPV: mean platelet volume, PCT: plateletcrit, PLR: platelet/lymphocyte ratio, NLR: neutrophil/lymphocyte ratio, PDW: platelet distribution volume, CRP: C-reactive protein

When the treatment methods were examined, it was seen that 77% of the patient group received medical treatment and 23% received surgical treatment. Compared with the control group, lymphocyte, hemoglobin and hematocrit values were significantly lower in the patient group ($p<0.001$), whereas neutrophil and WBC counts were significantly higher in the patient group ($p<0.001$). PLR and NLR were significantly higher in the patient group ($p<0.001$). There was no significant difference between patient and control groups in terms of platelet count, MPV, PCT and PDW values ($p>0.05$).

The correlation analyses of CRP and WBC values and other hematological parameters of the subjects in the patient group are shown in Table 2. While there was a significant positive correlation between NLR and PLR values and CRP values ($r=0.398$, $p<0.001$ and $r=0.282$, $p=0.002$, respectively), there was a significant negative correlation between MPV and CRP values ($r=-0,185$, $p=0.041$). There was no significant correlation between PCT and PDW values and CRP values ($p>0.05$). While there was a significant positive correlation between NLR and WBC values ($r=0.593$, $p<0.001$), there was no significant correlation between PCT, MPV, PDW and PLR values and WBC values ($p>0.05$).

In receiver operator characteristic analysis, sensitivity and specificity of neutrophil count in the diagnosis of PID were found to be 82% with a cut-off value of 5.63, and sensitivity was 80.3% and specificity was 78.3% for a cut-off value of 2.58 for NLR. When the cut-off value for WBC count was taken as 8.42, its sensitivity and specificity were 80.3% and 70.4%, respectively (Table 3).

Table 2. Correlation analysis of CRP, WBC and other hematological parameters

	CRP (n=122)		WBC (n=122)	
	Rho	p	Rho	p
WBC	0.270*	0.003	-	-
PCT	0.047	0.607	0.146	0.108
NLR	0.398**	<0.001	0.593**	<0.001
PLR	0.282*	0.002	0.048	0.601
MPV	-0.185*	0.041	-0.094	0.304
PDW	-0.037	0.686	0.100	0.274

CRP: C-reactive protein, WBC: white cell count, PCT: plateletcrit, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, MPV: mean platelet volume, PDW: platelet distribution volume, Rho: Spearman's r, *: p<0.05, **: p<0.001

Discussion

In this retrospective study, we investigated whether NLR, PLR, MPV, and PDW could be used as a diagnostic marker in PID. Our hypothesis in this study was that these parameters might be diagnostic markers such as CRP and increased WBC count used in the diagnosis of PID. In accordance with our hypothesis, in our study, NLR and PLR values were found to be higher in patients with PID compared to the control group. As a result of this study, these parameters were found to have an important role in the diagnosis of PID as inflammatory markers. In addition, the sensitivity and specificity of NLR in the diagnosis was found to be high. As a result of our study, the sensitivity of NLR was similar to the increase in WBC count and the specificity was higher in the diagnosis of PID. The sensitivity and specificity of NLR was found to be close to neutrophil count, which is an important inflammatory marker, and was the second most valuable marker in the diagnosis of PID after neutrophil count.

PID is an inflammatory disorder of the female upper genital system and includes different clinical features such as endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis. The clinical diagnosis is 65-90%, even in the most experienced hands (2,6). Early diagnosis not only reduces the risk of infection spread but also reduces the complication rates. Although laparoscopy is the gold standard for diagnosis, it is a costly and invasive procedure that limits its use. Although the diagnosis of PID is mainly made clinically, laboratory tests are used as auxiliary diagnostic tools. Since clinical findings are non-specific and obscure in many cases, laboratory tests play an important role in supporting the diagnosis (2,3). In the meta-analysis of the diagnostic value of the markers used in the diagnosis of PID, Kahn et al. (7) concluded that there was no biomarker that could be used alone or in combination in the diagnosis of PID. In 10 of the 12 studies examined in this meta-analysis, laparoscopy was considered the gold standard in diagnosis, while the sensitivity of CRP was reported to be 74-93% and the sensitivity of sedimentation was reported to be 64-81%. CRP begins to increase 48 hours after the onset of symptoms. Increased CRP and sedimentation may also be associated with non-inflammatory factors such as age, anemia, gender, and renal failure (8). Therefore, the use of these two

Table 3. Diagnostic values of complete blood count parameters in pelvic inflammatory disease

	AUC	Cut-off	Sensitivity	Specificity	PPV	NPV
NLR	0.864	2.58	80.3	78.7	75.4	83.1
Neutrophil	0.863	5.63	82.0	82.0	78.7	84.8
WBC	0.827	8.42	80.3	70.4	71.5	82.2
PLR	0.679	127	68.0	60.0	58.0	69.8
Lymphocyte	0.330	2.11	66.4	61.3	58.3	69.2
MPV	0.421	9.35	61.5	49.3	50.0	61.5
PCT	0.509	0.252	52.5	47.3	44.8	55.0
PLT	0.533	279.5	50.8	50.7	45.6	55.9
PDW	0.465	16.1	50.8	47.3	44.0	54.2

AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, NLR: neutrophil/lymphocyte ratio, WBC: white cell count, PLR: platelet/lymphocyte ratio, MPV: mean platelet volume, PCT: plateletcrit, PLT: platelet, PDW: platelet distribution width

parameters in diagnosis is limited. This necessitates the evaluation of additional inflammatory markers in the diagnosis of PID.

As a result of neutrophil activation caused by tissue destruction, the release of enzymes such as myeloperoxidase, acid phosphatase and elastase increases and neutrophil dominance is observed and thus NLR increases. In recent studies, NLR has been evaluated as an inflammatory marker (9-12). AKopuz et al. (10) reported that NLR values were significantly higher in patients diagnosed with PID compared to the control group before treatment, and in these patients they found that clinical improvement and NLR regressed to normal levels after treatment. They concluded that NLR could be used as a marker of clinical improvement in PID. In a study investigating the diagnostic value of complete blood count (CBC) parameters and CRP in PID cases, Seçkin et al. (11) found that NLR had the highest sensitivity and specificity in the diagnosis of PID and had similar sensitivity and specificity to CRP. They concluded that NLR could be used together with other CBC parameters in the diagnosis of PID.

Consistent with the literature, in our study, NLR was significantly higher in the PID group than in the control group ($p<0.001$). It was observed that NLR had the second highest sensitivity (80.3%) and specificity (78.7%) after neutrophil count among all CBC parameters. Thus, we found that NLR has higher sensitivity and specificity in the diagnosis of PID compared to WBC, and PDW, PLR and MPV, which are examined as inflammatory markers in recent studies, and consequently that NLR is a valuable inflammatory marker that can be used in the diagnosis of PID, such as CRP. Compared with similar studies in the literature, the high number of cases may be considered as the superior aspect of our study.

PLR has been shown to increase significantly in many inflammatory diseases (11,13-15). Consistent with the literature, in our study, PLR was found to be significantly higher in patients with PID, whereas sensitivity (68%) and specificity (60%) of PLR were lower than NLR and WBC, and higher than MPV and PDW.

MPV, which is a marker of function and activation of platelets, is altered by platelet activation (12,13). MPV has been shown to decrease in inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease in recent studies (16,17). In the study of Incebiyik et al. (12), MPV was significantly lower in patients with PID and MPV was a more valuable marker in the diagnosis of PID than leukocyte count. Although Seçkin et al. (11) found that MPV was significantly lower in patients with PID; they suggested that MPV was not a valuable marker in the diagnosis of PID (11). Contrary to these studies, no statistically significant difference was found between patient and control groups for MPV. In the diagnosis of PID, sensitivity (61.5%) and specificity (49.3) of MPV were lower than NLR and PLR. While PDW values were not different between the patient and control groups, the sensitivity (50.8%) and specificity (47.3%) of PDW were not considered as a valuable marker in the diagnosis of PID.

Retrospective design of the study, lack of CRP values in the control group and the effect of treatment on the parameters examined were the main limitations of our study. In addition, the fact that the presence of pelvic abscess, an important complication of PID, on the studied parameters has not been investigated is another limitation of our study.

Conclusion

It was found that NLR was more specific and sensitive than MPV, PDW, PLR parameters in the diagnosis of PID. In addition, it was concluded that NLR, which has a higher sensitivity and specificity than WBC count and similar sensitivity and specificity to neutrophil count, has an important role in the diagnosis of PID. Further studies are needed on this subject.

Ethics Committee Approval: Ethics committee approval was obtained for the study (İstanbul Training and Research Hospital Ethics Committee (decision no: 914, date: 06.01.2017).

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Time to Terminate Vacuum-assisted Closure and Convert to Primary Abdominal Closure in Intra-abdominal Sepsis

İntra-abdominal Sepsiste Vakum-yardımlı Kapama Sonlandırma ve Primer Abdominal Kapamaya Dönüştürme Zamanı

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ABSTRACT

Introduction: There is no widely accepted surgical technique in intra-abdominal sepsis and there is also limited data on available surgical techniques and their outcomes. There is no significant difference between these techniques. The aim of the laparotomy, which is performed to control the source of sepsis, is to reduce mortality. This retrospective study was performed to investigate daily analysis of the effects of vacuum-assisted closure (VAC) on intra-abdominal inflammation, sepsis and mortality.

Methods: The study included 159 patients who underwent VAC technique between January 2010 and April 2017. Statistical analysis of the effects of VAC technique was performed on a daily basis using APACHE IV score, Mannheim peritonitis index (MPI) and Sepsis-Related Organ Failure Assessment (SOFA) score.

Results: VAC changes had a significant effect on APACHE IV score, MPI and SOFA score (p=0.0001). Although there was no significant difference in the SOFA scores between the 1st and 2nd changes or between the 3rd and 4th changes, there was a decrease in values over time.

Conclusion: In the treatment of abdominal contamination with sepsis, VAC use had a positive effect on contamination by decreasing the predicted mortality rate on a daily basis. Although it had a positive effect on sepsis, the effect of VAC on sepsis alone was not significant.

Keywords: Vacuum-assisted closure, intra-abdominal sepsis, controlled exploration, treatment

ÖZ

Amaç: İntra-abdominal sepsis durumunda yaygın kabul gören cerrahi teknik yoktur, mevcut teknikler ve sonuçları hakkında da sınırlı veri bulunmaktadır. Bu teknikler arasında anlamlı farklılık yoktur. Sepsis kaynağının kontrolü için yapılan laparotomilerde amaç mortaliteyi azaltmaktır. Bu retrospektif çalışma; vakum-yardımlı kapama (VAK) uygulamasının günler bazında intraabdominal enflamasyona, sepsis tablosuna ve mortaliteye etkisini araştırmak amacıyla planlandı.

Yöntemler: Çalışmaya 2010 Ocak-2017 Nisan tarihleri arasında VAK uygulaması yapılan 159 hasta dahil edildi. APACHE IV skoru, Mainhaim peritonit indeksi (MPİ) ve Sepsisle İlgili Organ Yetmezliği Değerlendirmesi (SOFA) skoru kullanılarak VAK uygulamasının günler bazında etkilerinin istatistiksel analizi yapıldı.

Bulgular: VAK değişimlerinin APACHE IV skoru, MPİ, SOFA değerleri üzerinde anlamlı etkiye sahipdi (p=0,0001). SOFA skorlarında 1. değişim ile 2. değişim arasında, 3. değişim ile 4. değişim arasında anlamlı farklılık olmamasına rağmen değerlerde zamana göre bir azalma vardı.

Sonuç: Sepsis tablosuyla kombine abdominal kontaminasyon tedavisinde, VAK uygulamasının günler bazında, beklenen mortalite oranını azaltarak kontaminasyon üzerine olumlu etkiye sahip olduğu tespit edilmiştir. Sepsis tablosuna olumlu etkisi olmasına rağmen, VAK'nin sadece sepsise üzerine etkisi anlamlı değildi.

Anahtar Kelimeler: Vakum-yardımlı kapama, intra-abdominal sepsis, kontrollü eksplorasyon, tedavi

Introduction

The main objective of damage control surgery is to manage high intra-abdominal pressure and abdominal contamination, as initially identified during trauma surgery in cases of intra-abdominal sepsis (1-3). In these cases, there are no widely accepted surgical techniques. There is limited data on surgical techniques and outcomes in cases of intra-abdominal sepsis, which can be considered a disaster chain (4), and no significant difference was found between different surgical techniques (5). In the 1990s, Wittmann reported that repeated laparotomies within 48-72 hours in abdominal sepsis reduced the mortality rate from 43% to 28% compared to that the use of primary abdominal closure (PAC) based on

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the APACHE II score (6). The usefulness of the vacuum-assisted closure (VAC) system, described in the late 1990s, has been supported by studies reporting that the system decreased the pressure caused by intra-abdominal contamination in sepsis; moreover, that the system allowed determination of postoperative edema and facilitated patient transport. VAC system also allows patients to remain mobile and enables improved nursing services (7,8). Nonetheless, there is insufficient data to allow a complete evaluation of the efficacy of VAC in cases of sepsis caused by intra-abdominal contamination, as well as the effect on the predicted survival rate.

In this retrospective study of a large patient cohort, the early effects of the VAC system on predicted survival rates, peritonitis, and the severity of sepsis according to the APACHE IV score (it was useful for quality assessment and predicting mortality in intensive care units), the Mannheim peritonitis index, and the Sequential Organ Failure Assessment (SOFA) score were evaluated in cases of intra-abdominal sepsis.

Methods

The records of 159 patients, who underwent emergency surgery between January 2010 and April 2017 for acute abdominal conditions, with subsequent use of VAC due to intra-abdominal contamination and high pressure, were reviewed. The study protocol was approved by the Ethics Committee of the İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2019/245). Informed consent was obtained from the patients. VAC is an aspiration system that is placed in the abdominal cavity after exploration under general anesthesia. It is used for control of intraabdominal pressure and sepsis source. For this purpose, VAC was performed in patients with anastomotic leak. Daily changes in APACHE IV, Mannheim peritonitis index (MPI) and SOFA scores were not investigated in patients with PAC. Patients who underwent VAC due to trauma, necrotizing fasciitis or Fournier gangrene and patients who were explored before 72 hours were excluded from this study.

Data on the 1st, 2nd, 3rd and 4th VAC application days were evaluated to assess early efficacy. VAC system applied following source control was changed within 72 hours after evaluation of peritoneal contamination, intestinal edema, hemodynamic instability, and intra-abdominal compartment criteria.

On the preoperative day and postoperative 3rd, 6th and 9th days, patients with available data on history, age, gender, American Society of Anesthesiologists score, temperature, heart rate, respiratory rate, PaO_2/FiO_2 mmHg, PO_2, PCO_2, use of mechanical ventilation, arterial pH, Na+, platelet count, bilirubin, albumin, hematocrit, leukocyte count, mean arterial pressure, Glasgow Coma scale score, creatinine, urine output and preoperative intra-abdominal contamination findings were included in this study. The effects of VAC application on the predicted mortality rate, peritonitis findings and sepsis were evaluated on a daily basis according to the APACHE IV, MPI, and SOFA scores.

Statistical Analysis

Qualitative variables were expressed as frequencies and percentages, and quantitative variables were expressed as mean and standard deviation. Repeated measures analysis of variance (ANOVA) was used to detect temporal changes in the APACHE IV, MPI and SOFA scores. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using Number Cruncher Statistical System 11 software.

Results

The mean age of the patients was 55 years (range: 19-84). The study included 61 women and 98 men. VAC was used for large bowel perforation in 23 patients, small bowel perforation in 20, mesenteric ischemia in 18, anastomotic failure in 47, necrotizing pancreatitis in four, gastric perforation in 17 and biliary complications in 20 patients (Table 1).

VAC changes had a significant effect on the APACHE IV score (p=0.0001), accounting for 89.1% of the variations in the APACHE IV measurements. The Bonferroni test revealed significant differences between the 1st and 2nd changes (p=0.0001), between the 1st and 3rd changes (p=0.0001), between the 1st and 4th changes (p=0.0001), between the 2nd and 3rd changes (p=0.0001), between the 2nd and 4th changes (p=0.0001), and between the 3rd and 4th changes (p=0.0001). When the mean values of the measurements were examined, VAC change was observed to decrease APACHE IV scores (Table 2).

VAC changes had a significant effect on MPI (p=0.0001), accounting for 92.2% of the changes in the MPI. There were significant differences between the 1st and 2nd changes (p=0.0001), between the 1st and 3rd changes (p=0.0001), between the 1st and 4th changes (p=0.0001),

Table 1. Demographic data of the study

	n	Age	Women/Men	VAC technic (4 times)
Large bowel perforation	23	53 (20-84)	5/18	92
Small bowel perforation	20	53 (22-72)	9/11	80
Ischemia/Infarct	18	60 (46-77)	6/12	72
Anastomotic failure	47	60 (20-83)	19/28	188
Abscess	10	56 (36-79)	5/5	40
Necrotizing pancreatitis	4	43 (27-62)	1/3	16
Gastric Perforation	17	54 (19-73)	6/11	68
Biliary complication	20	61 (22-77)	10/10	80
TOTAL	159	55 (19-84)	-	636

VAC: vacuum-assisted closure

between the 2nd and 3rd changes (p=0.0001), between the 2nd and 4th changes (p=0.0001), and between the 3rd and 4th changes (p=0.0001). When the mean values of the measurements were examined, VAC changes were observed to decrease MPI (Table 3).

Table 2. Assessment of the APACHE 4 score according to time

APACHE 4	Mean ± SD	Median (maximum-minimum)	p*	Eta-squared
Day 1	70.97±13.93	67.00 (99.00-42.00)	0.0001	0.891
Day 2	67.49±14.81	64.00 (98.00-40.00)	-	-
Day 3	60.08±14.67	55.00 (92.00-39.00)	-	-
Day 4	53.09±14.26	47.00 (90.00-38.00)	-	-
Bonferroni post-hoc test				
	p**	-	-	-
Day 1/Day 2	0.0001	-	-	-
Day 1/Day 3	0.0001	-	-	-
Day 1/Day 4	0.0001	-	-	-
Day 2/Day 3	0.0001	-	-	-
Day 2/Day 4	0.0001	-	-	-
Day 3/Day 4	0.0001	-	-	-

*ANOVA Test, **Bonferroni Test
SD: standard deviation

Table 3. Assessment of Mannheim peritonitis indices according to time

Mannheim	Mean ± SD	Median (maximum-minimum)	p*	Eta-Squared
Day 1	37.87±5.57	38.00 (53.00-27.00)	0.0001	0.922
Day 2	32.78±6.46	33.00 (48.00-16.00)	-	-
Day 3	25.69±6.26	25.00 (39.00-10.00)	-	-
Day 4	18.01±5.80	17.00 (32.00-3.00)	-	-
Bonferroni post-hoc test				
	p**	-	-	-
Day 1/ Day 2	0.0001	-	-	-
Day 1/ Day 3	0.0001	-	-	-
Day 1/ Day 4	0.0001	-	-	-
Day 2/ Day 3	0.0001	-	-	-
Day 2/ Day 4	0.0001	-	-	-
Day 3/ Day 4	0.0001	-	-	-

*ANOVA Test, **Bonferroni Test
SD: standard deviation

Table 4. Assessment of SOFA values according to time

SOFA	Mean ± SD	Median (maximum-minimum)	p*	Eta-Squared
Day 1	1.86±0.79	2.00 (3.00-1.00)	0.0001	0.240
Day 2	1.82±0.87	2.00 (3.00-0.00)	-	-
Day 3	1.40±1.09	1.00 (3.00-0.00)	-	-
Day 4	1.26±1.45	0.00 (4.00-0.00)	-	-
Bonferroni Post-Hoc test				
	p**	-	-	-
Day 1/Day 2	1.00	-	-	-
Day 1/Day 3	0.0001	-	-	-
Day 1/Day 4	0.0001	-	-	-
Day 2/Day 3	0.0001	-	-	-
Day 2/Day 4	0.0001	-	-	-
Day 3/Day 4	0.079	-	-	-

*ANOVA test, **Bonferroni Test
SD: standard deviation

VAC change had a significant effect on SOFA scores (p=0.0001), accounting for 24% of the changes in SOFA measurements. Significant differences were observed between the 1st and 3rd changes (p=0.0001), between the 1st and 4th changes (p=0.0001), between the 2nd and 3rd changes (p=0.0001), and between the 2nd and 4th changes (p=0.0001). No significant difference was observed between the 1st and 2nd changes (p=1.00) or between the 3rd and 4th changes (p=0.079). Although there was no significant difference between the 1st and 2nd changes, or between the 3rd and 4th changes, a temporal decrease was observed when the mean measurement values were examined (Table 4).

Discussion

Intra-abdominal sepsis may gradually progress to severe sepsis, septic shock and even organ failure in some cases (9). The concept of repeat laparotomy for the treatment of severe peritonitis has long been discussed. Although not routinely recommended for intra-abdominal sepsis in the current guidelines, the open abdominal approach is still accepted as an important strategy (10). It has been reported that this approach can provide better source control and enable anastomosis under better conditions, while also preventing intra-abdominal compartment syndrome (11-13).

Although studies have reported that negative pressure therapy, which is commonly used in cases of increased intra-abdominal pressure and sepsis, is effective in the abdominal wall formation, few studies have evaluated the effects of this method on intra-abdominal peritonitis and sepsis. Negative pressure therapy, however, has been reported as a promising method, particularly in source control (14).

The findings showed that VAC had a positive effect on predicted survival rates, based on the APACHE IV score, which is used to determine the predicted survival rate of patients in the intensive care unit. The decrease in the APACHE IV score was found to be statistically significant (p=0.0001), and a statistically significant difference was also found between the APACHE IV score on the day VAC was applied and on the daily scores (p=0.0001). Every day of VAC application, the APACHE IV score was observed to decrease, and thus the predicted mortality rate decreased.

This positive effect of VAC on APACHE IV scores was detected in MPI (p=0.0001). In particular, VAC application, which had a positive effect on contamination and intestinal edema, had a positive effect on MPI (p=0.0001). It is apparent that use of the VAC system for an open abdominal protocol may have positive effects on peritoneal contamination and intestinal edema. Our results showed that VAC application provided good source control.

It was noted that changes in the SOFA score between VAC application days were not statistically significant, although VAC had a positive effect on the SOFA score. This finding suggests that VAC application has a positive effect on the local effects of peritonitis, although the expected positive systemic effects were not observed at the expected level. VAC therapy increased peritoneal fluid concentrations of interleukin (IL)-6, IL-17, IL-5, and human growth factor more than PAC, therefore increased peritoneal cytokines were found to lead to progression of abdominal sepsis in a study (15). The application of an abdominal management method in cases of abdominal sepsis has several advantages, including the diagnosis and treatment of residual infections, infection source control, removal of infected and cytokine-loaded peritoneal fluids, and prevention of abdominal compartment syndrome, and can serve as a temporizing measure pending permanent intervention until the patient is appropriately resuscitated and hemodynamically stabilized (16). However, our findings suggest that VAC application does not reduce sepsis control. VAC should be terminated with PAC application in patients who achieve source control and normalized intra-abdominal pressure (i.e., as early as possible).

This retrospective study revealed that VAC application for intra-abdominal sepsis could provide source control, and could reduce the local effects of contamination, control intra-abdominal pressure, and simplify patient care. However, it was also found that VAC offers little promise in the treatment of sepsis. The basic criteria for the termination of VAC therapy and initiation of PAC should aim to prevent peritonitis and regression of intestinal edema, and control contamination. In case of prolonged VAC application, it is believed that peritoneal cytokines will increase, with a negative effect on sepsis. Inflammatory peritoneal fluid findings should be investigated in future studies with a larger cohort of patients. Such an evaluation may validate our findings.

Study Limitations

Limitations of our study was that the effects of VAC system on mortality could not be completely evaluated as they did not provide standardization for survival, the effects on APACHE IV, MPI, and SOFA scores could be assessed within 12 days.

Conclusion

The effects on peritonitis macroscopy and expected mortality rate of VAC system used in intraabdominal sepsis were evaluated positively. However, this study defined that the sepsis decreasing effect of VAC was not sufficient. Improvement of peritonitis macroscopy and regression of intraabdominal pressure to normal values were the most important criteria in terminating VAC system and converting to PAC.

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of the İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (decision no: 2019/245).

Informed Consent: Informed consent was obtained from the patients.

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