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Comparison of three techniques for appendiceal stump closure during laparoscopy

Laparoskopik apendektomide güdük kapatmak için kullanılan üç tekniğin karşılaştırılması

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Abstract

Aim: Laparoscopic appendectomy is the gold standard treatment of acute appendicitis. However, there is no consensus about the technique to apply when closing the appendix stump. This study compares three techniques to close the appendix stump: Laparoscopic purse-string suture (LPS), metal clips, and Hem-o-lok clips. The aim is to evaluate the advantages, safety, and costs of these three methods.

Methods: We conducted a retrospective cohort study which included 220 patients who underwent laparoscopic appendectomy operations for acute appendicitis between May 2017 and December 2019. The cases were divided into three groups and evaluated. Group A received LPS, group B received metal clips, and group C received Hem-o-lok clips. The demographic features of the patients, American Society of Anesthesiology (ASA) scores, duration of surgery, postoperative complications, hospital stay, and cost were evaluated retrospectively from patient files.

Results: There were 79 patients in group A, 91 patients in group B, and 50 patients in group C. There was no difference between the groups with respect to demographic features, ASA physiological state scores, and laboratuary values. The operation time and postoperative complication rates did not differ between groups (P>0.05). Group C had longer hospital stays (P=0.001), and group A had lower costs (P=0.001).

Conclusion: In the laparoscopic appendectomy technique, the use of LPS for appendix stump closure is safe and effective. Furthermore, technical consumables and hospital treatment costs are significantly reduced.

Keywords: Acute appendicitis, Laparoscopic appendectomy, Laparoscopic purse string, Hem-o-lok clip

Öz

Amaç: Laparoskopik apendektomi akut apandisit tedavisinde altın standarttır. Bununla birlikte, apendiks güdüğünü kapatırken uygulanacak teknik hakkında henüz bir fikir birliği yoktur. Bu çalışma, apendiks güdüğünü kapatmak için uygulanan teknikleri karşılaştırmaktadır: Laparoskopik sütur uygulama, metal klips uygulama ve Hem-o-lok klips uygulama. Amacımız bu üç yöntemin avantajlarını, güvenliğini ve maliyetlerini değerlendirmektir.

Yöntemler: Mayıs 2017-Aralık 2019 tarihleri arasında akut apandisit nedeniyle laparoskopik apendektomi operasyonu geçiren 220 hastanın dahil edildiği retrospektif kohort çalışma planlandık. Olgular üç gruba ayrılarak değerlendirildi. A Grubunda apendiks güdüğü laparoskopik sütur yöntemi ile kapatılanlar yer aldı. B grubunda metal klips C grubunda ise Hem-o-lok klips uygulanarak apendiks güdüğü kapatılan olgular yer aldı. Hastaların demografik özellikleri, Amerikan Anesteziyoloji Derneği (ASA) skorları, ameliyat süresi, postoperatif komplikasyonlar, hastanede kalış süresi ve maliyeti değerlendirildi.

Bulgular: Grup A'da 79 hasta, grup B'de 91 hasta ve grup C'de 50 hasta vardı. Demografik özellikler, ASA skorları, laboratuar değerleri açısından gruplar arasında fark yoktu. Ameliyat süresi ve ameliyat sonrası komplikasyon oranları gruplar arasında farklılık göstermedi (P>0,05). Grup C'de daha uzun hastanede kalış süresi vardı (P=0,001) ve grup A daha düşük maliyete sahipti (P=0,001).

Sonuç: Laparoskopik apendektomide, apendiks güdüğünün sütur kullanılarak kapatılması tekniği güvenli ve etkilidir. Ayrıca bu tekniğin sarf malzeme kullanımını ve hastane tedavi maliyetlerini önemli ölçüde azalttığı görülmüştür.

Anahtar kelimeler: Akut apandisit, Laparoskopik apendektomi, Laparoskopik sütur, Hem-o-lok klip

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Introduction

Laparoscopic appendectomy (LA) is a globally accepted surgical method for the treatment of acute appendicitis [1]. The benefits of LA compared to open treatment include faster recovery, less surgical pain, reduced wound infections, shorter hospitalization, and early return to daily activities [1,2]. Although the technique is an accepted method, concerns remain regarding the technique that should be used for appendiceal stump closure [3]. A number of techniques have been described, such as endoloops, the intracorporeal suture technique, bipolar coagulation, metal clips, Hem-o-lok polymeric clips, and endostaplers [3-7]. Discussions about the effectiveness and safety of these new materials are still ongoing [3-9].

All the techniques offer obvious advantages and disadvantages at various clinical stages of acute appendicitis. Prospective clinical studies have evaluated the effectiveness, but the number of patients in these studies is low, and sufficient data on cost are not included [10,11]. Given the materials used in LA surgery, a safe and low-cost technique is required to reduce costs for the hospital and the patient.

A polymeric clip seems easier to use, faster, and at least as secure as a knot. It is also cheaper than an endostapler. Polymeric clips have found a wider range of application in daily practice [7,10,12-14]. With the widespread use of titanium endoclips in surgery, endoscopic procedures have been made easier, and operation times have significantly shortened. They can also be easily applied and do not require surgeons to have advanced surgical skills.

Many studies have been conducted on the use of metal clips to close the appendix stump [3,6,15]. However, there are serious concerns that clips do not provide adequate security, especially in cases where the appendix diameter increases significantly [16]. In a study on laparoscopic purse-string sutures (LPS), no difference was found between the groups regarding the use of polymeric clips and intracorpereal sutures [17].

The aim of the present clinical study is to evaluate the safety and effectiveness of three techniques under routine conditions: LPS, metal clips, and Hem-o-lok clips. The aim is to evaluate the advantages, safety, and costs of the methods.

Materials and methods

The clinical, paraclinical, and intraoperative data files of patients who underwent LA between May 2017 and December 2019 were examined. A retrospective comparative analysis was performed for appendix stump closure for three groups with different surgical techniques. Group A received LPS, group B received metal clips, and group C received Hem-o-lok clips.

Patients were excluded if they had an American Society of Anesthesiology (ASA) score ≥ III, a history of anesthetic or narcotic analgesic allergy, abdominal surgery, were pregnant or aged less than 18 years. The diagnosis of acute appendicitis and surgery was always made by an experienced surgeon. All operations were performed by surgeons who are experienced in LA. The groups were compared in terms of age, gender, ASA score, body mass index (BMI), comorbidity, complications, duration of surgery, length of hospital stay, and cost of hospitalization. After discharge, the patients were followed up in the outpatient clinic at one-week intervals for the monitoring of complications and full recovery. Post-operative outpatient records were reviewed. 220 patients who came to the outpatient clinic controls and whose file records were accessed were included. Fifty patients whose data were missing or did not show up for control visits were excluded from the study.

The surgical procedure followed a standard protocol. All patients were given a dose of first-generation cephalosporin for antibiotic prophylaxis before surgery. LA was performed using the classic three-port technique. Pneumoperitoneum was created using an open technique or a closed Veress needle technique depending on the surgeon's preferences, with carbon dioxide (CO2). Intra-abdominal pressure was adjusted to 10-12 mmHg. An 11-mm trocar (Johnson and Johnson, USA) was placed under the navel. A 5-mm trocar was then inserted into the left lower quadrant with a 5-mm trocar under direct vision of the right iliac fossa.

A 30-degree 10-mm laparoscope and 5-mm laparoscopic instruments such as an endograsper and an endoligasure were used. The patients were placed in the reverse inclined Trendelenburg position. The distal ileum was pushed to the left side of the abdomen to help reveal the appendix. After the appendix became visible, the mesoappendix was ligated with endoligasure (LigaSure, Covidien, Boulder, CO). After the appendix radix was introduced, the appendix stump was managed as follows:

In Group A, two intracorporeal knots and one intracorporeal knot 5 mm above the last were made in the base of the appendix, and resection was performed by cutting between these knots. The specimen was taken out of the abdomen in an endobag. Then, a sac suture was tied with 1.0-cm 3/0 vicryl around the base of the appendix (Figure 1E,F). By holding the two ends of the suture, the stump was inverted, buried, and knotted with the help of an endograsper.

In Group B, two titanium metal clips (LIGACLIP Extra Ligating Clip, Large, Ethicon Endo-Surgery, LLC, Cincinnati, OH) were placed on the base of the appendix, and one metal clip was placed 5 mm above them (Figure 1A,B). Cuts were made just above the two clips on the base of the appendix. The specimen was placed in the endobag and taken out of the abdomen from the 11-mm trocar.

In Group C, two Hem-o-lok clips (Hem-o-lok clips, Weck, Research Triangle Park, NC) were placed on the base of the appendix, and another Hem-o-lok clip was placed 5 mm above them (Figure 1C,D) through the trocar. Cuts were made just above the two Hem-o-lok clips on the base of the appendix. The specimen was placed in the endobag and taken out of the abdomen from the 11-mm trocar.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 24.0 was used for statistical analysis. A one-way ANOVA test was used for intergroup comparisons of normally distributed parameters. Non-normally distributed parameters, which were presented with descriptive statistics (mean, standard deviation, median, frequency, rate, minimum, maximum) were compared with Kruskall-Wallis test. Pearson's chi-squared test was used to analyze qualitative data. *P*-value <0.05 were considered statistically significant.

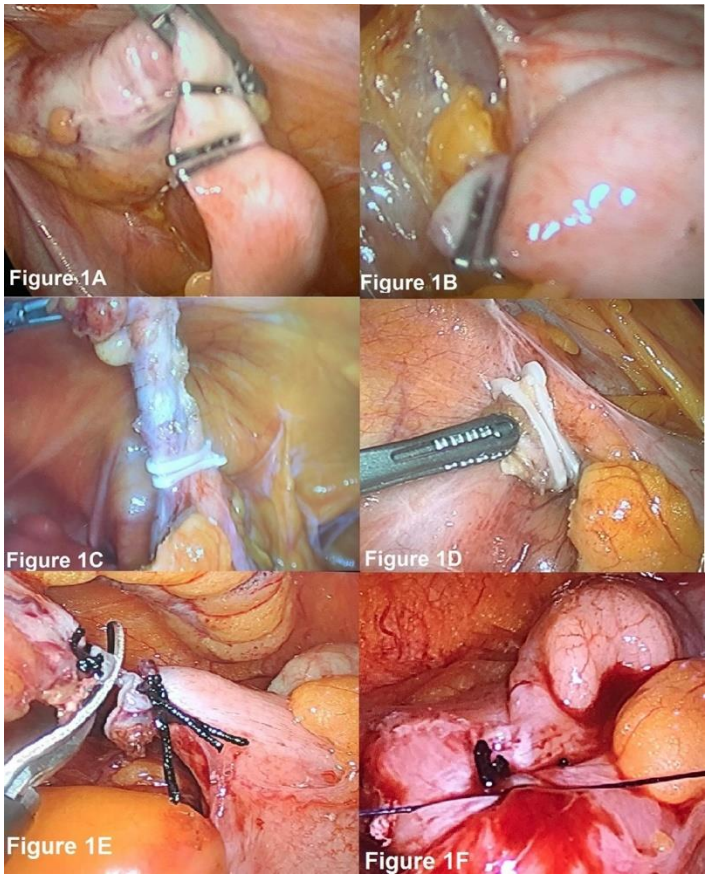

Figure 1: Laparoscopic view of closing the appendix stump. (1A) Intraoperative view of applied metal clips in laparoscopic appendectomy. (1B) Intraoperative view of appendix stump after applied metal clips. (1C) Intraoperative view of applied hem-o-lok clips in laparoscopic appendectomy. (1D) Intraoperative view of appendix stump after applied hem-o-lok clips. (1E) Intraoperative view of intracorporeal knots in laparoscopic appendectomy. (1F) Intraoperative view of appendix stump after applied intracorporeal knots.

Results

This retrospective study initially included 270 patients with acute appendicitis. Their history, physical examination, abdominal ultrasonography, and computerized tomography results were used for the diagnosis. Fifty patients were excluded from the study due to missing data and loss to follow-up. There were 79 patients in group A, 91 patients in group B, and 50 patients in group C. All surgical operations were completed successfully with the laparoscopic technique. The diagnosis was uncomplicated acute appendicitis for 188 patients and complicated acute appendicitis for 32 patients.

There was no significant difference between the two groups with respect to demographic features, ASA scores, white blood cell (WBC) counts, and neutrophil counts (Table 1). The mean durations of the procedure were 53.7 (19.6) minutes in group A, 51.9 (20.2) minutes in group B, and 47.8 (16.3) minutes in group C (Table 2). The rates of postoperative complications did not significantly differ between groups (P=0.474) (Table 2).

Patients were discharged at postoperative days 1–3 and controlled daily for 1 week. The Douglas space was drained due to perforated appendicitis in 8 patients in group A, 8 patients in group B, and 4 patients in group C. All drains were pulled out on postoperative days 5 or 6. There was no significant difference between three groups (P=0.256) (Table 2).

The mean hospitalization period after LA was 27.8 (48.3) hours in group A, 22.8 (19.0) hours in group B, and 34.1 (34.6) hours in group C. The total length of hospital stay varied significantly (P=0.001) (Table 2). According to the binary comparisons, the total length of stay was significantly higher in group C than groups B (P=0.002) and A (P=0.001). There was no significant difference between groups A and B (P=0.785) (Table 3).

The mean cost of the procedure was 247.9 (26.4) dollars in group A, 260.4 (24.9) dollars in group B, and 281.8 (38.5) dollars in group C. The costs differed significantly between groups (P=0.001) (Table 2). According to the binary comparisons, group A's costs were significantly lower than those of group B (P=0.001) and group C (P=0.001). Group B's costs were significantly lower than those of group C (P=0.001) (Table 3).

Table 1: Demographic data of patients

		Suture (n:79)	Metal clip (n:91)	Hem-o-lok clip (n:50)	*P*-value
Age (years) Mean (SD)		30.01 (2.59)	30.07 (13.42)	33.70 (14.74)	[a]0.220
Gender (n)(%)	Male	43(54.4)	59(64.8)	29(58)	[b]0.111
	Female	36(45.6)	32(35.2)	21(42)	
BMI (kg/m2) Mean (SD)		28.12 (4.07)	27.84 (4.52)	28.23 (3.59)	[a]0.912
ASA score (n)(%)	I	44(55.7)	49(53.8)	29(58)	
	II	31(39.2)	32(35.1)	17(34)	[a]0.564
	III	4(5.1)	10(11.1)	4(8)	
WBC (cell/mm3) Mean (SD)		14006 (4049)	14398 (3987)	13381 (3472)	[a]0.335
Neutrophil (cell/mm3) Mean (SD)		11010 (4163)	11785 (3706)	10366 (3507)	[a]0.099
Co-morbidities (n) (%)		18(22.7)	21(23.1)	11(22)	[a]0.756
Diagnostic imaging (n) (%)	CT	54(68.3)	61(67.1)	32(64)	[a]0.876
	US	25(31.7)	30(32.9)	18(36)	

BMI: Body mass index, ASA score: American Society of Anesthesiologists physical classification system, WBC: White blood cell, CT: Computed tomography, US: Ultrasonography

Table 2: The characteristics of the operation results

		Suture (n:79)	Metal clip (n:91)	Hem-o-lok clip (n:50)	*P*-value
LGS* Score (n) (%)	LGS* 0, 1, 2	52(65.8)	78 (85.7)	42 (84)	
	LGS* 3a	12 (15.2)	8 (8.7)	3 (6)	[a]0.032
	LGS* 3b	8 (10.1)	0	0	
	LGS* 4a	3 (3.7)	2 (2.1)	2 (4)	
	LGS* 4b	2 (2.5)	1 (1.1)	1 (2)	
	LGS* 5	2 (2.5)	2 (2.1)	2 (2)	
Postoperative complications (n) (%)		8 (10.1)	5 (5.5)	5 (10)	[b]0.474
Trocar site infection (n) (%)		4 (5.1)	7 (7.7)	7 (14)	[b]0.192
Drain (n) (%)		8 (10.1)	8 (8.8)	4 (8)	[b]0.256
Hospital stay (hours) Mean (SD)		27.8 (48.3)	22.8 (19.0)	34.1 (34.6)	[c]0.001
Operative time (minute) Mean (SD)		53.7(19.6)	51.9 (20.2)	47.8 (16.3)	[a]0.233
Hospital cost (dollar) Mean (SD)		247.9 (26.4)	260.4 (24.9)	281.8 (38.5)	[c]0.001
Price (dollar)		3.2[x]	6.42[y]	20.71[z]	[c]0.001

[a] One-Way Anova Test, [b] Pearson Chi-Square Test, [c] Kruskall Wallis, LGS*: Laparoscopic grading system of acute appendicitis according to Gomes Score [16] (the appendix was graded based upon its appearance: Grade 0 (normal looking), 1 (redness and edema), 2 (fibrin), 3a (segmental necrosis), 3b (base necrosis), 4a (abscess), 4b (regional peritonitis), and 5 (diffuse peritonitis), x: The price of three silk suture, y: The price of three metal clips, z: The price of three Hem-o-lok clips.

Table 3: Post-Hoc results

	Techniques	*P*-value
Hospital stay	Suture/Metal clip	0.785
	Suture/Hem-o-lok clip	<0.001*
	Metal clip/Hem-o-lok clip	<0.002*
Hospital cost	Suture/Metal clip	<0.001*
	Suture/Hem-o-lok clip	<0.001*
	Metal clip/Hem-o-lok clip	<0.001*

Mann Whitney U test, * P<0.01

The total complication rates of Group A, Group B, and Group C were 15.1, 13.1 and 24%, respectively (Table 2). There was no significant difference between the groups in terms of wound infection, intra-abdominal abscess, and postoperative ileus. Antibiotic treatment was administered in 5 patients in Group A, 4 patients in group B, and 4 patients in group C. In group B, 2 patients were treated with USG-guided percutaneous drainage and antibiotic therapy. Ileus developed in 1 patient in each group and healed with medical treatment. Four patients in group A, 7 patients in group B and 7 patients in group C

developed wound infections that were treated with antibiotic therapy.

Discussion

Due to faster recovery, less pain, and less surgical complications in the treatment of acute appendicitis, laparoscopic treatment has been widely accepted worldwide [1,2]. LA is a safe procedure for the treatment of uncomplicated acute appendicitis, but there is no common consensus for the laparoscopic treatment of complicated appendicitis due to studies showing high and low rates of post-operative intra-abdominal abscess (POIAA) [2,18-22]. Peroperative classification of complicated and uncomplicated acute appendicitis is highly valuable [16].

Postoperative complication rates are higher in complicated appendicitis, regardless of the appendix stump closure technique, and include intraabdominal abscess formation, wound infection, and paralytic ileus [1-8,23]. This suggests that the main determinant of postoperative complications depends on the degree of the disease rather than the method used. It is reasonable to consider that the presence and extent of peritonitis may be risk factors for POIAA, and perforated appendicitis without pus in the abdominal cavity may have lower rates than in those complicated with peritonitis.

Despite the shorter hospital stay and lower perioperative complication rates of LA, the hospital cost is still high compared to open appendectomy [22]. The appendix stump closure technique and the materials used are important in LA. Safe closure of the appendix stump is important to prevent potential postoperative complications (such as postoperative peritonitis, sepsis, and fistulas) and reoperation. Numerous studies have been carried out on techniques such as the endoloop, endostapler, metal clips, and Hem-o-lok clips, and intracorporeal knot for the closure of the appendix stump [3-13]. However, there is still no consensus on the ideal technique. The closure technique of embedding the stump used in open appendectomy was attempted using alternative techniques in a laparoscopic procedure.

Studies using endostaples to close the appendix stump have been carried out, but this method requires advanced laparoscopic training [5,11,14,15,24]. Staples are safe to use but very expensive. In addition, lost staple clips have been shown to cause peritoneal adhesions that lead to complications such as small bowel obstruction or ileus [15,24,25]. The appendix stump closure selection is up to the surgeon's preference, but an endostapler is recommended in cases of necrosis and inflammation of the base of the appendix [25].

Endoloops are also widely used and are one of surgeons' preferences [4,5,12,25]. The endostapler and endoloop methods were compared in a clinical prospective, observational, multicenter, high-case cohort study conducted by Van Rossem et al. There was no significant difference between the groups in terms of postoperative intraabdominal infections. Nevertheless, they recommended using endoloops in terms of cost. In this study, a double endoloop proximal to base of the appendix was proposed in the presence of inflammation.

Another method used for appendix stump closure is the titanium metal clip technique. Studies suggest that titanium metal clips are safe and cost effective for fixing the base of the appendix in LA [3,6,16]. In a clinical study, the metal clip technique was evaluated in patients with complicated appendicitis. Acute appendicitis grading was evaluated and classified according to peroperative laparoscopic findings. It was emphasized that the presence of local and diffuse peritonitis does not cause difficulty for the metal clip technique. Nine of twelve patients with appendicular base necrosis were safely treated with laparoscopic suture and laparotomy, and the metal clip technique is not recommended in these cases [16].

Recently, the use of simple non-absorbable clips, such as the Hem-o-lok clip, has become widespread for the closure of the appendix stump. The advantages of these clips are effortless application, low cost, and robust and safe stump closure [10-15]. In a clinical study, Delibegovic et al. stated that the method is effective and safe for closure of the appendix stump.

In our study, a secure closure was achieved by tying the appendix stump with 2 intracorporeal knots, suturing 1 cm from the stump, and embedding it in the cecum. Our technique provides a safe closure in cases with appendix radix necrosis, which is defined as 3D in the classification made by Gomez et al. We defined the LPS technique in our clinical study in 2017 [26]. In a similar study, Shadhu et al. compared the intracorporeal knot, Hem-o-lok clip, and laparoscopic purse string suture techniques and stated that all techniques are safe in cases of complicated appendicitis [17].

The stump closure techniques affect the operation times. While devices such as the Hem-o-lok clip, metal clip, and endostapler can be applied easily [6-13,27], techniques such as the intracorporeal knot, endoloop, and LPS techniques require surgical skills and experience [3-5]. A Cochrane review published in 2017 compared the results of endostapler and ligation methods (endoloop and intracorporeal knot) and found that the endostapler technique significantly reduced the operation time [28]. Again, both Hem-o-lok clip and metal clip applications significantly decreased the operation times compared to ligation techniques.

In a randomized clinical study conducted by Begovic et al. [27], the endoloop group had significantly longer operations than the endostapler group with clip techniques. The metal clip technique had a shorter time than the endostapler technique, but there was no significant difference between the Hem-o-lok clip and the endostapler group. In the same study, the operation time was significantly shorter in the Hem-o-lok group than the metal clip group [27]. In a retrospective clinical study by Shadhu et al. there was no significant difference in the duration of surgery in the intracorporeal knot, Hem-o-lok clip, and LPS techniques. It is much more difficult to apply LPS near the appendicular stump during LA, and it requires some experience in laparoscopic suturing [17].

In our study, even the LPS technique could not be applied in some serious cases due to cecum edema, and partial cecal resection was performed with an endostapler in these cases. The Hem-o-lok polymeric clip technique has been found feasible and safe for the appendicular stump [6-11]. However, the safe use of Hem-o-lok and metal clips is significantly limited by the maximum diameter of the 10-mm closure insert. In our study, the LPS technique was applied to patients who could not receive the Hem-o-lok clip technique.

The most common complications after LA are of infectious origin, and the most serious is intra-abdominal abscess formation [1,2]. This complication has important clinical consequences because frequent intervention or hospitalization is required. In a meta-analysis of 11 studies, wound-related infections were present in 92 (4.2%) of 2175 operated patients with acute complicated appendicitis [29]. In the same study, the postoperative intraabdominal abscess rate was 5.9% (1059/63) [29]. Abundant irrigation of the abdominal cavity with 0.9% saline solution has been stated as a possible cause of this development, and rational local irrigation with aspiration and gauze application was recommended [2]. The type of appendix stump closure has not been proven to affect this complication.

In a Cochrane systematic review, there was no significant difference in the postoperative complications between endoscopic clip and ligation techniques (endoloop and intracorporeal knots) for closure of the appendix stump [28]. This meta-analysis showed a significant decrease in postoperative complications with the use of the endostapler device compared to the ligation techniques [28]. This decrease in postoperative complications revealed that the endostapler technique triggered a reduction in postoperative superficial wound infections compared to ligation techniques.

There was no significant difference between groups in terms of POIAA or postoperative ileus [28]. In a retrospective clinical study, Shadhu et al. stated that there was no significant difference between LPS, Hem-o-lok clip and intracorporeal knot groups in terms of wound infection and POIAA. In our study, no significant difference was found between LPS, metal clips and Hem-o-lok clips in terms of postoperative complications.

It is accepted worldwide that LA is a costly method compared to open appendectomy. For this reason, a safe and low-cost technique is required to close the appendix stump to reduce costs for the hospital and the patient. Cost analysis is limited to data on consumable costs, and data on indirect costs are not available [28]. Consumable prices also differ from country to country [28,30]. Unfortunately, there is no study in which appendix suture closure techniques are compared in terms of hospital costs. Shadhu et al. compared LPS, hemoclip, and intracorporeal knot techniques, but no cost was given.

In our study, hospital costs differed significantly among groups. According to binary comparisons, the hospital costs in LPS were significantly different than those in which clips were used. Hospital costs in patients with metal clips were significantly lower than those with local clips. Consumable costs differed significantly by group.

Limitations

Our study has some limitations. The study was retrospective and allocated to one or another treatment arm because of the individual decision of the treating surgeon, so both groups of patients differed in disease severity. Therefore, no conclusions could be drawn regarding the equivalence of stump closure by LPS, metal clip or Hem-o-lok clip at the same disease stage. In addition, because of inflammation and necrosis (Gomez classification 3B), the LPS technique was applied in patients in which metal clip could not be used, because the appendix stump diameter was over 10 mm.

Conclusion

The use of LPS for appendix stump closure in LA operations is safe and effective. Our data clearly show that a significant percentage of routine LA (32%) is suitable for clip closure without an increase in intra- and postoperative complications. This technique significantly reduces consumables and hospital treatment costs. Our study supports the use of the LPS technique in complicated appendicitis cases with necrosis and perforation of the appendix base.

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Is overactive bladder a risk factor for erectile dysfunction? A cross-sectional study

Aşırı aktif mesane erektil disfonksiyon için bir risk faktörü müdür? Kesitsel çalışma

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Abstract

Aim: Erectile dysfunction (ED) is a sexual dysfunction characterized by the inability to achieve or maintain penile erection during sexual activity. Many risk factors have been identified in ED-related epidemiological studies. In experimental studies, a relationship is thought to exist between Overactive Bladder (OAB) and ED. We investigated the relationship between OAB and ED, its clinical reflections, and the odds ratio of OAB for ED.

Methods: We conducted this cross-sectional prospective study between January-July 2020. Sixty patients referred to the urology outpatient clinic with complaints of OAB (Group 1) and 66 patients without urological complaints (Group 2) were included in the study. Patients' erectile functions were evaluated with the IIEF-5 form. OAB was evaluated with the OAB-V8 form.

Results: The groups were similar in terms of age, body mass index, comorbidity, and smoking status. IIEF-5 scores were higher in Group 2 [20.52 (3.51)] compared to Group 1 [18.17 (5.46)] (P=0.036). Correlation analysis between IEF-5 and OAB-V8 scores revealed a negative correlation; it was observed that the IIEF-5 score decreased as the OAB-V8 score increased (r=-0.260, P=0.045). The odds ratio of decreasing IIEF-5 score with each 1-unit increase of OAB-V8 score was 0.164 (P=0.04). It was observed that the patients diagnosed with OAB had lower IIEF-5 scores when they had nocturia.

Conclusion: OAB is a risk factor for ED. The presence of nocturia symptoms is remarkable for ED in OAB patients. The effect of OAB should not be ignored in the treatment of ED.

Keywords: Erectile dysfunction, IIEF-5, OAB, Overactive bladder

Öz

Amaç: Erektil disfonksiyon (ED), cinsel aktivite sırasında penis ereksiyonunun sağlanamaması veya sürdürülememesi ile karakterize bir cinsel işlev bozukluğudur. ED ile ilişkili epidemiyolojik çalışmalarda birçok risk faktörü tanımlanmıştır. Deneysel çalışmalarda Aşırı Aktif Mesane (OAB) ile ED arasında bir ilişki olduğu düşünülmektedir. Bu çalışmamızda OAB ve ED arasındaki ilişkiyi, klinik yansımalarını ve ED için OAB'nin risk oranını araştırmayı amaçladık.

Yöntemler: Bu kesitsel çalışmayı Ocak 2020 ve Temmuz 2020 arasında gerçekleştirdik. OAB (Grup 1) şikayetleri ile üroloji polikliniğine başvuran 60 hasta ve ürolojik şikayeti olmayan 66 hasta (Grup 2) çalışmaya dahil edildi. Hastaların erektil fonksiyonları IIEF-5 formu ile aşırı aktif mesane sorgulaması OAB-V8 formu ile değerlendirildi.

Bulgular: Gruplar yaş, vücut kitle indeksi, komorbidite ve sigara içme durumu açısından benzerdi. IIEF-5 skorları Grup 2'de [20,52 (3,51)] Grup-1'e [18,17 (5,46)] göre daha yüksek bulundu (P=0,036). IEF-5 score ve OAB-V8 score arasında yapılan korelasyon analizinde negatif korelasyon saptandı; OAB-V8 skoru arttıkça IIEF-5 skorunun düştüğü gözlendi (r -0,260, P=0,045). OAB-V8 skorunun her 1 birim artışında IIEF-5 puanınında ki azalma risk oranı 0,164 olarak bulunmuştur (P=0,04). OAB tanısı alan hastalarda noktüri varlığında IIEF-5 skorlarının daha düşük olduğu gözlendi.

Sonuç: OAB, ED için bir risk faktörüdür. Noktüri semptomlarının varlığı OAB hastalarında ED için dikkat çekicidir. ED tedavisinde OAB'nin etkisi göz ardı edilmemelidir.

Anahtar kelimeler: Erektil disfonksiyon, IIEF-5, OAB, Aşırı aktif mesane

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Introduction

Erectile dysfunction (ED) is a sexual dysfunction characterized by the inability to achieve or maintain penile erection during sexual activity [1]. It is a quite common disease among adult males and its incidence increases with age. With the aging US population, it is predicted that more than 35 million American men will experience ED and that 50% of men will be affected by ED until the age of 50 [2]. In epidemiological studies on ED, the main risk factors were divided into 4 categories: 1- Urological and andrological risk factors, 2- Cardiovascular and metabolic risk factors, 3- Psychiatric diseases and 4- Lifestyle-related risk factors [3]. The relationship between ED and LUTS under the title of urological and andrological risk factors is confirmed by epidemiological studies and potential common biological mechanisms [4].

According to OAB definition of ICS 2002 [5], overactive bladder (OAB) is a syndrome characterized by symptoms of urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia (increased night-time urination). It includes lower urinary system symptoms (LUTS). The association of OAB, including lower urinary tract symptoms, with Erectile Dysfunction (ED), which is a urological disorder, was also investigated in the literature [6-10]. It was also indicated that ED had a strong relationship with OAB symptoms [9]. OAB affects 11.8-27.2% of men [8,11,12]. The prevalence of overactive bladder also increases with age, as in ED. Both diseases negatively affect health-related quality of life and psychology [13].

Experimental studies demonstrated that mirabegron, which is used in the treatment of OAB, led to the relaxation of the corpus cavernosum by alpha-1 adrenoceptor blockade and that avanafil, which is a type 5 PDH inhibitor, inhibited the activation of detrusor activated by potassium chloride [14,15]. Both experimental studies and the relationship of ED with LUTS suggest that these two urological diseases may be each other's risk factors or comorbid conditions.

In these studies, the relationship between the Overactive Bladder 8-Question Awareness Tool (OAB-V8) scores and The International Erectile Function Index Questionnaire (IIEF-5) scores of OAB patients and the OAB-V8 scores and IIEF-5 scores of control patients randomly selected from the community without OAB, and the clinical reflections of their responses to the IIEF-5 questions were not investigated.

In this study, we conducted an observational study to investigate this relationship and its clinical reflections and calculate the odds ratio of OAB for ED.

Materials and methods

Study design

This study was designed as a cross-sectional study. The present study protocol was reviewed and approved by the Institutional Review Board of Hitit University School of Medicine Ethics Committee (ethics committee approval date-number: 2020-207). Informed consent was obtained from all subjects when they were enrolled. This study was conducted in accordance with STROBE guidelines for reporting observational studies (www.strobestatement.org).

Study population

As a result of the sample size analysis based on other research findings in the literature, the minimum number of participants in each group was determined as 60 with a 95% confidence level and 80% power.

Sixty patients referred to the urology outpatient clinic with complaints of OAB (diagnosed with OAB for the first time and never received anticholinergic treatment) between January 2020 - July 2020, and 66 control patients without urological complaints were included in the study. The patients were informed about the study and written consent forms were received for participation. Patients' age, height, weight, Body Mass Index (BMI), comorbid disease states, and smoking status were examined.

Evaluation of ED

The sexual activity status of the patients with active sexual lives for the last 12 months in the last 4 weeks was evaluated using the 5-question version of the International Erectile Function Index questionnaire (IIEF-5) (16). This questionnaire consists of 4 questions about sexual function and 1 question about sexual satisfaction. Each question is scored between 1-5 points. Patients who stated that they were using PDH-5 inhibitor were not included in the study.

Evaluation of OAB

OAB was evaluated according to the 2002 ICS definition using the OAB-V8 (Overactive Bladder 8-Question Awareness Tool- V8) form consisting of 8 questions developed by Acquadro et al. [17] for symptom scoring in 2006. In this form, each question is scored between 0-5 points. Among the patients with complaints of OAB, those with active urinary tract infections, interstitial cystitis, neurogenic bladder, excessive fluid intake, and patients using diuretics and similar drugs were excluded from the study. In addition, patients were evaluated in terms of benign prostatic hyperplasia. Patients with uroflowmetry maximum flow rate (Qmax) below 15 milliliters/second and patients with obstructive, stenotic, intermittent voiding patterns were not included in the study. Likewise, according to the EAU and AUA guidelines on digital rectal examination and PSA, patients with suspicious findings were excluded.

Statistical analysis

Statistical analyses were performed using the SPSS version 22 software. The distribution of variables was tested by the Shapiro-Wilk test. Descriptive statistics were presented as mean and standard deviation for normally distributed variables, median, minimum, maximum values for ordered ordinal data, and number and percentage for categorical variables. In the evaluation of numerical data between the groups, the parameters with normal distribution were evaluated by student t test, ordinal data were evaluated by Mann-Whitney U test, and categorical data were evaluated by chi-square test. The relationship between the IIEF-5 score and the OAB-V8 score was examined with the Pearson and Spearman’s correlation test. The independent effects of the OAB-V8 score on IIEF-5 score were examined with the linear regression model. The model fit was analyzed with the required residual and fit statistics. The cases with a Type-1 error level below 0.5% were statistically evaluated.

Results

A total of 126 patients, including 60 patients diagnosed with OAB (Group 1) and 66 patients in the control group (Group 2), were included in our study. The mean ages of Groups 1 and 2 were 44.30 (12.63) years and 40.15 (13.41) years, respectively. BMI values were 27.95 (5.85) kg/m^2 and 26.62 (4.68) kg/m^2 in Groups 1 and 2, respectively. There was no difference between the groups in terms of age and BMI values (P=0.056, P=0.073). IIEF-5 scores were higher in Group 2 [20.52 (3.51)] compared to Group 1 [18.17 (5.46)] (P=0.036). No difference was found between the groups in terms of diabetes, hypertension comorbidity and smoking. The main demographic data of the groups are presented in Table 1.

When the responses to the questions of the IIEF-5 form between the groups were examined, OAB patients were found to have lower scores in question 2 (When you had erections with sexual stimulation, how often were your erections hard enough for penetration?), question 3 (During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?) and question 5 (When you attempted sexual intercourse, how often was it satisfactory for you?) compared to control patients (P=0.010, P=0.048, P=0.006, respectively). The scores of IIEF-5 questions among the groups are presented in Table 2 and Figure 1.

Table 1: Demographic characteristics of the patients

		Group 1 (OAB) n=60 Mean (SD)	Group 2 (Control) n=66 Mean (SD)	*P*-value
Age (year)		44.30 (12.63)	40.15 (13.41)	0.056
BMI (kg/m^2)		27.95 (5.85)	26.62 (4.68)	0.073
IIEF-5 score		18.17 (5.46)	20.52 (3.51)	0.036
Diabetes Mellitus	Yes n (%)	8 (13.3)	8 (12.1)	0.838
	No n (%)	52 (86.7)	58 (87.9)	
Hypertension	Yes n (%)	10 (16.7)	7 (10.6)	0.320
	No n (%)	50 (83.3)	59 (89.4)	
Smoking	Yes n (%)	21 (35)	23 (34.8)	0.986
	No n (%)	39 (65)	43 (65.2)	

BMI: Body Mass Index, IIEF-5: International Index of Erectile Function-5 Score, SD: Standard deviation

Table 2: Comparison of the responses of the groups to the IIEF-5 questions

IIEF-5 questions	Group 1 (OAB) n=60 median (min-max)	Group 2 (Control) n=66 median (min-max)	*P*-value
1. How do you rate your confidence that you could get and keep an erection?	3 (1-5)	5 (2-5)	0.083
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?	4 (1-5)	4.5 (2-5)	0.010
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	4 (1-5)	4 (2-5)	0.048
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	4 (1-5)	4 (2-5)	0.051
5. When you attempted sexual intercourse, how often was it satisfactory for you?	4 (1-5)	5 (3-5)	0.006

IIEF-5: International Index of Erectile Function-5 Score, OAB: Overactive Bladder

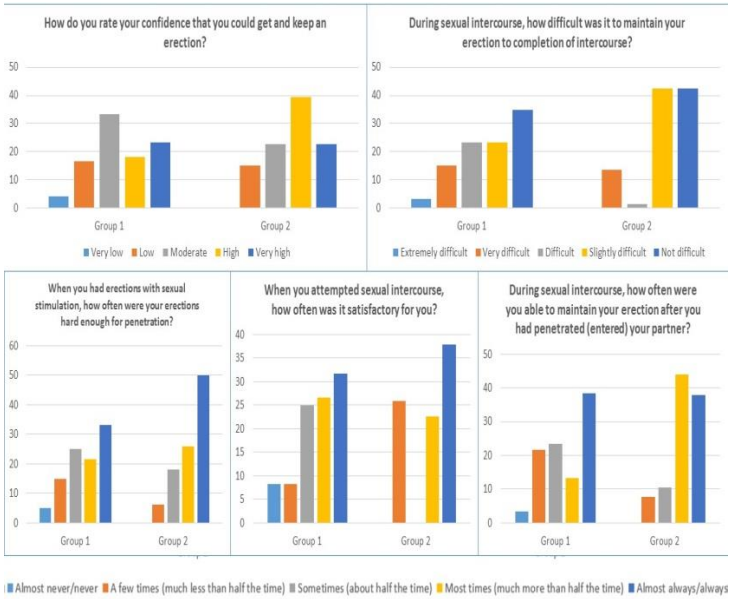

Figure 1: Graphical representation of scores given to IIEF-5 questions between groups

In the correlation analysis of OAB-V8 and IIEF-5 scores of OAB patients, IIEF-5 score was determined to decrease (developed erectile dysfunction) as the OAB-V8 score increased (r -0.260, P=0.045). A statistically significant correlation was found between IIEF-5 scores and the questions on Nighttime urination and Waking up at night because you had to urinate (rho -0.283, P=0.028 and rho -0.316, P=0.014, respectively) (Table 3). Linear regression analysis of OAB-V8 and IIEF-5 scores revealed that the odds ratio of decreasing IIEF-5 score for each 1-unit increase of OAB-V8 score was 0.164 (95% CI: 0.325-0.004, P=0.04).

Table 3: Correlation analysis between IIEF-5 score and OAB-V8 questions

OAB-V8 questions	IIEF-5 score Correlation coefficient	*P*-value
1. Frequent urination during the daytime hours?	0.579	0.550
2. An uncomfortable urge to urinate?	-0.132	0.316
3. A sudden urge to urinate with little or no warning?	-0.098	0.458
4. Accidental loss of tiny amounts of urine?	-0.207	0.113
5. Nighttime urination?	-0.283	0.028
6. Waking up at night because you had to urinate?	-0.316	0.014
7. An uncontrollable urge to urinate?	-0.071	0.590
8. Urinary incontinence associated with a powerful desire to urinate?	-0.158	0.229

OAB-V8: Overactive Bladder Version 8-Question Awareness Tool

Discussion

This is an observational study investigating the relationship between OAB and ED using ICS definitions. In previous studies, it was indicated that sexual activity and satisfaction decreased with LUTS [18-20]. The association of OAB, including lower urinary tract symptoms, with ED was also investigated [6-10]. In the study of Liu et al., it was stated that the groups were affected by the age factor [21]. Aging, diabetes, and hypertension were defined as the risk factors for ED [22]. In our study, fewer elderly population, and the fact that the groups had similar average age minimizes the effect of age on ED and OAB. Furthermore, similar comorbidities also provided isolated examination of ED and OAB.

In their study including 502 OAB patients, Erwin et al. [10] found the risk coefficient of OAB for ED as 1.5. They also found that the odds ratio of OAB was similar to the ED odds ratio of hypertension and diabetes [10]. Amano et al. [23] indicated that OAB was a risk factor of ED and that this odds ratio was 1.12. Liu et al. [7] found that the odds ratio of severe ED for OAB was 2.36 in patients with type 2 diabetes. In another

study, LUTS ED odds ratio was reported as 2.2 [24]. In our study, OAB was determined as a risk factor for ED. This odds ratio was lower than the odds ratios indicated in the literature. However, in our study, the study groups were fewer, they were diagnosed with OAB for the first time and had not received prior treatment for OAB. The similarity between the patients with OAB and the control group patients in terms of risk factors such as hypertension, diabetes, and smoking defined for ED may have led to the lower result of this ratio.

With regards to the relationship between OAB and ED, Erwin et al. [10] showed that urinary symptoms decreased the frequency of sexual activity or prevented participation in sexual activity. In the same study, it was also stated that nocturia and urge incontinence had strong negative effects on ED. Similarly, Liu et al. [7] determined that urge and nocturia had strong effects on ED. In our study, we determined that the patients with OAB had lower IIEF-5 scores compared to the healthy control group. We think that OAB may have a negative effect on Erectile function. Akin to the literature, we determined that nighttime urination and waking up at night because you had to urinate negatively affected IIEF-5 scores. However, we could not find comparable results for urge incontinence. In our study, unlike the literature, we determined that the scores of questions 2, 3 and 5 (erection for penetration, maintaining the erection and satisfaction with sexual intercourse) in the IIEF-5 inquiry form were lower among men with OAB compared to healthy controls. One of the results we obtained in our study was that the responses given to these questions (although there is a need to be supported by studies with a larger number of patients) may be inexpressible OAB symptoms. The effect of OAB should not be ignored in the treatment of ED. OAB should be investigated in those who do not respond to ED treatment. In the literature, sexual functions were reported to improve after anticholinergic treatment in female patients with OAB [25-27]. This was not studied for male patients. There is a need for studies examining the erectile functions of ED patients with OAB after OAB treatment.

Limitations

This study has some limitations, one of which was the small study population. Regarding other reasons, although the study groups were similar in terms of hypertension, diabetes, and smoking, which are known risk factors for ED, patients with these factors were affected by the time they had these risk factors. The effects of nocturia on sleep quality and quality of life may also have effects on erectile function. Furthermore, patients diagnosed with OAB may also be affected by these factors since it was unknown how long the disease existed.

Conclusion

OAB and ED prevalence increase with age. OAB is a risk factor for ED. ED patients with OAB have difficulties in achieving and maintaining erection for penetration and sexual satisfaction. The presence of the symptoms of nocturia is remarkable for ED in OAB patients. The effect of OAB should not be ignored in the treatment of ED, and there is a need for studies examining the erectile functions of ED patients with OAB following OAB treatment.

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Assessment of quality and accuracy of YouTube videos on percutaneous transthoracic biopsy

Transtorasik akciğer biyopsisi hakkındaki YouTube videolarının kalite ve doğruluğunun değerlendirilmesi

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Abstract

Aim: YouTube is an essential source of medical information for patients, but may also be misleading, depending on the kind of content quality. The aim of this study is to evaluate the quality of YouTube videos on percutaneous transthoracic lung biopsy.

Methods: A search on YouTube was performed with the terms 'Lung Biopsy,' 'CT-Guided Lung Biopsy,' 'US-Guided Lung Biopsy,' and 'Percutaneous Transthoracic Biopsy.' Relevant English videos were examined and scored by two reviewers. Video characteristics, uploaded sources, and content quality were assessed using different indices. Correlation analysis was conducted to investigate the possible correlation for global quality score.

Results: Fifteen videos (47%) were uploaded by a healthcare professional, nine videos (28%) by a product company, six videos (19%) by an individual user, and 2 (6%) by an academic institution. The videos had a median (IQR) quality score of 2 (range 1-5), and a median (IQR) length of 235 (46-751) seconds. The quality of the videos varied, depending on the uploaded sources as well as whether they were uploaded by academic institutions, which had the highest quality. Some important components regarding the biopsy procedure, such as complications, were not evaluated in most videos.

Conclusion: YouTube videos on percutaneous transthoracic lung biopsy (PTLB) had a low median content quality score, while some important points were grossly overlooked. Thus, YouTube videos may be a misleading source of patient information. Academic institutions and healthcare professionals should be creating accurate multimedia content for patients seeking informative medical information.

Keywords: YouTube, Social media, Biopsy, Patient education

Öz

Amaç: YouTube, hastalar için önemli bir tıbbi bilgi kaynağıdır. Ancak içerik kalitesine bağlı olarak yanıltıcı bilgiler de verebilmektedir. Bu çalışmanın amacı, perkütan transtorasik akciğer biyopsisi ile ilgili YouTube videolarının kalitesini değerlendirmektir.

Yöntemler: YouTube'da 'Lung Biopsy', 'CT-Guided Lung Biopsy' 'US-Guided Lung Biopsy' ve 'percutaneous Transthoracic Biopsy' terimleri ile arama yapıldı. İlintili İngilizce videolar iki kişi tarafından incelendi. Video karakteristikleri, yüklendiği kaynak ve içerik kalitesi değerlendirildi. Global kalite skorunu değerlendirmek için korelasyon analizi yapıldı.

Bulgular: On beş video (%47) profesyonel sağlık çalışanları, 9 video (%28) firmalar, 6 video (%19) kişisel hesaplar ve 2 (%6) video ise akademik kurum tarafından yüklenmişti. Videoların ortanca (IQR) kalite skoru 2 (aralık 1-5), ortanca uzunluğu ise 235 (46-751) saniye olarak hesaplandı. Videoların kalitesi, yüklendiği kaynağa göre değişiklik göstermekte olup, akademik kurumlar tarafından yüklenen videolar en yüksek kaliteye sahipti. Komplikasyonlar gibi önemli biyopsi prosedürü komponentleri, çoğu videoda değerlendirilmemişti.

Sonuç: Perkütan transtorasik akciğer biyopsisi (PTLB) ile ilgili YouTube videolarında bazı önemli noktalar göz ardı edildiğinden dolayı, düşük bir ortanca içerik kalite puanına sahip oldukları gözlendi. Bu nedenle, YouTube videoları yanıltıcı bir hasta bilgisi kaynağı olabilir. Akademik kurumlar ve sağlık uzmanları, bilgilendirici tıbbi bilgi arayan hastalar için doğru multimedya içeriği oluşturmalıdır.

Anahtar kelimeler: YouTube, Sosyal medya, Biyopsi, Hasta eğitimi

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Introduction

YouTube is the second most popular website, which serves 95% of web surfers in 80 different languages [1,2]. Entertainment and educational sources, including medical videos, are also commonly used with YouTube. Explanatory videos about medical procedures and operations are often appreciated by medical students, as well as patients.

Lung cancer is the 3rd most frequent malignancy in both genders, and the most frequent malignancy in males. Approximately 2 million new patients were diagnosed with lung cancer in 2018. Although lung cancer mortality rates tend to decrease in the male population, as a function of decreased smoking prevalence, overall rates in women continue to increase. Lung cancer accounts for the highest mortality rate in the overall population [3,4]. Its presentation for most patients in the advanced stages emphasizes the importance of early diagnosis and treatment.

Lung biopsy procedures, as part of the diagnosis for lung cancer, are either performed by bronchoscopy, percutaneous interventions, or open surgery. Percutaneous transthoracic lung biopsy (PTLB) is an image-guided radiological biopsy method used in the diagnosis of lung cancer for patients with peripheral masses. Fluoroscopy, computed tomography (CT) and ultrasound (US) are often selected for imaging during the PTLB procedure [5]. Occasionally, patients find the information from their primary physicians about the PTLB procedure insufficient, since it is usually performed by radiologists. As patients try to overcome the lack of information from website sources, YouTube videos serve as a substantial resource. Even if most videos enlighten the patients and answer their questions accurately, there is a risk of misinformation, which cannot be underestimated. Misleading video content may have negative consequences, such as avoidance of the procedure. The quality of information received by patients via medical YouTube videos has immense value.

The primary aim of this study was to evaluate the quality of YouTube videos on PTLB. As such, video characteristics via the upload source, reliability scores, and popularity indices were assessed.

Materials and methods

A search was performed on YouTube with the search terms 'Lung Biopsy,' 'CT-Guided Lung Biopsy,' 'US-Guided Lung Biopsy,' and 'Percutaneous Transthoracic Biopsy.' The study was performed on 6.6.2019. The videos were sorted by relevance as well as other default filter settings. The first 60 videos for each search term were analyzed and viewed, since internet search engine studies show that users primarily view the first three pages [6]. Non-English videos are irrelevant, while nonverbal and duplicate videos were excluded. Number of likes/dislikes, total number of views, video length, uploading date, and number of comments and likes per 1000 views were recorded for the enrolled videos. They were analyzed and scored independently by two investigators. One was a radiologist, experienced with lung biopsies, the other was an experienced pulmonary physician.

The videos were categorized according to four uploading sources: Academic institutions, healthcare professionals (physician and non-physician), product companies, and individual users. Four questions adapted from the DISCERN tool [7] were used for determining reliability of YouTube videos (ROV): (1) Are the aims clearly stated? (2) Is the source of information informative and reliable? (3) Is the presented information objective and unbiased? (4) Are uncertain elements noted? 'Yes' answers scored 1 point and 'no' answers, 0 points. A lung biopsy scoring tool (LBST) was created for evaluating the accuracy of the videos, which were adjusted from previous studies [8,9] (Table 1). Each item scored 1 point, with a maximum of 12 points. The educational content value of the videos was evaluated by Global Quality Score (GQS), which was adapted from a previous study [10], using a scale of 1 to 5: (1) Poor quality, not useful for patients; (2) Poor quality and flow, but partially useful; (3) Moderate quality, useful with some important details missing; (4) Generally good flow and quality; and (5) Excellent quality and flow, including very useful information. Video power index (VPI) could evaluate popularity of the videos, described by the formula: ratio*view ratio/100 [11].

Table 1: Lung biopsy scoring tool for accuracy of the videos (scored from 0 to 12)

Topic	Content	Maximum points available
Purpose of the procedure	To determine if the lesion is benign or malignant and to analyze the tumor stage, for evaluating diffuse lung disease	3
Alternative to percutaneous transthoracic lung biopsy	Follow-up, excisional biopsy	2
Preparation	Stop antiaggregant 5-7 days, oral anticoagulants 3-5 days before the procedure. No intake of solid foods before procedure for 6 hours and water for 2 hours	2
Method	The entry localization should be sterilized and then local anesthetic is injected. Position depends on depth and size of the lesion. Biopsy needle should be inserted while patient holds inspiration. Duration is 20 to 120 minutes.	2
Side effects	Px, pulmonary hemorrhage, hemothorax, tumor seeding cardiac tamponade, chest infection.	2
After procedure	Chest radiograph should be performed 0.5-1 hour later than the procedure.	1
Results	2-10 days after the procedure	1
Further information	Further information sources	1

Px: pneumothorax

Statistical analysis

The statistical analysis was performed with IBM SPSS Statistics 22.0 (Armonk, NY, USA: IBM Corp.). Shapiro-Wilk test was used to assess the normality of variable distributions, which were also included. A Spearman correlation analysis was conducted to examine associations between GQS and VPI, and ROV and ICGIP. For all analyses, a P-value < 0.05 was considered significant.

Results

Among 240 screened videos, 32 fulfilled inclusion criteria and were analyzed for the study (Excluded videos (n=208): Non-English (61), Irrelevant (95), Non-verbal (22), Duplicate videos (31)). Fifteen videos (47%) were uploaded by a healthcare professional, 9 videos (28%) by a product company, 6 videos (19%) by an individual user, and 2 (6%) by an academic institution. Median (IQR) length of the videos was 235 (46-751) seconds, while median (IQR) number of views was 6385 (57-63128). There was a significant correlation between duration of

the video and number of views (P=0.04) (Table 2). Based on reviewers' GQSs, 12 videos were rated 1 point (poor quality, not useful for patients), and only 1 was rated as 5 points (excellent quality and flow, includes very useful information), out of a total of 32 videos. Median quality score was 2.00. The highest median quality score (3) belonged to videos uploaded by academic institutions and the lowest median score (1) belonged to videos uploaded by healthcare professionals (Table 3). The median ROV was 2 out of 4. Academic institutions had the highest ROV median score (2.5). The median number of likes from product companies and individual user videos were 28 and 26, respectively, which were higher than other uploaded sources. The video with the highest number of dislikes was uploaded by a product company with the longest duration (751 seconds). Video content was not assessed for all components of LBST. The highest score was 11 out of 12, uploaded by individual users. Thirteen videos (40%) mentioned side effects, which was shown in 5 videos (33%) uploaded by healthcare providers. The purpose of the procedure was noted in most (81%) videos. Those that focused on methods had higher dislike counts (P=0.02). The videos with the highest and lowest median VPI scores were from academic institutions and healthcare workers, respectively (38.83 and 1.64, respectively). GQS demonstrated a significant correlation with ROV and ICIGP, but not with VPI (P<0.001, P<0.001, P=0.067, respectively) (Table 4). GQS did not show a significant correlation between number of views and video length (P=0.31, P=0.62, respectively). Videos clarifying the purpose of the procedure showed a significant correlation with GQS (P<0.001 in both). Interclass correlation coefficients ranged between 0.911 and 0.984 for intra-rater reliability, and between 0.925 and 0.941 for interrater reliability. Ethical committee approval was not required for the present study, since open access data were used.

Table 2: Characteristics of the evaluated videos

	Mean	SD	Median	Minimum	Maximum
Video length (seconds)	259	161	235	46	751
Number of likes	58	123	17	1	676
Number of dislikes	5	7	1	1	26
Total number of views	16079	19778	6385	57	63128
Total number of comments	9	29	1	0	162
Days since upload	1333	961	1165	28	3547
View ratio	19.68	40.48	7.33	0.07	209.43
Like ratio	80.61	17.04	87.30	50.00	98.67
VPI	17.66	38.33	5.78	0.04	205.75
ROV (0-4)	1.94	1.22	2.00	0.00	4.00
LBST (0-12)	3.44	2.82	3.00	1.00	11.00
GQS (1-5)	2.16	1.14	2.00	1.00	5.00

LBST: lung biopsy scoring tool, VPI: video power index, ROV: reliability of YouTube videos, GQS: global quality score

Table 3: Characteristics of the YouTube videos by source

Source		VPI	ROV (0-4)	ICIGP (0-12)	GQS (1-5)
Academic institutions	Mean	38.83	2.50	5.50	3.00
	Median	38.83	2.50	5.50	3.00
	SD	44.15	2.12	6.36	2.83
Healthcare professionals(physician and non-physician)	Mean	7.83	1.73	2.40	1.80
	Median	1.64	1.00	2.00	1.00
	SD	10.71	1.10	2.10	1.01
Product companies	Mean	29.28	2.22	3.22	2.44
	Median	5.97	2.00	3.00	2.00
	SD	66.40	1.09	1.99	0.88
Individual users	Mean	17.77	1.83	5.67	2.33
	Median	11.71	2.00	5.00	2.50
	SD	25.07	1.60	3.39	1.21

Abbreviations: LBST, lung biopsy scoring tool; VPI, video power index; ROV, reliability of YouTube videos; GQS, global quality score

Table 4: Correlation of GQS

	Correlation coefficient	P-value
Number of likes	0.050	0.976
ROV	0.813	<0.001
ICIGP	0.799	<0.001
VPI	0.078	0.673

LBST: lung biopsy scoring tool, VPI: video power index, ROV: reliability of YouTube videos, GQS: global quality score

Discussion

While there is a large number of medical studies on YouTube related to patient education, over the last 10 years, these studies have generally focused on diseases and treatments, the use of medical materials, and operations. In our literature review, we found only one study about image-guided biopsy. For lung biopsy, no such studies were conducted so far.

Patients receiving detailed information from their physicians before the biopsy and operation becomes more difficult as the number of patients increase, as the time allocated for each patient shortens. Healthcare associations provide information to patients and their families in numerous ways for educational purposes. However, special procedures such as a biopsy become more understandable when supported by visual content, such as videos. Although pulmonary and oncology clinicians examine the patient with malignant diseases of the lung and refer them for biopsy, the procedures are often performed by radiologists. Disorderly information regarding the procedure cause confusion. Lung cancer has the highest mortality rate and early diagnosis is crucial for quality medicine. To increase patient compliance prior to the biopsy, which is necessary for an early diagnosis, online information is especially helpful [12].

In this study, the median values of GQS, ROV, and LBST of the videos were extremely low. These results show that the quality, reliability, and accuracy of the videos on transthoracic lung biopsy were also low. In terms of upload source, the highest median ROV, LBST, and GQS scores were affiliated with academic institutions. The lowest median of all groups belonged to healthcare professionals. In terms of VPI, the videos uploaded had the lowest average. It was also found that these videos included little explanation, often containing biopsy patient images in the CT unit with poor informative content and quality. The popularity scores for these videos were also low, due to lack of satisfactory information for the audience. For example, one of the most important subjects for a patient is the complication rate that may occur after the procedure. The most common is pneumothorax, which can be seen in a wide range of patients, from 0 to 61%. Moreover, 3.3% to 15% of patients may also need a chest tube [13,14]. When patients and their relatives do not receive enough information about these issues, they can be troubled by hearsay information, and sometimes refuse the procedure due to misleading information. Videos uploaded by healthcare groups stated that this was rare. This shows that videos displaying the process content, with too much visual detail for patients (and not acknowledging focus topics, such as side effects), receive negative reactions.

LBST was a tool that was adapted by us from two separate studies, to evaluate videos about lung biopsy in terms of accuracy. LBST being significantly correlated with GQS suggested that this tool was useful. It also allowed us to make unique inferences about the videos during a subgroup evaluation.

For example, the dislike ratio of videos that discussed the method was high. The most mentioned topic was the purpose of the procedure. In general, this was noted in all videos uploaded by individual users, focusing on their biopsy stories from subjective experiences. We find that the mean LBST score of individual users, being higher than other groups, needs further consideration.

As stated, the highest VPI scores belonged to academic institutions and product companies, respectively. We attributed this to the fact that both groups create their videos with higher quality and offer their content in a more organized manner. Since it may be possible to get higher search rankings on YouTube with Search Engine Optimization (SEO) [15], increasing the number of views via various advertising routes by the product companies may have positively contributed to the VPI scores. To keep up with changing YouTube search algorithms, appropriate optimization of title, description, and keywords must also be performed for videos uploaded by healthcare professionals.

The lack of correlation between GQS and VPI revealed that video uploaders neglected factors that created quality content, while tending to increase video popularity for users. ROV developed from the DISCERN tool, which was created about 10 years before the first YouTube video was made, was also correlated with GQS. This indicates that the tool was up-to-date and could evaluate educational videos.

Limitations

The fact that only videos in English were examined was one of the limitations of our study. Like previous studies, two reviewers were included, which may also be considered a potential limitation. Furthermore, new content could be available in YouTube, while old content may have been removed. This is also a limitation for our study.

Conclusion

In this study where we examined the contents of the educational videos on YouTube for transthoracic lung biopsy procedure, we found that the quality of the videos was low. Moreover, we observed that the subjects about which the patients were often curious, such as complications that may occur after the procedure, were not adequately addressed. Professional associations and academic institutions need to keep up with changes in ways of learning, provide online healthcare information more accurately and address a broader audience to minimize patients' anxiety about the procedure and any refusal of procedure.

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Is language disability a risk factor for complicated appendicitis? A retrospective cohort study

Dil engeli, komplike apandisit için bir risk faktörü müdür? Geriye dönük kohort çalışma

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Abstract

Aim: Acute appendicitis is the most common emergent surgical disease and complicated appendicitis is an indicator of disrupted access to healthcare. Language disability has become more important in the healthcare sector with increasing migration in the last decade. We aimed to evaluate language disability as a risk factor for complicated appendicitis.

Methods: From January 2014 to December 2018, patients who were operated for acute appendicitis were evaluated retrospectively. Patients' age, gender, language disability (LD) (no (C) or yes (F)), whether surgical drainage was required, pathological findings (appendix diameter, severity as uncomplicated (UCA) or complicated (CA), and presence of local peritonitis), levels of C-Reactive Protein (CRP), White Blood Cells (Wbc), Neutrophil% (Neu%), and ultrasonography (USG) and computed tomography (CT) results were noted and compared.

Results: Six hundered twenty-eight patients were included in the study, among which 15.1% (n=95) were considered F, and 12% (n=74) were CA. Age and gender did not significantly differ in terms of LD and severity (P=0.15, P=0.24 and P=0.2, P=0.21, respectively). Drainage requirement, local peritonitis, levels of CRP, Wbc, and Neu% were significantly higher in the CA group (P<0.001, P<0.001, P<0.001, P=0.009, and P<0.001, respectively). Drainage, appendix diameter, levels of CRP, and Neu% were significantly higher in the F group (P=0.01, P=0.04, P=0.007, and P=0.046, respectively). CA rate was insignificantly higher in the F group (17% vs 11%) (P=0.72). The false-negative ratio of USG and CT was higher in F patients with CA (56.2% vs. 37.5%).

Conclusion: This study showed that language disability could be a risk factor for complicated appendicitis with higher drainage ratio, appendix diameter, levels of CRP, and Neu%.

Keywords: Appendicitis, Severity, Language disability

Öz

Amaç: Akut apandisit en sık acil cerrahi hastalık ve komplike apandisit sağlık kuruluşlarına erişebilme göstergesidir. Son on yılda göçlerin artması ile dil engeli sağlık için önemli hale gelmiştir. Dil engelinin komplike apandisit için risk faktörü olarak değerlendirmeyi amaçladık.

Yöntemler: Ocak 2014'den Aralık 2018 tarihleri arasında akut apandisit nedeni ile opere edilen hastalar geriye dönük değerlendirildi. Hastaların yaş, cinsiyet, dil engeli (DE) (var (Y) yok (V)), drenaj uygulanması, patolojisi (apandiks çapı, şiddeti komplike olan (KA), komplike olmayan (KOA), ve lokal peritonit varlığı), C-Reaktif Proteini (CRP), beyaz küre (BK), nötrofil yüzdesi (Nöt%), ultrasonografi (US) ve bilgisayarlı tomografi (BT) sonuçları istatistiksel olarak değerlendirildi.

Bulgular: Altı yüz yirmi sekiz hasta çalışmaya dahil edildi. %15,1'i (n=95) Y, ve %12'si (n=74) KA idi. DE ve şiddet açısından yaş ve cinsiyet farkı istatistiksel olarak anlamlı saptanmadı (sırasıyla P=0,15, P=0,24 ve P=0,2, P=0,21). Drenaj, lokal peritonit, CRP, BK ve Nöt% KA grubunda anlamlı olarak yüksek saptandı (sırasıyla P<0,001, P<0,001, P<0,001, P=0,009, ve P<0,001). Drenaj, apandiks çapı, CRP ve Nöt% seviyesi Y gurunda anlamlı olarak yüksek saptandı (sırasıyla P=0,01, P=0,04, P=0,007 ve P=0,046). KA oranı Y grubunda daha fazla olmasına rağmen (%17 karşı %11) istatistiksel olarak anlamlı (P=0,72). US ve BT'nin yalancı negatiflik oranı KA'lı Y grubunda daha yüksek saptandı (%56,2 karşı %37,5).

Sonuç: Bu çalışma dil engelinin; yüksek drenaj oranı, apandiks çapı, CRP ve Nöt% seviyeleri ile komplike apandisit için bir risk faktörü olabileceğini göstermiştir.

Anahtar kelimeler: Apandisit, Şiddet, Dil engeli

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Ethics Committee Approval: Approval was received from Okmeydanı Training and Research Hospital Ethical Committee, May 14, 2019 date and 1148 number. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Onay Okmeydanı Eğitim ve Araştırma Hastanesi Etik Kurulu, 14 Mayıs 2019 tarih ve 1148 sayı onay numarası ile alınmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Introduction

Ten percent of Europe and 4.8% of Turkey are foreigners (immigrants, tourists, etc.) with language disability [1,2]. The language disability, difficulty in accessing healthcare, or lack of health insurance are the most important disadvantages of foreign healthcare [3,4]. Language disability decreased with the second generation of immigrants due to their learning of the primary language. Lack of access to healthcare or health insurance are not valid factors for all foreigners admitted to the emergency department Turkey. However, language disability remains a severe problem and causes complications.

Acute abdominal pain is an important, frequent complaint which was observed in 10% of the emergency department admissions and only 1.9% were caused by acute appendicitis [5,6]. Acute abdominal pain has a 10.5% false-positive and 18,6% false-negative decision risk. False-positive decisions cause unnecessary appendectomies with increased morbidity and mortality, and false-negative decisions increase perforation or abscess risk [7]. Complicated acute appendicitis is considered an indicator of lack of access to healthcare in children based on communication disabilities [8]. Foreigners have increased risk of perforated/complicated appendicitis or unnecessary surgery for acute abdominal pain [9,10].

Radiological (USG and CT), scoring systems (Alvarado, etc.), or inflammatory markers such as C-Reactive Protein (CRP), White Blood Cells (Wbc), and Neutrophil % (Neu%) are used to evaluate the severity of acute appendicitis [11-14].

Ten percent of admissions for emergency surgery consisted of foreigners with or without language disability, and appendicitis is the most common emergency surgical disease in our hospital. We aimed to evaluate language disability as a risk factor for complicated appendicitis.

Materials and methods

After receiving institutional approval from the ethics committee of Okmeydanı Training and Research Hospital (14 May 2019 date, and 1148 number), records of patients who were operated for acute appendicitis between January 2014 and December 2018 were evaluated retrospectively. The foreigner patients who can speak Turkish, English or other common languages were excluded from the group of patients with language disability (Figure 1).

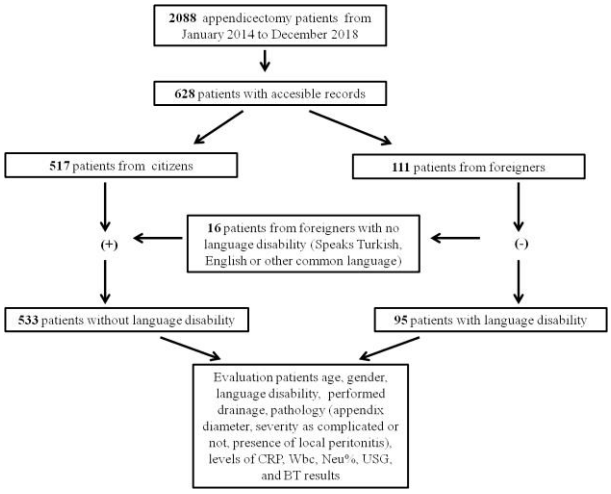

Figure 1: Flow diagram of the study. (CRP: C-reactive protein, Wbc: White Blood Cell, Neu%: Neutrophil %, USG: Ultrasonography, CT: Computed Tomography)

Age, gender, language disability, operation type, whether surgical drainage was performed, pathological findings (diameter of the appendix, severity, the presence of local peritonitis, and fecaloid), levels of C-reactive protein (CRP), white blood cells (Wbc), neutrophil % (Neu%), results of ultrasonography (USG) and computed tomography (CT) were evaluated retrospectively.

Language disability was evaluated as without (C) or with (F), and gender, as male or female. Operation methods were either open or laparoscopic, and whether surgical drainage was performed was noted. The severity of pathology was evaluated as uncomplicated (UCA) (appendicitis, phlegmonous, and suppurative) or complicated appendicitis (CA) (gangrenous and perforated). Local peritonitis and fecaloids were evaluated as yes or no. USG and CT were either (0) not performed, (1) performed but negative, or (2) performed and positive for acute appendicitis.

Severity of appendicitis and language disability were assessed with respect to age, gender, need for surgical drainage, appendix diameter, presence of local peritonitis, levels of CRP, Wbc, and Neu%. USG and CT results of patients with and without language disability were compared with regards to severity of appendicitis.

Statistical analysis

Statical analysis was performed with SPSS 15.0. T-test was used to evaluate age, diameter, CRP (mg/dl), Wbc (10^3/uL), Neu% (%) (Mean (Standard derivation)). The ratio of males to females, language disability, drainage requirement, local peritonitis, USG, and CT were calculated in percentages. Chi-Square, Mann Whitney U, and T-Test were used for assessment, and $P<0.05$ was considered statistically significant. ROC analysis was performed for language disability, CRP, WBC, Neu% according to CA. Cut off values, sensitivity, and specificity of CRP, Wbc and Neu% were noted.

Results

Six hundred twenty-eight patients were included in the study, 15.1% (n=95) of which had language disability (foreigners (F) not citizens (C)). The mean age was 30.31 (12.6) years, and 67% (n=421) of the patients were males. Among all, 55.7% (n=350) of the operations were performed laparoscopically, 13% (n=81) had surgical drainage. The mean appendix diameter was 10.54 (5.4) mm. Twelve percent (n=74) of the patients had CA, 63% (n=397) had local peritonitis, and 62.9% (n=395) had fecaloids. The mean CRP, WBC, and Neu% values were 54.5 (79.4) mg/dL, 14.6 (4.6) 10^6/uL, and 77.4% (10.3), respectively (Table 1).

The mean age was 29.86 (12.28) years among the UCA group, and 33.66 (14.86) years among those with CA. 66.2% of the UCA and 73% of the CA patients were male. 8.3% (n=46) of patients with UCA and 47.3% (n=35) of CA patients required surgical drainage, the difference between which was statistically significant ($P<0.001$). The mean diameter of the appendix was 10.39 (5.56) mm in UCA, and 11.68 (3.69) mm in CA groups ($P=0.055$). The language disability rates were 14.3% (n=79) and 21.6% (n=16) among those with UCA and CA, respectively, which were similar ($P=0.97$). 59% (n=327) of the UCA and

94.6% (n=70) of the CA patients had local peritonitis, which was significantly higher in the CA group (*P*<0.001) (Table 2).

Table 1: Age, gender, language disability, operation type, drainage, diameter, severity of appendicitis, local peritonitis, fecaloids, CRP, Wbc and Neu% values of included patients

Age (years)*	30.31 (12.6)	
Gender	n	%
Male	421	67
Female	207	33
Language Disability	n	%
No (C)	533	84.9
Yes (F)	95	15.1
Operation type	n	%
Open	278	44.3
Laparoscopic	350	55.7
Drainage	n	%
No	547	87
Yes	81	13
Diameter (mm)*	10.54 (5.4)	
Severity of Appendicitis	n	%
Uncomplicated	554	88
Complicated	74	12
Local Peritonitis	n	%
No	231	37
Yes	397	63
Fecaloid	n	%
No	233	37.1
Yes	395	62.9
CRP (mg/dl)*	54.5 (79.4)	
Wbc (103/uL)*	14.6 (4.6)	
Neu%*	77.4 (10.3)	

* Mean (Standard Derivation), C: Citizens, F: Foreigners. CR*P*= C-reactive protein, Wbc: White Blood Cell, Neu%: Neutrophil %

Table 2: Comparison of the severity of appendicitis with regards to age, gender, drainage, appendix diameter, language disability, local peritonitis, CRP, Wbc and Neu%

	Severity of Appendicitis				*P*-value
	Uncomplicated (n=554)		Complicated (n=74)		
Age (years)*	29.86 (12.28)		33.66 (14.86)		0.15
Gender	n	%	n	%	0.24
Male	367	66.2	54	73	
Female	187	33.8	20	27	
Drainage	n	%	n	%	
No	508	91.7	39	52.7	<0.001
Yes	46	8.3	35	47.3	
Diameter (mm)*	10.39 (5.56)		11.68 (3.69)		0.55
Language Disability	N	%	n	%	0.97
No	475	85.7	58	78.4	
Yes	79	14.3	16	21.6	
Local Peritonitis	n	%	n	%	<0.001
C	227	41	4	5.4	
F	327	59	70	94.6	
CRP (mg/dl)*	44.97 (71.77)		124.61 (97.17)		<0.001
Wbc (103/uL)*	14.47 (4.43)		15.97 (5.59)		0.009
Neu%*	76.83 (10.5)		81.87 (7.36)		<0.001

* Mean (Standard Derivation), C: Citizens, F: Foreigners. CRP: C-reactive protein, Wbc: White Blood Cell, Neu%: Neutrophil %

The mean CRP value of those in the CA group was significantly higher than those in the UCA group (124.61 (97.17) mg/dl vs. 44.97 (71.77)) (*P*=0,001). The same applied for WBC and Neu% values (15.97 (5.59) 10^3/uL vs. 14.47 (4.43) 10^3/uL (*P*=0.009) and 81.87% (7.36) vs. 76.83% (10.5) (*P*=0.001), respectively) (Table 2).

The mean ages of C and F patients were 30.58 (13.16) and 28.77 (9.26) years, respectively. 66% (n=352) of C and 72.6% (n=69) of F patients were male. 11% (n=59) of C and 23.2% (n=22) of F patients required surgical drainage, the difference between which was statistically significant (*P*=0.01). The mean diameter of the appendix was 10.36 (4.29) mm among C, and 11.59 (9.39) mm among F groups (*P*=0.04). 11% (n=58) of the C and 17% (n=16) of F patients had CA (*P*=0.72). 63.4% (n=338) of the C and 62.1% (n=59) of the F patients had local peritonitis (*P*=0.80) (Table 3).

The mean CRP value was 50.76 (77.38) mg/dl among C and 74.64 (87.62) mg/dl among F patients (*P*=0.007). In the C and F groups, the mean WBC values were 14.68 (4.47) 10^3/uL and 14.45 (5.34) 10^3/uL, respectively (*P*=0.654), and mean Neu% values were 77.08 (9.91) % and and 79.34 (12.18) % (*P*=0.046), respectively (Table 3).

Comparison of USG and CT results between UCA and CA groups is presented in Table 4. USG or CT was not performed in 0.8% (n=4) of C, and 1.3% (n=1) of F patients in the UCA group. CT was not performed in 63.3% (n=301) of C, and 64.5% (n=51) of F patients in UCA, and 48.3% (n=28) of those in C, and 50% (n=8) of F patients in CA. The false negative USG rate in UCA was 27.8% (n=131/470) among C, and 26.9% (n=21/78) among F patients. The false negative USG rates among the CA group was 43.1% (n=25/58) in C, and 56.2% (n=9/16) in F patients. The false negative CT among UCA was 9.3% (n=16/173) in C, and 21.4% (n=6/28) in F patients. The false negative CT in CA was 3.3% (n=1/30) in C, and 37.5% (n=3/8) in F patients. Comparisons of USG and CT yielded statistically significant results in both C and F patients with UCA (*P*<0.001, *P*=0.014 respectively), and significant results in F patients with CA (*P*=0.036).

In CA, the Area Under Curve (AUC) value was 0.530 (*P*=0.354) for language disability, and 0.782 (*P*<0.001) for CRP. The cut off value was 44.17 with 77% sensitivity and 72% specificity in CA. The AUC value was 0.567 (*P*=0.063) for WBC, while the cut off value was 14.5 with 55% sensitivity and 54% specificity in CA. The AUC value for Neu% was 0.641 (*P*<0.001), the cut off value being 80.45 with 65% sensitivity and 57% specificity in CA (Table 5) (Figure 2).

Table 3: Comparison age, gender, drainage, diameter, severity of appendicitis, local peritonitis, CRP, Wbc and Neu% with respect to language disability

	Language disability				*P*-value
	C (n=533)		F (n=95)		
Age (years)*	30.58 (13.16)		28.77 (9.26)		0.20
Gender	n	%	n	%	0.21
Male	352	66	69	72.6	
Female	181	34	26	27.4	
Drainage	n	%	n	%	
No	474	89	73	76.8	0.01
Yes	59	11	22	23.2	
Diameter (mm)*	10.36 (4.29)		11.59 (9.39)		0.04
Severity of appendicitis	n	%	n	%	0.72
Uncomplicated	475	89	79	83	
Complicated	58	11	16	17	
Local peritonitis	n	%	n	%	0.80
No	195	36.6	36	37.9	
Yes	338	63.4	59	62.1	
CRP (mg/dl)*	50.76 (77.38)		74.64 (87.62)		0.007
Wbc (103/uL)*	14.68 (4.47)		14.45 (5.34)		0.654
Neu%*	77.08 (9.91)		79.34 (12.18)		0.046

* Mean (Standard Derivation), C: Citizens, F: Foreigners. CRP: C-reactive protein, Wbc: White Blood Cell, Neu%: Neutrophil %

Table 4: Comparison the severity of pathology and language disability between ultrasonography (USG), computed tomography (CT)

Pathology	Language disability	USG	BT			*P*-value
			0	1	2	
UCA	C	0	4	1	0	<0.001
		1	44	6	81	
		2	253	10	76	
	F	0	1	0	0	0.014
		1	8	1	12	
		2	42	5	10	
CA	C	1	9	0	16	0.146
		2	19	1	13	
	F	1	2	3	4	0.036
		2	6	0	1	

C: Citizens, F: Foreigners, USG: Ultrasonography, CT: Computed Tomography, 0: Not Performed, 1: Performed but Negative, 2: Performed and Positive

Table 5: ROC analysis results of language disability, CRP, Wbc, and Neu% according to severity of appendicitis

Parameters	AUC	SE	*P*-value	95% CI		Cut-off value	Sensitivity (%)	Specificity (%)
				Lower	Upper			
Language Disability	0.530	0.033	0.354	0.465	0.595	---	---	---
CRP	0.782	0.029	<0.001	0.726	0.839	44.17	77	72
Wbc	0.567	0.036	0.063	0.496	0.638	14.5	55	54
Neu%	0.641	0.031	<0.001	0.579	0.702	80.45	65	57

ROC: Reciever Operating Caracteristics, CRP: C-reactive protein, Wbc: White blood cell, Neu: Neutrophil. AUC: Area Under Curve, SE: Standard Error, CI: Confidence Interval

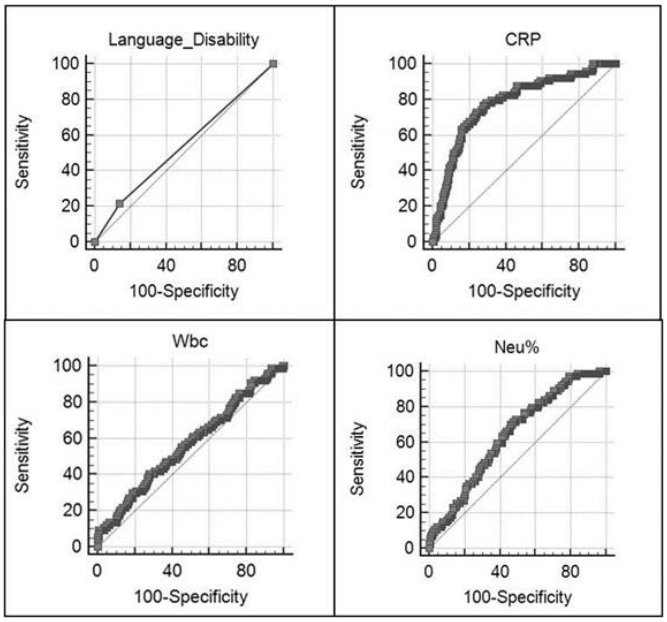

Figure 2: ROC curve of language disability, CRP, Wbc, and Neu% according to severity of appendicitis. (CRP: C-reactive protein, Wbc: White Blood Cell, Neu%: Neutrophil %)

Discussion

Among all, 16.5-24.4% of the appendicitis cases were complicated. CA is reported as an indicator of delayed access to healthcare, and a sign of late diagnosis. Prediction of complicated appendicitis is important for preventing further complications, morbidity, and mortality. Numerous studies are performed for predicting the risk factors of CA with clinical, radiological, biochemical, or mixed parameters. Various scoring systems were also developed for predicting CA [11-16].

The number of patients with language disability has increased with migration. Diagnosis of the disease can be difficult, and misdiagnosis is possible when the patient and doctor have language disabilities, which is a potential risk factor for complicated diseases such as CA [17,18]. The ratio of acute appendicitis in patients with language disability is reportedly 1.5-3.28% [9,10]. In a recent study, the ratio of acute appendictis in patients with language disability was higher than that reported in the literature, with 5.8% (n=111/2088).

Both CA and UCA are mostly seen in males. 53.6% of all appendectomies, 54% of CA, and 53.3% of the F appendectomies were performed males, as reported in the literature [2,9,10,19,20]. Another recent study found that the ratio of males was insignificantly higher than the literature.

Requiring drainage at surgery and finding of local peritonitis at pathological examination are signs of CA, for which increased diameter appendix (>12 mm) is reported as a risk factor [12,21]. A recent study reported higher rates of drainage requirement, local peritonitis, and increased appendix diameter in CA. Increased rate of the above-mentioned findings in F patients showed that language disability was a risk factor for CA.

For CA, the sensitivity and specificity of CRP, WBC, and Neu% were 51.4-78.57% and 60.31-85.7%, 43-67.5% and 36.3-73.8%, 58.5-60.1% and 60.1-90.9%, respectively [22-25]. In another study, the sensitivity and specificity of CRP for CA was 77% and 72%, with a cut-off value of 44.17. Mean CRP levels were significantly higher in CA as well as in F patients. The sensitivity and specificity of WBC were 55% and 54%, respectively, for CA, with a cut-off value of 14.5. Mean WBC levels were significantly higher in CA, but not in F patients. The sensitivity and specificity of Neu% were 65% and 57%, respectively, for CA with a cut-off value of 80.45. Mean Neu% levels were significantly higher in CA and F patients. In a recent study, increased CRP, and Neu% were significant predictors of CA. Also, higher CRP, and Neu% in F patients showed that language disability was a risk factor for CA.

The false diagnosis of appendicitis varies from 12 to 42% in literature. USG is the initial imaging modality for diagnosis of acute appendicitis with 44-90% sensitivity and 47-95% specificity. It has a 15-30% false-negative ratio for acute appendicitis. The sensitivity and specificity of CT is 72-97% and 91-99% respectively; however, the prevalence of positive findings was 23.5% [26,27]. In one of the latest studies, the false-negativity ratios of USG in CA among C and F patients (27.8% vs 26.9%) were similar to that reported in the literature, but the ratio in CA was higher in both C and F (43.1% vs 56.2%). The false-negativity ratios of CT in both CA and UCA were higher in F than C patients (21.4% vs 9.3% in UCA, and 37.5% vs 3.3% in CA). The development of complicated appendicitis for patients with language disability is also affected from false negative radiologic results.

Limitations

The retrospective nature of this study was its first limitation. Prospective randomized clinical trials with large numbers of patients, and translators, will provide further evidence regarding language disability being a risk factor for severe diseases.

Conclusions

Language disability becomes a more important risk factor for complicated diseases among immigrants until they can speak the main language of that country or an international language such as English. It could be a risk factor for complicated appendicitis with significantly higher drainage requirement rates, increased CRP, and Neu%. Higher false negative ratios of USG and CT must keep in the mind when evaluating the patients with language disability for acute appendicitis.

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Rhabdomyosarcoma as a very rare tumor in adult: Case series

Erişkinde nadir bir tümör olarak rabdomiyosarkom: Vaka serisi

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Abstract

Aim: Rhabdomyosarcoma is more frequent and has a better prognosis in children. In adults, it is relatively rare and has a worse prognosis. The most effective treatment is achieved with a multimodal approach. We aimed to share the clinical, pathological and survival results of 14 patients with adult rhabdomyosarcoma.

Methods: In our study, we evaluated 14 patients with RMS who were followed up and treated between January 2000 and January 2018 in three medical oncology departments in Turkey. The uses of surgery, chemotherapy and radiotherapy for curative and palliative purposes were considered multimodal in all patients.

Results: The median age of all patients was 44.5 years (range: 16-83). Ten (71.4%) of our patients were male. The tumors of nine (64.3%) of 14 patients were localized and 5 (35.7%) patients had metastatic disease. Five (55.6%) of 9 patients with localized disease developed relapse. Histological examination of the patients revealed that 10 (71.4%) had pleomorphic, 3 (21.4%) had alveolar and 1 (7.1%) had undifferentiated RMS. The median follow-up period of all patients was 14.6 (range; 2.3-267) months. Relapse-free survival (RFS) was 15.17 months (95% CI; 1.1-29.2). The time to progression of disease after metastatic first-line treatment (PFS) was 10.18 (95% CI; 7.08-13.2) months. At evaluation of the data, 9 patients had died. Median overall survival (OS) at local and metastatic stages were 29.3 months (95% CI; 20.8-37.9) and 11.2 months (95% CI; 9.29-13.1), respectively, while the OS of all participants was 22.8 months (95% CI; 0-47). Five-year OS was 28.2% (Standard error (SE); 13.4%) and 5-year relapse-free survival was 41.2% (SE; 17.3%).

Conclusions: The multimodal approach is the best option in early and advanced stage rhabdomyosarcoma. Among our few patient series, clinic and survival results are consistent with the literature.

Keywords: Adult rhabdomyosarcoma, Multimodality, Survival, Clinic and pathology

Öz

Amaç: Çocuklarda daha sık ve daha iyi prognozlu olan rabdomiyosarkom, erişkinlerde çocukların aksine daha nadir ve daha kötü prognozludur. En etkili tedavi yöntemi multimodaliter yaklaşımdır. Bu çalışmamızda 14 hastalık erişkin rabdomiyosarkom hastamızın klinik, patolojik ve sağkalım sonuçlarını paylaşmayı amaçladık.

Yöntemler: Çalışmamızda, Türkiye'nin üç tıbbi onkoloji bölümünde 2000 Ocak ve Ocak 2018 tarihleri arasında takip edilen ve tedavi edilen 14 RMS hastası değerlendirildi. Hastaların tamamında, küratif ve palyatif amaçlı cerrahi, kemoterapi ve radyoterapinin kullanılması multimodaliter olarak benimsenmiştir.

Bulgular: Tüm hastaların ortanca yaşı 44,5 (dağılım: 16-83) yıl olarak bulundu. Hastalarımızın 10'u (%71,4) erkektir. On dört hastanın 9'unda (%64,3) lokalize, 5'inde (%35,7) metastatik hastalık mevcuttu. Lokalize hastalığı olan 9 hastanın 5 (%55,6) inde nüks gelişti. Hastaların histolojik özelliklerine bakıldığında 10 (%71,4) hasta pleomorfik, 3 (%21,4) alveoler ve 1 (%7,1) hastada pleomorfik rabdomiyosarkom (RMS)vardı. Tüm hastaların ortanca takip süresi 14,6 (dağılım; 2.3-267) aydı. Nükssüz geçen sağkalım (RFS) 15,17 aydı (%95 Güvenlik Aralığı (GA); 1,1-29,2). Metastatik hastalarda birinci basamak tedavi için progresyonsuz sağkalım süresi (PFS) 10,18 (%95 CI; 7,08-13,2) ay olarak saptandı. Hastalardan 9 unda ölüm gerçekleşmişti. Lokal evrede toplam sağkalım (OS) 29,3 ay (%95 GA; 20,8-37,9), metastatik evrede 11,2 ay (%95 GA; 9,29-13,1) ve tüm hasta grubunda 22,8 (%95 GA; 0-47) ay olarak bulundu. Beş yıllık OS %28,2 (Standart hata (SH); %13,4) ve 5 yıllık RFS %41,2 (SH; %17,3) idi.

Sonuç: Multimodaliter tedavi yaklaşımı erken ve ileri evre rabdomiyosarkom için en iyi seçenektir. On dört hastalık serimizin klinik ve sağkalım sonuçları literatürle uyumludur.

Anahtar kelimeler: Yetişkin rabdomiyosarkom, Multimodalite, Sağkalım, Klinik ve patoloji

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Introduction

Soft tissue sarcomas constitute 1% of all adult malignancies [1,2]. Although rhabdomyosarcoma (RMS) is common in children, it is very rare in adults [3]. In a study in Europe where adult sarcomas were evaluated retrospectively, rhabdomyosarcomas constituted 10.6% of all soft tissue sarcomas [4,5].

While the overall 5-year overall survival (OS) in localized RMS in children exceeds 70%, the prognosis is worse in the adult age group. Five-year overall survival in localized disease in RMS in the adult age group is around 20-43%, while this rate is around 5% in metastatic disease. Treatment of RMS in adult patients is difficult, the most important reasons being its rarity and heterogeneous distribution [6,7].

Alveolar and embryonic RMS are treated according to pediatric guidelines. RMSs seen in the adult age group are treated by adhering to pediatric treatment protocols and with multidisciplinary approaches [8,9].

In systemic treatment of alveolar and embryonic RMS, agents such as doxorubicin, actinomycin, cyclophosphamide, vincristine, ifosfamide and etoposide are used. Pleomorphic RMS is treated like other soft tissue sarcomas in the adult age group [4,10,11].

We aimed to share the clinical features, treatment, and follow-up results of 14 adult rhabdomyosarcoma patients, 9 of which had localized and 5 had metastatic disease.

Materials and methods

This study involved the evaluation of 14 patients who were treated for and followed-up with a diagnosis of RMS at three medical centers between January 2000 and December 2018.

Soft tissue sarcoma staging of the American joint committee on cancer (AJCC, 2017, 8th edition) staging system was used. The classification determined by the World Health Organization was utilized for side effect assessment. Treatment choices were made taking into account the studies of international sarcoma study groups and the National Comprehensive Cancer Network guideline (NCCN).

VAC (vincristine, actinomycin, cyclophosphamide, mesna), ICE (ifosfamide, carna, adriamycin) and oral pazopanib were used for chemotherapy. Multidisciplinary treatment, including surgery, adjuvant chemotherapy and radiotherapy, was required in 9 patients with localized disease. Considering adjuvant treatment protocols, 7 pleomorphic RMS and 1 alveolar RMS patients received VAC chemotherapy, while 1 alveolar RMS patient received IMA. When all stage 4 patients were evaluated in terms of 1st line treatment, 1 undifferentiated RMS, 2 alveolar RMS and 4 pleomorphic RMS patients were administered VAC chemotherapy, and 3 pleomorphic RMS patients, IMA chemotherapy. Total anthracycline dose was decisive in the selection of first-line treatment in patients with recurrence. In the second line treatment of stage 4 patients, 2 patients with pleomorphic RMS received oral pazopanib treatment and 1 patient with alveolar RMS received ICE chemotherapy. No patients received third-line treatment.

Statistical analysis

The SPSS 18.0 program was used to estimate survival rate, and descriptive data were calculated through the use of the same program. Kaplan-Meier curves and a Log-rank test were used to analyze the survival data, and *P*-values of <0.05 were considered statistically significant.

Results

The median age of all patients was 44.5 (Range: 16-83) years. Ten (71.4%) patients were male. Nine (64.3%) of 14 patients had localized tumors, while 5 (35.7%) were in stage 4 at diagnosis. Five localized patients (35.7%) had stage 2, 4 patients (28.6%) had stage 3 disease. During the diagnosis, 1 (20%) RMS patient with a single metastatic nodule in the lung underwent metastasectomy. In 4 (80%) patients with metastatic disease, surgery could not be performed due to extensive metastasis. R1 resection was performed in 2 (22%) of 9 patients with localized disease, while R0 resection was performed in the remaining 7 (88%) patients. The primary sites of 5 patients (35.7%) were lower limbs, 2 patients (14.3%), upper limbs, 2 patients (14.5%), the head and neck, 2 patients (14.5%), the trunk, 2 patients (14.5%), the genitourinary system, and 1 patient (7.1%), the ophthalmic area. Histopathologically, 10 (71.4%) patients had pleomorphic, 3 (21.4%) patients had alveolar, 1 (7.1%) patients had undifferentiated RMS (Table 1, 2).

Recurrence occurred in 5 (55.6%) of 9 patients with localized disease. Local recurrence was more common, followed by inguinal region and lung recurrence. Considering the metastasis sites in patients who had metastases at diagnosis or later, 5 patients (55.6%) had metastasis in the lung, 2 patients (22.2%), in the skin, 3 patients (33.3%), in the bone, 1 patient (11.1%) in the breast, and 1 (11.1%) in the inguinal lymph node.

Primary GCSF prophylaxis was performed in the treatment of VAC, IMA and ICE. Hematological toxicity was grade 3-4 in seven patients and grade 1-2 in 5 patients. Among non-hematologic toxicities, 4 patients had grade 3 mucositis and one patient using VAC developed severe type demyelinating polyneuropathy. The use of pazopanib in the second-line treatment of metastatic pleomorphic sarcoma was well tolerated.

Median overall survival (OS) at local and metastatic stages were 29.3 months (95% CI; 20.8-37.9) and 11.2 months (95% CI; 9.29-13.1), respectively, while the OS of all participants was 22.8 months (95% CI; 0-47). Five-year OS was 28.2% (Standard error (SE); 13.4%), the median survival time to relapse (RFS) was 15.17 months (95% CI; 1.1-29.2), and 5-year RFS was 41.2% (SE; 17.3%). Progression-free survival (PFS) was 10.18 (95% CI; 7.08-13.2) months after first-line treatment in metastatic disease. Three patients were able to receive second-line treatment in metastatic disease: Two patients with Pleomorphic RMS received pazopanib, and PFS was 3.2 and 7.2 months. The PFS of the patient with alveolar RMS who received ICE chemotherapy in the second line was 7.2 months (Tables 1, 2).

Table 1: Underwent surgery patients who are early stage (stage 2-3) at diagnosis

Patient Number	Age	Gender	Localization	Pathology	Stage	Adjuvant Treatment	Recurrence Area	RFS (Month)	Name and Response of First line Treatment in advance disease	PFS of First line Treatment in advance disease (Month)	Name and Response of second line treatment of advance disease	PFS of second line treatment of advance disease	OS (Month)	Exitus
1	30	Male	Genitourinary	Alveolar	Stage 3	6×IMA Local RT	Local Recurrence Lung	15.1	4×VAC SD	4.99	3×ICE SD	7.23	28.85	Yes
2	53	Male	Trunk	Pleomorphic	Stage 3	6×VAC Local RT	İnguinal LAP	8.8	6×IMA PR	8.28	6 ×Pazopanib (Month) SD	7.2	29.37	Yes
3	43	Male	Limbs	Pleomorphıc	Stage 2	6×VAC Local RT	No						59.3	No
4	16	Male	Genitourinary	Alveolar	Stage 2	6×VAC Local RT	No						215.1	No
5	68	Male	Limbs	Pleomorphıc	Stage 2	5×VAC Local RT	No						13.37	No
6	33	Female	Limbs	Pleomorphıc	Stage 2	6×VAC Local RT	Lung	7.26	6×IMA SD	8.05	3 ×Pazopanib (Month) PD	3.22	23.85	Yes
7	46	Male	Head and Neck	Pleomorphıc	Stage 2	3×VAC		9.43					10.3	Yes
8	16	Male	Head and Neck	Pleomorphıc	Stage 3	6×VAC	No						267	No
9	83	Female	Limbs	Pleomorphıc	Stage 3	No	No	2.43					2.43	Yes

IMA: Iphosphamide-Mesna-Adriamycin, VAC: Vincristin-Actynomycin-Cyclophosphamide-Mesna, ICE: Iphosphamide-Carboplatin-Etoposide-Mesna, RT: Radiotherapy, LAP: Lymphadenopathy, RFS: Recurrence Free Survival, PFS: Progression Free Survival, OS: Overall Survival, PR: Partial Response, SD: Stabil Disease, PD: Progression Disease

Table 2: Patients who are advance disease at diagnosis

Patient Number	Age (Years)	Gender	Primary Localization	Pathology	Palliative RT	Metastasıs Area	Name and response of firstline in advance disease	PFS of Firstline in advance disease (Month)	OS	Exitus
10	26	Female	Ophthalmic	Undifferentiated	Bone	Bone	6×VAC PR	9.17	10.32	Yes
11	68	Male	Scapula	Pleomorphıc	Bone	Lung Skin	1×VAC PD	0.43	0.79	Yes
12	32	Female	Limbs	Alveolar	Bone	Bone Breast	3×VAC PD	4.47	14.52	No
13	52	Male	Limbs	Pleomorphic	Bone	Bone	6×VAC PR	11.20	11.20	Yes
14	48	Male	Limbs	Pleomorphic	No	Lung	6×VAC PD	8.02	11.96	Yes

Discussion

We shared the clinical, follow-up and treatment results of 14 patients with adult rhabdomyosarcoma. In this case series, the 5-year OS was 28%. In the literature, the 5-year OS in adults is reported as 27%, regardless of stage [3]. Among histologic sub-types, alveolar and pleomorphic RMS were the majority in our case series. While alveolar histology was seen in early ages, pleomorphic histology was dominant in later years, which was coherent with the literature. Since RMS is less common in the adult age group, chemotherapy protocols used in childhood were predominantly applied in our cases. A multidisciplinary approach was demonstrated in all of our patients. Combined treatment approach including surgery, radiotherapy and chemotherapy was adopted in those with localized disease. While median OS was 22.8 months in all patient groups, it was 11.2 months in the metastatic group. Although the number of patients in our study was low, survival data were similar to the literature. The OS of one patient was 17.9 years, and he was still alive. Even though grade 3-4 toxicities developed from time to time with the chemotherapy protocols applied, they were manageable.

In the study with the largest patient series regarding adult RMS and comparing adult and child age group RMS, the 5-year OS was around 82% in children with localized disease, and around 47% in adults. Age, histological subtype, primary location, stage, surgery and radiotherapy and local control were the most important predictors for survival in multivariate analysis [3].

In a study in which French national data were compiled, when survival according to histopathologic subtypes were examined, the median OS in localized disease was 24, 42, 66 months for alveolar, pleomorphic, and embryonic RMS, respectively, and 9, 13 and 28 months for metastatic alveolar, pleomorphic and embryonic RMS, respectively. In the Multivariate analysis performed for OS in localized disease, it was observed that patients with non-alveolar histology, young age, R0 resection, radiotherapy and pediatric KT protocol had better survival. In the multivariate analysis for advanced RMS, non-alveolar histology, R0 resection and RT use were found to have better OS [6].

In the study from MD Anderson cancer center involving 239 patients, median OS was 3.8 years in the nonmetastatic group. In multivariate analysis of localized disease, age >50 years was associated with shorter OS and RFS. Median OS in metastatic disease was 1.4 years. Multimodal therapy has been shown to be associated with longer survival in localized and metastatic disease [7].

At the 2018 American Society of Clinical oncology (ASCO) congress, the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) phase 3 study showed that maintenance metronomic chemotherapy increased OS in patients with high-risk RMS after standard chemotherapy in patients aged 6-21 years. Additional studies and time are needed to evaluate this as a standard approach [12].

Limitations

The main deficiencies in our study are the low number of patients, lack of multi-center data and retrospective evaluation. Due to the low number of patients, a complete statistical evaluation of the factors affecting treatment efficacy and survival could not be made. Case reports and case series on adult rhabdomyosarcoma have an important place in the literature. The number of studies with large patient series and prospective studies is very low. For these reasons, we think that our series of 14 cases will contribute to the literature.

Conclusion

In our series of patients with rhabdomyosarcoma, which we rarely see in adults, we have seen that our patients with multimodal approach can have better results on a case-by-case basis. In our patients, we experienced that multimodal treatment was tolerable with a manageable toxicity profile.

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The effects of first-trimester hemoglobin on adverse pregnancy outcomes

İlk trimester hemoglobin değerinin olumsuz gebelik sonuçları üzerine etkileri

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Abstract

Aim: Previous studies have demonstrated that variable hemoglobin levels are associated with adverse pregnancy outcomes such as postpartum hemorrhage, pregnancy-induced hypertension, intrauterine growth restriction, gestational diabetes mellitus and perinatal mortality. Here, we aimed to investigate the effects of hemoglobin (Hb) levels measured in the first trimester of pregnancy on pregnancy outcomes and identify the predictive value of Hb on adverse pregnancy outcomes.

Methods: This single-center, retrospective study included a total of 8,916 pregnant women who were diagnosed, followed, and delivered their babies in our Obstetrics and Gynecology clinic. The patients were divided into three groups according to their Hb levels as anemic (Hb <11 g/dL, n=1,846), normal (Hb <12.5 g/dL, n=4,898), and elevated (Hb ≥12.5 g/dL, n=2,172). Demographic and clinical features of the patients were obtained from hospital records. Adverse pregnancy outcomes were also noted.

Results: The mean age of the patients was 27.50 (4.45) years and BMI value was 25.03 (3.39) kg/m^2. The mean Hb level was 11.83 (0.88) g/dL and the mean hematocrit value was 36.004 (2.75%). Irrespective of Hb levels, among all patients, rate of pregnancy loss was 6.5%, rate of impaired glucose tolerance, 4.9%, gestational diabetes mellitus, 5.1%, pregnancy-induced hypertension, 7.4%, preterm birth 3.8%. The rate of newborns in need of neonatal intensive care unit was 3.5%, while 3.8% were born with low APGAR scores. Placenta previa was observed in 2.4% of patients, and placental abruption was seen in 1.3%. About 39.3% had a cesarean-section (C/S) delivery, 5.9% gave birth to low birth-weight neonates, and premature rupture of membranes was observed in 9.7% patients. There were no significant differences with respect to adverse pregnancy outcomes between the three groups (P>0.05 for all).

Conclusion: Our study results showed no significant differences between the three groups categorized by Hb concentrations measured in the first trimester in terms of adverse pregnancy outcomes.

Keywords: Anemia, First trimester, Hemoglobin, Pregnancy outcomes

Öz

Amaç: Literatürde yapılan çalışmalarda farklı hemoglobin (Hb) düzeylerinin postpartum hemoraji, gebelik ile indüklenen hipertansiyon, intrauterin gelişme geriliği, gestasyonel diabetes mellitus ve perinatal mortalite gibi olumsuz gebelik sonuçları ile ilişkisi gösterilmiştir. Bu çalışmanın amacı gebeliğin ilk üç ayında ölçülen hemoglobin (Hb) düzeylerinin gebelik sonuçları üzerindeki etkilerini araştırmak ve Hb'nin olumsuz gebelik sonuçları üzerindeki prediktif değerini belirlemektir.

Yöntemler: Bu tek merkezli, retrospektif çalışma, kadın hastalıkları ve jinekoloji kliniğimizde teşhis, takip ve doğumları yapılan toplam 8.916 gebeyi kapsamaktadır. Hastalar Hb düzeylerine göre anemik (Hb<11 g/dL, n=1.846), normal (Hb 11-12,5 g/dL, n=4.898) ve yüksek (Hb ≥12,5 g/dL, n=2.172) olmak üzere üç gruba ayrıldı. Hastaların demografik ve klinik özellikleri hastane kayıtlarından elde edilerek olumsuz gebelik sonuçları kaydedildi.

Bulgular: Hastaların ortalama yaşı 27,50 (4,45) yıl ve vücut kitle indeksi değeri (VKİ) değeri 25,03 (3,39) kg/m^2 idi. Ortalama Hb düzeyi 11,83 (0,88) g/dL ve ortalama hematokrit değeri %36 (%2,75)'ti. Hemoglobin seviyelerinden bağımsız olarak tüm çalışma grubunda gebelik kaybı %6,5, bozulmuş glukoz toleransı %4,9, gestasyonel diabetes mellitus %5,1, gebelik ile indüklenen hipertansiyon %7,4, erken doğum %3,8, yenidoğan yoğun bakım ünitesine duyulan ihtiyaç %3,5, düşük APGAR skorları %3,8, plasenta previa %2,4, plasental ablasyon %1,3, sezaryen (C/S) doğum %39,3, düşük doğum ağırlığı %5,9 ve erken membran rüptürü %9,7 oranında saptandı. Hemoglobin seviyeleri ve olumsuz gebelik sonuçlarını oluşturan değişkenler açısından anlamlı bir fark yoktu (Tümü için P>0,05).

Sonuç: Çalışmamızda ilk trimesterde ölçülen Hb konsantrasyonlarına göre ayrılan gruplar arasında olumsuz gebelik sonuçları açısından anlamlı bir farklılık saptanmadı.

Anahtar kelimeler: Anemi, İlk trimester, Hemoglobin, Gebelik sonuçları

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Introduction

Alterations in the hematological parameters occur depending on the trimester of pregnancy. In healthy pregnancies, major hematological changes which activate adaptation mechanisms of the human body include expanded plasma volume and red blood cell count, physiological anemia, mild neutrophilia, and mildly prothrombotic state to accommodate the growing and developing fetoplacental unit [1].

Hemoglobin (Hb) is the standard measure to assess physical capacity and anemia of pregnant women in the first perinatal visit. Physiological anemia is characterized by reduced Hb levels with a peak at late second trimester, followed by an increase during the third trimester [2].

Anemia is typically caused by decreased oxygen-carrying capacity of the blood or red blood cells depending on the age, gender, and pregnancy [3]. Due to physiological alterations in pregnant women, the diagnosis of anemia differs among pregnant women and non-pregnant women of reproductive age [3]. According to the World Health Organization (WHO), anemia is defined as Hb levels of <11 g/dL (hematocrit <33%) in the first and third trimesters and as <10.5 g/dL (hematocrit <32%) in the second trimester [4]. Accordingly, the prevalence of anemia is about 24.8% among pregnant women worldwide, leading to a major maternal and fetal health concern [5].

Previous studies have demonstrated controversial findings regarding the effects of Hb on pregnancy outcomes. The discrepancy between the findings can be attributed to the use of different study designs and sample sizes and the measurement of Hb at different time points. Nonetheless, it has been well-established that maternal anemia dramatically affects the fetal health [6].

Anemic hypoxia plays a key role in the dilation of the placental blood vessels. Although iron deficiency is the leading cause of anemia, compromised immune system, malnutrition with vitamin B12 and folic acid deficiency, decreased physical and mental capacity, sedentary lifestyle, low socioeconomic status, hemoglobinopathies, age (<20 years or >35 years), adolescent pregnancy, alcohol and tobacco use, short intervals between pregnancies, and infections can also pose an increased risk for anemia [7]. In a recent systematic review, an increased incidence of low-birthweight (LBW) and preterm birth was reported among anemic patients with low Hb levels related to maternal iron deficiency [8]. In addition, maternal anemia was shown to increase perinatal morbidity and mortality due to preterm birth and intrauterine growth restriction (IUGR) [9].

Although previous studies have demonstrated that maternal anemia is associated with adverse pregnancy outcomes with an increased rate of postpartum hemorrhage (PPH) and cesarean-section (C/S) delivery, the effects of maternal anemia on pregnancy outcomes are still unclear. Recent studies have, however, shown elevated red blood cell counts and hypercoagulability due to increased plasma volume during pregnancy, leading to pregnancy-induced hypertension (PIH), IUGR, gestational diabetes mellitus (GDM), and perinatal mortality [5,10].

In the present study, we aimed to investigate the effects of Hb levels measured in the first trimester of pregnancy on pregnancy outcomes and to identify the predictive value of Hb on adverse pregnancy outcomes.

Materials and methods

Study population and study design

This single-center, cross-sectional, retrospective study was conducted at a tertiary hospital between January 2018 and June 2019. A total of 8,916 pregnant women who were diagnosed, followed, and delivered their babies in our Obstetrics and Gynecology clinic were retrospectively reviewed. According to the WHO criteria, the patients were divided into three groups based on their Hb levels as anemic (Hb <11 g/dL, n=1,846), normal (Hb 11-12.5 g/dL, n=4,898), and elevated (Hb ≥12.5 g/dL, n=2,172). The anemic patients were considered to have mild anemia (10 to 10.9 g/dL) according to the WHO criteria, as the lowest Hb level was 10 g/dL in our study. None of the patients had moderate (7 to 9.9 g/dL) or severe (<7 g/dL) anemia. Exclusion criteria were as follows: Having irregular screening visits during pregnancy, missing birth data, missing Hb levels in the first trimester, age <16 years or >35 years, multiple pregnancies, congenital abnormalities, hepatic and renal impairment, diabetes mellitus, PPH, a history of preterm birth, recurrent pregnancy loss, previous placental abnormalities, complicated pregnancy, a body mass index (BMI) of ≥30 kg/m^2, hypothyroidism or hyperthyroidism, and alcohol or tobacco use. A written informed consent was obtained from each participant. The study protocol was approved by the University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Ethics Committee (2011-KAEK -25-2020/06-07). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

Demographic and clinical characteristics of the patients were obtained from hospital records. In addition, pregnancy complications, type of delivery, birth weight, Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores, the need for neonatal intensive care unit (NICU) were noted. Complete blood count analysis was performed using the Coulter LH780 analyzer (Beckman Coulter Inc., CA, USA). Adverse pregnancy outcomes included pregnancy loss, GDM, PIH, preterm birth, need for NICU, placenta previa or placental abruption, C/S delivery, premature rupture of membranes (PROM), and low APGAR scores (<7). Pregnancy loss was defined as any natural miscarriage occurring before 20 weeks of gestation. LBW was defined as a birth weight of less than 2,500 g, while preterm birth was defined as a live birth occurring at <37 completed weeks of gestation. PROM was defined as spontaneous rupture of fetal membranes prior to the onset of labor. The NICU stay was needed in case of jaundice, respiratory distress, preterm birth, neonatal sepsis requiring cardiorespiratory support [11].

Impaired glucose tolerance (IGT) was defined as an elevated fasting plasma glucose concentration (100 to 126 mg/dL). The diagnosis of GDM was made based on a 75-g oral glucose tolerance test (OGTT) results (a fasting blood glucose of >92 mg/dL, ≥180 mg/dL at one hour, and ≥153 mg/dL at two hours). The patients with elevated glucose levels (≥140 mg/dL)

in 50-g OGTT underwent 100-g OGTT and those with two or more elevated glucose results were diagnosed as having GDM (a fasting blood glucose level of ≥95 mg/dL, ≥180 mg/dL at one hour, ≥155 mg/dL at two hours, and ≥140 mg/dL at three hours). The patients with a fasting blood glucose level of ≥200 mg/dL at two hours were also diagnosed with GDM [12]. The diagnosis of PIH was made based on a systolic blood pressure of ≥140 mmHg and/or a diastolic blood pressure of ≥90 mmHg after 20 weeks of gestation [13]. Placenta previa was defined as the abnormal implantation of the placenta into the lower uterine segment, covering the cervical opening partially or completely [14]. Placental abruption was defined as the separation of a normally implanted placenta before delivery of the fetus [14].

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean (standard deviation (SD)), median (min-max), or number and frequency. The Kolmogorov-Smirnov test was used to assess the normality of data. One-way analysis of variance (ANOVA) was performed to analyze significant differences between the groups and the Bonferroni test was used to test significance. The Pearson chi-square test was applied to evaluate the relationship between categorical variables. Binary multiple logistic regression analysis was carried out to identify the effects of age, BMI, and Hb and hematocrit levels on adverse pregnancy outcomes. A *p* value of <0.05 was considered statistically significant.

Results

Of a total of 8,916 pregnant women included in the study, 20.7% (n=1,846) were anemic, 54.9% (n=4,898) had normal Hb levels, and 24.4% (n=2,172) had elevated Hb levels. Irrespective of Hb levels, pregnancy loss was observed in 6.5%, IGT in 4.9%, GDM in 5.1%, PIH in 7.4%, preterm birth in 3.8%, need for NICU in 3.5%, low APGAR scores in 3.8%, placenta previa in 2.4%, placental abruption in 1.3%, C/S delivery in 39.3%, delivery with LBW in 5.9%, and PROM in 9.7% patients. The patient groups according to the Hb levels and adverse pregnancy outcomes are shown in Table 1.

The mean age of the patients was 27.50 (4.45) years. The mean BMI value was 25.032 (3.39) kg/m^2. The mean Hb level was 11.827 (0.882) g/dL and the mean hematocrit value was 36.004 (2.75%) Descriptive data of the patients are summarized in Table 2.

Age and BMI values were evaluated among the three groups according to the Hb levels (Table 3). There was a significant difference only in the mean BMI value among the groups (*P*=0.001). Multivariate analysis was performed to examine the reason for significance. Accordingly, the mean BMI value was significantly lower in the anemic group than those with normal and elevated Hb levels (*P*=0.001 and *P*=0.001, respectively).

Categorical variables were compared between three groups. There was no statistically significant difference between three Hb groups in terms of pregnancy loss (*P*=0.165), impaired glucose tolerance (*P*=0.769), gestational diabetes mellitus (*P*=0.916), pregnancy induced hypertension (*P*=0.841), preterm delivery (*P*=0.257), NICU admission (*P*=0.482), low APGAR scores (*P*=0.118), placenta previa (*P*=0.708), placental abruption (*P*=0.311), cesarean-section (C/S) delivery (*P*=0.474), low birth weight (*P*=0.588) and PROM (*P*=0.956) (Table 4).

Table 1: Patient groups according to hemoglobin levels and adverse pregnancy outcomes

Variable		n	%
Hb (g/dL)	Mild anemic	1,846	20.7
	Normal	4,898	54.9
	Elevated	2,172	24.4
Pregnancy loss	No	8,334	93.5
	Yes	582	6.5
IGT	No	7,924	95.1
	Yes	411	4.9
GDM	No	7,910	94.9
	Yes	425	5.1
PIH	No	7,722	92.6
	Yes	613	7.4
Preterm birth	No	8,021	96.2
	Yes	314	3.8
NICU	No	8,040	96.5
	Yes	295	3.5
APGAR <7	No	8,012	96.2
	Yes	315	3.8
Placenta previa	No	6,093	97.6
	Yes	150	2.4
Placental abruption	No	6,159	98.7
	Yes	84	1.3
C/S delivery	No	3,787	60.7
	Yes	2,456	39.3
LBW	No	5,875	94.1
	Yes	368	5.9
PROM	No	5,637	90.3
	Yes	606	9.7

Data are given in number and percentage, unless otherwise stated. Hb: hemoglobin, IGT: impaired glucose tolerance, GMD: gestational diabetes mellitus, PIH: pregnancy-induced hypertension, NICU: neonatal intensive care unit, APGAR: Appearance, Pulse, Grimace, Activity, and Respiration; C/S: cesarean-section, LBW: low birth weight, PROM: premature rupture of membranes.

Table 2: Descriptive characteristics of patients

	Mean	Median	SD	Min	Max	IQR
Age, year	27.50	28.00	4.458	18	35	7
BMI, kg/m^2	25.032	25.100	3.394	18.5	34.7	5.3
Hb (g/dL)	11.827	11.800	0.882	10.0	13.8	1.3

SD: standard deviation, min: minimum, max: maximum, IQR: interquartile range, BMI: body mass index, Hb: hemoglobin

Table 3: Quantitative measurements according to hemoglobin concentrations

	Mild decrease (Hb <11 g/dL)		Normal (Hb 11-12.5 g/dL)		Elevated Hb (Hb ≥12.5 g/dL)		*P*-value [a]
	Mean	SD	Mean	SD	Mean	SD	
Age, year	27.49	4.480	27.50	4.466	27.50	4.424	0.997
BMI, kg/m^2	24.606	3.529	25.106	3.310	25.225	3.434	0.001

[a] One-way analysis of variance (ANOVA), SD: standard deviation, BMI: body mass index

Table 4: Categorical variables according to hemoglobin concentrations

		Mild decrease (Hb <11 g/dL)		Normal (Hb 11-12.5 g/dL)		Elevated Hb (Hb ≥12.5 g/dL)		*P*-value[a]
		n	%	n	%	n	%	
Pregnancy loss	No	1,729	93.7	4,558	93.1	2,047	94.2	0.165
	Yes	117	6.3	340	6.9	125	5.8	
IGT	No	1,638	94.7	4,339	95.2	1,947	95.1	0.769
	Yes	91	5.3	220	4.8	100	4.9	
GDM	No	1,642	95.0	4,329	95.0	1,939	94.7	0.916
	Yes	87	5.0	230	5.0	108	5.3	
PIH	No	1,597	92.4	4,224	92.7	1,901	92.9	0.841
	Yes	132	7.6	335	7.3	146	7.1	
Preterm birth	No	1,656	95.8	4,384	96.2	1,981	96.8	0.257
	Yes	73	4.2	175	3.8	66	3.2	
NICU	No	1,663	96.2	4,391	96.3	1,986	97.0	0.482
	Yes	66	3.8	168	3.7	61	3.0	
APGAR <7	No	1,651	95.6	4,379	96.2	1,982	96.9	0.118
	Yes	76	4.4	175	3.8	64	3.1	
Placenta previa	No	1,254	97.9	3,322	97.5	1,517	97.6	0.708
	Yes	27	2.1	86	2.5	37	2.4	
Placental abruption	No	1,260	98.4	3,369	98.9	1,530	98.5	0.311
	Yes	21	1.6	39	1.1	24	1.5	
C/S delivery	No	791	61.7	2,071	60.8	925	59.5	0.474
	Yes	490	38.3	1,337	39.2	629	40.5	
LBW	No	1,200	93.7	3,217	94.4	1,458	93.8	0.558
	Yes	81	6.3	191	5.6	96	6.2	
PROM	No	1,154	90.1	3,080	90.4	1,403	90.3	0.956
	Yes	127	9.9	328	9.6	151	9.7	

[a] Pearson chi-square test. Data are given in number and percentage, unless otherwise stated. Hb, hemoglobin; IGT, impaired glucose tolerance; GMD, gestational diabetes mellitus; PIH, pregnancy-induced hypertension; NICU, neonatal intensive care unit; APGAR, Appearance, Pulse, Grimace, Activity, and Respiration; C/S, cesarean-section; LBW, low birth weight; PROM: premature rupture of membranes.

Discussion

Anemia is one of the most common medical disorders during pregnancy and its prevalence and severity vary depending on the populations studied. Although there are many studies investigating the relationship between anemia and maternal morbidity, mortality, and adverse pregnancy outcomes in the literature, controversial results have been reported [15-17]. The discrepancies among the studies primarily result from the gestational week in which Hb levels are measured and the severity of anemia. Due to increased plasma volume, Hb and hematocrit levels tend to decrease with increasing gestational week. Screening for anemia is recommended before 20 weeks of gestation due to the occurrence of physiological anemia in later weeks [15]. In the light of these data, we, therefore, investigated the effects of Hb levels measured in the first trimester of pregnancy on pregnancy outcomes and identified the predictive value of Hb on adverse pregnancy outcomes. According to the WHO criteria, we divided the patients into three groups according to their Hb levels as anemic (Hb <11 g/dL), normal (Hb <12.5 g/dL), and elevated (Hb ≥12.5 g/dL). Our study results showed that 20.7% of the patients had mild anemia, which is consistent with a previous study conducted in Europe [15,18]. However, we were unable to find a significant difference in the incidence of PIH, GDM, preterm birth, LBW, C/S delivery, PROM, and placental abruption among the three groups.

In a study conducted in Turkey, Vural et al. [10] examined the effect of anemia on preterm birth (<37 weeks), LBW (<2,500 g), and anemia (Hb <11 g/dL) in different stages of pregnancy and reviewed medical records of 39,587 Turkish pregnant women. They divided the participants into three groups as Hb <10 g/dL, Hb 10-11 g/dL, and Hb >11 g/dL. They found a significant increase in LBW and preterm birth rates in the Hb <10 g/dL group compared to the non-anemic group. In addition, C/S rates were significantly higher in the anemic group. In another study, Hamalainen et al. [19] evaluated adverse pregnancy outcomes in pregnant women with anemia during three trimesters and found that maternal anemia detected only in the first trimester was associated with LBW, using a cut-off value of 100 g/L for anemia. However, they were unable to find a significant correlation between anemia in the first trimester and small for gestational age and preterm birth. In their population-based study, Levy et al. [20] showed that maternal anemia (Hb <10 g/dL) measured in the first trimester was an independent risk factor for both preterm birth and LBW. However, they were unable to identify a significant correlation between maternal anemia and adverse perinatal outcomes. Similarly, Sehgal et al. [21] examined the effect of anemia on course and pregnancy outcomes in anemic (8-10.9 g/dL) and non-anemic (≥11 g/dL) primigravidas aged 20 to 30 years with a gestational age of 16 to 18 weeks and found no significant difference in the IUGR and LBW rates between the study groups. In addition, there was no increase in the LBW and preterm birth in the anemic group. No significant correlation between anemia and week and type of delivery was observed. Based on these findings, the authors concluded that mild to moderately anemic pregnant women had similar outcomes as a normal pregnancy, if anemia could be detected early in pregnancy and treated appropriately. Unlike the aforementioned studies, patients with moderate (7 to 9.9 g/dL) or severe (<7 g/dL) anemia were excluded from our study. The inclusion of only mild anemic women in the study yielded no significant correlation between mild anemia and preterm birth, PROM, LBW, and C/S rates.

Preeclampsia (PE) is another pregnancy complication which has been extensively studied for its possible association with Hb levels in the first trimester. Some authors have proposed that the link between PE and Hb concentrations lies beneath increased blood viscosity: Hyperviscosity decreases blood flow in the placental tissue, leading to impaired perfusion and reduced oxygenation. In addition, Hb has been thought to have a direct effect on nitric oxide (NO) regulation and endothelial functions. Free Hb binds to NO and depletes it, resulting in vasoconstriction [22]. In patients with PE, the increase in blood volume is not likely to be adequate compared to those with normal Hb levels and, thus, Hb concentrations tend to increase [23]. In the light of these data, several studies have been conducted considering that these alterations may occur even in early stage of pregnancy, i.e., the first trimester [16,22,23]. In a study, Wang et al. [22] reported that the risk for PE increased, when Hb levels exceeded ≥150 g/L. However, there was a significant correlation between elevated Hb levels and an increased risk for PE in women with a pre-pregnancy BMI of ≥24 kg/m^2, although it became non-significant after adjusting for confounders. Cakmak et al. [16] evaluated the relationship between Hb levels in the first trimester and adverse pregnancy outcomes in a Turkish population and found PIH to be more common in the women with a Hb level of ≥13 g/dL compared to the others. However, in this study, the effect of BMI on PE development could not be assessed due to missing BMI data of the participants. In another study, Aghamohammadi et al. [23] examined whether high maternal Hb levels in the first trimester was associated with PIH in Iranian nulliparous women aged 20 to 34 years with a BMI value of <26 kg/m^2 and found that high maternal Hb levels (≥13.2 g/dL) in the first trimester was a risk factor for PE. Consistent with this study, we included a similar study population and found no significant increase in the PE risk in the patients with elevated Hb levels, although the sample size was relatively high in our study.

Iron is an essential micronutrient which plays a role in several physiological processes. Previous studies have shown that excess iron increases oxidative stress and insulin resistance, resulting in GDM by exerting toxic effects to the β-cells [24-26]. Gao et al. [27] examined the relation of Hb concentrations in the first trimester and GDM and found significantly higher Hb levels in GDM patients compared to the control group. In addition, the number of patients who were overweight or obese according to the pre-pregnancy BMI values was significantly higher among those with elevated Hb levels, yielding a higher number of GDM patients. Logistic regression analysis also revealed that a Hb level of ≥13 g/dL was an independent risk factor for GDM. In another study including 21,577 singleton pregnancies, Wang et al. [22] investigated whether Hb levels in early pregnancy were associated with the risk of GDM, PE, and preterm birth. The women with GDM and PE had significantly elevated Hb levels in the first trimester of pregnancy compared to the control group. In addition, the Hb levels were significantly higher in the women

with a pre-pregnancy BMI of ≥24 kg/m^2; however, the correlation between GDM and pre-pregnancy BMI values among the women with a BMI of ≥24 kg/m^2 and <24 kg/m^2 became non-significant, after adjusting for confounders. Beibei et al. [24] assessed the relation of serum iron concentration, Hb level, and iron supplements before and during pregnancy with GDM risk and observed a U-shaped correlation between serum iron concentration and GDM risk, indicating that iron supplements before pregnancy increased the risk of GDM. However, although elevated Hb levels were associated with an increased GDM risk in the early pregnancy, this association became non-significant after pre-pregnancy BMI values and systolic and diastolic blood pressures were included in the analysis as adjustments. In addition, the authors found no significant correlation between iron supplementation in the first and second trimester and GDM risk. Consistent with these findings, we observed no significant difference in GDM risk among the women with mild anemia and normal and elevated Hb levels. Similarly, the women with mild anemia in the first trimester had lower BMI values, consistent with previous studies. Also, although the women with normal and elevated Hb levels had similar BMI values in our study, we found no significant increase in the GDM risk in the women with elevated Hb concentrations.

Strength and limitations

There are some limitations to this study. Due to the retrospective nature of the study, the data regarding iron supplementation are missing in the women with mild anemia detected in the first trimester. Although iron supplementation is recommended in our routine clinical practice for all pregnant women, the number of women receiving iron supplements is unclear. However, some of the previous studies demonstrated that anemia treatment in early pregnancy did not significantly affect the incidence of PPH, preterm birth, small for gestational age, LBW, and stillbirth [17,28]. In a study, treatment of mild anemia in early pregnancy reduced adverse maternal and perinatal outcomes [15]. Another limitation of the current study is that it included Hb levels measured only in the early trimester. However, several studies reported that the first-trimester Hb measurement was more valuable and clinically relevant than the second- and third-trimester measurements [29]. The main strength of the present study is the large sample size, which can theoretically detect statistically significant effects. Also, it is optimally representative of the Turkish young healthy pregnant women.

Conclusions

In conclusion, our study results showed no significant difference between the Hb concentrations in the first trimester and adverse pregnancy outcomes. However, the present study included low-risk women with mild anemia rather than women with complicated pregnancies and, therefore, further large-scale, prospective studies including different severities of anemia and data regarding iron supplementation are needed to draw a definite conclusion.

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Evaluation of axillary nerve integrity and shoulder functions in patients who underwent lateral deltoid splitting approach

Lateral deltoid splitting yaklaşım uygulanan hastalarda aksiller sinir bütünlüğünün ve omuz fonksiyonlarının değerlendirilmesi

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Abstract

Aim: The most common complication of the Lateral deltoid splitting approach (LDSA), which is used in the shoulder area, especially for posterior extension fractures and other soft tissue pathologies, is axillary nerve injury. Determining the frequency of nerve injuries that may occur after LDSA is decisive for the applicability of this approach. Therefore, in our study, we aimed to evaluate the axillary nerve integrity and shoulder functions in patients who underwent LDSA.

Methods: In this prospective cohort study, 55 patients who were operated with LDSA for proximal humerus fractures between February 2015 and July 2018 were evaluated. Among these patients, 35 were selected and included in the study. Six months later Electrophysiological tests (Electroneuromyelography – ENMG) and Constant Shoulder Score (CSS) were used for evaluation of each operated and non-operated shoulder. CSS difference between the operated and non-operated sides was graded as mild (11-20 point), moderate (21-30) and severe (>30).

Results: Mean age of the group was 66 (9) years. Twenty-five patients were female and 10 were male. Mean follow-up time was 4 (1) years. Mean latencies of axillary nerve were 4.6 (1.8) msn, 3.7 (0.54) msn and mean amplitudes of axillary nerve were 6.6 (2.21) mV, 8.4 (2.80) mV in the operated and non-operated shoulders, respectively. There was no statically significant difference between the operated and non-operated sides according to latency and amplitude (latency P=0.25, amplitude P=0.16). Mean CSS of the patients were 28.7. CSS of 12 patients were severe (mean: 39.08), 18 patients, moderate (mean 25.4) and 5 patients, mild (mean 16). There was no statically significant correlation between CSS and axillary nerve latency / amplitude (P= 0.62, r=0.267 / P=0.98, r=-0.339). Fracture type and CSS showed a statically significant correlation (P=0.032, r=0.829).

Conclusion: This study revealed that LDSA provides wide and versatile fracture control without compromising the deltoid muscle functions and axillary nerve, especially in fractures extending to the posterior part of the proximal humerus.

Keywords: Proximal humeral fractures, Deltoid-splitting approach, Nerve crush, Electromyography

Öz

Amaç: Omuz bölgesinin özellikle posterior uzanımlı kırıklarında ve diğer yumuşak doku patolojilerinde uygulanmakta olan Lateral deltoid splitting yaklaşım (LDSY)'ın en bilinen komplikasyonu aksiller sinir yaralanmasıdır. LDSY sonrası oluşabilecek sinir yaralanmalarının sıklığını belirlemek bu yaklaşımın uygulanabilirliği açısından belirleyicidir. Bu nedenle çalışmamızda, LDSY uygulanan vakalarda aksiller sinir bütünlüğünü ve omuz fonksiyonlarını değerlendirmek amaçlanmıştır.

Yöntemler: Prospektif kohort tipteki bu çalışmada Şubat 2015-Temmuz 2018 tarihleri arasında proksimal humerus kırığı nedeniyle LDSA uygulanarak opere edilen 55 hastanın verileri incelendi. Bu hastalar arasından seçilen 35 hasta çalışmaya alındı. Altı ay sonra tüm hastaların opere edilen ve edilmeyen omuzları elektrofizyolojik testler (Elektronöromiyelografi - ENMG) ve Constant Omuz Skoru (CSS) ile karşılaştırmalı olarak değerlendirildi. Opere edilen ve edilmeyen omuzların CSS farkları hafif (11-20), orta (21-30), şiddetli (>30) olarak derecelendirildi.

Bulgular: Hastaların yaş ortalaması 66(9) idi. Hastaların 25'i kadın, 10'u erkek hasta idi. Ortalama takip süresi 4(1) yıl idi. Opere olan ve olmayan omuz bölgelerinde yapılan ENMG incelemelerinde aksiller sinirin ortalama latansı sırasıyla 4,6(1,8) msn, 3,7(0,54) msn ve ortalama amplitude'u sırasıyla 6,6(2,21) mV, 8,4(2,80) mV idi. Latans ve amplitude değerlerine göre ameliyat edilen ve ameliyat edilmeyen taraflar arasında istatistiksel olarak anlamlı bir fark saptanmadı (latans P=0,25, amplitude P=0,16). Hastaların ortalama CSS skoru 28,7 idi. CSS'in 12 hastada şiddetli (ortalama: 39,08), 18 hastada orta (ortalama 25,4) ve 5 hastada hafif (ortalama 16) olduğu saptandı. CSS ve aksiller sinir latans / amplitude değerleri arasında istatistiksel olarak anlamlı bir korelasyon saptanmadı (P=0,62, r=0,267 / P=0,98, r=-0,339). Kırık tipi ve CSS arasında ise istatistiksel olarak anlamlı korelasyon olduğu görüldü (P=0,032, r=0,829).

Sonuç: Bu çalışma sonucunda, LDSA'nın aksiller sinir'e ve omuz fonksiyonlarına zarar vermeden özellikle proksimal humerusun arka kısmına uzanan kırıklarda geniş ve çok yönlü kırık kontrolü sağladığı saptanmıştır.

Anahtar kelimeler: Proksimal humerus kırıkları, Deltoid-splitting yaklaşım, Sinir yaralanması, Elektromiyografi

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Introduction

Nowadays, proximal humerus fractures have become the most widespread problem of the aging population. Preserving blood supply and neurologic innervation of the shoulder region are the challenging issues about fracture surgery. The deltopectoral approach is most used to fixate proximal humerus fractures [1]. However, some authors have argued that this approach involves extensive soft tissue dissection and muscle retraction to gain adequate exposure to the lateral aspect of the humerus [2,3]. Additionally, the amount of dissection is thought to further contribute to the devascularization of proximal humerus fractures at the time of internal fixation [4,5]. Especially proximal humerus fractures which extend to the posterior part of humeral head need more lateral exposure. For this reason, lateral deltoid splitting approach (LDSA) is described as an alternative, especially for proximal humeral fractures extending to the lateral and posterior parts of the humeral head. It has also been used for other shoulder region pathologies, such as impingement syndrome or rotator cuff tears [6]. The main complication of this approach is axillary nerve injury, which is widely recognized [2,7].

Axillary nerve originates from the posterior cord of the brachial plexus at the level of the axilla in the posterior division of the upper trunk. It carries nerve fibers from C5 and C6. The axillary nerve travels with the posterior circumflex humeral artery and vein through the quadrangular space which is formed by teres minor, teres major, long head of triceps and medial border of humerus. It gives anterior and lateral branches to enter and innervate the deltoid muscle after it travels around the humerus. This route of the axillary nerve runs transversely 5-7 cm distal to the edge of the acromion from the posterior to anterior [8].

LDSA is a useful approach, especially in posteriorly extending proximal humerus fractures, but it is limited by the position of the axillary nerve. The aim of this study is to evaluate axillary nerve integrity and shoulder function after proximal humeral fracture surgery using LDSA.

Materials and methods

In this prospective cohort study, the records of 55 patients who were operated for proximal humerus fracture between February 2015 – July 2018 were evaluated. Among these, 35 patients were selected according to inclusion criteria, which comprised being operated for proximal humerus fractures with LDSA, having the proximal humerus anatomic plate used for fracture fixation and having passed minimum 6 months after surgery. The study was approved by the ethics committee of Maltepe University Faculty of Medicine on 08.05.2020 (No:2020/900/24).

Surgical technique

For preoperative planning, axillary nerve route and bony landmarks were determined with a marker. A skin incision was made beginning at the anterolateral tip of the acromion extending distally approximately 5 cm (Figure 1).

The skin, subcutaneous tissue, fascia, and deltoid muscle were sharply dissected, and the greater tuberosity was exposed. The axillary nerve was not fully exposed, but identified and protected (Figure 2).

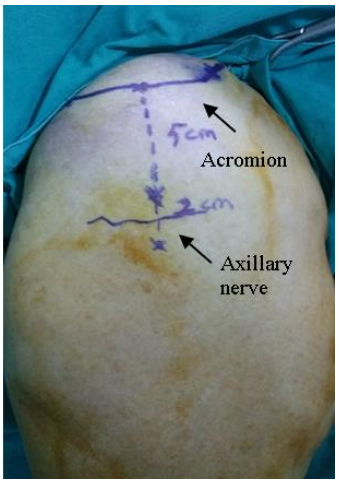

Figure 1: Preoperative planning

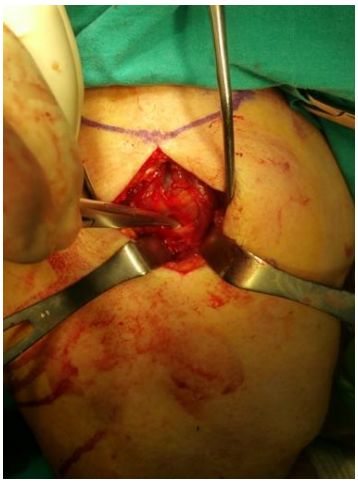

Figure 2: Intraoperative limited axillary nerve exposure

Fracture parts were fixed with proximal humerus anatomic plate and screws (Proximal humerus anatomic plate, Truemed, Istanbul, Turkey). After fixation, axillary nerve integrity was checked (Figure 3) and the wound was closed.

Figure 3: Checking axillary nerve integrity after fracture fixation

Evaluation of the patients

Physical and electrophysiological examination of the shoulder and Constant Shoulder Score (CSS) were used to evaluate axillary nerve integrity and functional status of the shoulder joint. Physical examination including inspection, palpation and touching sensation of the deltoid muscle was performed for investigation of atrophy and hypoesthesia of the shoulder. For the electrophysiological evaluation of the axillary nerve, electroneuromyography (ENMG) was performed on both upper limbs, earliest at the 6th postoperative month. In ENMG examination, axillary motor nerve's latency and amplitude were recorded on the operated and non-operated sides. An active electrode was placed in the middle of deltoid muscle; a reference electrode was placed over the acromion. Supramaximal stimulation was given at Erb's point. In needle electromyography, the electrode was inserted into the belly of deltoid muscle (Nihon Kohden Neuropack, Tokyo, Japan). Functional status of the operated shoulder was evaluated with CSS, which was performed to both healthy and operated sides. Difference of the scores were graded as > 30: severe, 21-30: moderate, 11-20: mild and <11: normal [9].

Statistical analysis

SPSS 25.0 statistics program was used for statistical analysis of results. Frequency analysis was used for demographic data. Bilateral latency and amplitude values of the axillary nerve were compared with student-t test. CSS, latency, and amplitude values of the axillary nerve were compared with correlation analysis. ANOVA test was used to compare CSS groups and latency – amplitude values. A *P*-value <0.05 was considered statically significant.

Results

Mean age of the patients was 66(9) years. Twenty-five patients were females and 10 patients were males. Mean follow-up time was 4(1) years. According Neer classification, 10 patients had surgical neck fractures (group III), 19 patients had a 3-part fracture (13 group IV, 4 group V, and 2 group VI), and 6 patients had a 4-part fracture (4 group IV, 2 group VI) (Table 1). In physical examination, none of the patients had deltoid atrophy or hypoesthesia at the lateral side of the shoulder. Mean latency and amplitude were 4.6(1.8) msn and 6.6(2.21) mV, respectively, on the operated side and 3.7(0.54) msn and 8.4(2.80) mV on the non-operated side, the difference between which were insignificant (latency *P*=0.25, amplitude *P*=0.16). There were no denervation potentials in needle electromyography, neither on the operated side nor on the non-operated sides (Table 2).

Mean CSS of all patients was 28.7. 12 patients were in bad condition (mean 39.08), 18 patients were in fair condition (mean 25.4), and 5 patients were in good condition (mean 16) at the last control visit. According to the correlation analysis, axillary nerve latency was prolonged and amplitude was low in patients with high CSS but there was no statically significant correlation between CSS and axillary nerve latency / amplitudes (*P*=0.62, r=0.267 / *P*=0.98, r=-0.339).When CSS groups were compared, there was no statically significant difference between groups with regards to EMG parameters (*P*=0.084). Correlation analysis between CSS and fracture type revealed that there was a negative correlation between functional scores and comminution of the fracture which means functional scores were bad or fair for more fragmented fractures (*P*=0.032, r=0.829).

Table 1: Demographics of the patients

Demographics	n
Mean age (min. – max.)	66.7 (53 - 79)
Gender (W/M) (n)	25 / 10
Mean follow-up (min. – max.) (year)	4.8 (3 – 7)
Side of humerus fracture (R / L)	19 / 16
Neer Classification	
Surgical Neck Fracture	10 (group III)
3-part fracture	19 (13 group IV, 4 group V, 2 group VI)
4-part fracture	6 (4 group IV, 2 group VI)

Min: minimum, max: maximum, W: woman, M: men, R: right, L: left

Table 2: The electrophysiological evaluation of axillary nerve

ENMG parameters	Operated side	Non-operated side	*P*-value
Mean latency (msn) (SD)	4.6 (1.8)	3.7 (0.54)	0.25
Mean amplitude (mV) (SD)	6.6 (2.21)	8.4 (2.8)	0.16

ENMG: Electroneuromyography, msn: millisecond, mV: millivolt, SD: standard deviation

Discussion

The deltopectoral approach is the most used approach in the shoulder region [10]. However, in some cases, LDSA may be preferred due to characteristics of the pathology and necessity of extended approach. The main complication of the LDSA is iatrogenic axillary nerve injury [11]. In this study, we evaluated the patients who were operated for proximal humerus fracture with LDSA with regards to axillary nerve integrity and shoulder functions. The results revealed that LDSA is a safe method for axillary nerve injury with careful dissection and fracture fixation. Additionally, functional scores of the shoulder joint were dependent to severity of the fracture.

One of the major upper extremity fractures is proximal humerus fracture and surgical treatment is usually necessary for comminuted fractures. The deltopectoral approach is well known and more commonly used for proximal humerus fractures. It has a relatively low complication rate and enhances exposure for fracture fixation, but deltopectoral approach may be insufficient for some comminuted and posterior extended fractures [11]. Some complications were defined for this exposure in these fractures [4,12]. Extended dissection to reach posterior part of humeral head may cause more disruption of the integrity of periosteum. Additionally, reduction of displaced greater tuberosity may become difficult with the deltopectoral approach. Deltoid muscle retraction during this approach may cause dysfunction of the muscle [13].

LDSA can solve this problem and provide more control on extreme fractures for fixing the posterior part of humeral head [14]. Especially for posteriorly extending proximal humerus fractures, LDSA can provide adequate exposure with a smaller incision than the deltopectoral approach. It affects postoperative functional outcomes of the shoulder joint [14, 15]. Isiklar et al. [16] demonstrated that constant scores in patients operated with LDSA were significantly better than patients who were operated using the deltopectoral approach at an earlier time. Additionally, this approach preserves periosteal blood supply by adequate exposure with limited incision. Despite these benefits, branches of axillary nerve are in danger due to its proximity to the surgical field, and iatrogenic axillary nerve injury is the main complication. Cheung et al. [17] investigated axillary nerve placement with a cadaver study and revealed that the axillary nerve lies about 5 cm distal from the mid-acromion. The risky area for axillary nerve is between 5 cm to 9 cm from mid-acromion.

Axillary nerve injury and shoulder functions after fixation of proximal humerus fracture were evaluated in many studies [15,18]. Khan et al. [15] reported that none of patients had an axillary nerve injury after lateral deltoid splitting approach with shoulder strap incision. In their surgical technique, axillary nerve is visualized and protected during fixation. Laflamme et al. [18] also reported that axillary nerve injury was not seen in their case series who were operated due to proximal humerus fractures with 2 different incisions, using mini open lateral deltoid splitting approach. They did not visualize the axillary nerve. In our study, postoperative 6th month ENMG results revealed that there were no significant differences between the operated and non-operated side axillary nerve functions. None of the patients complained about hypoesthesia at the lateral side of the shoulder.

Many injuries, especially proximal humerus fractures affect the functional status of the shoulder joint negatively. Severity of the fracture is the main predictor of the functional outcome of the shoulder joint. Robinson et al. [19] pointed that proximal humerus fractures with tuberosity involvement had poor functional outcome. Especially proximal humerus fractures

with varus angulation have high complication rates [20,21]. Disruption of the medial vascular supply to the humeral head is stated as the possible cause [22]. Besides, metaphysical impaction and displacement of medial hinge are strong predictors of osteonecrosis of the humeral head [20,23]. Fisher et al. [24] revealed that more complex fracture patterns may be associated with worse outcomes after proximal humerus fracture surgery. In this study, a correlation between CSS and fracture type was determined and lower CSS scores were recorded more frequently in comminuted fractures.

Due to the spherical anatomical structure of the shoulder area, it is difficult to control the entire shoulder with a single surgical approach. Although the deltopectoral approach is a suitable surgical approach for many shoulder pathologies, it may be insufficient, especially in surgeries involving the posterior shoulder area. LDSA provides adequate exposure at the lateral and posterior parts of the shoulder but may cause axillary nerve injury due to its proximity. The results of our study, in which we evaluated the rate of axillary nerve injury and its effect on shoulder functions in patients undergoing LDSA, show that this approach can be used safely.

Limitations

Main limitation of this study is the number of the participants which should be much higher for more accurate results. Another limitation is that only patients who underwent LDSA were evaluated and the effects of deltopectoral approach could not be compared with LDSA, especially for posteriorly extending proximal humerus fractures.

Conclusions

Clinical and electrophysiological findings of this study have revealed that LDSA is an effective and safe approach if it is performed by carefully exploring the axillary nerve. It provides wide and versatile fracture control without compromising the deltoid muscle functions and axillary nerve integrity, especially in fractures extending to the posterior part of the proximal humerus.

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Knowledge, attitudes, and practices of orthopedic patients towards COVID-19 outbreak

Ortopedi hastalarının COVID-19 salgınına yönelik bilgi, tutum ve uygulamaları

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Ethics Committee Approval: The study was approved by Kirikkale University Ethics Committee (Date: 5/20/2020, No. 2020.04.08) and performed in the Department of Orthopedics and Traumatology at Kirikkale University School of Medicine. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Çalışma Kırıkkale Üniversitesi Etik Kurulu tarafından onaylanmış (Tarih: 20.05.2020, No. 2020.04.08) Kırıkkale Üniversitesi Tıp Fakültesi Ortopedi ve Travmatoloji Anabilim Dalı'nda gerçekleştirilmiştir. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: Public education and awareness levels play a prominent role in effective, timely prevention and control of a public health crisis. We aimed to determine the level and defective sides of knowledge, perceptions, and awareness of the population who were referred to the outpatient clinic of the Orthopedics and Traumatology on pandemic days.

Methods: In this prospective cross-sectional study, a total of 467 patients who were referred to the orthopedics outpatient clinic between May 21, 2020 and June 21, 2020 were surveyed. We used the questionnaire which was previously described by Khan et al. A total of 276 volunteer patients aged over 16 years were included. Patients' knowledge, perceptions, and awareness level regarding COVID-19 were evaluated in terms of spread of the COVID-19 pandemic, prevention, and control policies.

Results: Out of these respondents, 58.3% were males and 41.7% were females. Around 50% of patients were aged less than 45 years, while 50% were above 45 years. The majority of the participants (question-5 [n=271; 98.2%], question-6 [n=231; 83.7%], question-7 [n=221; 80.1%]) had knowledge about the name, origin, signs and symptoms of COVID-19 infection, although their knowledge about the spread of coronavirus was relatively low. 225 participants (81.5%) did not receive any form of training or orientation about infection prevention and control. The mean age those who preferred newspapers and advertisements, friends and family, and other sources (51.09 (17.63) years) was higher than those who preferred social media and the internet (37.85 (16.45) years) (P<0.001).

Conclusion: There is a lack of information about spread routes, hence, protection from COVID-19 in the society. We suggest that health care providers develop, and release content-checked health education programs that aim to increase the knowledge level among the people and control COVID-19 spread.

Keywords: COVID-19, Knowledge, Attitudes, Practice, SARS-CoV-2, Coronavirus

Öz

Amaç: Halkın eğitimi ve farkındalık seviyeleri, bir halk sağlığı krizinin etkili, zamanında önlenmesi ve kontrolünde önemli bir rol oynar. Biz pandemi günlerinde Ortopedi ve Travmatoloji polikliniğine başvuran insanların bilgi, algı ve farkındalık düzeylerini ve kusurlu taraflarını belirlemeyi amaçladık.

Yöntemler: Bu prospektif kesitsel çalışmada, 21 Mayıs 2020 ile 21 Haziran 2020 tarihleri arasında ortopedi polikliniğine başvuran toplam 467 hasta incelendi. Çalışmada Khan ve arkadaşlarının tanımladığı anket kullanılmıştır. Çalışmaya 16 yaş üstü toplam 276 gönüllü hasta dahil edildi. Hastaların COVID-19 hakkındaki bilgi, algı ve farkındalık düzeyleri COVID-19 pandemisinin yayılma, önleme ve kontrol politikalarına göre değerlendirildi.

Bulgular: Katılımcıların %58,3'ü erkek, %41,7'si kadındı. Hastaların toplam %50'si 45 yaş altındayken, %50'si 45 yaş üzerindeydi. Katılımcıların çoğunluğunun koronavirüsün yayılmasına ilişkin bilgi düzeyleri nispeten düşük olmasına rağmen (soru-5 [n=271; %98,2], soru-6 [n=231;% 83,7], soru-7 [n=221; %80,1]) isim, köken, COVID-19 enfeksiyonunun belirti ve semptomları hakkında yeterli bilgi sahibi idi. 225 katılımcı (%81,5) enfeksiyon önleme ve kontrol konusunda herhangi bir eğitim veya yönlendirme almamıştı. Bilgiye erişimde gazete, reklam, arkadaş, aile ve diğer kaynakları tercih edenlerin yaş ortalaması (51,09 (17,63) yıl), sosyal medya ve interneti tercih edenlerden (37,85 (16,45) yıl) daha yüksekti (P<0.001).

Sonuç: Toplumda yayılma yolları ve dolayısıyla COVID-19'dan korunma hakkında bilgi eksikliği vardır. Sağlık hizmeti sağlayıcılarının, insanlar arasında bilgi düzeyini ve dolayısıyla COVID-19'un yayılmasını kontrol altına almayı amaçlayan içerik kontrollü sağlık eğitimi programları geliştirmelerini ve yayınlamalarını öneriyoruz.

Anahtar kelimeler: COVID-19, Bilgi, Tutumlar, Uygulama, SARS-CoV-2, Koronavirüs

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Introduction

The novel coronavirus disease-2019 (COVID-19, also known as severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was first reported as unknown cases of systemic acute respiratory syndrome from Wuhan, Hubei, mainland China on December 8th, 2019 [1-4]. COVID-19, which is thought to have spread from a seafood market in Wuhan, was declared a pandemic by the World Health Organization (WHO) after having been reported in more than 100 countries on March 11th, 2020 [5].

Turkey was threatened by the COVID-19 pandemic, like the rest of the world. Strict measures were taken to prevent this pandemic, so it did not lead to a national health crisis. The Republic of Turkey, Ministry of Health declared a guideline for infection control, which was based on science board recommendations, after the first case was seen on March 11th, 2020. According to this guideline, only emergency patients, patients with severe comorbid disease, oncological diseases, and those in the postoperative follow-up period were able to present to the outpatient clinics to prevent transmission of the coronavirus among patients with comorbid diseases [6]. Moreover, patients who presented to the hospital were checked in terms of signs and symptoms of COVID-19. Thus, the number of patients who were referred to the outpatient clinics decreased. However, the orthopedic outpatient clinic was the most crowded one in those days, especially due to the high population of elderly patients with degenerative musculoskeletal diseases and those in the postoperative follow-up period. In addition, the pediatric patient population also raised as the schools were closed and the children became more active in daily life.

The implementation of basic infection control protocols is only possible when individuals are aware of public health policies. Public education and awareness levels play a prominent role in effective, timely prevention and control of a public health crisis. In addition, the assessment of knowledge and perceptions of populations about rapidly spreading infectious disease outbreaks, such as COVID-19, should be accomplished in a brief period to provide information to public health institutions.

In the present study, we aimed to determine the level and defective sides of knowledge, perceptions, and awareness of the population who visited the Orthopedics and Traumatology outpatient clinic regarding COVID-19, and provide data to guide health care providers and hospital managers in informing the patients about COVID-19 and probable future pandemics.

Materials and methods

This study was approved by the Kırıkkale University Ethics Committee (Date: 5/20/2020, No. 2020.04.08). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

In this prospective cross-sectional study, a total of 467 patients who visited the orthopedics outpatient clinic between May 21, 2020 and June 21, 2020 were surveyed. A total of 276 volunteers aged over 16 years were included. The sample size was calculated with the formula which was previously used by Zhong et al. [7] as follows: Sample size= (Zα2 * (P) * (1-P)) / C2. Z value for 99% confidence interval =2.576, P=0.900, C=0.05). It was determined that at least 239 individuals had to be recruited to the study for 99% confidence interval, 5% margin of error, and 90.0% prevalence. Patients under 16 years of age and those who did not volunteer to participate were excluded. Patients' knowledge, perceptions, and awareness levels on COVID-19 were evaluated in terms of COVID-19 spread, prevention, and control policies. We used the questionnaire which was previously described by Khan et al. [8]. The questionnaire was translated into Turkish by the authors (Table 1). It includes demographic features and 21 different questions to measure patients' basic knowledge of infection, their attitudes, standard practices during the infection outbreak, control programs and policies, awareness of origin, transmission, and signs and symptoms.

Table 1: Questionnaire on COVID-19

Questionnaire-based analysis of infection prevention and control in Turkey regarding Coronavirus
* Required

Q1	Age *
Q2	Gender * • Male • Female • Other….
Q3	Profession *
Q4	Organization * • Government Hospital • Private Hospital • Educational Institutes
Q5	Do you know the name of Coronavirus? * • Yes • No • Maybe
Q6	Do you know the origin of Coronavirus? * • Yes • No • Maybe
Q7	Are you aware of common signs and symptoms of Coronavirus? * • Yes • No • Maybe
Q8	Does having fever, flue, and cough mean that you are infected? * • Yes • No • Maybe
Q9	Can you get Coronavirus from a parcel coming from china? * • Yes • No • Maybe
Q10	Can you get it from pets? * • Yes • No • Maybe
Q11	Do you have knowledge of other pandemic viral infections in the past? * • Yes • No • Maybe
Q12	Can we stop the viral spread in Turkey? * • Yes • No • Maybe
Q13	Is there an infection control program in the hospital you are applying for? * • Yes • No • Maybe
Q14	Does your country have any infection control policies and guidelines? * • Yes • No • Maybe
Q15	Have you received some form of training or orientation about infection prevention and control? * • Yes • No • Maybe
Q16	Does your organization have an emerging infectious disease task force (dealing with outbreaks)? * • Yes • No • Maybe
Q17	Do you think that all residents in your city are promptly following infection control policies and rules? * • Yes • No • Maybe
Q18	Do you think your country is prepared for any infection outbreak? * • Yes • No • Maybe
Q19	Is Coronavirus curable? * • Yes • No • Maybe
Q20	Do you think that going to school, hospital or any organization is safe? * • Yes • No • Maybe
Q21	Where can you get further information about Coronavirus? * • Internet • Social media • Newspapers and advertisements • Friends and family • Others ……..

Q: Question

Statistical analysis

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) for Windows version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented in mean (standard deviation (SD)), median (min-max), or number and frequency. The variables were examined using visual (histogram and probability plots) and analytical methods (Shapiro-Wilk test) to determine whether they were normally distributed. The Kruskal-Wallis test was conducted to compare the non-normally distributed parameters and three and more independent variables. The chi-square automatic interaction detector (CHAID) analysis was performed to identify

the factors affecting the variables of "age" and "sources" (friends and family, internet, newspapers and advertisements, social media, or Others). The CHAID analysis is one of the decision tree methods dividing the selected variable (main node) into subgroups according to their importance by categories. If the main selected variable is continuous, it is divided into groups by F tests. If it is a categorical variable, it is divided into groups by the chi-square test. It was decided to divide into subgroups according to the *P*-value (≤0.05) using the Bonferroni correction. The decision tree included the following criteria: The number of maximum levels was 3, the number of decision nodes was 25, the number of terminal nodes was 10, and *P*≤0.05. A *P*-value of <0.05 was considered statistically significant.

Results

Characteristics of participants

Out of these respondents, 58.3% were males and 41.7% were females. A total of 50% patients were aged less than 45 years, while 50% were above 45 years. Most of the participants (n=49) were workers. Details of demographic characteristics are summarized in Table 2.

Knowledge assessment of participants

The majority of the participants (question-5 [n=271; 98.2%], question-6 [n=231; 83.7%], question-7 [n=221; 80.1%]) had knowledge about the name, origin, signs and symptoms of COVID-19 infection, although their knowledge about the transmission of coronavirus was relatively low. 225 participants (81.5%) did not receive any form of training or orientation about infection prevention and control. Of the 276 participants, 211 (76,4%) believed that policies regarding infection prevention, control, and guidelines were implemented in our hospital and 196 thought that they were implemented in Turkey (71%). In addition, 178 participants (64.5%) believed that Turkey was ready for a pandemic, while 61 (22.1%) were indecisive. Distribution of responses to the questions is presented in Table 3.

Table 2: Sociodemographic characteristics of participants

	n (%)
Gender	
Female	115 (41.7)
Male	161 (58.3)
Age	
Mean (SD)	45.63 (18.33)
Median (Min-Max)	45.5 (7-90)
Occupation	
Academician	1 (0.4)
Civil servant	29 (10.5)
Coach	3 (1.1)
Engineer	1 (0.4)
Farmer	3 (1.1)
Health care worker	7 (2.5)
Homemaker	73 (26.4)
Police Officer	1 (0.4)
Retired	44 (15.9)
Soldier	3 (1.1)
Student	35 (12.7)
Teacher	3 (1.1)
Tradesman	24 (8.6)
Worker	49 (17.8)

Table 3: Distribution of responses by age

	Age			
	n (%)	Mean (SD)	Median (Min-Max)	*P*-value
Q5				
Yes	271(98.2)	45.19 (18.14)	45(16-86)	
No	3(1.1)	76 (13.11)	74(64-90)	0.023*
Maybe	2(0.7)	59 (1.41)	59(58-60)	
Q6				
Yes	231(83.7)	44.24 (18.03)	43(16-86)	0.020*
No	40(14.5)	53.18 (17.93)	50(16-90)	
Maybe	5(1.8)	49.2 (23.69)	45(21-81)	
Q7				
Yes	221(80.1)	44.07 (18.32)	43(16-86)	0.014*
No	17(6.2)	55.24 (20.19)	54(16-90)	
Maybe	38(13.8)	50.39 (15.64)	51(16-72)	
Q8				
Yes	141(51.1)	44.56 (17.25)	46(16-85)	0.569
No	54(19.6)	46.13 (22.21)	45(16-86)	
Maybe	81(29.3)	47.15 (17.49	45(16-90)	
Q9				
Yes	162(58.7)	45.33 (18.91)	47(16-85)	
No	47(17)	44.38 (17.73)	39(18-86)	0.617
Maybe	67(24.3)	47.21 (17.47)	47(16-90)	
Q10				
Yes	131(47.5)	46.86 (18.83)	47(16-85)	
No	92(33.3)	43.35 (19.3)	39.5(16-90)	0.210
Maybe	53(19.2)	46.53 (15.00)	46(16-74)	
Q11				
Yes	131(47.5)	44.52 (19.13)	44(16-86)	0.267
No	112(40.6)	47.77 (17.86)	47(16-90)	
Maybe	33(12)	42.76 (16.29)	39(16-78)	
Q12				
Yes	211(76.4)	45.91 (18.51)	46(16-90)	0.828
No	14(5.1)	46.64 (19.92)	48(16-78)	
Maybe	51(18.5)	44.18 (17.42)	43(16-77)	
Q13				
Yes	211(76.4)	45.19 (18.76)	44(16-90)	0.374
No	12(4.3)	41.83 (18.98)	38(16-78)	
Maybe	53(19.2)	48.23 (16.4)	49(16-78)	
Q14				
Yes	196(71)	44.92 (17.96)	43(16-86)	0.246
No	29(10.5)	51.31 (21.63)	57(16-90)	
Maybe	51(18.5)	45.12 (17.52)	47(16-81)	
Q15				
Yes	42(15.2)	41.81 (18.49)	37(16-75)	
No	225(81.5)	46.31 (18.14)	47(16-90)	0.331
Maybe	9(3.3)	46.44 (22.19)	46(16-78)	
Q16				
Yes	211(76.4)	46.02 (18.26)	46(16-90)	
No	33(12)	46.52 (19.31)	48(20-80)	0.574
Maybe	32(11.6)	42.09 (17.95)	43.5(16-81)	
Q17				
Yes	111(40.2)	46.77 (19.06)	47(16-86)	0.402
No	119(43.1)	44.18 (17.74)	42(16-90)	
Maybe	46(16.7)	46.61 (18.18)	47.5(16-78)	
Q18				
Yes	178(64.5)	45.94 (18.91)	47(16-86)	0.785
No	37(13.4)	46.57 (19.77)	46(16-90)	
Maybe	61(22.1)	44.15 (15.73)	43(16-78)	
Q19				
Yes	129(46.7)	44.39 (19.18)	42(16-85)	0.223
No	37(13.4)	43.65 (18.02)	40(16-78)	
Maybe	110(39.9)	47.75 (17.35)	48.5(16-90)	
Q20				
Yes	87(31.5)	48.06 (17.91)	48(16-86)	0.177
No	159(57.6)	43.91 (18.34)	43(16-90)	
Maybe	30(10.9)	47.7 (19.08)	51(16-78)	

Q: Question, * There is a significant difference in Q5, 6 and 7 between yes and no answers

Age and source-based awareness

Social media (n=77) was the most preferred source of information about the COVID-19 outbreak. Details of distribution of sources are shown in Figure 1. In the CHAID analysis of source, the participants who were over 45 years of age preferred friends and family, while those who were less than 45 years of age preferred social media as the source of knowledge about COVID-19 (*P*<0.001). A significantly higher number of participants under 45 years old who had knowledge about past viral pandemic infections (Question 3) used the others as a source of information (*P*=0.020). We found that the majority of the participants who were under 45 years who responded the 'Do you have knowledge of other pandemic viral infections in the past?' (Question 11) as 'No' or 'Maybe' and believed that COVID-19 was curable used social media as the source of information (*P*=0.016). On the other hand, a

significantly higher number of participants who were aware of the previous viral outbreaks and considered that all cough and fever symptoms were related to COVID-19 infection (Question 8) used social media as the source (P=0.023). Details of CHAID analysis of source are shown in Figure 2.

The mean age those who preferred newspapers and advertisements, friends and family, and other sources (51.09 (17.63) years) was higher than those who preferred social media and the internet (37.85 (16.45) years) (P<0.001). The mean age of those who did not know the name of coronavirus (76 (13.11) years) was significantly higher than those who knew its name (45.19 (18.14) years; P=0.023). Moreover, the mean age of those who did not know the origin of coronavirus (Question 6) (53.18 (17.93) years) was significantly higher than those who did (44.24 (18.03) years; P=0.020). The mean age of those who recognized the common signs and symptoms of COVID-19 (44.07 (18.32) years) was significantly less than those who did not know (55.24 (20.19) years; P=0.014). However, there was no significant difference between the mean ages of those who knew or did not know the common signs and symptoms of COVID-19 (P=0.569). There was no significant difference in terms of mean age between those who answered "Yes", "No" or "Maybe" to other questions. Details of distribution of age-based responses are summarized in Table 3. In CHAID analysis, the mean age of those who use social media and internet as a source of information about COVID-19 was significantly less than those who used the newspapers and advertisements, friends and family, and others (P<0.001). A significantly higher number (n=131) of those who used the newspapers and advertisements, friends and family, and others as sources had knowledge about the origin of COVID-19 (P=0.007). Among these 131 individuals, the mean age of women (52.40 (18.33) years) who knew the origin of COVID-19 was significantly higher than that of men (45.67 (16.38) years) (P=0.029). Details of CHAID analysis of age are shown in Figure 3.

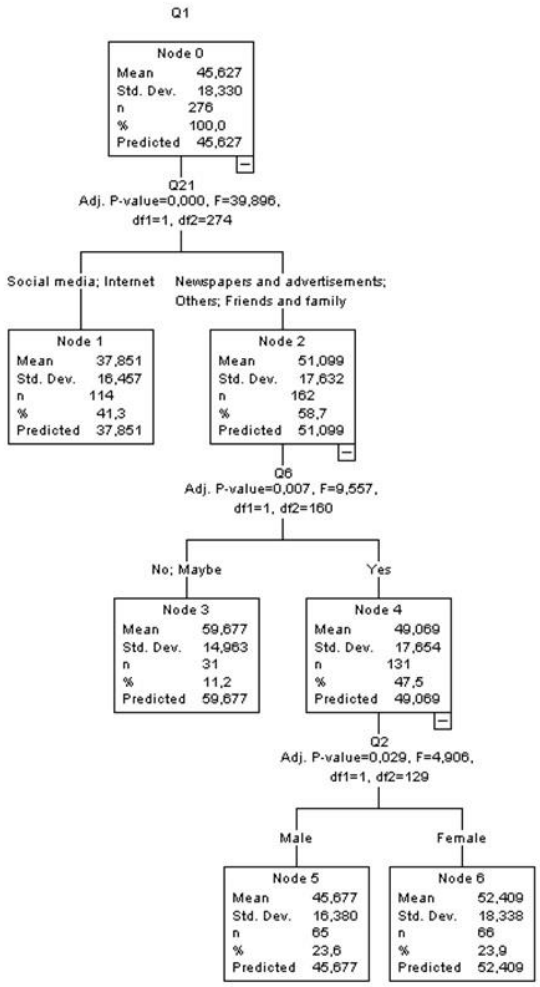

Figure 3: Aged-based decision tree of CHAID analysis

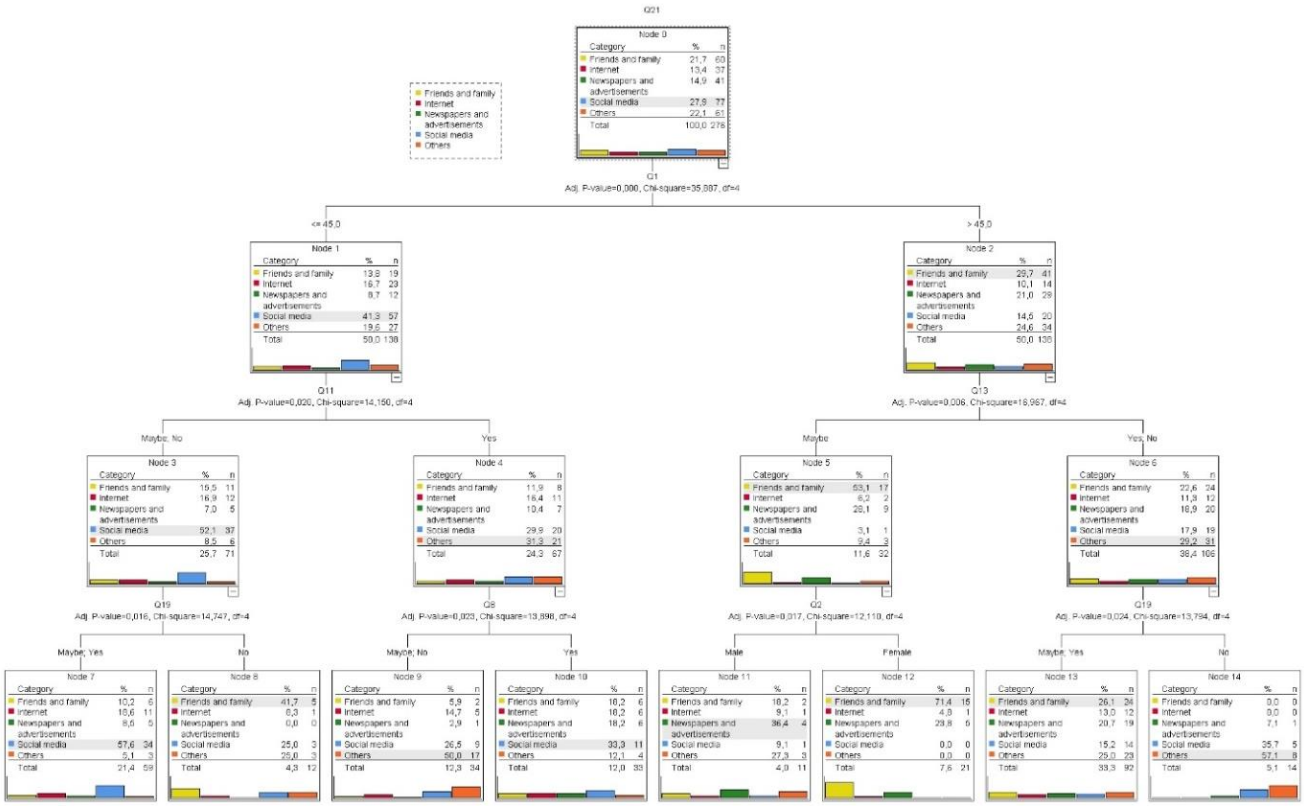

Figure 2: Source-based decision tree of CHAID analysis

Discussion

Turkey is one of the largest countries between the Middle East and Europe with more than 80 million citizens. To the best of our knowledge, this is the first study in the Turkish population examining the knowledge, attitudes, and practices toward COVID-19 among patients.

The implementation of basic infection control protocols is possible when individuals are aware of public health policies. Moreover, public education and awareness levels play a vital role in timely prevention and control of a public health crisis such as COVID-19. The most attractive finding of our study was the lack of knowledge of the participants about the spread of coronavirus. It was well documented by WHO [9] that the disease spreads primarily from human to human through small droplets from the nose or mouth, which are expelled when a person with COVID-19 coughs, sneezes, or speaks. People can catch COVID-19 if they breathe in these droplets from a person infected with the virus. It is important to stay at least 1 meter away from others. These droplets can land on objects and surfaces around the person such as tables, doorknobs, and handrails [9]. People can become infected by touching these objects or surfaces, then touching their eyes, nose, or mouth. Thus, it was highly recommended to wash your hands regularly with soap and water or clean with alcohol-based hand rubs. The lack of information about the transmission routes of coronavirus may play a significant role in the spread of COVID-19. People may misbehave with regards to individual protection from COVID-19. Incorrect usage of the masks and gloves, insufficient handwashing, and application errors of social distance in business life and in the specific events to our country, such as weddings and enlistment ceremonies, increase the transmission of the virus around substantial number of citizens. Thus, the effectiveness of common public education programs plays the key role for protection in epidemics.

Our study also revealed that, 81.5% of the participants did not receive any form of training or orientation about infection prevention and control. Zhong et al. [7] stated that health education programs aimed at improving COVID-19 knowledge are helpful for maintaining safe practices. In another study, Abdelhafiz et al. [10] reported that vaccine development is estimated to require months, and thus management of the COVID-19 outbreak depends primarily on people's knowledge, attitudes, and practices. Practicing hand and respiratory hygiene is important at outbreaks such as SARS and COVID-19 and is the best way to protect oneself. It was also underlined by WHO that since some infected individuals may be asymptomatic or their symptoms may be mild, maintaining at least a 1-meter distance with everyone is needed if you are in an area where COVID-19 is circulating, and particularly important when you are standing by someone who is coughing or sneezing [9]. Therefore, we believe that in preventing the spread of epidemic diseases, the public education programs must include detailed data about transmission routes of the agent, protection methods and public and individual protection policies.

In the current study, patients had a vast knowledge of name, origin, signs, and symptoms of COVID-19, and optimistic attitudes toward SARS-CoV-2. In a pandemic, people should not be pessimistic, however, ignorant optimism may lead to inadequate implementation of protective measures, which can lead to an out-of-control increase of infected individuals. Even if the ideal training program is implemented, indifference due to optimism can cause a deficiency in the purpose of education programs.

In our study, social media and internet were the most preferred sources of information, instead of more traditional media platforms; namely, newspapers and advertisements for patients under 45 years of age, while friends and family were the most popular sources for patients over 45 years of age. A concern in this regard is the spread of dis- and misinformation about COVID-19 on social media. WHO Director General Tedros Adhanom Ghebreyesus stated that a global epidemic of misinformation spreading rapidly through social media platforms and other outlets pose a severe problem for public health [11]. Since social media can include unverified information, it may be a source of false information. We believe that in such a public health crisis, both the ministry of health and non-governmental health organizations should work together to reveal the most accurate information and deliver it to all parts of the population using all informing platforms such as the social media, visual, and printed media, while keeping content under control.

Limitations

The main limitation of the present study includes the methodological limitations of the survey. There may be some reporting bias. Data were self-reported and data from non-respondents could not be obtained. In addition, the questionnaire was not pilot tested, which would have increased its reliability. Finally, this study included only those living in a single city; thus, further large-scale, and multi-center studies are needed.

Conclusion

There is a lack of information about spread routes and hence protection from COVID-19 in the society due to the limited ways of accurately informing large populations. Therefore, the content-checked health education programs such as printed brochures and advertisements, public information videos on TVs and social media that aim to increase knowledge level among the people and control the spread of COVID-19 should be developed and released in cooperation with the ministry of health and non-governmental health organizations.

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The value of adenosine deaminase level in assessing activation of inflammatory bowel disease

İnflamatuar bağırsak hastalığının aktivasyonunun değerlendirilmesinde adenosin deaminaz düzeyinin kullanımı

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Abstract

Aim: There is still a need for an ideal laboratory test that can determine the type of disease, the degree of its activity, predict its course, and monitor treatment response in patients with inflammatory bowel disease (IBD). This study aims to investigate the relationship between disease types and activity with Adenosine deaminase (ADA) levels in patients with IBD.

Methods: A total of 92 patients with IBD [43 with Crohn's disease (CD) and 49 with ulcerative colitis (UC)] and 31 healthy control (HC) volunteers were included in this case-control study. Patients' age, gender, body mass index, location and severity of the disease, medication, endoscopic examination, hemogram, C-reactive Protein (CRP), and ADA results were evaluated.

Results: The mean ADA level was 24.87 (9.6 - 74.9) IU/L in the IBD group and 20.8 (13.7 - 38.9) IU/L in the HC group. The difference between the IBD and HC groups was statistically significant (P<0.013), while that between UC and CD groups was not (P=0.76). Mean ADA level was significantly higher in active UC patients than in inactive ones (P<0.001). To distinguish active UC patients from those in remission, a cut-off level of 21.64 U/L was determined for ADA with 77.6% confidence interval, 89% sensitivity and 60% specificity. Mean ADA level was significantly higher in the CD group compared to the HC group.

Conclusion: ADA level may be used as an alternative marker to distinguish active UC patients from those in remission, regardless of the disease location and the extent of the affected area.

Keywords: Ulcerative colitis, Crohn's disease, Adenosine deaminase

Öz

Amaç: Günümüzde, inflamatuar barsak hastalığı (İBH) hastalarda hastalığın türünü, aktivitesinin derecesini belirleyebilen, seyrini tahmin edebilen ve tedavi yanıtını izleyebilen ideal bir laboratuvar testine hala ihtiyaç vardır. Bu çalışmada İBH olan hastalarda hastalık aktivitesi ile adenozin deaminaz ADA düzeyleri arasındaki ilişki araştırıldı.

Yöntemler: Bu vaka-kontrol çalışmasına toplam olarak 92 IBH hastası [43 Crohn hastalığı (CD) ve 49 ülseratif kolit (UC)] ve 31 sağlıklı kontrol (HC) gönüllüsü dahil edildi. Hastaların yaşı, cinsiyeti, vücut kitle indeksi, hastalığın yeri ve şiddeti, ilaç tedavisi, endoskopik muayene, hemogram, C-reaktif Protein (CRP) ve ADA sonuçları retrospektif olarak değerlendirildi.

Bulgular: Ortalama ADA seviyesi IBH grubunda 24,87 (9,6 - 74,9) IU/L ve HC grubunda 20,8 (13,7 - 38,9) IU/L idi. IBH ve HC grubu arasındaki fark istatistiksel olarak anlamlıydı (P<0,013), ancak UC ve CD grubu arasındaki fark istatistiksel olarak anlamlı değildi (P=0,76). Ortalama ADA düzeyi aktif UC hastalarında inaktif olanlardan anlamlı olarak yüksekti (P<0,001). Aktif UC hastalarını remisyonda UC hastalarından ayırt etmek için, eğer ADA düzeyinin eşik değeri 77,6 güven aralığında 21,64 U/L olarak kabul edilirse, duyarlılık %89 ve özgüllük %60 olarak hesaplandı. Ortalama ADA düzeyi CD grubunda HC grubuna göre anlamlı derecede yüksekti.

Sonuç: ADA seviyesi, hastalığın bulunduğu yere ve etkilenen alanın boyutuna bakılmaksızın, aktif UC hastalarını remisyondaki UC hastalarından ayırmak için alternatif bir belirteç olarak kullanılabilir.

Anahtar kelimeler: Ülseratif kolit, Crohn hastalığı, Adenozin deaminaz

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Introduction

Inflammatory bowel diseases (IBD) are chronic inflammatory pathologies without any curative medical treatment, which develop due to recurrent immune system activation and inflammation, and course with gastrointestinal tract remission and exacerbations. Crohn's disease (CD) and ulcerative colitis (UC) are two types of IBD with similar epidemiology, etiology, and clinical features [1-3]. Many clinical activity predictors and noninvasive markers have been used to identify disease activity and plan treatment for patients with IBD. However, none of them has yet provided a definitive finding in detecting inflammatory activity as much as histopathological and endoscopic examinations [4]. An ideal laboratory test that would be able to identify the type of disease, determine the degree of disease activity, predict the course of the disease, and monitor the treatment response in patients with IBD would be beneficial for physicians. However, there is no laboratory marker with sufficient sensitivity and specificity to provide this convenience alone.

Adenosine deaminase (ADA) enzyme plays a role in the catabolism of purine nucleotides and catabolizes the conversion of adenosine and deoxyadenosine to inosine and deoxycinosine irreversibly [5]. It is widely available in body fluids and tissues. The most important biological activity of ADA is seen in lymphoid tissues: It plays an essential role, especially in the differentiation and proliferation of T lymphocytes [6]. ADA level is ten times higher in lymphocytic cells than in erythrocytes, and more common in T lymphocytes than B lymphocytes [7]. It is considered a non-specific marker of T cell activation and cellular immunity. ADA level increases in autoimmune diseases and inflammation and is used as an indicator of cellular immunity for tuberculosis, rheumatoid arthritis, Graves' disease, celiac disease, systemic lupus erythematosus, acute pancreatitis, acute appendicitis, and other infectious diseases [8-14]. However, studies regarding the level of ADA as an effective biomarker in the evaluation of intestinal inflammation and disease activity are ongoing [15].

The aim of this study is to investigate the relationship between ADA levels and diagnosis, as well as clinical and endoscopic activity of the disease in patients with UC and CD.

Materials and methods

A case-control study was conducted on patients with IBD followed in the gastroenterology clinic. All patients were definitively diagnosed with IBD by clinical, endoscopic, histopathologic, and radiologic examinations. Patients with abdominal abscess, intestinal obstruction, active gastrointestinal bleeding, chronic liver disease, other active infections, tuberculosis, malignant disease, chronic kidney failure, pregnancy, and those younger than 18 years of age were not included in the study. Thirty-one volunteer participants with similar characteristics in terms of age, gender, and body mass index included to constitute the healthy control (HC) group. These participants were selected from individuals who visited our hospital for routine health checks and without a history of any disease, malignancy, or chronic drug use.

The patients' ages, genders, body mass indexes, findings, durations, and severity of the disease, affected area of the intestine, medications, and previous operations were recorded. Endoscopic examination and laboratory blood tests of the patients were performed on the same day. The endoscopic examination of the patients was carried out by gastroenterologists with at least five years of experience. Smoking and alcohol use habits of the patients were recorded in detail.

In patients with UC, Truelove-Witts [16] and clinical colitis activity index (CCAI) criteria [17] were used to calculate clinical severity. Endoscopic Mayo Score [18] was used to categorize endoscopic severity. UC patients with CCAI index scores ≤4 were considered clinically inactive. Bloodless defecation 1-2 times a day, normal hemoglobin, and erythrocyte sedimentation rate, as well as the absence of fever and tachycardia, are characteristics of inactive disease according to the Truelove-Witts score.

UC patients with Mayo Scores between 0 and 1 considered to be in endoscopic remission. CD activity index (CDAI) [19] and a simple endoscopic score (SES-CD) [20] were used for patients with CD. CD patients with a CDAI value <150 were considered to have clinically inactive disease. Clinically active CD patients were divided into three subgroups as mildly active (CDAI was between 150-220), moderately active (CDAI was between 221-450), and severely active (CDAI> 450). Patients were also evaluated endoscopically according to SES-CD, and scores between 0-2 were considered as endoscopically inactive, and scores above 2 were considered as endoscopically active disease.

ADA level was determined in all patients for biochemical evaluation of disease activity. For laboratory tests, venous blood was collected from the patients and control groups after 10-12 hours of fasting (to eliminate possible lipemia) into tubes containing EDTA, sodium citrate, and gel (Becton Dickinson, USA). The gel tubes were centrifuged for 10 minutes in 3500 RPM (1300g) after resting for 30 minutes. Whole blood count (EDTA blood samples) and erythrocyte sedimentation rates (ESR) (performed using the Westergreen method from sodium citrate blood sample) were measured with the Sed Rate Screener 100 (SRS 100, Greiner Bio-one GmbH, Austria) device. CRP was measured from serum samples with the nephelometric method (Immage, Beckmann Coulter, USA).

The serum samples were kept at -70ºC for measuring ADA levels later, and frozen samples were thawed and studied just before the analysis. Repeated freezing and thawing were avoided. ADA levels of all patients were measured using the Enzymatic-spectrophotometric method. Total ADA levels were evaluated by the Giusti and Galanti method [21]. Samples incubated with adenosine and free ammonium ions were measured. The concentration of ammonium ions formed in 1 minute was expressed in U/L and defined as the ADA level.

Ethical considerations

This study was approved by the Ethics Committee of Health Science University İstanbul Haydarpaşa Training and Research Hospital (HNEAH-KAEK 2013/KK/62) and carried out according to the principles of the Helsinki Declaration.

Written informed consent was obtained from all patients and volunteer participants.

Statistical analysis

Nonparametric tests were used to evaluate non-normally distributed study data. Descriptive statistical methods (median) were used, and the nonparametric Kruskal Wallis test was utilized to compare quantitative data between groups. Mann Whitney U test was used to identify groups with differences. The mean rank values were considered in determining the source of group differences. Nonparametric Kendall's Taub relation test was made use of for the correlation analysis of parameters. Power analysis was performed using the computer-aided statistics program G-power. According to previous studies [22,23] in the literature, the smallest sample size to represent the population with 95% strength was calculated as 36 participants with 1.25 effect size and 5% alpha error margin. IBM SPSS (Statistical Package for Social Sciences) Statistics 20 program was used for statistical analysis in evaluating the study findings.

Results

Ninety-two IBD patients (43/49, CD/UC) and 31 healthy volunteers were included in this study. There were 19 female and 24 male patients in the CD group, 27 female, and 22 male patients in the UC group, and 15 female, 16 male patients in the control group. The median ages of the CD, UC and control groups were 39 years (24-66), 37 years (16-74), and 39 years (25-55), respectively. IBD group patients and healthy volunteers, as well as UC and CD subgroup patients were similar in terms of mean age and gender distribution (Table 1).

The mean ADA level was 24.87 (9.6 - 74.9) IU/L in the IBH group and 20.8 (13.7 - 38.9) IU/L in the healthy volunteer group. The mean ADA level of all IBD patients was significantly higher than that of the healthy volunteer group (P=0.013). Also, the mean ADA levels of CD [26.48 (13.8-74.9) IU/L] and UC [23.8 (9.6-43) IU/L] groups were statistically significantly higher (P=0.028, P=0.027 respectively) compared with the healthy volunteer control group. However, ADA levels of patients in the UC and CD groups were similar (P=0.76).

When ADA levels were compared in the CD subgroups according to disease localization (Normal: no active disease as diagnosed by endoscopy; Localization: Colonic, ileal, ileocolonic) and CDAI (<150; mild, 150-219; moderate and >220; severe), the results were similar (Table 2). When the patients with CD were classified into those with clinically active and inactive disease according to CDAI (<150; inactive, ≥150; active) and SES-CD (0-2; inactive, >2; active), there was no significant difference between ADA levels and disease activity (Table 3). However, in patients with CD, ESR, and CRP values were significantly higher in the active group than the inactive group with respect to the CDAI classification (P=0.002, P=0.035, respectively).

No significant differences were found between the disease types in the CD subgroups (stricting, penetrating, nonpenetrating-nonstricturing) and the ADA levels (Table 2). When the patients with UC were compared between subgroups according to CCAI (score between 0-4: subgroup 0, between 5-10: subgroup 1, 11-17: subgroup 2, 18 and above: subgroup 3), subgroup 0, which had the lowest disease activity, was found to significantly differ in terms of ADA levels, ESR, and CRP values from the other groups (P=0.002, P=0.001, P=0.010 respectively) (table 2).

Table 1: The characteristics of study and control groups

Characteristic	HC	IBD	CD	UC	*P*-value
Patients, n	31	92	43	49	
Gender / Male Female	15/16	46/46	19/24	27/22	0.30
Median Age (Range, Years)	39 (24-55)	36.8 (16-74)	36 (19-63)	37.2 (16-74)	0.29
Median BMI (Range kg/m2)	24.2 (18.4-37.9)	22.82 (13.7-37.5)	22.4 (16.2-35.2)	23.15 (13.7-37.5)	0.38
Smoke (+/-)	10 /21	28 / 64	11 / 32	17 / 32	0.28
Years of Disease (Median)	---	5.5 (1-16)	6.1 (1-15)	5.0 (1-16)	---

HC: healthy controls, IBD: inflammatory bowel disease, CD: crohn's disease, UC: ulcerative colitis, BMI: body mass index

Table 2: Serum ADA, CRP and ESR levels in IBD classified by potential categorical coverable

Variable	n	ADA (IU/L)	*P*-value	CRP (mg/dl)	*P*-value	ESR (mm/h)	*P*-value
Crohn's disease							
Disease location							
Normal	5	17.98(13.8-23.4)		1.03(0.13-2.13)		22.8(10-45)	0.53
Colonic	6	33.25(15-74.9)	0.093	5.5(0.13-14)	0.142	45.6(19-64)	
Ileal	16	22.43(14.9-47.6)		2.71(0.1-12)		22.8(21-71)	
Ileocolonic	16	28.6(14.5-48.7)		3.07(0.16-14)		39.06(21-14.9)	
CDAI							
<150	24	23.5(13.8-74.9)		1(0.1-14)		19(0.21-58)	<0.001
150-219	11	23(15-38.4)	0.832	2(0.13-14)	0.009	46(20-79)	
>220	8	22.1(14.9-34.9)		3.51(2-10)		55(35-90)	
Disease behavior							
B1	21	24.3(13.8-74.9)		1.65(0.1-14)		3510-90)	0.724
B2	12	23(14.9-47.6)	0.606	1.94(011-14)	0.980	29(0.21-71)	
B3	10	21.65(14.5-41)		1.64(0.13-6.44)		35(14-54)	
Ulcerative colitis							
Disease location							
Proctitis	4	19.95(9.6-28)		0.5(0.26-1.3)		26(16-34)	0.946
Left side	27	22(12.2-42.9)		1.2(0.1-6)		28(6-70)	
Pancolitis	18	23.8(11-43)	0.615	1.17(0.1-7.3)	0.522	29(10-83)	
CCAI							.
<4	21	20.9(11-28.7)		0.31(0.1-7.3)		19(6-54)	0.010
5-10	14	28.95(20-43)		0.94(0.11-2.28)	0.001	42(12-70)	
11-17	14	23.4(9.6-36.3)	0.002	4.4(0,4-6)		34(28-83)	
>18	7	24.9(20.9-42.9)		1.54(0.4-5.3)		25(10-83)	
Truleove-Wits index							
0	4	28.35(17-29.4)		0.28(0.26-0.31)		21.5(12-32)	0.031
1	12	21.35(11-42.7)		0.29(0.1-3.59)		18.5(6-61)	
2	22	22(9.6-43)	0.757	1.25(0.11-6)	<0.001	34(12-70)	
3	11	24.7(12.4-42.9)		4.4(0.4-7.3)		28(10-83)	
Mayo score							
0	5	28(17-29.4)		0.26(0.1-0.31)		14(12-32)	0.110
1	4	29.95(18.5-29.9)	.596	0.44(0.28-0.63)	.001	12(6-61)	
2	23	22(11-43)		0.98(0.11-6)		28(12-70)	
3	17	22.7(9.6-36.3)		2.2(0.4-7.3)		30(10-83)	

Data presented as median (IQR), ADA: Adenosine deaminase, IBD: Inflammatory bowel disease, CDAI: Crohn's disease activity index, CCAI: Clinical colitis activity index

Table 3: Serum ADA, CRP and ESR levels in inactive-active IBD

Variable	n	ADA (IU/ml)	*P*-value	CRP (mg/dl)	*P*-value	ESR (mm/h)	*P*-value
Crohn's disease							
CDAI							
Inactive	26	24.25(13.8-74.9)	0.032	1.05(0.1-14)	0.035	20(0.21-67)	0.002
Active	12	21.70(14.9-38.4)		2(0.13-14)		45(20-90)	
SES-CD							
Inactive	31	21.90(13.8-74.9)	0.832	0.47(0.11-14)	0.003	18.5(10-57)	<0.001
Active	8	23(14.5-47.6)		1.65(0.1-14)		35(0.21-90)	
Ulcerative Colitis							
CCAI							
Inactive	28	20.9(11-28.7)	0.001	0.31 (0.1-7.30)	0.005	19(6-54)	0.002
Active	21	25.65(9.6-43)		1.53(0.11-6)		34(10-83)	

Data are presented as median (IQR), ADA: Adenosin deaminase, IBD: Inflammatory bowel disease, CDAI: Crohn disease activity index, CCAI: Clinical colitis activity index, SES-CD: Simple Endoscopic Score for Crohn's Disease

The patients with CD were divided into six subgroups regarding the medicine they used. ADA levels were compared between the medicine subgroups (mesalazine (n:3), azathioprine (n:23), budesonide (n:2), azathioprine + budesonide (n:3), anti-

TNF (n:8), and azathioprine + steroid (n:4)), and no differences found (P>0.05).

As the UC group was classified into active and inactive subgroups according to CCAI, ADA levels, CRP, and ESR values were higher in the active UC subgroup than the inactive subgroup (P=0.001, P=0.005, P=0.002, respectively), but ADA levels were comparable (Table 2). The cut-off level for the value of ADA in differentiating active UC patients from inactive ones was determined as 21.64 IU/L, with 76.8% power of discernment, 89% sensitivity, and 60% specificity by the ROC curve. The cut-off for CRP was 0.80, with 74% power of discernment, 68% sensitivity, and 42% specificity, and for ESR, it was 18mm/s, with 85% discrimination power, sensitivity 85.6%, and specificity 30% (Figure 1).

There was no significant difference in ADA levels between UC patients according to endoscopic Mayo score and Truelove-Witts clinical activity index (P=0.596, P=0.757, respectively).

ADA levels of UC patients did not differ according to the drugs they used, which were as follows: 5-ASA (n=30), steroid (n=1), 5-ASA+azathioprine (n=6), 5-ASA+azathioprine+steroid (n=3), 5-ASA+steroid (n=8), anti-TNF+azathioprine (n=1). In addition, the ADA levels of the smokers and non-smokers among CD and UC patients were similar (P=0.29, P=0.27 respectively).

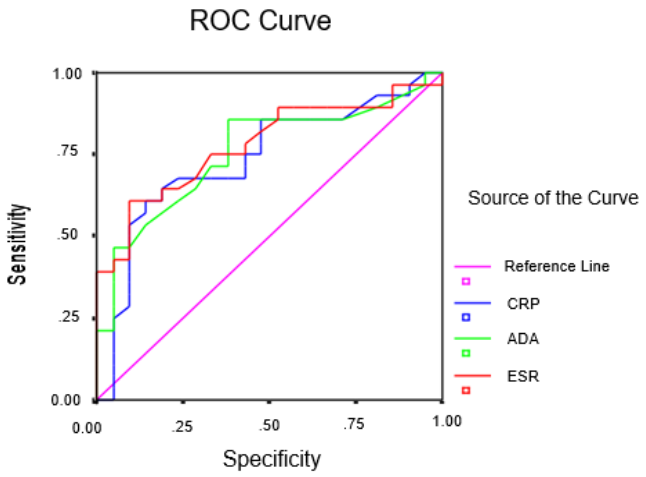

Figure 1: ROC curve of CRP, ESR, and ADA levels in Ulcerative Colitis patients

Discussion

IBD is a chronic inflammatory pathology of the gastrointestinal tract without curative medical treatment and is triggered by environmental, genetic, microbial, or immunoregulatory factors. IBD has remission and exacerbation periods. CD and UC are two main forms of IBD, and the underlying causes are similar in terms of epidemiological and clinical features [1]. Diagnosis, activity, and treatment results in patients with IBD are evaluated by the combination of clinical examination, laboratory tests, radiology, endoscopic and histological findings. Although clinical, endoscopic, and histopathological methods are one step ahead in terms of diagnostic importance, the benefits of laboratory findings should not be overlooked.

In the recent years, many noninvasive tests have been studied in the evaluation of intestinal inflammation, but a simple, widely available, and successful one is yet to be found. CRP, ESR, white blood cell (WBC) count, fecal calprotectin, and polymorphonuclear neutrophil elastase were noninvasive tests used for this purpose. While CRP value correlates with disease activity, especially in patients with CD, this correlation is weaker in patients with UC [4]. Fecal calprotectin has been used in recent years as a noninvasive sensitive stool test to detect intestinal inflammation in both UC and CD patients. It has proven to be a better predictor, especially in patients with UC. On the other hand, ESR is less used in clinical practice because it has a longer half-life, and its relationship with inflammation is weaker compared to that of CRP. Due to the limitations of the current noninvasive tests, the search for the optimal test, which can be used in both diagnosis and activity determination of patients with IBD will likely continue.

ADA plays a role in the maturation and function of monocytes and macrophages. It is the main enzyme involved in lymphoid cell differentiation, and the highest ADA activity is detected in lymphocytes, especially T lymphocytes and monocytes. ADA activity is higher in CD + 4 lymphocytes than in CD + 8 lymphocytes [24-27]. As a non-specific marker of T cell activation and cellular immunity, ADA levels increase in a variety of autoimmune and inflammatory diseases that cause cell-mediated immune response [8-14].

It seems rational to use inflammatory markers for diagnosis and activity determination in IBD, the main pathogenetic mechanism of which is T-cell activation and chronic intestinal inflammation. In our study investigating the diagnostic benefit of ADA level as a marker of T cell activation and cellular immunity in patients with IBD, it was significantly higher in patients with IBD compared to the control group. ADA levels were also higher in patients with active disease compared to the HC group and patients with inactive disease in the UC group. However, there was no significant difference in ADA levels between patients with clinically active and inactive disease in the CD group.

Although it is known that ADA level increases in IBD, few studies have evaluated its relationship with disease activity in the literature. The relationship between ADA levels and clinical and endoscopic disease activation was investigated in patients with CD by Maor et al. [22] and in patients with UC by Beyazıt et al. [23]. In both studies, akin to the results in our study, ADA level was higher in patients with UC and CD compared to the HC group. WBC, CRP, and ESR values were frequently used inflammatory markers to determine IBD activity in clinical practice. These parameters may vary with the severity of inflammation. However, they are not sufficient to reflect disease activity, as they have low sensitivity and specificity for intestinal inflammation [4,28].

In our study, ADA level was significantly higher in the UC group compared to the CD group, in which CRP and ESR values were also higher. When patients with active and inactive UC were compared, CRP, ESR, and ADA levels were significantly higher in the active disease group. In their study, Beyazıt et al. [23] evaluated ADA level as a marker of disease activity in patients with UC and found it to be significantly higher in patients with active UC compared to those with inactive disease. In that study, ADA cut-off value was 9.45 U/L, and its predictive accuracy of active disease was 83.7%

(sensitivity 83.3%, specificity 84.2%). In our study, the results were similar, and ADA level was higher in patients with UC compared to the HC group. ADA was significantly higher in the active disease group than the inactive disease group. According to our calculations, the diagnostic value of ADA was similar to other non-invasive laboratory parameters such as CRP and ESR.

In our study, there was no correlation between ADA levels, CRP, and WBC values in the UC patient group. Contrary to our study, Beyazıt et al. [23] found a correlation between ADA level, WBC, and CRP values in patients with UC. However, in their study, ADA cut off value was lower than ours. Differences in the kits used, the time of blood drawing, and in the process of handling and processing serum samples may play a role in the formation of divergent results. As a result of their study, Maor et al. [22] found that ADA and CRP values were higher in patients with active CD compared to HC participants. Additionally, they reported a significantly lower ADA level and CRP value in patients with inactive CD (CDAI <150). They also reported a significantly positive correlation between ADA and CRP values in patients with CD. They claimed that ADA levels could distinguish between active and nonactive CD. However, in our study, while ADA level was higher in the CD group compared to the HC group, there were no significant differences between active and inactive patients with CD. Additionally, we did not observe any correlation between ADA levels and other inflammatory parameters (CRP, ESR, WBC) in the CD group. The results of ADA levels in patients with CD by Sajjadi M et al. [29] were similar to our results. They also could not demonstrate that ADA level was associated with disease activity and other inflammatory markers (CRP, ESR, and fecal calprotectin) in patients with CD.

The effects of drugs used by patients on inflammation may alter ADA levels. Therefore, patient groups were also compared in terms of the drugs they used in our study. There was no difference in ADA levels between patient groups using different pharmacological agents. Additionally, in patients with active UC, although ADA level was high, no relationship was demonstrated between the degree of severity and endoscopic and clinical activity. ADA levels were negatively correlated with drugs used in patients with UC. Evaluation of all these data suggest that with the use of more potent immunoregulatory drugs in patients with higher inflammation and clinical activity, ADA levels are expected to be relatively lower.

Limitation

Possible limitations of ADA level measurement and its use in clinical practice should be considered. Because tuberculosis patients are prominent in our country, the use of ADA levels in determining IBD activity is limited, especially in patients with suspected intestinal tuberculosis. In these patients, the diagnosis of intestinal tuberculosis should be ruled out first. Undoubtedly, easily applicable, and reproducible noninvasive tests will be preferred more. This feature should also be provided for ADA measurement. The cut-off values used in studies conducted with ADA levels differ from each other, and even its mean value in one study may be the same as that of healthy controls in another study. For this reason, ADA level measurements should be standardized before common use recommendations. As inflammatory markers, ADA levels, which are elevated in patients with IBD and appear to be associated with high inflammatory response, especially in patients with active UC, seem to be usable in determination of the clinical activity.

In our study, the potential of ADA levels to distinguish the active disease from inactive disease was similar to that of commonly used CRP since it is cheaper, reproducible, and easier in routine. However, an elevated serum CRP level is not a specific finding and may vary due to several inflammatory and non-inflammatory responses. It has been shown that serum CRP levels are independently related with serum albumin level and cardiovascular diseases [30]. Many factors such as age, gender, smoking addiction, body mass index, liver failure, lipid levels, and blood pressure can affect baseline CRP levels. In addition, it has been shown that healthy postmenopausal women receiving hormone replacement therapy have high CRP levels and, in these cases, CRP is the most affected inflammatory marker. Also, some drugs used for other diseases, such as HMG CoA-reductase inhibitors, have also been shown to reduce high CRP levels [31].

Conclusion

ADA level was higher in patients with IBD than HC volunteers, reflecting inflammation in the gastrointestinal tract. It was found effective in distinguishing active disease from inactive disease in UC patients. However, its effectiveness was similar that of CRP, which is widely used in daily practice. Especially considering the low sensitivity of CRP in the determination of activity in the UC patient group, ADA level measurement may be beneficial for patients in which a definitive decision regarding disease activity cannot be made, despite evaluation of the CRP value. Although its routine use is not yet recommended, ADA level is useful in determining the clinical activity of IBD and can be preferred in selected cases. Additionally, before the widespread use of ADA levels is recommended, it should be ensured that it is easily applicable in larger populations.

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Fixation of femoral neck fractures with three cannulated screws: biomechanical changes at critical fracture angles

Femur boyun kırıklarında üç kanüllü vida ile tespit: kritik kırık açılarında biyomekanik değişiklikler

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Ethics Committee Approval: This article is not a study with human participants. There are no experiments on animals. There is no identifying information of participants.
Etik Kurul Onayı: Bu makale, insan katılımcılarla yapılan bir çalışma değildir. Hayvanlar üzerinde deney yoktur. Katılımcıların tanımlayıcı bilgisi yoktur.

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Abstract

Aim: Increased fracture angle in the coronal plane results in more instability and complications in femoral neck fractures. Our aim in this study was to analyze biomechanical changes at critical fracture angles (30 degrees, 50 degrees, and 70 degrees) as described in Pauwels classification.

Methods: A femur model was obtained by 3D computerized tomography (CT) scanning. The angle of femoral neck fracture in the coronal plane observed on the CT image was created on the model at 30, 50 and 70-degree angles. Three cannulated screws were placed in the inverted triangle position. Screws were named “anterior-superior” (A), “posterior -superior” (B), and “inferior” (C). The obtained three different models were transferred to the ANSYS Workbench program. Von Mises stress distribution on the screws and distal fracture surfaces were recorded.

Results: In the 30-degree fracture model, the maximum stress was 18.062 MPa on the "A" screw. It was 22.13 MPa on screw "B" and 16.21 MPa on screw "C". In the 50-degree fracture model, the maximum stress values were 68.04 MPa, 89.52 MPa and 48.94 MPa in screws "A", "B", and "C", respectively. In the 70-degree fracture model, the maximum stress values were 120.02 MPa, 138.32 MPa and 98.37 MPa in screws "A", "B", and "C", respectively. The stress values on the distal fracture surfaces were 13.54 MPa, 43.80 MPa, and 50.07 MPa in the 30, 50, and 70-degree models, respectively.

Conclusion: Increasing fracture angle from 30 to 50 degrees in femoral neck fractures significantly increases the stress on the distal fracture surface and implants. However, this increase is minimal at angles higher than 50 degrees.

Keywords: Femoral neck fractures, Pauwels classification, Cannulated screw fixation, Finite element study

Öz

Amaç: Femur boyun kırıklarında koronal planda kırık açısının artması instabiliteyi ve komplikasyonları arttırmaktadır. Bu çalışmadaki amacımız Pauwels sınıflamasında belirlenmiş olan kritik açılardaki (30 derece, 50 derece, 70 derece) biyomekanik değişiklikleri analiz etmektir.

Yöntemler: 3D bilgisayarlı tomografi taramasından elde edilen femur modelinde koronal plandaki kırık açısına göre 30, 50 ve 70 derece femur boyun kırığı oluşturuldu. Inverted triangle pozisyonunda 3 adet kanüllü vida yerleştirildi. Vidalar anterior-superior (A), posterior –süperior (B) ve inferior (C) olarak isimlendirildi. Üç model Ansys Workbench programına aktarılarak vidalardaki ve distal kırık yüzeyindeki von mises stres dağılımları kaydedildi.

Bulgular: Maximum stres 30 derece kırık modelinde A vidasında 18,06 mpa idi. B vidasında ise 22,13 MPa, C vidasında 16,21 MPa olarak bulundu. 50 derece kırık modeline baktığımızda max stres değerleri A vidasında 68,04 MPa iken B vidasında 89,52 MPa, C vidasında ise 48,94 MPa olarak bulundu. 70 derece kırık modelinde A vidasında maximum stres 120,02 MPa, B vidasında 138,32 MPa idi. C vidasında ise 98,37 MPa olarak bulundu. Distal kırık yüzeyindeki stres değerleri ise 30, 50, 70 derece modellerde sırası ile 13,54 MPa, 43,80 MPa ve 50,07 MPa idi.

Sonuç: Femur boyun kırıklarında kırık açısının 30 dereceden 50 dereceye yükseltilmesi distal kırık yüzeyi ve implantlar üzerindeki gerilimi önemli ölçüde artırmaktadır. Ancak bu artış 50 derecenin üzerindeki açılarda minimumdur.

Anahtar kelimeler: Femur boyun kırığı, Pauwels sınıflaması, Kanüllü vida ile fiksasyon, Sonlu elemanlar analizi

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Introduction

Femoral neck fractures are common injuries [1]. Anatomically, they occur in the area between the intertrochanteric region and the femoral head [2]. While they occur due to high-energy traumas in young patients, the mechanism is mostly a low-energy trauma in the elderly [3,4].

Anatomical reduction and stable fixation in femoral neck fractures are critical factors to achieve success. Fixation with cannulated screws is a frequently used treatment method [5]. The most common complications of femoral neck fractures are avascular necrosis (AVN) and nonunion. The occurrence of these complications requires reoperations at a rate of 20% [6].

Pauwels classification is a frequently used system to classify femoral neck fractures. Based on the angle of the fracture line in the coronal plane, angles of up to 30 degrees are classified as type 1, angles between 30 degrees-50 degrees are classified as type 2, and angles higher than 50 degrees are classified as type 3 [7]. Several studies report that high fracture angles in the coronal plane increase the likelihood of failure after fixation with cannulated screws, thereby, resulting in increased rates of postoperative complications [8,9].

Despite many studies investigating this subject matter in the literature, more studies are needed to understand biomechanical changes and complications that may occur in association with different fracture configurations [10].

Our aim in this study is to contribute to the treatment of femoral neck fractures by examining the stress changes on the implants and distal fracture surface at different fracture angles.

Materials and methods

Finite Element Method (FEM) is a mathematical based computational technique used in solving complicated analytically structural problems. In this way, one creates a model similar to the real body with solid modeling programs such as Solid Works. This model is obtained by using real computerized tomography (CT) images from real CT scans. Modified solid models are generated in a solid modeling program based on the problem, then sent to a Finite Element Analysis software such as Ansys Workbench, which is a useful tool for especially engineers to solve various engineering problems.

The femur model used in our study was obtained from a three-dimensional (3D) computerized tomography (CT) scan. Fracture angles of 30 (30º), 50 (50º), and 70 degrees (70º) were created on the obtained femur model based on the fracture angles in the coronal plane. Three cannulated screws were placed in the inverted triangle position (Figure 1).

Screws were named as anterior-superior (A), posterior-superior (B), and inferior (C) (Figure 2). The obtained three different models were transferred to the ANSYS Workbench program and von Misess stress distribution on the screws and distal fracture surfaces were recorded.

All models were applied a force of 1650N at a 15-degree (15º) angle with the femoral shaft axis. The force applied was limited along the femoral shaft (Figure 3).

High-resolution 3D elements of 1mm are used for the construction of the mesh. The Elasticity Modules were taken as 16.8G Pa and 206 GPa for the femur and screws, respectively. The Poisson ratio was selected to be 0.3 for both the femur and the screws. The Linear Elastic Isotropic Model was used for material deformation in the analyses [11].

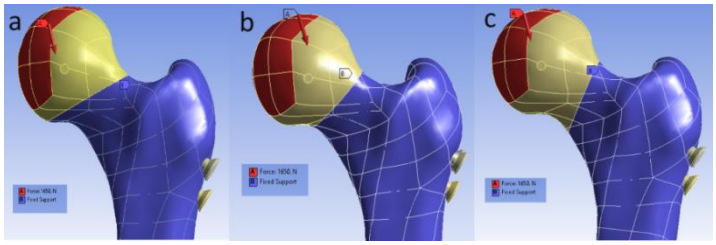

Figure 1: Shows the fracture angle models of 30º, 50º, and 70º

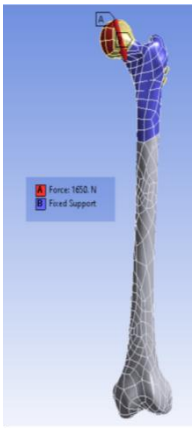

Figure 2: Screw placements: anterior-superior (A), posterior –superior (B), and inferior (C)

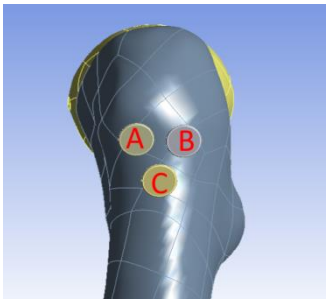

Figure 3: Schematic representation of the loads applied to the models. A 1650N load at an angle of 15 º

Results

The examination of the von Mises stress distribution on the screws revealed that maximum values occurred at the points where the screws crossed the fracture line and superiorly. In the 30-degree fracture model, the maximum stress was 18.062 MPa on the "A" screw. It was 22.13 MPa on screw "B" and 16.21 MPa on screw "C". In the 50-degree fracture model, the maximum stress values were 68.04 MPa, 89.52 MPa and 48.94 MPa in screws "A", "B", and "C", respectively. In the 70-degree fracture model, the maximum stress values were 120.02 MPa, 138.32 MPa and 98.37 MPa in screws "A", "B", and "C", respectively (Table 1) (Figure 4).

The maximum stress values on the distal fracture surfaces, obtained in the inferior cortex, were 13.54 MPa, 43.80 MPa, and 50.07 MPa in the 30, 50, and 70-degree models, respectively. (Table 2) (Figure 5).

Table 1: Maximum stress values on screws in fracture models

	Max stress (MPa) on screw locations		
Angle	A(screw)	B(screw)	C(screw)
30º	18.06 MPa	22.13 MPa	16.21 MPa
50º	68.04 MPa	89.52 MPa	48.94 MPa
70º	120.02 MPa	138.32 MPa	98.37 MPa

Table 2: Maximum stress values on distal fracture surfaces in fracture models

Angle	Distal fracture surface stresses (MPa)
30º	13.54 MPa
50º	43.80 MPa
70º	50.07 MPa

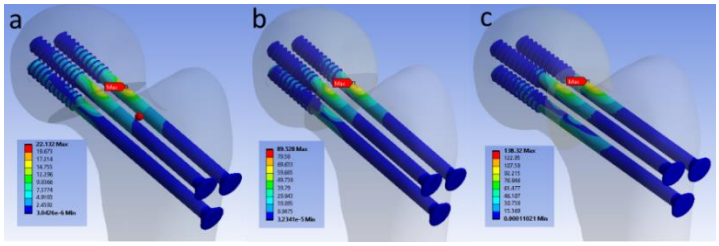

Figure 4: Von Mises stress distribution on screws by the fracture angles

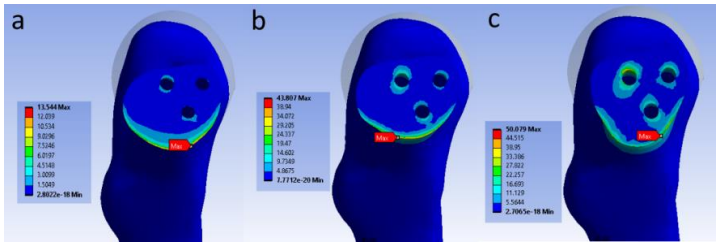

Figure 5: The stress distribution on distal fracture surfaces by fracture angles

Discussion

Despite the availability of several studies regarding the effects of fracture configuration and the type of implants on the success of stabilization in femoral neck fractures, no consensus has been achieved on this subject matter [12-17]. Jiantao et al. [18] investigated the optimal placement of cannulated screws in the treatment of femoral neck fractures. In their study, they stated that the most stable model was the inverted triangle model. In our study, we examined biomechanical changes by fracture angles in cannulated screw fixation performed by applying an inverted triangle model.

Hoshono et al. [3] and Collinge et al. [19] reported that a high fracture angle may lead to instability and implant and treatment failures. In our study, we observed that as the fracture angle increases, so does the stress intensity on both the implant and the distal fracture surface. In this sense, we suggest that high angles of fractures may impair stability, increase complications, and lead to treatment failures. When we analyzed the data we obtained on the distal fracture surface in detail, we observed that increasing the angle of the fracture from 30º to 50º raised the maximum stress value on the distal fracture surface approximately by fourfold. However, an increase in the angle from 50 º to 70º is associated only with a 16% increase. These findings demonstrate that the critical level of a biomechanical change is more notable with fracture angles ranging from 30º to 50º and that angles of more than 50º are not associated with significant differences across models. When these data are interpreted clinically, it is obvious that increasing the angle of fracture results in increased instability. In the Pauwels classification, fracture angles of more than 50º are classified as Type 3 and these angles are associated with high instability and complication rates [3,8,20,21]. However, our study results show that notable differences occur across fracture angles ranging from 30º to 50º, whereas biomechanical differences occur less at angles of more than 50 º. When the loads on the screws are examined, it is observed that a shift in the angle from 30º to 50º increases the load on all screws approximately by 4-fold but an increase from 50º to 70º results in an increase by approximately 2-fold. Furthermore, the load on the screws increases with the increasing load on the distal fracture surface. After examining the overall results of the study, we can argue that Pauwels type 2 fractures are at least as much unstable as type 3 fractures. Pauwels classification is important from a biomechanical aspect; however, we suggest that critical angle values for instability be reviewed and the classification be revised accordingly.

In a study on young patients with displaced femoral neck fractures, Hoshino et al. [19] reported lower complication rates with the use of fixed-angle devices used in anatomical reduction compared to fixation with screws. The authors reported that they did not know the reason for this finding, warranting further studies. Studies comparing various implant systems report that many implants provide sufficient stability despite some differences across implant types [5,7,11,22]. In our study, we obtained the stress values on inferior cortices of distal fracture surfaces. In cases with no inferior cortical contact, that is, when an anatomical reduction cannot be performed, the stress generated in the proximal fracture fragment will not be transferred to the distal fracture surface and the calcar region, impacting on the implant directly. Consequently, implant and treatment failures result. From this point of view, we argue that achieving a proper anatomical reduction is important for stability and success rather than the type of the implant in the treatment of femoral neck fractures.

In our study, we measured the highest stress value on the superior-posterior (B) screw compared to A and C screws. We think that the cause of high stress levels may be the 15º anteversion angle in the femoral neck. More comprehensive biomechanical studies are needed on this subject matter.

Limitations

A limitation of our study is its biomechanical computer-based design, warranting further clinical studies and studies on cadavers to support the results. Secondly, in our study, we examined the biomechanical effects of different angles but only on 3 models. Further studies to be conducted on more models with different angles may demonstrate biomechanical changes more appropriately. The results we obtained in this study should be supported by more comprehensive clinical and biomechanical studies.

Conclusion

In femoral neck fractures, a higher fracture angle in the coronal plane is associated with increased stress values on the distal fracture surface and cannulated screws. While the changes are more notable with increasing fracture angles from 30 º to 50º, they become minimal with angles of more than 50º.

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The relation of visceral adiposity index and lipid accumulation product with metabolic, anthropometric, and hormonal parameters in patients with polycystic ovary syndrome

Polikistikover sendromlu hastalarda visseral adiposite indeksi ve lipid birikim ürünlerinin metabolik, antropometrik ve hormonal parametrelerle ilişkisi

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Abstract

Aim: Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in women of reproductive age and is associated with glucose intolerance, central obesity, hypertension, and dyslipidemia. The Visceral Adiposity Index (VAI) and Lipid Accumulation Product (LAP) are effective indices for predicting insulin resistance are associated with cardiovascular and cerebrovascular events. In this study, we aimed to investigate the relationship of VAI and LAP with metabolic, anthropometric, and hormonal parameters in PCOS patients.

Methods: A total of 106 patients with PCOS who were diagnosed according to the Rotterdam criteria and 66 healthy controls without PCOS aged 18-35 years were included in this prospective, case-control study. Patients with diabetes mellitus, Cushing syndrome, hyperprolactinemia, congenital adrenal hyperplasia, hypertension, or thyroid disorder were excluded. The VAI and LAP were calculated based on the high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) levels.

Results: There was a negative, significant correlation between LAP and HDL-C (r=-0.644), a positive, significant correlation between TG (r=0.706) and hip circumference (r=0.872), and a positive, significant correlation between VAI and waist circumference (r=0.625) in the PCOS group. There was also a positive, significant correlation between HOMA-IR and VAI in the PCOS group (r=0.462).

Conclusion: Our study results suggest that VAI seems to be a more useful index for predicting insulin resistance in PCOS patients.

Keywords: Lipid accumulation product, Polycystic ovary syndrome, Visceral adiposity index

Öz

Amaç: Polikistik over sendromu (PKOS) üreme çağında en sık görülen endokrinopati olup santral obezite, glukoz intoleransı, dislipidemi ve hipertansiyon ile ilişkilidir. Visseral adipozite indeksi (VAI) ve lipid birikim ürünleri (LAP) insülin duyarlılığı dışında kardiyovasküler ve serebrovasküler olaylar ile de ilişkili olduğu saptanmıştır. Bizler de, bu çalışmamızda PKOS ve kontrol grubu hastalarımızda VAI ve LAP ile metabolik, antropometrik ve hormonal parametreler arasındaki ilişkileri değerlendirdik.

Yöntemler: Çalışmaya 18-35 yaş aralığında 106'sı Rotterdam kriterlerine göre PKOS grubunda olmak üzere toplam 172 hasta dahil edildi. Diabetes mellitus, Cushing sendromu, hiperprolaktinemi, konjenital adrenal hiperplazi, hipertansiyon ve tiroid bozukluğu olan hastalar çalışmaya dahil edilmedi. LAP ve VAI indekslerinin hesaplanması için HDL ve trigliserid düzeylerine bakıldı.

Bulgular: PKOS'lu hasta grubunda LAP ile HDL-C (r=-0,644) arasında anlamlı negatif korelasyon saptanırken, trigliserid (r=0,706) ve kalça çevresi (r=0,872) arasında pozitif korelasyon saptandı. Yine VAI ile bel çevresi (r=0,625) ve HOMA-IR (r=0,462) arasında pozitif korelasyon saptandı.

Sonuç: Bu çalışmada PKOS hasta grubunda VAI'nın insülin direncini belirlemede yararlı bir indeks olduğu sonucuna varıldı.

Anahtar kelimeler: Polikistik over sendromu, Visseral adipozite indeksi, Lipid birikim ürünleri

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Introduction

Polycystic ovary syndrome (PCOS) is a common hormonal disorder in women of reproductive age characterized by ovulatory dysfunction, chronic anovulation, irregular menstruation, and clinic and/or biochemical hyperandrogenism [1]. A higher rate of women with PCOS suffer from insulin resistance, type 2 diabetes mellitus (DM), dyslipidemia, hypertension, and central obesity than those with regular menstruation. Insulin resistance is the main underlying cause of the pathophysiology of these metabolic disorders [2]. About 70% of women with PCOS have insulin resistance, while metabolic syndrome affects about 8 to 25% of these women with anovulatory PCOS phenotype [3,4].

Several studies have demonstrated that metabolic disorders are more frequently associated with the distribution of adipose tissue rather than absolute amount of the body fat [5]. Visceral obesity has been associated with increased insulin resistance, low-grade chronic inflammation, type 2 DM, dyslipidemia, and metabolic and cardiovascular diseases [6-8]. In about 50 to 60% of insulin-resistant PCOS patients, central adipose tissue distribution is present, irrespective of obesity [9].

Ultrasonography (USG), computed tomography (CT), and magnetic resonance imaging (MRI) are helpful imaging modalities for the assessment of visceral adiposity distribution. However, radiation exposure and excessive costs of these imaging modalities limit their use in daily clinical practice [10]. In previous studies, waist circumference (WC) and waist-to-hip ratio (WHR) were calculated for the assessment of visceral adipose tissue [11]. In more recent studies, the Visceral Adiposity Index (VAI) and Lipid Accumulation Product (LAP), which are effective indices for predicting insulin resistance, were used and shown to be useful for the evaluation of cardiometabolic risk-related adipose tissue dysfunction [12,13].

To date, several studies have used VAI for visceral adiposity dysfunction in patients with metabolic syndrome, type 2 DM, and PCOS [12,14-18]. In the present study, we aimed to investigate the relationship between VAI and LAP with metabolic, anthropometric, and hormonal parameters in PCOS patients.

Materials and methods

This prospective, case-control study was conducted at the Obstetrics and Gynecology outpatient clinics between January 2019 and July 2019. The patient group included a total of 106 patients diagnosed with PCOS according to the Rotterdam criteria [19]. The control group included 66 healthy individuals without PCOS. Those with DM, Cushing syndrome, hyperprolactinemia, thyroid disorder, hypertension, or congenital adrenal hyperplasia, and patients who received oral contraceptives, anti-androgens, insulin-sensitizing agents, or statins within the past six months were excluded. A written informed consent was obtained from each participant. The protocol of the study, which was conducted in accordance with the principles of the Declaration of Helsinki, was approved by the Ethics Committee (2011-KAEK-25 2019/10-02).

Blood samples were collected after a 12-hour overnight fast between 08.00 and 10.00 AM on Days 2 and 5 of the menstrual cycle. Laboratory tests including follicle-stimulating hormone (FSH), estradiol (E_2), total testosterone, prolactin (PRL), luteinizing hormone (LH), dehydroepiandrosterone sulfate (DHEA-S), insulin, and 17-hydroxyprogesterone (17-OHP) were analyzed (ARCHITECT®, Abbott Laboratories, Singapore). Fasting blood glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), HDL-C, and TG were measured using the Synchron LX20 analyzer (Beckman Coulter, CA, USA).

Insulin resistance was calculated using the Homeostatic Model Assessment Insulin Resistance (HOMA-IR) formula (fasting glucose (mg/dL) x fasting insulin (μU/mL)/405). LAP was calculated using the following formula: (WC [cm]-58) x (TG [mmol/L]) [13]. VAI was calculated using the following formula: (WC in cm/36.58 + [1.89 x BMI in kg/m2] x [TG/0.81] x [1.52/HDL-C mmol/L]) [12].

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean (standard deviation), median (IQR) values, and number and frequency. The Kolmogorov-Smirnov test was used to check the normality assumption. The Mann-Whitney U test was performed to compare unadjusted age and BMI variables between the patient and control groups. The analysis of covariance (ANCOVA) was used to compare adjusted age and BMI variables between the patient and control groups. The Spearman's rank correlation analysis was utilized to investigate the relationship between VAI and LAP and other variables. A *P*-value of <0.05 was considered statistically significant.

Results

Of a total of 172 participants included in the study, 106 were in the PCOS group and 66 were in the control group. Descriptive demographic and clinical characteristics of the patient and control groups (unadjusted) are shown in Table 1. The mean BMI, Ferriman-Gallwey Hirsutism scores, WC, HC, WHR, LH, total testosterone, 17-OHP, insulin, fasting blood glucose, TC, and LAP ($P<0.05$ for all) were significantly higher in the PCOS group compared to the control group.

Due to a significant difference in age and BMI values between the groups, these variables were included in the model as covariates. Descriptive demographic and clinical characteristics of the patient and control groups (adjusted) are shown in Table 2. Accordingly, there was no significant difference in the VAI and LAP between the groups. However, the mean WHR ($P=0.049$), LH ($P=0.005$), 17-OHP ($P=0.001$), TC ($P=0.049$), and HOMA-IR ($P=0.049$) were significantly higher in the PCOS group compared to the control group.

Correlation analysis results are summarized in Table 3. There was a significant difference in WC between the groups ($P=0.020$), indicating a positive, significant correlation of WC with VAI in the PCOS group(r=.625). However, there was a significant difference in the HC ($P=0.022$), HDL-C ($P=0.006$), and TG levels ($P=0.016$) between the groups, indicating a positive, significant correlation of HC(r=.872), HDL-C(r=-.644), TG(r=.706) with LAP in the PCOS group. Furthermore, there was a positive, significant correlation between the HOMA-IR

(r=0.462) and VAI in the PCOS group. There was a similar correlation between HOMA-IR and LAP measurements in both groups.

Table 1: Descriptive demographic and clinical characteristics of the patient and control groups (unadjusted)

	Control group n=66		PCOS group n=106		
Variable	Mean	SD	Mean	SD	*P*-value
Age (years)	27.67	4.68	24.90	4.95	0.001
BMI (kg/m^2)	23.69	3.87	26.44	5.65	0.001
FGH score	11.13	4.56	16.29	6.52	0.001
Waist circumference (cm)	74.29	12.37	81.05	15.51	0.007
Hip circumference (cm)	99.52	8.70	103.67	12.44	0.016
Waist-to-hip ratio (cm)	0.74	0.07	0.78	0.07	0.003
TSH (µU/ml)	2.48	1.15	2.14	1.29	0.019
PRL (ng/mL)	15.79	8.45	14.65	7.78	0.461
FSH (mIU/mL)	5.93	1.88	5.21	2.35	0.002
LH (mIU/mL)	5.02	3.02	7.40	6.30	0.005
Estradiol (pg/mL)	76.16	56.58	71.68	6476	0.248
Total testosterone , (ng/dL)	16.25	16.13	21.39	19.98	0.026
DHEA-S (µg/dL)	202.97	81.29	228.52	96.84	0.067
17-OHP (ng/mL)	0.52	0.49	0.94	0.84	0.001
Insulin (µIU/mL)	9.54	13.08	10.65	6.78	0.004
HOMA-IR	1.612	.916	2.430	1.742	0.001
FBG (mg/dL)	85.35	13.04	89.56	9.20	0.023
HDL-C (mg/dL)	54.26	12.72	53.49	11.64	0.788
LDL-C (mg/dL)	97.94	28.99	108.29	29.22	0.052
TC (mg/dL)	167.83	30.47	181.71	35.10	0.015
TG (mg/dL)	90.05	49.88	97.15	56.81	0.297
VAI	3.20	2.57	3.58	2.73	0.242
LAP	16.67	21.03	25.10	24.89	0.010

PCOS: polycystic ovary syndrome, TSH: thyroid-stimulating hormone, PRL: prolactin, FSH: follicle-stimulating hormone, LH: luteinizing hormone, DHEA-S: dehydroepiandrosterone sulfate, 17-OHP: 17-hydroxyprogesterone, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, FBG: fasting blood glucose, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, TC: total cholesterol, TG: triglyceride, VAI: Visceral Adiposity Index, LAP: Lipid Accumulation Product

Table 2: Descriptive demographic and clinical characteristics of the patient and control groups (adjusted)

Variable	Control group n=66		PCOS group n=106		*P*-value
	Mean	SD	Mean	SD	
Waist circumference (cm)	77.715	8.798	78.914	8.597	0.403
Hip circumference (cm)	102.831	5.825	101.605	5.693	0.197
Waist-to-hip ratio (cm)	0.751	0.065	0.771	0.062	0.049
TSH (µU/ml)	2.608	1.300	2.058	1.277	0.010
PRL (ng/mL)	15.930	8.603	14.569	8.412	0.331
FSH (mIU/mL)	5.905	2.332	5.221	2.275	0.073
LH (mIU/mL)	4.904	5.549	7.475	5.426	0.005
Estradiol (pg/mL)	64.405	62.011	78.992	60.621	0.149
Total testosterone (ng/dL)	16.450	18.466	21.271	17.997	0.109
DHEA-S (µg/dL)	213.536	94.255	221.940	92.146	0.584
17-OHP (ng/mL)	0.462	0.772	0.975	0.752	0.001
Insulin (µIU/mL)	9.857	10.082	10.450	9.863	0.718
HOMA-IR	86.728	10.919	88.697	10.677	0.268
FBG (mg/dL)	1.843	1.44	2.287	1.76	0.049
HDL-C (mg/dL)	53.636	11.431	53.877	11.181	0.897
LDL-C (mg/dL)	98.566	30.741	107.902	30.053	0.063
TC (mg/dL)	169.374	35.388	180.749	34.604	0.049
TG (mg/dL)	95.726	55.463	93.614	54.227	0.815
VAI	3.506	2.608	3.386	2.553	0.777
LAP	21.959	18.271	21.803	17.863	0.958

Table 3: Correlation analysis results

		r	*P*-value	r	*P*-value
Control n=66	Age (years)	0.397	0.001	0.227	0.067
	BMI (kg/m^2)	0.221	0.074	0.625	0.001
	FGH score	-0.143	0.253	-0.448	0.001
	Waist circumference (cm)	0.344	0.005	0.911	0.001
	Hip circumference (cm)	0.221	0.075	0.752	0.001
	Waist-to-hip ratio (cm)	0.432	0.001	0.828	0.001
	TSH (µU/ml)	0.006	0.959	-0.269	0.029
	PRL (ng/mL)	0.197	0.113	0.362	0.003
	FSH (mIU/mL)	-0.004	0.974	0.004	0.976
	LH (mIU/mL)	-0.078	0.534	-0.100	0.426
	Estradiol (pg/mL)	-0.168	0.177	-0.429	0.001
	Total testosterone (ng/dL)	-0.169	0.179	-0.515	0.001
	DHEA-S (µg/dL)	-0.017	0.891	-0.047	0.708
	17-OHP (ng/mL)	-0.142	0.257	-0.364	0.003
	Insulin (µIU/mL)	0.268	0.030	0.386	0.001
	FBG (mg/dL)	0.077	0.538	0.348	0.004
	HDL-C (mg/dL)	-0.657	0.001	-0.318	0.009
	LDL-C (mg/dL)	0.243	0.049	0.035	0.779
	TC (mg/dL)	0.231	0.062	0.150	0.229
	TG (mg/dL)	0.844	0.001	0.455	<0.001
	HOMA-IR	0.242	0.051	0.435	<0.001
PCOS n=106	Age (years)	0.145	0.139	0.304	0.002
	BMI (kg/m^2)	0.503	0.001	0.771	0.001
	FGH score	0.010	0.919	0.102	0.300
	Waist circumference (cm)	0.625	0.001	0.905	0.001
	Hip circumference (cm)	0.617	0.001	0.872	0.001
	Waist-to-hip ratio (cm)	0.519	0.001	0.771	0.001
	TSH (µU/ml)	0.092	0.348	0.064	0.517
	PRL (ng/mL)	-0.007	0.944	0.047	0.634
	FSH (mIU/mL)	-0.010	0.921	-0.057	0.565
	LH (mIU/mL)	-0.115	0.241	-0.219	0.024
	Estradiol (pg/mL)	-0.391	0.001	-0.508	0.001
	Total testosterone (ng/dL)	-0.336	0.001	-0.488	0.001
	DHEA-S (µg/dL)	0.127	0.196	0.166	0.090
	17-OHP (ng/mL)	-0.068	0.486	0.033	0.740
	Insulin (µIU/mL)	0.463	0.001	0.525	0.001
	FBG (mg/dL)	0.251	0.009	0.306	0.001
	HDL-C (mg/dL)	-0.730	0.001	-0.644	0.001
	LDL-C (mg/dL)	0.250	0.010	0.194	0.047
	TC (mg/dL)	0.230	0.018	0.207	0.033
	TG (mg/dL)	0.909	0.001	0.706	0.001
	HOMA-IR	0.462	<0.001	0.530	<0.001

Discussion

Polycystic ovary syndrome is typically characterized by chronic anovulation, hyperandrogenism, and morphological polycystic ovaries. Irrespective of insulin resistance and obesity, increased central adipose tissue is one of the main clinical manifestations of PCOS, suggesting that PCOS is a metabolic disorder [20,21]. Even with a normal body weight, women with PCOS have usually increased visceral adipose tissue [20,21]. Visceral obesity is associated with increased adipocytokine production, proinflammatory activity, and insulin resistance and hypertension, high TG and low HDL-C levels, atherosclerosis and high mortality rates [12,22,23]. Therefore, it is of utmost importance to assess visceral adiposity in PCOS patients to diagnose and treat cardiovascular diseases, irrespective of the obesity status.

The International Diabetes Federation recommends CT or MRI for the evaluation of visceral adiposity distribution [24]. Although both imaging modalities yield reliable results, radiation exposure and excessive costs limit their use in daily clinical practice. Previous studies have also established the role of anthropometric measurements in predicting insulin resistance, metabolic syndrome, and cardiovascular risks [15,25]. Recent studies have reported that VAI and LAP are more useful tools to estimate visceral obesity and visceral adiposity functionality [12,13]. VAI and LAP seem to be helpful in identifying cardiometabolic risk in many settings including PCOS [26,27]. Review of the literature reveals several studies investigating the relationship of VAI and LAP with cardiometabolic risk factors in women with PCOS. Agrawal et al. [28] examined the possible relationship between VAI and cardiometabolic risk factors in

patients with PCOS phenotypes classified according to the Rotterdam criteria and in healthy controls. They showed higher mean VAI values in the PCOS group. Although the patient and control groups were BMI-matched, higher VAI values were attributed to the increased WC and impaired lipid functions in PCOS patients. The authors concluded that VAI showed a strong correlation with cardiometabolic risk in PCOS patients and was, therefore, a useful index. The precise cut-off reference value of VAI for assessing cardiometabolic risk in this patient group should be identified in future studies.

In another study, which evaluated the performance of adiposity indices according to phenotypes of PCOS for the first time, Mario et al. [26] examined different adiposity indices to predict preclinical metabolic alterations and cardiovascular risk in PCOS patients with classic and ovulatory phenotype and healthy controls. They observed that LAP with a cut-off value of ≥34 and VAI with a cut-off value of ≥1.32 were the best markers for classic and ovulatory PCOS, respectively. Also, both indices were more useful than other indices for screening insulin resistance in PCOS. Similarly, in the present study, we examined the relation of VAI and LAP with metabolic, anthropometric, and hormonal parameters. Our study results showed a significant correlation between LAP and HDL-C, TG, and HC and between VAI and WC in the PCOS group.

It has been well established that insulin resistance plays a key role in the formation of reproductive and metabolic alterations in PCOS patients; however, it is often challenging to diagnose [14]. In a study using hyperinsulinemic-euglycemic clamp to assess insulin sensitivity in PCOS patients, Oh et al. [14] reported that VAI with a cut-off value of 1.79 could replace visceral CT scanning as a marker for visceral adiposity defined as a visceral fat area of >100 cm^2 on CT. In another study, VAI was strongly correlated with insulin resistance, indicating an independent correlation with cardiovascular and cerebrovascular events in the general population [12]. Similarly, in our study, we observed a significant correlation between HOMA-IR and VAI in the PCOS group.

On the other hand, there are controversial reports in the literature suggesting a stronger correlation between the insulin resistance, WC and BMI than those with VAI and LAP indices. Borruel et al. [11] compared several surrogate indices of visceral adiposity with USG and determined that WC and BMI showed the strongest correlations with USG measurements of visceral adiposity, while the WHR and VAI showed a weaker, but statistically significant correlation with USG measurements of the thickness of visceral adipose tissue depots. In addition, WC and BMI showed a stronger correlation with insulin resistance than VAI. In another study, Huang et al. [9] assessed insulin resistance in Chinese women with PCOS according to the body fat indices and reported that VAI and LAP were reliable indicators of insulin resistance in the normal weight group, while LAP, BMI, and waist-to-height ratio were more sensitive in overweight/obese group. Similarly, Ramezani et al. [15] compared the validity of available indicators in PCOS patients who participated in a large population-based study and found both VAI and LAP indices to be the best indicators for predicting insulin resistance; however, WC and VAI were the best predictors for predicting metabolic syndrome.

Limitations

Nonetheless, there are some limitations to this study. First, we used the HOMA-IR for screening insulin resistance. The hyperinsulinemic-euglycemic clamp is the gold standard for the evaluation of insulin sensitivity; however, HOMA-IR shows a strong correlation with this method and is helpful in identifying cardiovascular risk [29,30]. Second, we were unable to examine the performance of these indices according to PCOS phenotypes. However, previous studies have demonstrated that cardiovascular risk factors are less frequent in patients with normoandrogenic patients than hyperandrogenic ones [31,32].

Conclusions

Our study results showed a significant correlation between the HOMA-IR and VAI in the PCOS group than the control group. These findings suggest that VAI seems to be a more useful index for predicting insulin resistance in PCOS patients. However, further large-scale studies are needed to draw a definitive conclusion.

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Parental anxiety and depression levels associated with challenge tests in children with suspected drug and food allergies

Şüpheli ilaç ve gıda alerjisi olan çocukların ebeveynlerinde provokasyon testleri ile ilişkili anksiyete ve depresyon düzeyleri

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Abstract

Aim: Oral food challenges (OFCs) and drug provocation tests (DPTs) are currently the gold standards for evaluating food and drug hypersensitivity, respectively; however, use of these tests on children may generate anxiety and depression among their parents. Our aim was to explore depression and anxiety level among parents of children who were undergoing clinical evaluation via a DPT or OFC.

Methods: This cross-sectional study included parents of patients diagnosed with food or drug hypersensitivity reactions in the pediatric allergy clinic between September 2018 and October 2019. Children in Group 1 were subjected to DPT, Group 2 underwent OFC, and Group 3 were healthy controls. Before a child underwent an OFC or DPT, all parents (one parent per child) completed the Hospital Anxiety and Depression Scale, which is a serial assessment for symptoms of depression and anxiety.

Results: The study included parents of 105 children, among which Group 1 (n=50 children) were subjected to DPT, Group 2 (n=35 children) underwent OFC, and Group 3 (n=20 children) were healthy controls. In all three Groups, parents were primarily female (62.9%). Anxiety and depression scores were significantly higher among the parents of children in Groups 1 and 2 *vs.* those of children in Group 3 (P=0.002 and P=0.028, respectively). Anxiety scores were significantly higher among parents of children in Group 2 than those of children in Group 1 (P=0.017).

Conclusions: DPTs and OFCs have a significant impact on the emotional status of parents. Parents of children with suspected or documented food allergy experience particularly elevated levels of anxiety and depression before an OFC.

Keywords: Oral food challenge, Drug provocation test, Parental, Anxiety, Depression

Öz

Amaç: Oral besin ve ilaç provokasyon testleri, günümüzde besin ve ilaç aşırı duyarlılığını değerlendirmek için altın standart testlerdir; ancak bu testlerin çocuklar üzerinde kullanılması ebeveynleri arasında anksiyete ve depresyon oluşturabilir. Amacımız, bir provokasyon testi aracılığıyla klinik değerlendirmeye giren çocukların ebeveynleri arasındaki depresyon ve anksiyete düzeylerini araştırmak idi.

Yöntemler: Bu kesitsel çalışmaya Eylül 2018 ile Ekim 2019 tarihleri arasında çocuk alerji kliniğinde gıda veya ilaç aşırı duyarlılık reaksiyonları tanısı alan hastaların ebeveynleri dahil edilmiştir. Çalışma çocukların ebeveynlerini içeriyordu; grup 1 DPT'ye, grup 2'ye OFC'ye tabi tutulan ve grup 3 sağlıklı kontrollerden oluşmakta idi. Bir çocuğa provokasyon testi uygulanmadan önce tüm ebeveynlerden (çocuk başına bir ebeveyn) depresyon ve anksiyete belirtileri için seri bir değerlendirme olan Hastane Anksiyete ve Depresyon Ölçeğini doldurmaları istenmiştir.

Bulgular: Çalışmaya 105 çocuk alındı, grup 1 (n=50 çocuk) ilaç provokasyonu yapılan, grup 2 (n=35 çocuk) besin provokasyonu yapılan ve grup 3 (n=20 çocuk) sağlıklı kontrollerdi. Her üç grupta da, ebeveynler esas olarak kadındı (%62,9). Grup 1 ve 2'deki çocukların ebeveynlerinde anksiyete ve depresyon puanları, grup 3'teki çocukların ebeveynlerine göre anlamlı olarak daha yüksekti (sırasıyla P=0,002 ve P=0,028). Grup 2'deki çocukların ebeveynlerinin anksiyete puanları, grup 1'deki çocuklarınkinden anlamlı derecede yüksekti (P=0,017).

Sonuçlar: Çocuğa yapılan ilaç ve besin provokasyon testlerinin ebeveynlerinin duygusal durumu üzerinde önemli bir etkisi vardır. Özellikle şüpheli veya belgelenmiş besin alerjisi olan çocukların ebeveynleri, besin provokasyon testi öncesinde, daha yüksek düzeyde anksiyete ve depresyon yaşarlar.

Anahtar kelimeler: Besin provokasyon testi, İlaç provokasyon testi, Ebeveyn, Anksiyete, Depresyon

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Introduction

Food allergy is a developing problem with a growing incidence in industrialized countries. Food allergies are estimated to have an impact on ~10% of children worldwide, which can result in a substantial deterioration in the quality of life of both the child and the family [1]. They can also be a source of significant morbidity and mortality [2].

It is well known that diagnosing children with food allergies can result in significant stress for parents [3]. Results of previous studies indicate that quality of life both the child and the families underwent deterioration if food allergy is suspected or diagnosed [4-7]. Interestingly, impaired quality of life due to food allergy has been shown to be more significant than that resulting from chronic diseases such as rheumatoid arthritis and diabetes mellitus [8]. The factors with direct impact on quality of life include the overall emotional impact as well as ongoing social, and dietary restrictions. When quality of life scores are low, all family members may experience symptoms of anxiety and/or depression [8].

Like food allergy, drug allergy is a widespread problem for practicing allergists. An incorrect diagnosis of drug allergy can result in the use of less effective and/or more expensive therapeutic modalities [9]. Drug provocation tests (DPTs) and oral food challenges (OFCs) are currently gold standards for diagnosis of suspected allergies; these tests can also be used to find safe alternatives for allergenic substances [10]. Previous studies showed that DPTs may cause a significant anxiety in adults with drug hypersensitivity, who underwent these tests [11]. Parents are routinely informed about the risks of these tests, which may result in increased anxiety.

Although anxiety associated with DPTs and OFCs has been reported [12-14], to the best of our knowledge, no studies that provide a quantitative assessment of parental anxiety and depression associated with these evaluations have yet been performed.

In the present study**,** our goal was to evaluate parental anxiety and depression symptoms related to the performance of these provocation tests in children with suspected food or drug allergies.

Materials and methods

Study design and participants

This study included parents of children who were diagnosed with food or drug hypersensitivity in our pediatric allergy clinic between September 2018 and October 2019. A total of 105 children and their parents (one parent per child) were enrolled in this study. Power analysis was performed before the initiation of the study to determine the minimum number of subjects that should be included in the patient and control groups. In this study, the required minimum sample numbers were determined as 60 patients and 15 controls (using Cohen criteria), alpha=0.05 and power=0.80. The number of subjects who were with both parents were 4 in Group 1, 3 in Group 2, none in the control Group. Five of them were mothers. Control Group was defined as patients who visited the general pediatrics polyclinics with any reason and agreed to be participants in the study. Demographic data and a detailed history of drug or food allergy (the type of reaction, duration and culprit drug/food and related phenomena...) were recorded for each child.

Exclusion criteria

The children who had a history of severe life-threating drug reactions (toxic epidermal necrolysis, Stevens-Johnson syndrome, drug rash with eosinophilia and/or acute generalized exanthematous pustulosis) were excluded from the study, as were parents with a past or current psychiatric history, including diagnoses of depression or anxiety. Also excluded were children who had an acute reaction within the previous 4 to 6 weeks, who used antihistamines and steroids on a regular basis, and who were diagnosed with another disorder, including urticaria, uncontrolled asthma, cardiac dysfunction, renal-hepatic disease or current upper airway infection.

Drug provocation tests

Provocations with the suspected drugs were performed according to the European Network for Drug Allergy Guidelines [15]. Reactions were classified as immediate if they were detected within the first hour of drug administration and non-immediate (delayed) type when responses were detected >1 hour after administration [16]. The children who experienced both immediate (urticaria, angioedema and anaphylaxis) as well as non-immediate reactions, (maculopapular exanthema) were included in the study. If the suspected reaction was compatible with drug hypersensitivity, skin provocation tests (prick and intradermal) with the suspected drug were performed according to guidelines. For diagnosis, skin tests were performed if a skin testing material was available. Skin testing was not performed in children with mild non-immediate skin reactions. Drugs that elicited reactions in the Group 1 patient cohort included antibiotics, paracetamol, ibuprofen, and macrolides.

Oral food challenges

OFCs were performed to confirm the diagnosis of a suspected food allergy or to determine whether tolerance has developed in children who have already been diagnosed. The OFC begins with a minimal challenge followed by incremental increases in dose provided in 20-minute intervals until the total challenge dose is reached and/or the child experiences an adverse reaction. Parents of children who experienced an immediate (urticaria, angioedema and/or anaphylaxis) or a nonimmediate reaction (maculopapular exanthem) were included in Group 2. OFCs were performed to detect responses to both immunoglobulin E (IgE) and non-IgE mediated food allergy [17]. Foods that elicited reactions among the children in Group 2 included cow's milk, egg, and banana.

Hospital Anxiety and Depression Scale

Parents (one parent per child) were evaluated by the Hospital Anxiety and Depression Scale (HADS), which is a series of standardized screening tests designed to identify symptoms of depression and anxiety. The HADS includes 2 subscales each with 7 questions that independently assess both anxiety and depression. For each question, parent participants were invited to indicate the best option related to their emotional state on a scale from 0 to 3; the participants were permitted only one response for each question. The cutoff points for the Turkish population include Hospital Anxiety and Depression Scale-Anxiety (HADS-A) scores of 10/11 for anxiety and Hospital

Anxiety and Depression Scale-Depression (HADS-D) scores of 7/8 for depression [18].

Statistical analysis

Statistical analyses were performed using SPSS statistical software version 21 (SPSS Inc, Chicago, Illinois). Continuous data are presented as mean ± standard deviation. The Shapiro–Wilks test, histogram graphics, skewness and kurtosis values were examined to determine normal distribution. Mann–Whitney U test was used to compare two groups for non-normally distributed variables and the Kruskal–Wallis H test was used to compare more than two Groups. Categorical data from patient and control groups were compared using the Chi-Square test. Pearson correlation test was used to determine correlation in normally distributed groups. If not normally distributed, Spearman correlation test was used. A value of $P \leq 0.05$ was considered statistically significant.

Results

Study groups

The study groups included the parents of patients in Group 1 (DPT, n=50 children), parents of patients in Group 2 (OFC, n=35 children) and parents of children in Group 3 (healthy controls, n=20 children). There were no significant differences with respect to age of the child, age of the parent, gender, educational statuses, or occupation of the parents associated with each of the three groups ($P>0.05$). Demographic characteristic of patients in Groups 1 and 2 as well as the controls (Group 3) are included in Table 1. Parents of the children were primarily female in all three Groups (62.9%).

Evaluation of the children for drug allergies

The mean age (SD) was 5 (3.2) years for children and 35 (5.2) years for parents. Drug provocation testing was negative in 47 of the 50 children (94%) in Group 1. Of these, 20 children (40%) underwent DPT, 27 (54%) underwent both skin tests and DPTs, and 3 (6%) underwent skin tests alone. The most common etiologic agents were β-lactam antibiotics (62%) followed by paracetamol (12%) and ibuprofen (12%). The clinical presentations included cutaneous reactions in 38 (76%), and anaphylaxis in 12 (24%) of the children in Group 1. Responses including urticaria with or without angioedema were identified in 28 (56%) as the most common symptoms and immediate reactions were higher among those reporting hypersensitivities to antibiotics than to any other drugs ($P=0.001$).

Evaluation of the children for food allergies

The mean age (SD) was 5 (2.5) years for children in Group 2 and 34 (4.9) years for their parents. Cow's milk (74.2%) was the most common cause of hypersensitivity reactions followed by hen's egg (22.8%). Cutaneous symptoms were the most common reactions reported by those in Group 2 before OFC (n=27, or 77.1%). Anaphylaxis was observed in 8 children (22.8%). Time between the reaction and formal evaluation for allergy was 4(7) months. With respect to this parameter, there were no significant differences between the findings of Group 1 and Group 2 ($P>0.05$).

Positive challenge tests

Forty-seven (94%) children had negative responses to tests for drug allergy; 3 children (6%) responded positively. Similarly, thirty-four (97%) children had negative responses to food challenge; only one child (3%) had a positive result. Antihistamine therapy was used in patients who developed an allergic reaction to a food or drug; epinephrine was not required. Given the very few positive results to challenge tests, we eliminated this group from statistical analysis. A DPT was performed in 54% of the children in Group 1 for diagnostic purposes; 46% of the tests were performed to identify suitable alternative agents. The OFC was performed in 77.5% of the children in Group 2 for diagnostic purposes and in 22% to identify alternative agents. The DPTs performed to identify alternative agents typically used cephalosporins (18%). Most OFCs for diagnostic purposes were performed using cow's milk (54.2%).

Table 1: Demographic characteristics of patients and the control group

	Group 1 (DPT) n(%)	Group 2 (OFC) n(%)	Group 3 (Control) n(%)	*P*-value
Children				
Female	25(50)	16(45.7)	11(55)	0.799[b]
Male	25(50)	19(54.3)	9(45)	
Age (years)				
Mean (SD)	5(3.2)	5(2.5)	6(4)	0.66[a]
Parents				
Mother	30(60)	23(65.7)	13(65)	
Father	20(40)	12(34.3)	7(35)	0.845[b]
Age (years)				
Mean (SD)	35(5.2)	34(4.9)	35(4.1)	0.631[a]
Occupation				
Homemaker	25(50)	18(51.5)	11(55)	0.999[b]
Clerk	12(24)	8(22.9)	5(25)	
Office worker	10(10)	7(20.0)	3(15)	
Others	3(6)	2(8.6)	1(5)	
Education level				0.959[b]
Elementary education	10(20)	7(20)	5(25)	
High school	17(34)	14(40)	7(35)	
College	23(46)	14(40)	8(40)	
Total	50(100)	35(100)	20(100)	

[a] Kruskal Wallis H Test, [b] Pearson (Exact) Chi-Square Test

Assessment of parental depression-anxiety levels

The mean scores of parents who completed the Hospital Anxiety and Depression Scale are summarized in Table 2. Both HAD-A and HAD-D mean scores were significantly higher among the parents of children in Groups 1 and 2 than among those of children in the control Group ($P=0.002$ and; $P=0.028$, respectively). Also HAD-A scores were significantly higher in Group 2 than Group 1 ($P=0.017$). Mothers' anxiety level was higher than fathers' ($P=0.03$). HAD-A and HAD-D scores were significantly higher in the parents of children who had a history of anaphylaxis in both Groups 1 and Group 2 ($P=0.01$). No statistical difference was found between the groups in the tests performed to find diagnostic or alternative agents in terms of parents' HAD-A and HAD-D scores ($P>0.05$).

We compared mothers' (n=53) and fathers' (n=32) HAD-A and HAD-D scores. There were no significant differences between mothers' and fathers' HAD-A and HAD-D scores ($P=0.433$ and $P=0.777$ respectively) (Table 3). It was found that HAD-A and HAD-D scores were correlated with each other ($P<0.01$ and r:0.606) but not correlated with parental age, time to allergy work up and child age (Table 4).

Table 2. The mean scores of parents in the Hospital Anxiety and Depression Scale

	Parents of Group 1 (DPT) (n=50)	Parents of Group 2 (OFC) (n=35)	Parents of control Group (n=20)	*P* df	Comparison pattern
HADS-Anxiety Mean(SD)	5.82(4.14)	8.20(3.37)	4.83(2.85)	0.002[c] 2	0.002[a] 0.017[b]
HADS-Depression Mean(SD)	5.00(3.80)	5.85(2.83)	3.63(3.01)	0.028[c] 2	0.027[a]

HADS: Hospital Anxiety and Depression Scale *, [a] Comparison pattern indicates the standardized mean difference between Group 2 and Group 3, [b] Comparison pattern indicates the standardized mean difference between Group 1 and Group 2, [c] Kruskal- Wallis

Table 3: Comparison of fathers and mothers' HAD scores

	Fathers (n=32)	Mothers (n=53)	Total (n=85)	*P*-value
HADS-Anxiety Mean(SD)	5.00(0.67)	5.66(0.50)	5.41(3.68)	0.433[a]
HADS-Depression Mean(SD)	4.41(0.67)	4.45(0.47)	4.44(3.54)	0.777[a]

[a] Mann-Whitney U test

Table 4: Correlation test of variables

	Child age (r)	Parental age (r)	Time between reaction and allergy work- up (r)	HADS-A	HADS-D
HADS-A	0.162	0.160	-0.119	1	0.606[a]
HADS-D	0.185	0.065	0.023	0.606[a]	1

[a] Spearman's rho test

Discussion

The results of the current study indicate that the parents of children with suspected food allergy have higher anxiety and depression scores before OFC. In our study, the anxiety and depression levels of parents of the children with suspected drug allergy were higher than healthy controls' parents but lower than those with suspected or documented food allergy. The reasons may include the presence of fewer opportunities to encounter agents that elicit drug-related allergic reactions, and the fact that they are more easily managed than allergies to food substances. This information may decrease anxiety and depression levels in parents of children with suspected drug allergy. There might be many reasons to explain the differences regarding children's individual characteristics, family characteristics, previous medical history, and life events. One study compared the anxiety and depression levels with HADS of the mothers of children with suspected food allergy on the first clinical visit and second visit after 4–6 weeks [19]. The study reported no higher anxiety and depression scores; however, the children were not evaluated by OFC and the parents were evaluated during two visits only. The studies related to anxiety of parents of the children with suspected food allergy have been compared before and after OFC. The parents' anxiety level decreased after OFC [12-14].

In a randomized controlled adult study, it was aimed to define placebo reactions during DPT, the subjects' anxiety and depression symptoms were evaluated by HADS before DPT. It was shown that HADS positivity before the test was correlated to placebo reactions. It was recommended that evaluating psychiatric symptoms before DPT was important to define placebo reactions [20].

Anxiety and depression scale scores can differ between parents of an individual child [21,22]. King et al. [22] found that mothers of children with food allergies express more anxiety and stress than the fathers. Another study reported that the mothers of children with food allergy reported higher levels of impairment with respect to quality of life than did fathers, regardless of the type or severity of the allergy or the existence of comorbidities [14]. Knibb et al [23]. reported that the mothers experienced comparatively prominent levels of anxiety prior to an OFC. Not the only suspicion of food allergy, but the actual performance of the OFC may increase parental anxiety levels. However, quality of life of the families was positively affected by having access to clear-cut results [23].

Most of the parents involved in our study were mothers (62.9%); overall, their anxiety level was higher than that of the fathers. The findings were consistent with the literature [12,22,23]. Beken et al [12]. reported that the mothers of children with suspected food allergy had higher anxiety before OFC than the mothers of healthy control children. Parents' reactions to any condition impact children's feelings and behavior, and parental anxiety and depression level may impact compliance to the tests. Mothers typically play a larger role in caring for children, including making decisions on medications, preparing food, reading labels, and related activities, all of which may cause their anxiety levels to increase [22]. Thus, mothers of children who were to undergo challenge tests might be more anxious and depressive than the fathers. In our study, there were no significant differences between anxiety and depression scores of fathers and mothers. However, due to the difference in the number of mothers visiting the clinic, gender differences could not be determined.

To the best our knowledge, this is the first study which evaluates parents' anxiety and depression level before DPT that are performed to children with suspected drug allergy.

Limitations

The first limitation of this study is the fact that we did not reevaluate and compare anxiety and depression scores of the parents sometime after the results of these provocation tests. The second limitation is the lack of comparison of parents with same gender. It must be considered that there are differences between with mothers' and fathers' anxiety and depression level. The third limitation is that we did not evaluate parents' physical and mental health problems, children's' mental health and other medical problems, family relationship quality, family functioning and other familial or individual factors that may affect depression and anxiety levels. Further larger and well-controlled observational studies are required in the future to consolidate the association between parental anxiety-depression and challenges.

Conclusion

We determined that the anxiety and depression scores of parents whose children require DPT or OFC testing are uniformly high regardless of the test type. Parents' anxiety and depression level were higher when parents were informed about the risks of these tests. However, informing parents that DPT will reveal alternative agents decreases their anxiety and depression levels. It may be useful to limit parents' anxiety before any type of allergy-provocation test, as that will increase compliance with both the test and the treatments offered.

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Evaluation of cancer-related deaths in Turkey between 2009-2018: An epidemiological study

2009-2018 yılları arasında Türkiye'de kansere bağlı ölümlerin değerlendirilmesi: Bir epidemiyolojik çalışma

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Ethics Committee Approval: By the design of the study, Hitit University Faculty of Medicine Clinical Research Ethics Board approval was not required. The Turkish Statistical Institute permits the use of data on its official website for research purposes.
Etik Kurul Onayı: Hitit Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu başkanlığı tarafından çalışmanın tasarımı nedeniyle onayı gerekmedi. Türkiye İstatistik Kurumu, resmi web sitesindeki verilerin araştırma amacıyla kullanılmasına izin vermektedir.

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Abstract

Aim: Determination of cancer incidence and mortality data for all countries is essential for cancer control. These data can affect public health and clinical service planning. In this study, we aimed to examine the variability of cancer deaths in Turkey in terms of age groups, gender, geographic region, and years according to the cancer types between 2009-2018.

Methods: In this epidemiological study, cancer-related mortality statistics data presented at the website of Turkey Statistical Institute (TSI) were used. Cancer-related deaths between 2009-2018 were evaluated in terms of ratio to total deaths, age groups, cancer types, geographical regions, and gender. Data were presented as percentages.

Results: Cancer-related deaths were observed to increase between 2009-2018. The highest cancer-related mortality rate was seen in the Marmara Region, while it was lowest in the Southeastern Anatolia Region. Cancer-related death rate was higher in males than females, and it was highest in the 65-74 years age range. The most common cause of death in males is lung cancer, and in females, breast cancer.

Conclusion: Cancer is responsible for 1/6 of all deaths in the world. Similarly, cancer-related deaths are responsible for approximately 1/5 of all deaths in our country. The risk of cancer in >60 years age group is higher in males than in females. In our country, all kinds of cancers, except female cancers, cause more deaths in males than females.

Keywords: Cancer, Mortality, Pathology, Death

Öz

Amaç: Tüm ülkeler için kanser insidansı ve mortalite verilerinin belirlenmesi; kanserin kontrolü için esastır. Bu veriler halk sağlığına ve klinik hizmet planlamasına etki edebilmektedir. Bu çalışmada 2009-2018 yılları arasında Türkiye'de kansere bağlı ölümlerin yıllara göre değişimini, yaş gruplarına, cinsiyete ve coğrafi bölgelere göre farklılıklarını, kanser türlerine göre değişkenlikleri incelemeyi amaçladık.

Yöntemler: Çalışmada Türkiye İstatistik Kurumu (TÜİK) web sitesinde sunulan kanser ilişkili ölüm istatistik verileri kullanıldı. 2009-2018 yılları arasında kansere bağlı ölümlerin coğrafi bölgelere göre toplam ölümlere oranı değerlendirildi. 2009-2018 yılları arasında yaş gruplarına ve cinsiyete göre kansere bağlı ölümler değerlendirildi. 2009-2018 yılları arasında kanser türlerine ve cinsiyete göre kansere bağlı ölümler değerlendirildi. Veriler yüzde olarak sunuldu. Çalışma epidemiyolojik olarak tasarlanmıştır.

Bulgular: Kansere bağlı ölümlerin 2009-2018 yılları arasında arttığı görülmüştür. Toplam ölümlere kıyasla kansere bağlı ölüm oranının en yüksek olduğu bölge Marmara Bölgesi iken en düşük olduğu bölge Güneydoğu Anadolu Bölgesidir. Tüm yaş gruplarında; erkekler, kadınlara göre kanser nedeniyle daha fazla ölmektedir. Kansere bağlı ölümler en yüksek seviyesine 65-74 yaş aralığında ulaşmaktadır. Erkeklerde ölüme en çok neden kanser türü akciğer, kadınlarda ise meme kanseridir.

Sonuç: Kanser dünyada meydana gelen tüm ölümlerin 1/6'sından sorumludur. Benzer şekilde ülkemizde kansere bağlı ölümler, tüm ölümlerin yaklaşık 1/5'inden sorumludur. 60 yaşın üzerinde erkeklerde kanser riski kadınlara oranla daha fazladır. Ülkemizde kadın kanserleri dışında her türlü kanserin erkeklerde daha fazla ölüme neden olduğu tespit edilmiştir.

Anahtar kelimeler: Kanser, Mortalite, Patoloji, Ölüm

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Introduction

Investigation of rates, numbers, and causes of death is important for the development of health systems, preventive medicine, understanding the effects of diseases on people and the effective use of treatment resources [1-3]. Cancer is a group of diseases characterized by uncontrolled proliferation and spread of abnormal cells. If the spread cannot be controlled, it can result in death [4]. Cancer is the leading cause of death for all levels of income and socioeconomic groups worldwide [5]. Determination of cancer incidence and mortality data is essential for the control of cancer in all countries. These data may affect public health and clinical service planning [6]. Ratings and measurements made according to age groups are not affected by population size and structure. Changes in incidence rates are the main indicator of changes in prevalence [7]. In 2018, it was estimated that there were 18 million cancer cases worldwide, and 9.8 million people died of cancer [6,8]. Age, alcohol, familial predisposition, cancer-causing substances, chronic inflammation, diet, hormones, immunosuppression, infectious agents, obesity, radiation, sunlight, and tobacco are the most frequently researched cancer risk factors. Although some of these risk factors can be avoided, some are unavoidable [9]. Today, there are changes in behavior and habits of society due to industrialization and rapid urbanization, which shows that cancer risk factors may change over time [10]. With the increase in urbanization and development, cancer risk factors, such as the adoption of a sedentary lifestyle, increase in the elderly population, decrease in fertility, diet, and environmental pollution, change. However, with the development of healthcare and imaging methods, early diagnosis and effective treatment have become more possible [11]. Cancer risk factors and treatment options are affected by the regions and socioeconomic status [12,13]. By evaluating cancer mortality and incidence from a socioeconomic and regional perspective, inequalities in the healthcare system can be recognized, and beneficial health arrangements can be made [14,15]. In this study, we aimed to investigate the changes by years, age group, gender, geographic region according to the types of cancer seen in Turkey between 2009-2018.

Materials and methods

In this epidemiological study, we used the death statistics data shared by Turkey Statistical Institute (TSI) on its website [16]. TSI allows the use of their data for research. The causes of death, mortality rates, and population data between 2009 and 2018 were collected, analyzed, classified in terms of age, gender, geographical region, and disease groups, and evaluated with descriptive statistics using the Statistical Package for Social Sciences (SPSS) 22.0 software to be presented in percentage (%).

Results

Cancer-related deaths are more frequent in males than in females. It is observed that deaths due to cancer regularly increased among both genders between 2009 and 2018. Compared to 2009, cancer-related deaths had increased by 28.6% in total, by 27.5% among males, and 30.5% among females by 2018. Deaths due to cancer by gender between 2009-2018 are shown in the figure 1.

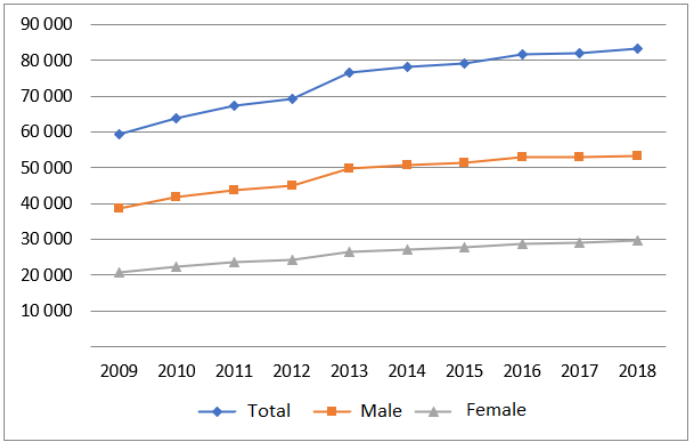

Figure 1: Cancer-related deaths between 2009 and 2018

The highest cancer-related mortality rate was seen in the Marmara Region, while it was lowest in the Southeastern Anatolia Region. In all regions but the Southeastern Anatolia, cancer-related deaths are responsible for 1/5 of all deaths (Table 1).

Table 1: The ratio of cancer-related deaths to total deaths between 2009-2018 by geographical regions

Geographical Regions	Total Death	Cancer-related deaths	%
Marmara	1070733	249186	23.3
Aegean	574355	116268	20.2
Mediterranean	412813	76908	18.6
Black Sea	470107	92003	19.6
Eastern Anatolia	215586	42894	19.9
Southeastern Anatolia	214454	31864	14.9
Central Anatolia	597801	124559	20.8

The cancer-related mortality rate is higher in males than females across all age groups. It reaches its highest level between the ages of 65-74 years. Cancer-related mortality rates are close to each other among males and females from birth until the age of 44 years; however, after 45 years of age, male predominance is observed (Table 2).

Table 2: Cancer-related deaths by age groups and gender between 2009 and 2018

Age groups	Total	%	Male	%	Female	%
0 – 14	6235	0.8	3149	0.7	3086	1.2
15 – 24	6191	0.9	3747	0.8	2444	0.9
25 – 34	10824	1.5	5843	1.2	4981	1.9
35 – 44	30597	4.1	15184	3.2	15413	5.9
45 – 54	89017	12.0	55643	11.5	33374	12.9
55 – 64	174697	23.6	123136	25.7	51561	19.9
65 – 74	202035	27.3	139350	29.1	62685	24.1
75 – 84	171138	23.2	108309	22.6	62829	24.2
85+	48435	6.6	25168	5.2	23267	9.0
Total	739169	100	479529	100	259640	100

Deaths due to all cancer types, except breast and gynecological cancers, are more frequent in males. The most common cancer types are lung, bronchus, larynx, and trachea cancer among both genders. Breast cancer was the most common cause of cancer-related mortality in females. Other common cancers included the lung, larynx, and trachea cancers (Table 3).

Table 3: Cancer-related deaths by cancer types and gender between 2009 and 2018

Cancer types	Cancer related deaths	%	Male	%	Female	%
Lip, Oral cavity, Pharynx	7965	1.3	5293	68.8	2672	31.2
Esophagus	7746	1.2	4544	58.7	3202	41.3
Stomach	62488	10.0	40970	65.6	21518	34.4
Column	51316	8.2	29311	57.1	22005	42.9
Rectum and anus	12218	2.0	7276	59.6	4942	40.4
Liver and bile ducts	27608	4.4	17775	64.4	9833	35.6
Pancreas	41351	6.6	24124	58.3	17227	41.7
Lung, larynx, trachea	225726	36.1	192410	85.2	33316	14.8
Skin	4457	0.7	2589	58.1	1868	41.9
Breast	35627	5.7	758	2.1	34869	97.9
Cervix	4703	0.8	0	0	4703	100
Other areas of the uterus	8241	1.3	0	0	8241	100
Over	13599	2.2	0	0	13599	100
Prostate	33042	5.3	33042	100	0	0
Kidney	9785	1.6	6661	68.1	3124	31.9
Bladder	19240	3.1	15993	83.1	3247	16.9
Lymphoid and hematopoietic	59738	9.6	34898	59.4	24839	40.6
Total	624850	100	415644	66.6	209206	33.4

Discussion

Old age is the most important risk factor for many types of cancer [17]. It is known that the proportion of elderly population has increased gradually in our country since 1935 [18]. Life expectancy in Turkey was 50 years in 1970, and it has risen to 78 years according to 2018 data. It is predicted that along with the ratio of elderly population, cancer cases will also increase. The number of cancer patients is growing due to the escalation of risk factors in underdeveloped and developing countries and due to the advances in diagnosis and treatment methods in developed countries. The increase in the number of cancer patients and the decrease in infection-related deaths because of the use of more effective antibiotics compared to the past also lead to a higher cancer-related mortality rate. In our country, cancer-related deaths increased by 28.6% in 2018 compared to 2009, and we think that this is due to the increase in the elderly population.

Cancers are the second most common causes of death in the world after cardiovascular diseases. It is also reported that cancer is responsible for 1/6 of all deaths worldwide [19]. Similarly, in our study, deaths due to cancer constituted approximately 1/5 of all deaths in all regions, except Southeastern Anatolia (Table 1). According to a study conducted by the National Cancer Institute in 2015, 25.4% of cancer cases were detected between the ages of 65-74 years (16). In our study, 27.3% of cancer-related deaths were seen in the 65-74 year-age group (Table 2). In Turkey, another study conducted by the Ministry of Health reported that breast cancer in women and lung cancer in men were increasing [20]. Currently, lung cancer is the most lethal type of cancer worldwide [19]. The most prominent reason is that tobacco use is more common among males. In European countries, the prevalence of lung cancer in females has approached that of males in the recent years [7]. A study conducted at a center in the eastern Anatolia region of Turkey examining lung biopsy reports showed that lung cancer has increased within the last decade [21].

In our study, the most common mortality-causing types were respiratory system malignancies among males and breast cancer among females (Table 3). Turkey's young population resides in Southeastern Anatolia the most and in Black Sea and Marmara regions the least [22]. Cancer risk increases with age [9]. In our study, in accordance with the above findings, we determined that cancer-related mortality rate was lower in the Southeastern Anatolia Region, where the proportion of the young population was higher. Expectedly, it was higher in the Marmara Region, where the rate of the elderly population was higher (Table 1). We think that the increase in some cancer risk factors such as diet, decrease in physical activity, obesity, and decrease in fertility rate may also contribute to the increase in cancer mortality rate in Marmara region. In general, it is known that the risk of cancer and cancer-related mortality are higher in males compared to that in females over the age of 60 years [22]. This may be caused by the fact that males consume more alcohol, cigarettes, are more exposed to the sun, and prone to various risk factors such as obesity [23]. Our study shows that all cancer types, except gynecological cancers, cause more deaths in men (Table 3). Classification according to geographical regions is especially important in terms of determining different risk factors, evaluating access to diagnosis and treatment, and healthcare planning. Although the most common type of cancer varies from country to country, different types of cancer can be predominant in different regions of the same country. While a decrease in lung cancer incidence is expected due to the tobacco ban in developed countries, it is still increasing in developing countries. Similarly, in terms of female cancers, while breast, ovarian and endometrial cancers increase with the decrease in fertility in developed countries, cervical cancer associated with HPV and multiparity is more common in developing countries [24-27]. In addition, liver cancer due to hepatitis B and C infections is more common because of inadequate hygiene in underdeveloped and developing countries, and rate of gastric cancer is relatively high because of contamination with *Helicobacter pylori* [28,29].

Around 85% of cancer risk factors are changeable and preventable. For this reason, risk factors, and their distribution according to regions, gender, and socioeconomic status can be revealed through statistics and studies. Thus, the necessary study for the target community will be performed more easily. In Turkey, 'Early Cancer Detection Screening and Training Centers' (KETEM) perform mammography for breast cancer. Family health centers perform fecal occult blood tests for colon cancer screening to those over the age of 50 years. It is also possible to detect cancer at an early stage and treat it effectively by recommending endoscopy and colonoscopy screening for patients with a family history of colon and stomach cancer. In 2008, the smoking ban in closed areas took effect in Turkey for the fight against cancer, reducing exposure to tobacco smoke. The government's publications about the harms of smoking and warnings about the relationship between tobacco and cancer on cigarette packages are positive developments in terms of fighting against cancer. Including the hepatitis A and B vaccines in the routine vaccination program will also likely reduce the risk of liver cancer in Turkey. Similarly, in some countries where HPV infection is prevalent, the routine use of the HPV vaccine is a preventive health plan for cervical cancer. Obesity is also an important problem associated with cancer in our era. It is predicted to increase the risk of many cancers such as those of the esophagus, colon, gallbladder, kidney, and breast. Obesity is a preventable disorder because it is associated with excessive calorie intake and reduced physical activity. By encouraging healthy and natural nutrition, raising awareness about obesity by

health institutions can reduce the incidence of cancer and contribute to the prevention of various diseases, such as cardiovascular diseases and diabetes [30]. We believe that inability to evaluate mortality rates of cancer types due to the lack of continuous reporting of annual new cancer case statistics is the primary limitation of our study. The distribution and mapping of cancer types according to geographical regions will help determine focus areas for the healthcare planning. In that regard, since mesothelioma is more frequent in Nevsehir, Turkey, the region's soil was examined, and it was found that soil comprises an excess amount of asbestos mineral. Therefore, some villages were relocated. Regarding geography, it is thought that some types of cancer, such as leukemia and thyroid cancer have increased in the Black Sea region after the Chernobyl disaster in 1986. In terms of cancer, differences in geographical regions may also be related to diet. In the eastern regions of Turkey, esophageal and stomach cancers are more common, and colorectal cancers predominate in the western regions. This is likely related to eating habits. It is known that pickled and smoked foods cause stomach cancer. In addition, excessively hot food consumption is a predisposing factor for esophageal cancer. A decrease in the incidence of stomach cancer is predicted due to easier access to fresh vegetables and better food preservation methods. Smoking also varies over time, according to the regions. While smoking rates decrease in developed countries, it continues to increase in underdeveloped and developing ones [31]. As a result, these countries, which are already challenged economically, will be in a difficult position against the global economic forces because of the cancer burden due to smoking [5]. Grouping new cancer cases according to their age of occurrence, reporting the time from the detection of the disease to death, and similar statistics will be important for decreasing cancer-related mortality and morbidity.

Limitations

As a result of incomplete reporting of data on cancer statistics, institutional errors can be considered as the limitation of our study.

Conclusions

We think that our study is notable since it covers a 10-year period and reveals differences according to age groups, gender, cancer types, and geographical regions. Cancer statistics are important in terms of developing health policies, bringing preventive healthcare to the fore, increasing cancer screening rates in risky individuals, and conducting studies for early cancer diagnosis. Early diagnosis of cancer will reduce the treatment costs of countries.

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Impact of tumor necrosis factor alpha antagonist treatment on antibody titer of hepatitis B surface antigen

Tümör nekroz faktörü alfa antagonisti tedavisinin hepatit B yüzey antijeninin antikor düzeyine etkisi

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Abstract

Aim: Tumor necrosis factor alpha antagonists (anti-TNF-α) have recently been used successfully in various diseases. On the other hand, due to their potential immunogenic effects, they cause hepatitis B virus (HBV) reactivation. The objective of this study is to examine the change in the levels of hepatitis B surface antigen (HBsAg) and antibody (anti-HBs) in patients with negative HBsAg who were administered different anti-TNF-α drugs as well as the factors that influence this change.

Methods: This research was designed as a retrospective cohort study. Patients with autoimmune diseases who were followed up at General Internal Medicine outpatient clinics between 2012 and 2019, screened for hepatitis B virus (HBV) infection prior to treatment, checked for serological markers (HBsAg, anti-HBs, hepatitis B core antigen antibody (anti-HBc)), and treated with anti-TNF for at least a year were included. The inclusion criteria were as follows: Patients with negative HBsAg and whose liver function tests were within normal limits, and the exclusion criteria included patients with positive HBsAg and whose liver function tests were above the normal upper limit.

Results: A total of 221 adult patients who were treated with anti-TNF-α were included in the study. The pretreatment anti-HBs levels of the patients were significantly higher than the posttreatment levels (P<0.001). Of the 211 patients with positive pretreatment anti-HBs levels, 17 patients had posttreatment anti-HBs levels below 10 IU/L. The anti-HBs levels of five patients with positive anti-HBc dropped below 10 IU/L.

Conclusions: The anti-HBs levels of the patients who were administered anti-TNF-α agent decreased significantly, whereas there was no reactivation of HBV or de novo HBV infection in HBsAg-negative patients. It was observed in a small group of patients (8.0%) that the levels of anti-HBs decreased to a risky level.

Keywords: Tumor necrosis factor antagonist, Hepatitis B surface antigen antibody, Autoimmune diseases

Öz

Amaç: Tümör nekroz faktör alfa antagonisleri (anti-TNF-α) bir çok hastalıkta başarıyla kullanılmaktadır. Öte yandan, potansiyel immünojenik etkileri nedeniyle, hepatit B virüsü (HBV) yeniden aktivasyonuna neden olurlar. Bu çalışmanın amacı, farklı anti-TNF- α ilaçları ile uygulanan hepatit B yüzey antijeni (HBsAg) negatif hastalarda, HBsAg antikoru (anti-HBs) düzeylerindeki değişimi ve etkileyen faktörleri incelemektir.

Yöntemler: Bu araştırma, retrospektif kohort çalışma olarak tasarlanmıştır. Otoimmün hastalıkları nedeniyle 2012-2019 yılları arasında Genel Dahiliye polikliniğine başvuran ve anti-TNF-α tedavi ile tedavi edilen ve en az 1 yıl bu tedaviyi alan ve Hepatit B virusu için tarama amaçlı serolojik belirteçleri (HBsAg, anti-HBs, hepatit B kor antijen antikoru (anti-HBc)) değerlendirilen hastalar çalışmaya alındı. Dahil edilme kriterleri; HBsAg negatif olan ve karaciğer fonksiyon testleri normal sınırlar içinde olan hastalar ve dışlama kriterleri ise; HBsAg pozitif ve karaciğer fonksiyon testleri yüksek olan hastalar.

Bulgular: Anti-TNF-α ile tedavi edilen toplam 221 erişkin hasta çalışmaya dahil edildi. Hastaların tedavi öncesi anti-HBs düzeyleri, tedavi sonrası düzeyler ile karşılaştırıldığında, anlamlı derecede yüksekti (P<0,001). Tedavi öncesi anti-HBs düzeyleri pozitif (titre ve aşılı veya virusla karşılaşmış) 211 hastanın 17'sinde tedavi sonrası anti-HBs düzeyleri 10 IU / L'nin altındaydı. Anti-HBc pozitif beş hastanın anti-HBs seviyeleri 10 IU / L'nin altına düştü.

Sonuç: Anti-TNF-α tedavi uygulanan hastalarda anti-HBs düzeyleri önemli ölçüde azalırken, HBsAg-negatif hastalarda HBV veya de novo HBV enfeksiyonu için reaktivasyon yoktu. Küçük bir grup hastada (%8,0) anti-HBs düzeylerinin riskli bir seviyeye düştüğü gözlendi.

Anahtar kelimeler: Tümör nekroz faktör antagonisti, Hepatit B yüzey antijeni antikoru, Otoimmun hastalık

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Introduction

Tumor necrosis factor alpha antagonists (anti-TNF-α) have recently been used successfully in various areas, primarily in autoimmune-based dermatological, gastroenterological, and rheumatologic diseases [1,2]. Besides, anti-TNF-α drugs increase the risks of infection, latent tuberculosis, and hepatitis B virus (HBV) reactivation due to their potential immunogenic side effects [3]. Due to such risks, patients who are administered anti-TNF-α are advised to get screened for tuberculosis and HBV [4]. Data on HBV reactivation under anti-TNF-α treatment are quite limited and mostly include retrospective studies and case reports [5-7].

The serologic markers screened for HBV infection in patients receiving anti-TNF-α treatment include hepatitis B surface antigen (HBsAg), hepatitis B surface antigen antibody (anti-HBs), and hepatitis B core antigen antibody (anti-HBc) [4,8]. Theoretically, TNF-α assists the elimination of HBV in hepatocytes and synergistically prevents HBV replication through interferons [9]. In patients receiving anti-TNF treatment, the risk of HBV infection may increase, the existing HBV replication may escalate, and clinical hepatitis may occur [10,11]. Studies in the literature focus on the reactivation risk in patients with chronic HBV infection who receive anti-TNF-α treatment [12,13]. The infection risk in HBsAg-positive patients was defined as 12%–39% when anti-TNF-α agents such as infliximab, adalimumab, and certolizumab were used [14]. It is reported that anti-TNF-α agents with lower potency such as etanercept pose lower risk of reactivation (1%–5%) in HBsAg-positive patients [6]. In addition, this risk was lower in HBsAg-negative and anti-HBc-IgG-positive patients [15].

There is limited information about the relationship between anti-HBs levels and anti-TNF-α treatment. Tamori et al. [16] reported that anti-HBS levels of the patients who were administered anti-TNF-α decreased significantly. Similarly, Vassilopoulos et al. [12] reported that the anti-HBS levels in 19 patients inoculated with HBV decreased significantly following anti-TNF-α treatment. Preclinical studies showed that TNF-α is essential in host defense against external pathogens [10,17]. Additionally, TNF-α is thought to play a crucial role in anti-HBs acquisition after HBV inoculation [18].

The objective of this study is to examine the change in pretreatment and posttreatment anti-HBs levels in patients with negative HBsAg who were administered anti-TNF-α drugs as well as the factors that influence this change.

Materials and methods

Patients with autoimmune diseases who were followed up at General Internal Medicine outpatient clinics between 2012 and 2019 and who received anti-TNF-α treatment for at least 1 year were included in the study. The study was approved by the local ethics committee (OMU KAEK, 12/26/2019, 2019/842). This research was designed as a retrospective cohort study. The inclusion criteria were as follows: Patients with negative HBsAg (negative ≤0.9 COI, gray zone ≥0.9 but <1 COI, positive ≥1 COI), whose liver function tests were within normal limits, whose anti-HBs (negative ≤10 IU/L, positive ≥10 IU/L) titers were checked at least once before and during the treatment, and who had positive or negative anti-HBc antibody (negative ≥1 COI, positive ≤1 COI) levels. The exclusion criteria included patients with positive HBsAg and whose liver function tests were higher than the normal upper limit. Hepatitis markers were examined using the COBAS E 601 device. Patients with positive HBsAg and HBV-DNA, those with positive hepatitis C virus (HCV), and alcoholic liver disease, primary biliary cholangitis, or autoimmune hepatitis were excluded from the study. Genders and ages of the patients, their autoimmune diseases, immunosuppressive drugs used, drug exposure time, and HBV markers checked during and throughout the treatment were retrospectively examined and recorded.

Statistical analysis

Statistical analysis was performed using the Wilcoxon rank test for comparison of quantitative variables between the different patient subgroups. For repeated measurements, the Wilcoxon signed ranks test for paired samples was used. The results were expressed as mean (standard deviation). Statistical significance was set at *P*-value <0.05 in a two-tailed test.

Results

A total of 221 adult patients were included in the study. The mean age of the patients was 47.3 (15.1) years, and 46.1% of them were female. The disease age was 2.54 (1.23) years, and most patients received anti-TNF-α treatment due to ankylosing spondylitis (32.1%). Total anti-HBc was positive in 52.3% of the patients. Table 1 summarizes the sociodemographic and clinical data of the patients.

The pretreatment anti-HBs levels (316.39 (356.57), mean rank: 102.99) in the anti-HBs–positive patient group were significantly higher than the posttreatment levels (251.62 (312.059), mean rank: 92.60) (Z:-6.839, *P*<0.001). The anti-HBs levels in the adalimumab, infliximab, and etanercept drug groups decreased significantly. The comparison of pre- and posttreatment anti-HBs levels in anti-TNF drug groups is presented in Table 2.

Of the 221 patients, 10 had no HBV exposure and their pre- and posttreatment anti-HBc / anti-HBs levels were negative. It was observed that the anti-HBs levels of 17 patients out of 221 patients with positive anti-HBs levels before the treatment fell below 10 IU/L posttreatment. Anti-HBs levels in five patients with positive anti-HBc dropped below 10 IU/L. Table 3 shows the change in anti-HBs levels throughout the treatment.

Table 1: Clinical and sociodemographic data of the patients

Age (year)	47.3 (15.1)	
Gender (female)	46.4%	
Disease age (years)	2.54 (1.23)	
Primary Diagnosis	Ankylosing Spondylitis	32.1% (n: 71)
	Psoriasis	27.6% (n: 61)
	Rheumatoid arthritis	13.1% (n: 29)
	Ulcerative colitis	11.8% (n: 26)
	Crohn's disease	9.0% (n: 20)
	Behçet's disease	6.3% (n: 14)
Anti-TNF drugs	Adalimumab	47.5% (n:105)
	Infliximab	32.6% (n: 72)
	Etanercept	14.5% (n: 32)
	Golimumab	3.1% (n: 7)
	Certolizumab	2.3% (n: 5)
HBV antibodies	No HBV exposure: HBsAg (-), Anti HBc total (-), Anti HBs (-)	10
	HBV vaccinated: HBsAg (-), Anti HBc total (-), Anti HBs (+)	91
	Previous HBV: HBsAg (-), Anti HBc total (+), Anti HBs (+)	110

Anti-TNF: Anti-Tumor Necrosis Factor, HBV: Hepatitis B Virus, HBsAg: Hepatitis B Surface Antigen, Anti HBc: Hepatitis B Core Antigen Antibody, Anti HBs: Hepatitis B Surface Antigen Antibody

Table 2: Comparison of anti-HBs levels before and after treatment in anti-TNF drug groups

Anti-TNF drug	Anti-HBs level before the treatment (mIU/mL)	Anti-HBs level after the treatment (mIU/mL)	*P*-value*
Adalimumab (n:105)	329.00 (348.15)	281.63 (318.09)	0.002
Infliximab (n: 72)	289.96 (365.72)	217.69 (306.70)	<0.001
Etanercept (n:32)	330.28 (382.25)	235.96 (326.12)	0.008
Golimumab (n:7)	422.63 (396.81)	328.25 (294.12)	0.068
Certolizumab (n:5)	169.80 (150.43)	93.20 (110.15)	0.052

Anti-TNFα: Anti-Tumor Necrosis Factor α, Anti-HBs: Hepatitis B Surface Antigen Antibody, *Wilcoxon Signed-Ranks was used.

Table 3: Effects of anti-TNF drugs on anti-HBs levels according to HBV exposure

HBV exposure	Anti-HBs level before treatment (mIU/mL)	Anti-HBs level after treatment (mIU/mL)	*P*-value*
HBV vaccinated (n: 91)	289.96 (365.72)	217.69 (306.70)	<0.001
Previous HBV (n: 110)	330.28 (382.25)	235.96 (326.12)	0.008

No HBV exposure: HBsAg (-), Anti HBc total (-), Anti HBs (-), HBV vaccinated: HBsAg (-), Anti HBc total (-), Anti HBs (+), Previous HBV: HBsAg (-), Anti HBc total (+), Anti HBs (+), *Wilcoxon Signed-Ranks was analyzed.

Discussion

This study evaluated 221 patients who were receiving anti-TNF-α drugs. Most of the patients were followed up for ankylosing spondylitis (32.1%) and psoriasis (27.6%). Biological therapies have improved disease management in many rheumatic diseases, and they will probably be used in various other fields in the coming years [19]. In many rheumatologic and dermatologic diseases, anti-TNF therapies in early phases are more successful than standard treatments and are recommended as primary therapy [20,21]. It is anticipated that the increased use of biological agents in the future may increase the concerns about the infection risk from anti-TNF agents as they inhibit mechanisms that play essential roles in host defense [22].

In the present study, reactivation was not observed in patients who received anti-TNF-α treatment, and the posttreatment anti-HBs levels of 17 patients (8.0%) out of 221 patents with positive pretreatment anti-HBs levels were observed to decrease below 10 IU/L posttreatment. In addition, anti-HBs levels in five anti-HBc–positive / anti-HBs–negative patients fell below 10 IU/L. In anti-HBc–positive patients, anti-HBs negativity is the only known risk factor for HBV reactivation. The low level of 10 mIU/mL in anti-HBs titer poses a significant risk [22]. Pauly et al. [23] reported that 178 patients out of 4.620 who received anti-TNF treatment were HBsAg-negative and anti-HBc-positive, and reactivation was observed in none of these patients. HBsAg-negative/anti-HBc–positive patient group is heterogeneous and anti-HBs test is advised for these patients [24]. In the present study, although there is no reactivation, the anti-HBs levels decreased to a risky level for HBV, which poses an apparent risk for our country where HBV is endemic [25].

A statistically significant decrease has been observed in the posttreatment anti-HBs levels in the adalimumab, infliximab, and etanercept groups. Charpin et al. [26] demonstrated that the anti-HBs levels in 21 HBsAg-negative / anti-HBs–positive patients who received adalimumab, infliximab, and etanercept decreased by >30%. It has been speculated that the decrease in anti-HBs may be related to the underlying chronic disease in addition to immunosuppressive treatment. Ballanti et al. [27] examined the effects of etanercept and adalimumab in 32 patients with rheumatoid arthritis and previous HBV or HCV infection and reported that there was no reactivation. However, there have been reports of occult HBV infection reactivation and de novo hepatitis B in patients with rheumatoid arthritis [28]. Moreover, fulminant, and fatal hepatitis have been reported in HBV carriers who were treated with immunosuppressants [29]. Mori et al. [30] have demonstrated an increase in HBV-DNA titers of only 1 patient out of 239 patients with rheumatoid arthritis who have been infected with HBV and reported that anti-TNF agents are safe and effective. Tamori et al. [16] have reported reactivation in only one (2.2%) patient throughout the 2-year period in patients who had undergone HBV infection and received anti-TNF treatment.

Limitations

As the present study is retrospective, the inability to examine HBV-DNA levels can be considered as a limitation regarding activation. However, no transaminase increase was observed in the patient population that may suggest activation. Moreover, anti-HBS levels were not compared as comparable numbers could not be attained among patient groups.

Conclusions

We observed that the anti-HBs levels of patients who received anti-TNF agents decreased significantly; however, there was no reactivation of HBV or de novo HBV infection in HBsAg-negative patients. It was observed that the anti-HBs levels of a small group of patients (8.0%) dropped to a risky level. Thus, intermittent booster doses of HBV vaccination can be useful after administering anti-TNF-α. Although anti-TNF agents are considered safe in anti-HBs positive patients, it would be appropriate to follow these patients in cooperation with a gastroenterologist or an infectious diseases specialist.

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Evaluation of mean platelet volume before and after cyclophosphamide treatment in systemic sclerosis associated interstitial lung disease

Sistemik skleroz ile ilişkili interstisyel akciğer hastalığında siklofosfamid tedavisi öncesi ve sonrası ortalama trombosit hacminin değerlendirilmesi

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Abstract

Aim: Studies carried out in patients with systemic sclerosis (SSc) have shown that mean platelet volume (MPV) is associated with more advanced stage of SSc. However, the effect of cyclophosphamide (CP) on MPV in systemic sclerosis-associated interstitial lung disease (SSc-ILD) is less clear. In this study, we aimed to investigate the MPV response to CP treatment in SSc-ILD.

Methods: Thirty-eight SSc-ILD patients who responded positively to CP were included in this retrospective cohort study. MPV values before the treatment were compared with third, sixth, and ninth months' values during treatment.

Results: Over the nine-year period, 82 patients were diagnosed with SSc in the rheumatology clinic of our hospital. Forty-three of them had SSc-ILD and all were administered CP treatment for 9 months. Thirty-eight clinically benefited from CP, among which 32 were females (84%) and 6 (16%) were males. The MPV levels in SSc-ILD patients after CP (9.44 fL) were significantly higher than those before CP (7.89 fL) (P=0.001).

Conclusion: Cyclophosphamide treatment causes an increase in MPV in SSc-ILD. MPV, a negative acute phase reactant, is considered an independent risk factor for coronary and peripheral artery diseases. Patients receiving CP should be followed more closely for such diseases.

Keywords: Cyclophosphamide, Mean platelet volume, Systemic sclerosis

Öz

Amaç: Sistemik sklerozlu (SSc) hastalarda yapılan çalışmalar ortalama trombosit hacminin (MPV) SSc ileri evresi ile ilişkili olduğunu göstermiştir. Bununla birlikte, sistemik skleroza sekonder interstisyel akciğer hastalığında (SSc-İAH), siklofosfamid (CP) tedavisinin MPV değeri üzerindeki etkisi bilinmemektedir. Bu çalışmada SSc-İAH'de, CP tedavisine MPV yanıtını araştırmayı amaçladık.

Yöntemler: Bu retrospektif kesitsel çalışmaya CP tedavisinden fayda görmüş 38 SSc-İAH hastası dahil edildi. Tedavi öncesi MPV değerleri ile tedavi sırasında üçüncü, altıncı ve dokuzuncu ayların MPV değerleri karşılaştırıldı.

Bulgular: Dokuz yıllık bir süre içinde hastanemiz romatoloji kliniğinde 82 hastaya SSc tanısı kondu. Hastaların 43'ünde SSc-İAH vardı ve bunların hepsinde 9 ay süre ile CP tedavisi uygulandı. CP'den klinik yarar gören 38 hastanın, 32'si (%84) kadın ve 6'sı (%16) erkek idi. SSc-İAH hastalarında CP tedavisi sonrası MPV düzeyleri (9,44 fL), CP tedavisi öncesine (7,89 fL) göre belirgin yüksek tespit edildi (P=0,001).

Sonuç: Siklofosfamid tedavisi, SSc-İAH'de MPV'de bir artışa neden olmaktadır. Negatif akut faz reaktanı olarak MPV'nin koroner ve periferik arter hastalığı için bağımsız bir risk faktörü olarak kabul edildiği bilinmektedir. Siklofosfamid alan hastalar bu tür hastalıklar için özellikle takip edilmelidir.

Anahtar kelimeler: Siklofosfamid, Ortalama trombosit volümü, Sistemik skleroz

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Introduction

The diagnosis of systemic sclerosis-related interstitial lung disease (SSc-ILD) is based on the presence of various respiratory symptoms, such as non-productive cough, dyspnea, fatigue and bibasilar fine inspiratory crackles at the lung bases on physical examination. Pulmonary function tests and high-resolution computed tomography remain the mainstay for the diagnosis of SSc-ILD [1]. Nonselective immunosuppressors are still the main treatment for SSc-ILD, with cyclophosphamide (CP) most widely used to obtain remission [1].

In our rheumatology clinic, we evaluate our systemic sclerosis (SSc) patients at least monthly. At the control visits, we perform a thorough physical examination, chest X-ray, and obtain a complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values. Spirometry and DLCO were performed at three-month intervals, while HRCT was not performed routinely. We usually request HRCT when there is a worsening of symptoms or pulmonary function tests. If the involvement in HRCT is 20% or more in patients diagnosed with SSc-ILD, we switch the treatment to CP. In our clinic, we prefer monthly intravenous CP administration for the management of patients with SSc-ILD. The initial dose is based upon the body surface area and adjusted for renal function, obesity, cachexia, and advanced age. Subsequent doses are based on response to treatment and white blood cell (WBC) counts.

Platelets play a large and complex physiological role in both health and disease, as they contribute to hemostasis, inflammation, tissue repair, and innate and adaptive immunity [2,3]. Increased mean platelet volume (MPV) may reflect either increased platelet activation or increased numbers of large, hyperaggregable platelets. There are reports in the literature that repeatedly document ongoing and chronic activation of platelets and/or their release of biologically of active molecules, which may contribute to vascular, immunologic, and connective tissue pathology in SSc [4,5]. However, responses of MPV and similar inflammatory markers to the CP treatment have not been investigated before. In this study, we aimed to study whether CP treatment influences MPV values.

Materials and methods

Patient selection

All patients diagnosed with SSc-ILD from January 2006 to December 2015 in Kahramanmaras Sutcu Imam University Hospital were retrospectively reviewed. Patients who benefited from CP and received the treatment for at least 9 months were included in the study. Over the nine-year period, 82 patients were diagnosed with SSc in the rheumatology clinic of our hospital. Of these, 43 (52%) had SSc-ILD and all of them were treated with CP, but only 38 (88%) patients benefited from CP treatment. CP was administered intravenously to all patients at a dose of 1000 mg / month. We compared the MPV values immediately preceding the initiation of CP with the third, sixth, and ninth month values after initiation of treatment.

Exclusion criteria included an involvement of less than 20% in HRCT, not benefiting from CP treatment, deterioration in FVC, worsening of dyspnea according to MMRC (Modified Medical Research Council), and radiologic progression. Flow diagram with exclusion criteria is summarized in Figure 1.

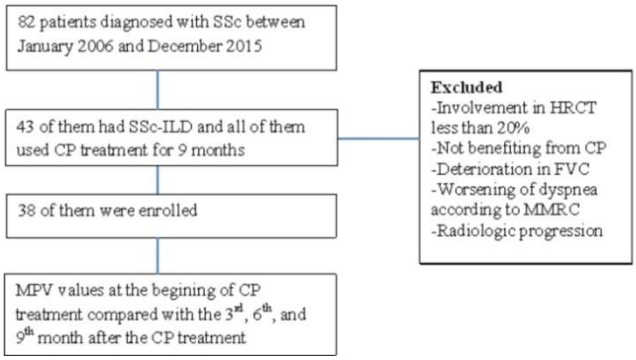

Figure 1: Flow diagram of the study (FVC:forced vital capacity, HRCT: high-resolution computed tomography, SSc-ILD: systemic sclerosis-related interstitial lung disease, CP: cyclophosphamide, MPV: mean platelet volume, MMRC: Modified Medical Research Council Dyspnea Scale)

Ethical approval

Approval for the study was granted by the Clinical Research Ethics Committee of Kahramanmaraş Sütçü Imam University. The study was conducted in accordance with the principles of Helsinki Declaration.

Statistical analysis

Statistical analysis was performed using the SPSS 22.0 statistics package (SPSS, Inc., Chicago, IL, USA). This was a retrospective cohort study. Descriptive statistics and T test were used to describe the features of the data and analysis of related samples (paired sample T test).

Results

The basic demographic findings of the patients are presented in Table 1. There were 32 females (84%) and 6 males (16%). Their mean age was 50.5 (13.6) years. Age at the onset of SSc was 34.2 years, mean disease duration (years) was 4.1 (4.2) years, mean pulmonary artery pressure (PAP) value was 24.4, scl-70 value was positive in 52%, antinuclear antibody (ANA) was positive in 89%, concomitant esophageal dilatation was present in 5 patients (13%), concomitant cardiomegaly was present in 7 patients (5.4%), and 8 patients had pleural thickening (21%).

Table 1: Sociodemographic characteristics of the study population

Age (years), mean (SD)	50.5 (13.6)
Gender (F/M)	32/6
Age at onset of SSc (years)	34.2
Disease duration (years), mean (SD)	4.1 (4.2)
Mean PAP	24.4
Scl-70 +/-	24/14
ANA +/-	34/4
Esophageal dilatation +/-	5/33
Cardiomegaly +/-	7/31
Pleural thickening +/-	8/30

SD: standard deviation, F: female, M: male, PAP: pulmonary artery pressure, ANA: antinuclear antibody

We found that the posttreatment MPV values were significantly higher than those before the treatment (P=0.001). The mean MPV levels of SSc-ILD patients before CP (7.89 fL) were significantly lower than those after 3 months (9.44 fL), 6 months (9.51 fL), and 9 months (9.48 fL) of treatment (P=0.001) (Figure 2).

According to the results in Table 2, there is a positive and significant relationship between the values before CP and 3 months (t= -10.957, P=0.001), 6 months (t= -12.34, P=0.001), and 9 months (t= -11.28, P=0.001) after treatment).

Table 2: Comparison of the difference between before and after CP treatment (CP: cyclophosphamide, MPV: mean platelet volume)

Before CP	MPV values After CP		t	*P*-value
7.89	3th month	9.44	-10.95	0.00
	6th month	9.51	-12.34	0.00
	9th month	9.48	-11.28	0.00

Discussion

To the best of our knowledge, this was the first study which showed the effect of CP on MPV in SSc-ILD patients. Our results showed that MPV values significantly increased after CP administration.

Cyclophosphamide is an alkylating agent of the nitrogen mustard type, which is used to treat cancers and autoimmune disorders such as SSc-ILD [6]. It is the most recommended agent in SSc-ILD, but the changes in blood parameters related to CP treatment in SSc-ILD is still unknown.

Platelets are small cells which include various granules, a microtubular system and an active membrane [7]. It is known that these granules produce and secrete many bodies which play an essential role in atherosclerotic coronary artery disease, atherothrombosis, coagulation, and inflammation processes [8]. On the other hand, MPV, which represents platelet volume, is one of the most studied parameters indicating the level of inflammation. Larger size platelets are more active metabolically and enzymatically than small ones. In other words, increase in MPV increases the risk of thrombosis [9]. The mean platelet volume may play a significant role in atherosclerotic and thrombotic pathways [10]. Aksoy et al. [11] found that low MPV values were associated with bone marrow aplasia after cytotoxic chemotreatment, splenomegaly, reactive thrombocytosis, and high-grade inflammation.

Systemic sclerosis, especially SSc-ILD, is a systemic inflammatory disease which leads to secretion of various pro-inflammatory cytokines, some of which cause secretion of hematopoietic cells into the circulation by affecting the maturation of hematopoietic cells in the bone marrow. Conditions associated with a high degree of inflammation (active inflammatory bowel disease, rheumatoid arthritis, FMF attack) are usually related to low MPV values [12]. In remission or anti-inflammatory drug use, MPV values remain high [13]. Patients included in our study were considered to have high degree inflammation, because all had active ILD. Some of the recent studies associated with rheumatologic disorders have investigated the potential relationship between MPV levels and disease activity in rheumatoid arthritis, ankylosing spondylitis, and synovitis with osteoarthritis. Previous studies have demonstrated decreased MPV levels in active patients with rheumatic diseases in contrast to the healthy population and inactive SSc patients [14-16]. In their study consisting of 596 patients with various rheumatic diseases, Sahin et al. [17] found a negative correlation between MPV and CRP, ESR. In another study involving 76 SSc patients and 45 healthy volunteers, Soydinc et al. [18] found that the mean MPV levels of SSc patients were significantly higher than those of the control group. On the other hand, as expected in any systemic high-grade inflammatory response, they found MPV levels decreasing in clinically active SSc patients. In this study, the authors compared the MPV values of patients with and without lung involvement. MPV values, regardless of CP usage in patients with lung involvement, were 9.42, lower than in patients without lung involvement (9.51). However, this result was not statistically significant. In our study, when we assessed SSc-ILD patients, MPV values were 9.07 and similar to the previous report.

The most crucial difference of our study from other studies is that we evaluated the relationship between CP treatment and MPV values. We found posttreatment MPV values significantly higher than those prior to treatment. Similarly, Gasparyan et al. [16] compared MPV values before and after TNF-α in 21 patients with rheumatoid arthritis. They found a statistically significant increase in MPV values after TNF-α administration (7.7 (0.9), 7.8 (1.1), and 8.4 (1.1) fL at baseline, 2, and 12 weeks, respectively).

The elevated level of MPV might increase the risk of arterial and venous thromboembolism. Therefore, physicians should be alert for thrombus in patients receiving CP treatment. It should also be remembered that MPV is not specific to the disease, and that the results may vary depending on many factors. Therefore, the changes in MPV level may be influenced by the other factors.

Limitations

Our study contains several limitations, one being its retrospective nature, the other, including results from a single center, and a relatively small sample size.

Conclusions

Our study shows that CP has led to the rise of MPV levels. However, further studies which are covering larger groups are required to verify our findings.

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Delay in starting insulin therapy in patients with type 2 Diabetes Mellitus

Tip 2 diyabetes mellitus hastalarında insülin tedavisine geç başlama

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Abstract

Aim: There are many problems with insulin initiation though required in diabetes mellitus patients. This study aims to determine why patients are unable to receive insulin treatments on time.

Methods: Approval from the ethics committee and consent from the volunteers was obtained for this cross sectional, single center study, in which patients with type 2 diabetes mellitus over the age of 18 years were included. Pregnant women, patients with cirrhosis, and psychiatric disorders were excluded. A questionnaire was used for data collection. Statistical analysis was performed with SPSS 18.0.

Results: A total of 1062 patients were included in this study. Diabetes mellitus was regulated in 34% of the patients. The number of patients who did not use insulin even though they should was 105. While physicians did not recommend any insulin treatment to 34 patients, 33 patients did not want insulin treatment due to fear of injection and 32 patients did not start insulin treatment because they had incorrect information regarding insulin. When 36 patients who stopped insulin treatment while they were using were questioned for the reason, it was learnt that 8 patients' insulin treatment was stopped by their physicians. The remaining 28 patients, on the other hand, stopped their insulin treatments most frequently because of the difficulty of injection and incorrect information they heard about insulin.

Conclusions: Providing outpatient conditions that increase patient-physician dialogue, ensuring that the injection pen and needle are seen and tested by the patient in person, and conferences for the patients and medical doctors to prevent getting the incorrect information would be the solution of the delay in starting insulin in diabetes mellitus.

Keywords: Diabetes Mellitus, Insulin, Early treatment

Öz

Amaç: Diabetes mellitus hastalarında gerekmesine rağmen insülin başlatılmasıyla ilgili birçok sorun vardır. Bu çalışmanın amacı hastaların niçin zamanında insülin tedavilerini alamadıklarını saptamak ve bu sorunlara değinmektir.

Yöntemler: Tek merkezde kesitsel yapılan bu çalışma için etik kurul'dan izin ve gönüllülerden onam alındı. 18 yaşından büyük, tip 2 diyabetes mellituslu hastalar çalışmaya dahil edildi. Hamileler, 18 yaşından küçükler, dekompanse karaciğer hastalığı olanlar, psikiyatrik bozukluğu olanlar, Tip 1 diyabeti olanlar çalışmaya alınmadı. Veri toplanması için anket kullanıldı. İstatistiksel analiz SPSS 18.0'da yapıldı.

Bulgular: Toplam 1062 hasta çalışmaya alındı. Hastaların %34'ü regüle idi. İnsülin kullanması gerektiği halde kullanmayan hasta sayısı 105'di. 105 hastadan 34 hastaya hekimler hiç insülin tedavisi önermemişken 33 hasta enjeksiyon korkusu nedeniyle insülin istememiş ve 32 hasta ise insülin hakkında yanlış bilgileri olduğu için insülin kullanmaya başlamamıştı. İnsülin kullanırken insülin tedavisine son veren 36 hasta sorgulandığında 8 hastanın insülin tedavisi hekimleri tarafından durdurulmuştu. Kalan 28 hasta ise insülin tedavilerini en sık enjeksiyon zorluğu ve insülin hakkında duyduğu yanlış bilgiler nedeni ile kendileri bırakmıştı.

Sonuçlar: Hasta hekim diyalogunu artıran poliklinik şartlarının sağlanması, enjeksiyon kaleminin ve iğnesinin bizzat hasta tarafından görülüp denenmesi, yanlış bilgi edinilmesinden kaçınmak için hastalara ve doktorlara yönelik konferanslar diyabetes mellitus'ta insülinin geç başlanmasına çözüm olabilir.

Anahtar kelimeler: Diyabetes Mellitus, İnsülin, Erken tedavi

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Introduction

Diabetes was first recognized by the ancient Egyptians 3500 years ago. The first clinical definition was made by Aretaeus, who lived in the Cappadocia region in about 120 years AD [1]. Diabetes Mellitus (DM) develops when the pancreas cannot produce enough insulin from beta cells or if the insulin produced cannot be used effectively.

DM is a chronic disease that can cause serious complications. Its complications can be macrovascular in the form of coronary, cerebral or peripheral artery disease, or microvascular, such as retinopathy, nephropathy, or neuropathy. The necessity of an effective treatment in preventing complications is an indisputable fact [2].

In addition to oral antidiabetic drugs, insulin also plays an important role in the treatment of DM. In the case of insulin deficiency, hyperglycemia and glucolipotoxicity due to increased fatty acids lead to apoptosis. In the pre-diabetes period, even during the impaired fasting glucose phase, more than 40% of pancreatic beta cells are lost. Therefore, insulin therapy is important in maintaining the beta-cell reserve [3-5].

Despite the long-term glycemic control and improving effects of insulin on the quality of life, the delay in starting insulin although treatment is indicated is due to various reasons. The reasons for this delay are associated with the physician, patient or both the physician and the patient [6].

This study aims to identify the main causes of delay in starting insulin treatment and provide solutions.

Materials and methods

Before starting this study, approval was obtained from the Ethics Committee of Prof. Dr. Cemil Taşcıoğlu City Hospital (9/25/2019/986) and informed consent was acquired from all patients who were willing to participate in the study before the data was received.

Patients with type 2 diabetes mellitus over the age of 18 years who applied to the internal medicine outpatient clinic of our tertiary hospital were included in this single center study. Pregnant women, those under the age of 18, patients with decompensated liver disease, or psychiatric disorders that prevent cognition or compliance, and those with Type 1 DM were excluded from the study.

All participants received a questionnaire specially designed by the physician. The survey included demographic information and personal diabetes treatment. Laboratory evaluations (fasting blood glucose, post prandial blood glucose, HbA1C) were performed at the hospital where the interviews were held. All laboratory parameters were measured using standard procedures.

Statistical analysis

Statistical analysis was performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean (SD) or continuous variables or as percentages for categorical variables. In the statistical evaluation of the data, *P*-value of <0.05 was considered significant.

Results

Within one year, 1062 patients with type 2 DM were included in the study. Among participants, 681 were female and 381 were male. The mean age of the study group was 59 (10) years, and the mean body mass index was 30 (5) kg/m^2. The mean fasting blood glucose level was 169 (70) mg/dl, the mean postprandial blood glucose, 234 (93) mg/dl, and the mean HbA1c, 8.1 (3.9) mg/dl. The mean diabetes duration was 9 (6) years, and the mean insulin usage period in patients under insulin treatment was 6 (5) years.

Considering that the HbA1c target was set at ≤7%, 330 patients (34%) were regulated, while 655 patients were not (Table 1). When the patients were divided into two groups according to HbA1c levels as ≤7% and >7%, it was seen that the group that was not regulated despite the treatment had diabetes for a significantly longer period.

The number and distribution of medications according to the drug active substances used by the patients were as follows: Metformin 842 (79.3%), Sulfonylurea 233 (21.9%), Acarbose 20 (1.9%), Glitazone 84 (7.9%), Glinides 6 (0.6), Gliptins 430 (40.5%), SGLT-2 inhibitors 103 (9.7%), GLP-1 agonists 9 (0.8%), rapid-acting insulins 210 (19.8%), basal insulins 340 (32%), ready-mix analog insulins 68 (6.4%) (Table 2).

Table 1: Demographic data

	HbA1c ≤7 (n=330)	HbA1c ≥7 (n=655)	Total (n=1062)	*P*-value
Gender (F/M)	207/123	426/229	681/381	0.609
Age (years)	59 (10)	60 (11)	59 (10)	0.300
BMI (kg/m²)	30 (5)	29 (5)	30 (5)	0.400
FBG (mg/dl)	118 (23)	194 (72)	169 (70)	0.001
PPBG (mg/dl)	163 (43)	270 (91)	234 (93)	0.001
Diabetes duration (years)	7 (5)	10 (6)	9 (6)	0.001
Insulin usage period (years)	5 (4)	6 (5)	6 (5)	0.307

BMI: Body mass index, FBG: Fasting Blood Glucose, PPBG: Postprandial Blood Glucose

Table 2: Distribution of patients included in the study according to the drug active substances they used

Drug active substances	n	%
Metformin	842	79.3
Gliptins	430	40.5
Sulfonylurea	233	21.9
SGLT-2 inhibitors	103	9.7
Glitazone	84	7.9
Acarbose	20	1.9
GLP-1 agonists	9	0.8
Glinides	6	0.6
Basal insulins	130	32
Ready-mix analog insulins	68	6.4
Rapid-acting insulins+basal insulins	210	19.8

Metformin was the most commonly used agent (n=239, 22.5%), which was followed by a combination of metformin and gliptin (n=109, 10.3%). Among insulin treatments, the combination of basal-acting insulin and fast-acting insulin was the most preferred (n=92, 8.7%) compared to all treatment options (Table 3).

Considering the patients who were using four or more oral antidiabetic agents or had HbA1c ≥9, 105 (9.9%) of the patients were not using insulin although it was indicated. When those 105 patients were asked why they did not use insulin, 34 (32.7%) stated that physicians did not recommend any insulin treatment so far, 33 (31.7%) rejected insulin because of fear of injection, and 32 (30.8%) did not start insulin because of the dreadful comments they had heard about insulin before. These dreadful comments included that insulin became habitual and caused kidney failure. Remaining three of our patients had not switched to insulin due to insufficient educational status, two

patients thought they would have hypoglycemia and one patient was afraid of gaining weight (Table 4).

Patients who interrupted insulin treatment while using insulin were questioned what the reason was. Based on the responses, they were divided into two as physician-induced and patient-induced to stop insulin treatment. In 8 (22%) of our patients, the treatment of insulin was stopped by the physician while 28 (78%) of our patients had stopped their insulin treatments themselves. In patients who interrupted their insulin treatment with the physicians' advice, the mean age (years), fasting blood sugar (mg/dl), postprandial blood sugar (mg/dl), HbA1c (mg/dl), diabetes duration (years), insulin usage period (years) and body mass index (kg/m^2) were 51, 174, 184, 7.8, 6, 8, and 24, respectively. In the same order, the values of the patients who quit insulin treatment on their terms were 57, 251, 308, 11, 9, 3, and 28 (Table 5). Reasons for physicians to stop insulin treatment in 8 patients included regulation of blood glucose in 6 patients and hypoglycemia in 2 patients. On the other hand, the reasons for 28 patients interrupting their insulin treatment were insufficient information on insulin in 10 (35%) patients, difficulty in injection in 9 (32%) patients, inadequate educational level and lack of helpers in 4 (14%) patients, hypoglycemia in 4 (14%) patients, and weight gain in one patient.

Table 3: The distribution of patients according to the drugs they use most frequently and the ratio of these treatments to the treatment combinations

Treatment choices	n	%
Barely Metformin	239	22.5
Barely Gliptin	18	1.7
Barely Sulfonylurea	14	1.3
Metformin+Gliptin	109	10.3
Metformin+Sulfonylurea	56	5.3
Metformin+Gliptin+SGLT-2	29	2.7
Metformin+Glitazone	14	1.3
Metformin+Sulfonylurea+Gliptin	72	6.8
Metformin+Glitazone+Gliptin	15	1.4
Metformin+Sulfonylurea+Glitazone	11	1
Barely Basal Insulin	14	1.3
Basal Insulin+Metformin	23	2.2
Basal Insulin+Metformin+Gliptin	31	2.9
Basal Insulin+Metformin+SGLT-2	12	1.1
Basal Insulin+Metformin+Sulfonylurea +Gliptin	14	1.3
Basal Insulin+Rapid-acting insulin	92	8.7
Basal Insulin+Rapid-acting insulin+Metformin	33	3.1
Basal Insulin+Rapid-acting insulin+Gliptin	12	1.1
Basal Insulin+Rapid-acting insulin+Metformin+Gliptin	45	4.2
Mix Insulin +Metformin	19	1.8
Mix Insulin+Metformin+Gliptin	13	1.2

Table 4: Distribution of reasons for not using insulin among patients using four or more oral antidiabetic drugs or HbA1c greater than 9 mg/dl

Reasons for not using insulin (n=105)	n	%
Physicians have not recommended	34	32.3
Fear of injection	33	31.4
Dreadful comments they had heard about insulin	32	30.4
Insufficient educational status	3	2.8
Fear of hypoglycemia	2	1.9
Afraid of gaining weight	1	0.9

Table 5: Comparison of patients whose insulin therapy was discontinued by the physician and those who discontinued their insulin treatments themselves

Patients whose insulin therapy was discontinued (n:36)	by the physician (n:8)	by themselves (n:28)	*P*-value
Age (years)	51 (9)	57 (9)	0.43
FBG (mg/dl)	174 (42)	251 (84)	0.01
PPBG(mg/dl)	184 (30)	308 (86)	0.10
HbA1c (mg/dl)	7.8 (1)	11 (2)	0.38
Diabetes duration (years)	6 (5)	9 (5)	0.69
Insulin usage period (years)	8 (9)	3 (5)	0.28
BMI (kg/m²)	24 (13)	28 (3)	0.03

FBG: Fasting Blood Glucose, PPBG: Postprandial Blood Glucose, BMI: Body mass index

Discussion

Type 2 DM has an increasing prevalence worldwide. This brings both increased treatment costs and complications of diabetes together with increased morbidity and mortality. Blood glucose regulation is important to prevent the development of complications of diabetes, and compliance with treatment algorithms is tremendously essential.

When looking at the insulin regimens used by patients, mixed insulins are the least preferred by physicians in treatment with a ratio of 16%, while basal + bolus treatment is administered with a rate of 51%. However, in parallel with the previous studies, in our study, we observed that we are still not at the desired point in the treatment of diabetes. In the recent TEMD study on this subject, Sonmez et al. [7] determined the mean HbA1c level as 7.7% in Type 2 diabetic patients followed in the endocrinology outpatient clinic, while in two separate studies conducted by Ilkova et al. [8] and Satman et al. [9] the HbA1c levels were reported as 8.1% and 8.6%, respectively. In our study, the mean HbA1c level was 8.1% in patients who visited the internal medicine outpatient clinic. Again, in the TEMD study, it was reported that only 40% of patients with Type 2 diabetes were achieving HbA1c targets. These rates were 29% and 23% in the studies of Ilkova et al. and Satman et al., respectively. The differences in the two ratios probably result from different HbA1c targets and the 5-year interval between the two study periods. In our study, when we accepted HbA1c ≤7 as the regulation criteria, we found that only 34% of our patients who visited the internal medicine outpatient clinic reached target HbA1c levels [10].

Insulin therapy has an important place in the treatment of diabetes mellitus. Achieving desired goals and maintaining pancreatic cell reserves should be the primary goals by ensuring the regulation of blood glucose levels in patients. There are more than one study showing the effectiveness of insulin therapy and early blood glucose regulation slowing the progression from prediabetes to diabetes and preventing its complications. The UKPDS study showed that while early glucose control reduces the risk of both macrovascular and microvascular complications, late control of diabetes is of little benefit to macrovascular complications [11-13].

In the study of Pennartz et al. [14] on patients with type 2 diabetes mellitus, who were not controlled sufficiently with metformin, a significant improvement in residual pancreatic cell function with early use of basal insulin was demonstrated.

However, when necessary, the delay in the transition to insulin therapy may be due to the physician, the patient or both the physician and the patient. The two most important reasons that emerged in our study were the patients' fear of injections and their dreadful ideas about insulin. Contrary to the expectations, lack of education is no longer an obstacle to starting insulin therapy. Besides, when the patients were divided into three classes according to HbA1c levels, the group with the highest HbA1c had the lowest rate of insulin offered by the physician, which suggests that the physicians had difficulty in changing the ossified misconceptions of the diabetic patients and they have stopped repeating their proposal.

Barriers to insulin initiation or continuation are worldwide problems. The main obstacles encountered after starting insulin therapy were determined by Lee et al. [15] as fear, misperception, and side effects. Insulin follow-up programs, multidisciplinary diabetes care teams, making glucometers and more easily accessible strips have become necessary to overcome these obstacles.

On the other hand, Karter et al. [16] attributed the reasons for the failure of starting insulin usually to the misinterpretations of the patients like the insulin itself has side effects such as blindness, kidney failure, causing amputation, increasing the risk of a heart attack, causing stroke or premature death, to their injection phobia, anxiety of hypoglycemia, negative impact on social life and work, and insufficient literacy.

The more difficult it is to start insulin for the patient who needs insulin treatment, the more difficult it is for the patient to continue the treatment. Oliveria et al. [17] reported that 86% of patients who required insulin treatment had never been recommended it by healthcare professionals, and 46% of patients who started insulin treatment had stopped. In this study, the average time between the patients' first and last prescriptions was 4.9 years. The most common causes of discontinuation of insulin were injection difficulty and the physicians' advice to no longer continuing. In their study, Khunti et al. [18] also emphasized the graveness of the delays to start insulin treatment and increase the dosages.

Yavuz et al. [19] reported that having negative perceptions about insulin treatment and basal-bolus insulin treatment regimen, young age, and starting new treatment were the most common difficulties for conformity to treatment.

In our study, when the reasons for quitting insulin were questioned, incorrect information previously obtained about insulin (45%) and fear of injection (47%) were the foremost patient reasons. Also, when the causes of insulin discontinuation associated with the physician or the patient are compared, the fasting blood glucose and BMI of the group in which the physicians stopped insulin treatment were statistically significantly lower than the other group. It is observed that physicians stop insulin treatment when they reach moderate HbA1c values with moderate postprandial glucose levels in young and thinner patients with near-normal fasting glucose levels. It is noteworthy that the patients who quit insulin by themselves were older, fatter, with a history of older diabetes, having poorly controlled diabetes, and having more newly started insulin therapy. Contrary to the expectations, only 14% of patients who quit insulin reveal the cause as hypoglycemia, while hypoglycemia was the reason for 25% of physicians to quit insulin. Therefore, it is possible to say that the fear of experiencing hypoglycemia resides in the physician rather than the patient.

Limitation

One potential limitation of this study is that it is based on data from a single center; therefore, composition of population, departmental protocols, resources, and staffing characteristics are potential limits to the generalizability of our results.

Conclusion

The most important physician-induced reasons of delay starting insulin are not to adequately inform the patient about insulin therapy and fear of hypoglycemia that the patient will experience. The most common patient-induced causes are fear of injections and dreadful ideas about insulin. The educational meetings for hypoglycemia and injection fears and enough time in outpatientclinic for patients can solve the problem of delay starting insulin in diabetes mellitus.

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Investigation of the effects of tadalafil and telmisartan in bleomycin-induced pulmonary fibrosis on rats

Tadalafil ve telmisartanın bleomisine bağlı akciğer fibrozisi üzerindeki etkilerinin sıçanlarda incelenmesi

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Abstract

Aim: Pulmonary toxicity related to bleomycin, an antitumor drug used in the treatment of several malignancies, is a challenge, and studies to find out molecules to prevent it are ongoing. In this study, we aimed to investigate the effectiveness of telmisartan and tadalafil in an experimental rat model of bleomycin-induced lung fibrosis.

Methods: A total of 32 male rats were divided into four groups: Control group, Bleomycin group, Bleomycin-plus-Tadalafil group and Bleomycin-plus-Telmisartan group. Lung fibrosis was achieved by intratracheal administration of bleomycin, and the same procedure was performed to the control group, but saline was substituted for bleomycin. Tadalafil and telmisartan were administered with an orogastric catheter for 14 days. Tissue malondialdehyde levels (MDA) were determined using colorimetric methods. Masson's trichrome staining was used in the histological examination of the tissue samples.

Results: The fibrosis scores of bleomycin-plus-tadalafil and bleomycin-plus-telmisartan groups were lower than that of the bleomycin group (P=0.007 and P=0.007, respectively). MDA levels did not differ among study groups.

Conclusion: Tadalafil and telmisartan were found to decrease fibrosis scores, which were increased with bleomycin, concluding that pulmonary toxicity was related to multiple processes and preventable.

Keywords: Pulmonary fibrosis, Bleomycin, Telmisartan, Tadalafil

Öz

Amaç: Farklı malignitelerin tedavisinde kullanılan bir antitümör ilaç olan bleomisin ile ilişkili pulmoner toksisite, önemli bir sorundur ve bu toksisiteyi önleyecek molekülleri bulmak için çalışmalar devam etmektedir. Bu deneysel çalışmada, ratlarda, bleomisinle indüklenen akciğer fibrozisinde telmisartan ve tadalafilin etkinliğini araştırmayı amaçladık.

Yöntemler: 32 erkek rat dört gruba ayrıldı: Kontrol grubu, Bleomisin grubu, Bleomisin+Tadalafil grubu, Bleomisin+Telmisartan grubu. Akciğer fibrozisi intratrakeal bleomisin uygulaması ile oluşturulurken aynı prosedür kontrol grubunda bleomisin yerine salin kullanılarak uygulandı. Tadalafil ve telmisartan gruplara göre 14 gün boyunca orogastrik kateter vasıtasıyla verildi. Doku MDA düzeyleri kalorimetrik yöntemler kullanılarak ölçüldü. Masson trikrom boyama uygulanarak histolojik değerlendirme yapıldı.

Bulgular: Bleomisin+tadalafil ve bleomisin+telmisartan gruplarının fibrozis skorları bleomisin grubuna göre daha düşüktü (P=0,007 ve P=0,007, sırasıyla). Gruplar arasında MDA düzeyleri açısından farklılık görülmedi.

Sonuç: Tadalafil ve telmisartanın bleomisine bağlı artan fibrozis skorlarını düşürdüğü ve pulmoner toksisitenin birden fazla süreçle ilişkili olduğu ve önlenebilir olduğu kanısındayız.

Anahtar kelimeler: Pulmoner fibrozis, Bleomisin, Telmisartan, Tadalafil

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Introduction

Bleomycin is an antitumor antibiotic that is used to treat a wide variety of malignancies, predominantly, germ cell tumors and Hodgkin lymphomas. However, pulmonary toxicities, interstitial pulmonary fibrosis being the most life-threatening variant, can be observed in around ten percent of patients receiving the drug [1,2]. The phosphodiesterase type 5 (PDE 5) inhibitors cause vasodilation in many tissues by blocking the degradation of cyclic guanosine monophosphate (cGMP), which results in prolongation of the action of various mediators, such as nitric oxide (NO). This effect of PDE 5 inhibitors are mostly seen in the penis and lung. There are diverse studies which demonstrated antiapoptotic, antifibrotic and anti-inflammatory effects of PDE 5 inhibitors in different tissues [3-6]. Angiotensin-II receptor blockers (ARBs) are used to treat high blood pressure, heart failure and diabetic kidney disease. Anti-apoptotic and antifibrotic effects of ARBs in lungs, heart and kidneys have been demonstrated in several studies [7-10]. Molecules which harbor antifibrotic potential are currently being studied in experimental settings, and we aimed to investigate the effects of tadalafil, a phosphodiesterase type-5 inhibitor, and telmisartan, an angiotensin receptor blocker, in bleomycin-treated rat model.

Materials and methods

The study was carried out with the approval of Karadeniz Technical University Animal Care and Ethical Committee (Date: 5/25/2011, Protocol number: 2011/22). A total of 32 male Sprague-Dawley rats, weighing between 250-300 grams, were used. The rats were randomized into four groups as follows: Control group, Bleomycin group, Bleomycin-plus-Tadalafil group and Bleomycin-plus-Telmisartan group. All rats were kept in steel cages at a room temperature of 22°C and fed on standard chow pellet diet, with *ad libitum* access to tap water.

After 8 hours of fasting, the rats were anesthetized with intraperitoneal injection of 50 mg/kg ketamine and 10 mg/kg xylazine. The Pulmonary Fibrosis Model was achieved by intratracheal administration of 0.2 ml of the designated solution (bleomycin 5 mg/kg in saline in all groups excluding controls, and 0.2 ml saline only in the control group) on day 0. In the following 14 days, saline, tadalafil or telmisartan were administered to the related groups through an orogastric catheter (10 mg/kg of tadalafil or 10 mg/kg telmisartan). On day 15, all rats were sacrificed, and their lungs were excised. The weights of right and left lungs of all rats were noted and the right lungs were used for histopathological examination, whereas the left lungs were used for biochemical assays.

Histopathological examination

The right lungs were fixed in 10% formaldehyde, after which paraffin blocks were prepared for light microscopic investigations. 3 μm-thick serial sections were made with a microtome and stained with hematoxylin-eosin and Masson's trichrome for evaluation of general morphology and fibrosis. Then the sections were analyzed under a light microscope (Olympus BX 51, Tokyo, Japan) at a high magnification by a histologist blinded to the animal groups. The histological sections were graded for pulmonary fibrosis, scores ranging from 0 (normal lung) to 8 (total fibrosis), using the grading system described by Aschcroft et al. (Grade 0 = Normal lung, Grade 1 = Minimal fibrous thickening of alveolar or bronchiolar walls, Grade 2-3 = Moderate thickening of walls obvious damage to lung architecture, Grade 4-5 = Increased fibrosis with definite damage to lung structure and formation of fibrous bands or small fibrous masses, Grade 6-7 = Severe distortion of structure and large fibrous areas, "honeycomb lung" is placed in this category and Grade 8 = Total fibrous obliteration of the field) [11] .

Biochemical assay (tissue MDA levels)

Tissue levels of MDA were measured spectrophotometrically with the method described by Uchiyama and Mihara on the thiobarbituric acid reactive substance (TBARS) [12]. Left lung tissues of the rats were cut on ice molds and weighed at 100 mg on a precision scale (Mettler Toledo AB 204-S Greifensee, Switzerland). 1 mL of cold homogenization buffer (1.15% KCl and 0.05% Triton X-100 solution) was placed and homogenized at 5000 rpm in a homogenizer (IKA- ultra turrax T 18, Staufen, Germany) for 30 s in a cold environment. After homogenization, samples were centrifuged at 1800g for 10 min. The supernatant fractions were analyzed at 512 nm by microplate reader (Molecular devices Versa Max, California, United States). Tetramethoxypropane was used as a standard, and MDA levels were calculated as nanomoles per gram wet tissue.

Statistical analysis

Data were expressed as median (interquartile range for 25-75 %). SPSS (version 23.0, Chicago, IL, USA) was used for statistical analysis of the data, where the groups were compared by Kruskal-Wallis analysis of variance (post-hoc evaluations were done by Mann-Whitney U test). A *P*-value of less than 0.05 was considered significant.

Results

The weights of the left lungs were similar in all groups. The weights of right lungs in two groups (bleomycin group and bleomycin-plus-tadalafil group) were higher compared to controls ($P=0.015$ and $P=0.003$, respectively).

The histopathological analysis of lung tissues from untreated, tadalafil and telmisartan-treated bleomycin groups revealed that both drugs had moderately protective effects on lung injury (Figure 1). The fibrosis scores of the bleomycin group were higher compared to the control group ($P<0.05$). The fibrosis scores of bleomycin-plus-tadalafil and bleomycin-plus-telmisartan groups were lower than the bleomycin group ($P=0.007$ and $P=0.007$, respectively). The scores from these two groups were comparable to the scores of the control group.

Analysis for tissue MDA levels did not show any difference for the studied groups. The results of the statistical analysis are presented in Table 1.

Table 1: A comparison of lung weight, MDA levels and fibrosis score in the groups

Variables	Control (n:8)	Bleomycin (n:8)	Bleomycin/ tadalafil (n:8)	Bleomycin/ telmisartan (n:8)	*P*-value
Lung Weight					
Right lung weight (mg)	1100 (1000-1275)	1450 (1300-1575)[a]	1550 (1325-1950)[a]	1300 (1125-1475)	0.015
Left lung weight (mg)	800 (625-1000)	850 (800-1050)	950 (800-1000)	1000 (850-1075)	0.421
Biochemical Variable					
MDA (nmol/mg wet tissue)	4.80 (4.32-5.44)	5.22 (4.31-5.70)	4.35 (3.43-4.95)	4.56 (4.19-5.60)	0.713
Histopathologic Variable					
Fibrosis Score	3.0 (1.0-3.0)	3.0 (1.0-6.50)[a]	1.0 (1.0-3.0)[b]	1.0 (1.0-3.0)[b]	0.018

Data were expressed as median (interquartile range for 25-75%). *P*-values according to Kruskal-Wallis Test, post hoc Mann Whitney U test. [a] $P<0.05$ compared with control group; [b] $P<0.05$ compared with Bleomycin group

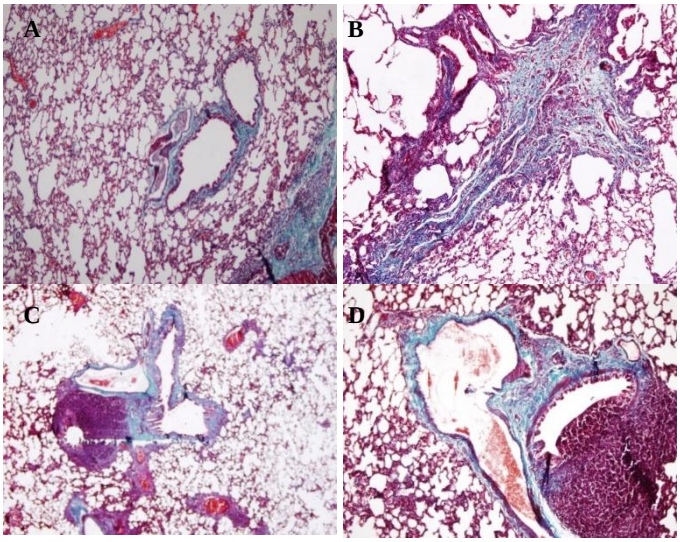

Figure 1: A: Normal appearance of lung parenchyma in control group B: Bleomycin group C: Bleomycin /Tadalafil Group D: Bleomycin/Telmisartan Group (Masson's trichrome staining, original magnifications ×40)

Discussion

Bleomycin is a prevalent drug in regimens for the treatment of testicular germ cell tumors (Bleomycin-Etoposide-Cisplatin (BEP), Cisplatin-Vinblastine-Bleomycin or Carboplatin-Vinblastine-Bleomycin) [13,14]. Pulmonary complications were found in 5% to 16% of patients treated with bleomycin for germ cell cancers [15]. In a study, it has been shown that long-term pulmonary complications persisted in 8% of the patients who received three cycles of BEP for germ cell tumors [16]. The pathophysiological process leading to pulmonary toxicity has not been clarified but oxidative damage, deficiency of bleomycin hydrolase, genetic susceptibility and inflammatory cytokines are thought to be relevant. Bleomycin hydrolase is known to inactivate bleomycin and decrease its effects [2]. Oxidative damage or chronic inflammation and fibrosis of pulmonary interstitial tissues may also play a role in bleomycin-related pulmonary injury. Bleomycin-induced oxidative stress, DNA breakage and epithelial cell obliteration provoke the accumulation of activated inflammatory cells, which release proinflammatory cytokines and growth factors. These fibrotic cytokines such as TNF-α, IL-1 and TGF-β are thought to increase inflammatory response, leading to myofibroblast activation, collagen deposition and remodeling progress. Imbalance between oxidants and antioxidants may play a significant role in pulmonary inflammation that induce fibrosis [17,18].

Antifibrotic and/or anti-inflammatory effects of PDE-5 inhibitors were shown in experimental studies. In a study, Marcus et al. showed that vardenafil inhibited myofibroblast transformation, collagen gel contraction and extracellular matrix production in a rat model of Peyronie's Disease [19]. In other studies, it was shown that tadalafil can reduce hepatic and circulating levels of TNF-α and limit the upregulation of pro-inflammatory cytokines [20-22]. Yildirim et al. reported that sildenafil lowered MDA levels and corrected antioxidant glutathione in a pulmonary fibrosis model (bleomycin-treated rats) [23]. However, our results were different from that of Yildirim's study, showing no significant changes in MDA levels. On the other hand, histopathologically, our results concluded that tadalafil was beneficial in preventing fibrosis in lungs.

TGF-β is an important profibrotic growth factor, controlling cell growth, extracellular matrix, and collagens. The role of reactive oxygen species and angiotensin on this process is well studied. Thus, angiotensin receptor blocked by telmisartan, is thought to be a potential target for preventing fibrosis in lungs [24]. Our histopathological findings were parallel to the hypothesis. We found that telmisartan can ameliorate the fibrosis in lungs. In a study where TGF- β levels were investigated, Waseda and colleagues showed that olmesartan, another angiotensin receptor blocker, had antifibrotic effects in rats with pulmonary fibrosis due to bleomycin, and they reported a decrease in TGF- β levels [8].

Limitations

The most important limitation of our study is the inadequate biochemical parameters. Another limitation of this research is that in vivo studies cannot be predicted in terms of possible effects.

Conclusion

We conclude that bleomycin-induced pulmonary fibrosis may be related to multiple processes and preventable. Our results with a phosphodiesterase type-5 inhibitor tadalafil and an angiotensin receptor blocker telmisartan may be considered promising and direct us to molecular studies to find the pathways related to pulmonary complications.

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Anxiety level and risk factors among pediatric patients in endoscopic procedures outside the operating room: A cross-sectional study

Pediatrik hastalarda ameliyathane dışı endoskopik işlemlerde anksiyete seviyesi ve risk faktörleri: Kesitsel çalışma

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Ethics Committee Approval: This study was approved by Necmettin Erbakan University Ethics Committee (2019/2059). All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
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Abstract

Aim: Endoscopy under anesthesia creates stress and anxiety in children and their parents. In this study, we aimed to determine the preoperative anxiety levels of parents and patients who were routinely informed before endoscopy and examine the relationship between children and parents' state and trait anxiety levels.

Methods: A cross-sectional study was planned in which pediatric patients and parents were included. The study comprised 104 ASA I-II patients, aged 6-14 years, who were scheduled for endoscopy under deep sedation, and their parents. Immediately after the child patient was taken to the treatment room, parents were asked to fill out the State-Trait Anxiety Inventory. The demographic characteristics of the patients were recorded. The children's anxiety level immediately after separation from parents was evaluated with Modified Yale Preoperative Anxiety Scale (m-YPAS). The patients were divided into two groups according to anxiety levels. Those with m-YPAS >30 were considered the anxiety (+) group, m-YPAS ≤30 were defined as the anxiety (-) group.

Results: The mean age of the patients was 11.8 (2.6) years (6-14). Twenty-nine patients had m-YPAS> 30, and 75 patients had m-YPAS ≤30. Parent anxiety levels were not significantly different between the two groups. There was a strong negative correlation (r=-0.589, *P*<0.001) between child's anxiety and child age, a negative moderate correlation between child's anxiety and parent age (r=-0.259, *P*=0.008), and weak positive correlation between child's anxiety and complications (r=0.218, *P*=0.026). Young age was determined as an independent risk factor for increased child anxiety (OR: 0.501, *P*<0.001, 95% CI: 0.390-0.643).

Conclusion: There is no relationship between preoperative anxiety in school-age children and parental anxiety. Young age is an independent risk factor for the development of anxiety in the child.

Keywords: Anxiety, m-YPAS, Parent anxiety, STAI

Öz

Amaç: Anestezi altında gerçekleştirilen endoskopi işlemi çocuklarda ve ebeveynlerinde stres ve kaygı yaratır. Bu çalışmada Endoskopi işlemi öncesi rutin bilgilendirilme yapılan ebeveynlerin ve hastaların preoperatif kaygı düzeylerini belirlemek ve çocuklar ile ebeveynlerin durum-sürekli kaygıları arasındaki ilişkiyi incelemeyi amaçladık.

Yöntemler: Çocuk hasta ve ebeveynlerin dahil edildiği kesitsel bir çalışma planlandı. Çalışmaya derin sedasyon altında endoskopi planlanan 6-14 yaş arası, ASA I-II, 104 çocuk hasta ve ebeveynleri dahil edildi. Çocuk hasta işlem odasına alındıktan hemen sonra ebeveynlerden Durum-Sürekli Kaygı Anketini doldurmaları istendi. Hastaların demografik özellikleri kayıt edildi. Çocukların kaygı seviyesi ebeveynlerinden ayrıldıktan hemen sonra Modifiye Yale Preoperatif Kaygı Skoru (m-YPAS) ile değerlendirildi. Hastalar anksiyete düzeylerine göre iki gruba ayrıldı. m-YPAS >30 anxiety (+) grup, m-YPAS ≤30 anxiety (-) grup olarak belirlendi.

Bulgular: Hastaların yaş ortalaması 11,8 (2,6) (6-14) yıldı. 29 hasta da m-YPAS >30, 75 hasta da m-YPAS ≤30'du. Ebeveyn kaygı seviyeleri iki grup arasında istatistiksel olarak anlamlı değildi. Çocuk kaygısı ile çocuk yaşı arasında negatif yönde kuvvetli (r=-0,589, *P*<0,001), ebeveyn yaşı arasında negatif yönde orta (r=-0,259, *P*=0,008), komplikasyon arasında pozitif yönde düşük (r=0,218, *P*=0,026) korelasyon vardı. Çocuk kaygı seviyesi için düşük çocuk yaşı bağımsız risk faktörü olarak belirlendi. (OR: 0,501, *P*<0,001, 95% CI: 0,390-0,643).

Sonuç: Okul çağı çocuklarda preoperatif kaygı ile ebeveyn kaygı arasında etkileşim yoktur. Küçük yaş, çocukta kaygı gelişimi için bağımsız risk faktörüdür.

Anahtar kelimeler: Kaygı, m-YPAS, Ebeveyn kaygı, STAI

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Introduction

Endoscopy is a diagnostic and treatment tool used by pediatric gastroenterologists to detect underlying organic pathologies in diseases of the gastrointestinal tract in the pediatric population. Endoscopy is usually performed under general anesthesia or deep sedation in children [1]. Medical procedures such as endoscopy can be a negative experience for children. Not only the child undergoing endoscopy, but the whole family can experience stress and anxiety [2]. The most common subject of anxiety among patients and parents are "Pain" and "Endoscopy-related accidents," respectively, before the procedure. The difficulty both patients and parents experience before and after the procedure regards "Hunger." By explaining these specific concerns, it is possible to reduce the anxiety of both patients and parents before endoscopy [3].

In addition, research has shown that the child's social compatibility, cognitive ability, temperament (sociability and activity) and age are predictors of preoperative anxiety [4,5]. Age and cognitive maturation are the most important predictors of preoperative anxiety in children [5]. In the preschool group, parents' anxiety level is higher. There is a close relationship with preoperative anxiety between preschool children and parents [6]. The presence of a close correlation between the periprocedural anxiety of parents and children provided further support for this observation [7,8].

The aim of this study is to determine the anxiety levels of the parents and patients who were routinely informed before the procedure and examine the relationship between children's and parents' state and trait anxiety.

Materials and methods

Setting and participants

Necmettin Erbakan University ethics committee (2019/2059) approval and written consent from the legal guardian of each patient were obtained for the study. The study included children aged 6-14 years undergoing endoscopy under deep sedation, with American Society of Anesthesiology (ASA) scores of I-II, and their parents.

Patients with major chronic disease and neurological disease, patients and parents with communication difficulties and psychiatric illnesses, illiterate parents, patients and parents who did not volunteer were excluded from the study.

G*Power Software was used to determine the sample size. A total of 100 patients were needed for the F test with 90% power, 5% type I error level, and 25% effect size. 104 patients were enrolled, considering the possibility of exclusion.

Survey study

Immediately after the pediatric patient was taken to the treatment room, the parents were given a questionnaire to complete in privacy and without any pressure. The parental questionnaire consisted of 2 groups: The parental demographic questionnaire and the State-Trait Anxiety Inventory (STAI). The first group demographic questionnaire includes questions regarding age, gender, siblings of the child, level of parent education (primary / high school / higher education), parental residence (province / district / town / village), the order of birth of the child who underwent the endoscopic procedure and whether they received anesthesia before.

State-Trait Anxiety Inventory

STAI is a self-reporting questionnaire that examines anxiety in parents. The scale consists of two separate measurements for trait (temperament or normal) anxiety and state (current or situational) anxiety, respectively [9]. The score ranges from 20 to 80 for each subscale and higher scores indicate higher levels of anxiety.

For each statement in the questionnaire, the participant was asked to choose between "almost never", "sometimes", "often" and "almost always". Items 3, 4, 6, 7, 9, 12, 13, 14, 17 and 18 were scored positively, while 1, 2, 5, 8, 10, 11, 15, 16, 19 and 20 were scored negatively. During the assessment, each item was scored between 1 (or -1) and 4 (or -4) (depending on its negative or positive value), and an additional 50 points were added to the total score.

Modified Yale Preoperative Anxiety Score

M-YPAS is used to assess children's preoperative anxiety. It contains 22 items in 5 categories (activity, emotional expression, state of arousal, vocalization, and use of parents).

Activity, emotional expression, state of arousal, and use of parents include four items, while vocalization includes six items. Each item is given 1 point.

Total corrected score is calculated by the following formula: (Activity / 4 + emotional expression / 4 + state of arousal / 4 + use of parents / 4 + vocalization / 6) × 100/5 [10].

M-YPAS can be used both in the premedication unit and at the beginning of anesthesia [11]. In this study, m-YPAS was applied before anesthesia induction. m-YPAS score ≥ 30 indicates anxiety [12,13].

Patient characteristics and anesthesia management

The day before the procedure, during preoperative preparation, the anesthesiologist explained the method and risks of administering anesthesia to parents, after which consent was obtained. On the same day, the pediatric gastroenterologist told the parents about the procedure and the risks that may occur in detail, and consent was obtained.

Demographic data (age, gender, ASA, weight) of the patients were recorded. Intravenous cannula was placed by an experienced nurse with topical (lidocaine) local anesthesia in the gastroenterology pediatric ward. No premedication was administered to the patients. The children's anxiety level, immediately after separation from parents, was evaluated with m-YPAS by an anesthesiologist who was not included in the study. Routine monitoring (electrocardiography, heart rate (HR), non-invasive blood pressure, peripheral oxygen saturation (SpO2), end-tidal carbon dioxide (Et-CO2)) were performed to the patients, and basal values and values after induction were recorded. Bispectral Index Monitoring (BIS 40-60) was performed and the depth of anesthesia was noted. Sedation level was evaluated with the Ramsay sedation scale (RSS). All patients were administered O2 at 4 L / min with nasal cannula. In accordance with the standard practice, midazolam 1 mg, ketamine 1 mg / kg, and propofol to obtain 40 <BIS <60 were used in anesthesia. Total propofol dose and anesthetic agent doses consumed at the end of the procedure were noted. Anesthesia management was carried out by the same experienced

anesthesiologist. The endoscopic procedure was performed by an experienced pediatric gastroenterologist.

The duration of the procedure (the time between the start and the end of the endoscopic procedure) and recovery time (the time until the patient's modified Aldred score (MAS) was 10 in the postoperative care unit) were recorded. Complications (nausea, vomiting desaturation, hypoxia, etc.) were noted during the procedure and in the recovery room. Patients with Modified Aldred Scores of 10 were sent home with their parents.

Grouping of the patients

The patients were divided into two groups according to their anxiety levels. m-YPAS> 30 was considered the anxiety (+) group, while m-YPAS ≤ 30 comprised the anxiety (-) group.

Statistical analysis

Results of the study were analyzed using SPSS 19.0 software. Continuous variables were expressed as mean (standard deviation), and categorical variables as frequency and percentage (n, %). Data were tested for normal distribution with the Kolmogorov-Smirnov test, histogram and ±SD. Non-parametric data of the groups were compared using Mann-Whitney test and parametric data, with Independent t test. Categorical data were analyzed using Chi-square test. Spearman correlation test was used to investigate the relationships between parameters. Logistic regression analysis was used to identify independent predictors of anxiety. Regression analysis was performed with the significant parameters (age, ASA, gender, parental age, parental anxiety, location, number of siblings) determined by univariate analysis. P<0.05 was considered statistically significant.

Results

Demographic data of the patients

The study included 104 children between the ages of 6 and 14 years, who were to undergo endoscopy, and their parents. The mean age of the patients was 11.8 (2.6) years (6-14 years). The age and gender of the anxiety (+) (n=29) and anxiety (-) (n=75) groups were 8.8 (2.7) years, 12.9 (1.5) years (P<0.001) and Female/Male ratios (F/M) of 20/9, 45/30, respectively (P=0.5). There was no statistically significant difference between ASA scores of the groups (ASAI / ASAII=20/9 (n=29), 59/16 (n=46), (P=0.315)). The difference in weight comparison between groups (27.89 (10.26) (n=29), 45.33 (7.70) (n=75)) was significant (P<0.001) (Table 1).

Anxiety evaluation

The comparison of the anxiety levels of the groups is shown in Table 2.

Evaluation of hemodynamic data and anesthesia duration

There was no significant difference between basal hemodynamic data of the groups and hemodynamic data after anesthesia induction. Comparison of the anxiety (+) and (-) groups yielded no significant differences between procedure duration, recovery times, or additional propofol dose. However, complication rate in the group with anxiety was significantly higher than that of the group without (P=0.001) (Table 3).

Parental demographic data and anxiety levels

The mean ages of parents in the anxiety (+) and (-) groups were 37.3 (7.4) years and 41.2 (5.6) years, respectively (P<0.001). Parental anxiety levels were not statistically significantly different between the two groups (P=0.543 / P=0.529). Parental education level in the anxiety (+) group was statistically significantly higher than that of the anxiety (-) group (P=0.011) (Table 4).

Table 1: Demographic Data of the Patients

	Anxiety (+) group (n=29) mean (SD)	Anxiety (-) group (n=75) mean (SD)	*P*-value
Age (years)	8.8 (2.7)	12.9 (1.5)	<0.001
Gender (F/M)	20/9	45/30	0.500
ASA (I/II)	20/9	59/16	0.315
Weight (kg)	27.8 (10.2)	45.3 (7.7)	<0.001

ASA: American Society of Anesthesiology

Table 2: Comparison of the m-YPAS scores of the groups

	Anxiety (+) group (n=29) mean (SD)	Anxiety (-) group (n=75) mean (SD)	*P*-value
Activity	1.7 (0.7)	1.0 (00)	<0.001
Vocalizations	2.5 (1.1)	1.0 (0.1)	<0.001
Emotional expressivity	2.6 (1.0)	1.0 (00)	<0.001
State of apparent arousal	2.6 (1.1)	1.0 (00)	<0.001
Use of parents	2.3 (1.0)	1.0 (0.1)	<0.001
Total m-YPAS	55.5 (18.3)	23.5 (0.8)	<0.001

m-YPAS: Modified Yale Preoperative Anxiety Scale

Table 3: Comparison of hemodynamic data, anesthetic dose, and duration of anesthesia of groups

	Anxiety (+) group (n=29) mean (SD)	Anxiety (-) group (n=75) mean (SD)	*P*-value
Basal MBP	85.4 (11.8)	89.0 (8.6)	0.087
Basal SpO2	98.5 (1.2)	98.4 (0.8)	0.470
Basal HR	86.6 (7.6)	90.1 (4.9)	0.025
Basal $EtCO_2$	39.8 (11.6)	38.4 (2.4)	0.307
MBP after anesthesia induction	82.6 (10.3)	85.6 (8.9)	0.143
SpO2 after anesthesia induction	98.8 (0.7)	98.6 (0.7)	0.174
HR after anesthesia induction	86.3 (8.5)	90.7 (5.3)	0.012
$EtCO_2$ after anesthesia induction	38.0 (2.7)	38.7 (2.8)	0.270
Ramsay Sedation Score	5.8 (0.3)	5.9 (0.2)	0.103
Duration of procedure (min)	7.1 (2.0)	6.8 (2.0)	0.476
Duration of recovery (min)	14.5 (3.8)	13.1 (4.1)	0.132
MAS	9.9 (0.2)	9.8 (0.3)	0.287
Propofol dose (mg)	12.4 (17.2)	12.9 (17.8)	0.893
Complication			0.001
Nausea (n, %)	5 (17.2)	4 (5.3)	
Vomiting (n, %)	0 (0)	2 (2.7)	
Desaturation (n, %)	4 (13.8)	0 (0)	

MBP: Mean Blood Pressure, SpO2: Peripheral Oxygen Saturation, HR: Heart Rate, Et-CO2: End-tidal Carbon dioxide, MAS: Modified Aldred Score

Table 4: Comparison of parental demographic data and anxiety levels

	Anxiety (+) group (n=29) mean (SD)	Anxiety (-) group (n=75) mean (SD)	*P*-value
Parents			
Age (years)	37.3 (7.4)	41.2 (5.6)	<0.001
Gender (F/M)	22/7	52/23	0.632
Number of children	2 (1-4)	3 (1-6)	0.197
STAI-state of the parents	44.4 (9.3)	43.0 (10.6)	0.543
STAI-trait of the parents	44.9 (6.4)	46.1 (8.8)	0.529
Education level			0.011
Primary school (n, %)	15 (51.7)	46 (61.3)	
High school (n, %)	2 (6.9)	17 (22.7)	
University (n, %)	12 (41.4)	12 (16)	
Residential area			0.112
City (n, %)	26 (89.7)	55 (73.3)	
Village/neighborhood (n, %)	3 (10.3)	20 (26.7)	
Anesthesia story (+/-)	7 (24.1%)/22 (75.9%)	12 (16.0%)/63 (84.0%)	0.398

STAI: State-Trait Anxiety Inventory

Spearman's Rho correlation analysis of parameters related to child's anxiety

There was a strong negative correlation between child age (P<0.001), a negative moderate correlation between parental age (P=0.008), and a weak positive correlation between complications (P=0.026) and child's anxiety. Spearman's rho correlation of anxiety-related parameters is shown in Figure 1a, 1b, 1c.

Regression analysis

Logistic regression analysis including age, ASA, gender, parental age, parental anxiety, location, number of siblings was performed to determine the independent risk factors

that are effective in the development of child anxiety. Young age was determined as an independent risk factor for increased levels of child anxiety (OR: 0.501, $P<0.001$, 95% CI: 0.390-0.643).

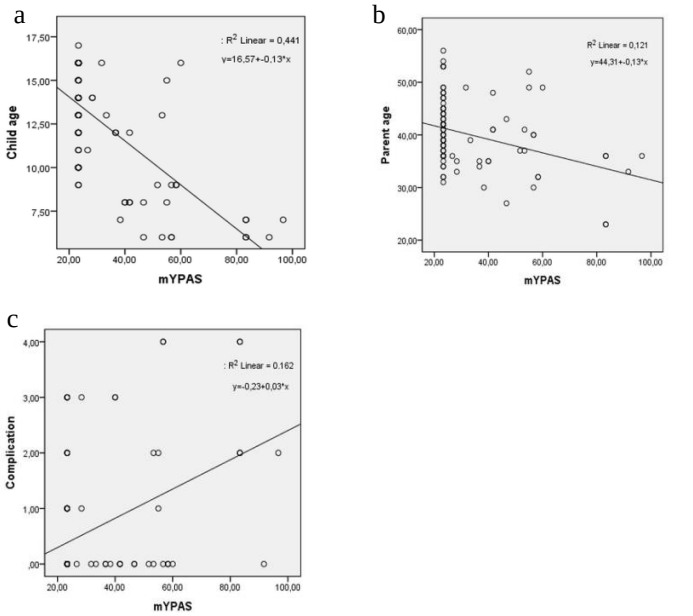

Figure 1: Spearman's Rho Correlation Analysis of parameters related to anxiety

Discussion

In this study, in which the anxiety level of school-age children who underwent gastrointestinal endoscopy was evaluated, young age was an important risk factor for anxiety development.

Many patients and parents are most concerned about the safety of endoscopy. Therefore, healthcare professionals performing pediatric gastrointestinal endoscopy should consider the anxiety of patients and parents before endoscopy [3]. Studies have found that the presence of an overly anxious parent during the induction of anesthesia does not benefit an anxious child and can increase anxiety in a calm child [14,15]. Intense anxiety and fear can cause poor cooperation, longer procedure time, increased sedation dose, and even increased complications [16]. It is known that there is a correlation between preoperative anxiety of children and parents' anxiety. The upcoming surgical stress can be perceived and transmitted between children and parents [17,18]. Emotional behaviors of parents have a significant impact on children modeling their parents' behavior [19], and coping mechanisms affect children's coping mechanisms [20]. However, such an interaction has been shown to be strong only in preschool children and their parents (state anxiety) [6].

In this study, routine information was given about the procedure and anesthesia. In this study, in which the study group was constituted by school-age children, it was observed that there was no relationship between child's preoperative anxiety and parental anxiety. There was a correlation between child age, parental age and child anxiety, and the rate of complications was significantly higher in highly anxious children. Schoolchildren are more independent and less affected by their parents, while preschoolers are still more dependent on their parents [6].

A study evaluating the preoperative anxiety levels in the parents of outpatients determined a relationship between the maternal anxiety score and the child's age [21]. In a child cohort evaluation including children between the ages of 2-16 years, they found that anxiety decreased with increasing age of children [22]. Young children are a risk factor for poor behavioral compatibility during induction [23]. Older children express less fear for preoperative preparations than younger children [24]. Older children can understand the necessity and requirements of the procedure, which helps them withstand it. Preparation of the child for the procedure and a pain-sensitive temperament can positively affect the child's response to a procedure [25,26].

In contrast to these studies, in a study that assessed the 3-12-year age group in Turkey, there was no significant correlation between the age of the child and maternal anxiety score [8].

While the mean age of the group with anxiety in the current study was 8.8 (2.7) years, it was 12.9 (1.5) years in the group without anxiety. In this study, although the study group comprised children in school age, the mean age of the children with anxiety was significantly lower. Young age was an independent risk factor anxiety. To reduce the preoperative anxiety of school-age children, it is useful to provide appropriate information directly to them [27].

Informing parents about procedures, communicating with doctors, and letting parents talk to other parents in a comparable situation reduces anxiety in parents and helps them support their children more effectively [4]. Factors that mothers thought would reduce maternal anxiety include getting more information from the doctor, talking with mothers who had anesthetic experience before, and being provided audiovisual information. It is thought that accompanying the child to the operating room and being present during the induction of anesthesia will decrease maternal anxiety [8].

A systematic psychological preparation provided to both parents and patients before endoscopy logically reduces the level of anxiety on procedures. Although the level of education affects the outcome of psychological preparation, it may not have a significant effect on the level of anxiety in parents [2]. One study reported that maternal education level had no effect on anxiety [28], while another stated that anxiety level increased with increasing maternal education level [29].

In our study, no information was provided to patients and parents other than routine information, since exclusive information and systematic psychological preparation is not always possible in intensive polyclinic conditions. It was observed that the education level of the parents of children with high anxiety was higher.

Limitations

This study was conducted in Turkey. There may be differences between pediatric gastrointestinal endoscopy-related anxiety situations between countries with diverse cultures. However, matching results have been emphasized in studies conducted in dissimilar cultures [6,22-25].

The second limitation of this study is that child anxiety risk factors were determined but their solutions were not mentioned. Future studies are needed to reduce anxiety, based on the results of this study.

Conclusion

This study showed that there was no interaction between preoperative anxiety in school-age children and parental anxiety.

Young age was determined as an independent risk factor for the development of anxiety in children. Attention should be paid to the height of anxiety in younger patients in the school age group and necessary precautions should be taken.

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Assessment of ear metric properties in young Turkish adults

Genç Türk erişkinlerde kulak metrik özelliklerinin değerlendirilmesi

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Ethics Committee Approval: This study was approved by Ethics Committee of Cukurova University on 1/10/2020; Meeting number: 95; Decision number: 36. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.
Etik Kurul Onayı: Bu çalışma, Çukurova Üniversitesi Etik Kurulu (10.01.2020: Toplantı no: 95; Karar no: 36) tarafından onaylanmıştır. İnsan katılımcıların katıldığı çalışmalardaki tüm prosedürler, 1964 Helsinki Deklarasyonu ve daha sonra yapılan değişiklikler uyarınca gerçekleştirilmiştir.

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Abstract

Aim: The ear is a critical component of the human face functionally and aesthetically. Studies in recent years have reported that the morphological properties of the outer ear show substantial differences based on sex and ethnic group. The data obtained in these studies are guiding for plastic surgeons.

Methods: This cross-sectional study was carried out on a Turkish population. Ear axis, antihelix angle, ear length, ear width, earlobe length and earlobe width measurements were made on 191 healthy adult volunteers (106 women, 85 men) between the ages of 18-25 years. Ear metric values mentioned above were compared between the genders, and correlation analysis was conducted for all.

Results: All values except the antihelix angle were larger in males (P=0.0486; P<0.001; P=0.004; P<0.001; P=0.038 for ear axis, length, width, ear lobule length and width respectively). The ear axis was positively correlated with the antihelix angle, the ear width and the ear lobule width and the ear length was positively correlated with the ear width and ear lobule length (P<0.001 for both).

Conclusion: Although our study has some limitations it includes noteworthy data about outer ear metric values of the young adult Turkish population which we believe is going to be beneficial to standardization and optimization in ear surgery.

Keywords: Pinna, Metric, Aesthetic, Anatomy

Öz

Amaç: Kulak, fonksiyonel ve estetik olarak insan yüzünün son derece önemli bir bileşenidir. Son yıllarda yapılan çalışmalar dış kulağın morfolojik özelliklerinin cinsiyete ve etnik gruba göre makul farklılıklar gösterdiğini raporlamıştır. Bu çalışmalardan elde edilen veriler plastik cerrahlar için yönlendiricidir.

Yöntemler: Çalışmamız Türk popülasyonu üzerinde gerçekleştirilmiştir. 18-25 yaşları arasında 191 sağlıklı yetişkin gönüllünün (106 kadın, 85 erkek) kulak ekseni, antiheliks açısı, kulak uzunluğu, kulak genişliği, kulak memesi uzunluğu ve kulak memesi genişliği ölçümleri yapılmıştır. Tüm parametreler cinsiyetler arasında karşılaştırılmıştır ve hepsi için korelasyon analizi yapılmıştır.

Bulgular: Anti heliks açısı dışında tüm değerler erkeklerde kadınlara göre daha büyük bulundu (P=0,0486; P<0,001; P=0,004; P<0,001; P=0,038 sırasıyla kulak ekseni, uzunluğu, genişliği, kulak memesi uzunluğu ve genişliği için). Kulak ekseni, antiheliks açısı, kulak genişliği ve kulak memesi genişliği ile pozitif korelasyon gösterdi ve kulak uzunluğu, kulak genişliği ve kulak memesi uzunluğu ile pozitif korelasyon gösterdi (her ikisi için P<0,001).

Sonuç: Çalışmamızın bazı sınırlılıkları olmakla birlikte, kulak cerrahisinde standardizasyon ve optimizasyon için faydalı olacağına inandığımız genç erişkin Türk popülasyonunun dış kulak ölçüm değerleri hakkında dikkate değer veriler içermektedir.

Anahtar kelimeler: Pinna, Metrik, Estetik, Anatomi

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Introduction

Reconstruction of the auricle (pinna) is technically difficult due to some factors. Before changing the shape of the ear, plastic surgeons need to have normal anatomical data that determine the normal shape, size, and direction limits of the ear. The auricle is one of the descriptive properties of the face. It is not a focus of beauty itself, but deviations in its symmetry, direction or projection may be easily noticed and divert a face from a sense of aesthetics [1]. Accordingly, some studies conducted recently have reported that every part of the outer ear is morphologically unique and shows substantial differences in individuals and population groups [2-4]. Additionally, the lateral notch found in its three-dimensional topography is a unique structure that contributes to a normal outer ear with its vertical placement and characteristic contour structure [1,2]. This unique structure of the ear may be helpful in determining the identity of individuals and in terms of anthropology and forensic medicine [4, 5].

A deformation in the shape and size of the auricle may indicate a possible congenital anomaly or syndrome in the patient [3]. The auricle is a flexible structure consisting of five main anatomical regions as the concha, helix, antihelix, tragus, and lobule formed by skin, cartilage and fat tissues [6]. A cartilaginous notch on the helix is known as “Darwin’s tubercle”, and it is a vestigial residue corresponding to the tip of the ear of some animals [4]. The contour of the auricle is determined by the configuration of the elastic cartilage frame [1, 4]. The skin of its lateral and medial surfaces contains hair with both sebaceous and sudoriferous glands. While the skin is laterally tightly connected to the perichondrium, medially, it is only loosely connected. The cartilage of the auricle is an extension of the meatus acusticus externus cartilage, and it is fixed on the cranium with a few ligaments and muscle connections [1].

Embryologically, the outer ear starts to form within 6 weeks of pregnancy and completes its formation up to the 18^{th} week. Six tissue elevations known as the hillocks of His develop. Each of these elevations shape different parts of the outer ear. The first three elevations originate from the first branchial arch and combine to form the tragus, helix, and antitragus, whereas the next three elevations originate from the second branchial arch and form the antihelix and concha. The ear lobule (lobule) does not originate from these elevations [6]. Tragus, on the other hand, does not contain cartilage tissue although it develops from the first branchial arch. Incomplete fusional conglomerations of the branchial arches lead to malformations of the outer ear. During arrangement of the formed deformities with otoplasty, instead of individual aesthetical perceptions, some ratios need to be used. Therefore, measurements that will provide reconstruction and aesthetical perception compatible with the social population are required. In many studies, the structure of the ear has been examined metrically to reveal societal differences. Most of such studies have reported that ear dimensions are metrically variable in individuals and populations, ear measurement parameters are larger in men than women, and the ears show bilateral asymmetry [2,4]. It may be stated that data obtained from studies making metric observations provide evidence-based indicators regarding the ratios of an aesthetically pleasing ear. In summary, ear morphology is aesthetically important and shows differences between ethnic groups and genders [2,3]. For this reason, in our study, which we want to become a significant guide for the Turkish population in auricular surgery, in Turkish male and female individuals, ear axis, antihelix angle, ear length, ear width, lobule length and lobule width measurements were made, and they were compared between the genders. Correlation analysis was conducted for all parameters.

Materials and methods

All authors declare that the study was carried out in accordance with the World Medical Association Helsinki Declaration "Ethical Principles for Medical Research on Human Subjects".

Participants

This cross-sectional study was conducted with 191 healthy adult volunteers (106 women, 55.497%; 85 men, 44.503%) between the ages of 18-25 years after obtaining approval from the Ethics Board of Cukurova University (Ethical permission no:2020/95). Participants were informed about the study and gave individual consent. It was aimed to include healthy individuals in the study. For this reason, the inclusion criteria were determined as not having had any facial surgical operation and not having a history of any neurological disease. Among the 200 volunteers who were included at the beginning of the study, 9 volunteers who later refused to participate were excluded.

Measurements

The photographs of the participants which covered their entire profile were taken with a Digital SLR camera with constant photographing values (Canon EOS 80D; ISO 100 f / 4.5). The photography system was set up by fixing the camera with an adjustable tripod. The tripod height was adjusted based on the height of each individual. In the photography procedure, each individual was firstly asked to stand up and relax, and they were then put into the Frankfurt Horizontal Plane (FHP) position, which is the natural head position. FHP is considered the natural anatomical position of the human skull. This plane passes through the lower edge of the orbita and the upper edge of the external auditory meatus and is a significant reference for surgeons [7]. Reports have stated that FHP is an adequately reliable reference plane for different treatments and studies [8]. For this reason, in our study, we preferred to use FHP while making the measurements. The images taken on this plane were then transferred to a computer. The ear axis, antihelix angle (angle between the antihelix and the vertical), ear length, ear width, lobule length and lobule width were measured by using the Image J 1.52a program. The physiognomic ear length was measured by following the long axis of the ear as the direct distance between the supra-auricula and sub-auricula. While measuring the ear length, the distance between the very tip of the lobule to the farthest point of the auricle was used. The physiognomic ear width was measured as the direct distance between the pre-auricula and post-auricula. The ear width was measured in two ways as a and b (Figure 1). The lobule length was measured as the direct distance between the incisura intertragica and the deepest point in the sub-auricula. The lobule

width was measured at the center point of the lobular length as the distance between the anterior lobule and posterior lobule. The ear axis angle was considered the angle between the axis where the ear length measurement was made and the vertical plane. The measurements were made with a precision of 1/100 mm.

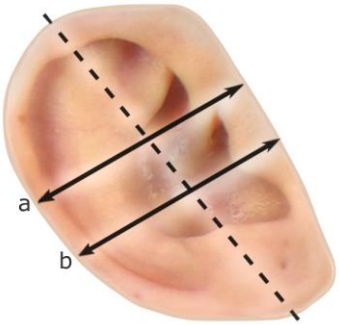

Figure 1: Presentation of ear width a and b measurement method on a volunteer

Statistical analysis

For the statistical analysis of the measurement results, the SPSS Windows version 24.0 package software was used. As n>30, Student's t-test was used to compare the variables between genders. The values are presented as mean (standard deviation). As n>30, the Pearson's correlation coefficient was used for correlation analysis. In all analyses, $P<0.05$ was considered statistically significant.

Results

In the comparison of the metric properties of the ear between the genders, almost all parameters turned out to be larger in the males than the females: The ear axis, ear length, ear width a and b, lobule length and width were all significantly higher in males ($P=0.049$, $P<0.001$, $P<0.001$, $P=0.004$, $P<0.001$ and $P=0.039$, respectively). There was no statistically significant difference between the genders in terms of the antihelix angle (Table 1).

Correlation analyses between ear metric properties yielded that there was a positive strong correlation between the ear axis and antihelix angle (r=0.417, $P=0.001$), the ear axis and ear width b (r=0.307, $P=0.001$) and the ear axis and lobule width (r=0.270, $P=0.001$). There was a significant positive correlation between the antihelix angle and ear width b (r=0.168, $P=0.020$), the ear length and ear width a (r=0.153, $P=0.034$), a positive strong correlation between the ear length and ear width b (r=0.660, $P=0.001$), ear length and lobule length (r=0.603, $P=0.001$) and ear length and lobule width (r=0.286, $P=0.001$). There were positive, strong and significant correlations between the ear width b and lobule length (r=0.361, $P=0.001$), ear width b and lobule width (r=0.530, $P=0.001$) and lobule length and lobule width (r=0.437, $P=0.001$) (Table 2).

Table 1: Comparison of ear metric properties between sexes

	Male (n=85)		Female (n=106)		*P*-value
	Mean	SD	Mean	SD	
Ear axis (°)	16.29	2.203	15.62	2.416	0.049
Antihelix angle (°)	61.95	8.586	60.76	9.152	0.360
Ear length (cm)	74.19	6.714	68.75	7.01	<0.001
Ear width a (cm)	41.04	4.584	37.6	3.987	<0.001
Ear width b (cm)	31.69	3.848	30.13	3.492	0.004
Ear lobule length (cm)	18.18	3.083	16.45	2.652	<0.001
Ear lobule width (cm)	22.32	3.848	21.21	3.306	0.039

SD: Standard deviation, cm: Centimeters

Table 2: Correlation analysis between ear metric properties

Variable 1	Variable 2	r	*P*-value
Ear axis (°)	Antihelix angle (°)	0.417	<0.001
Ear axis (°)	Ear width b (cm)	0.307	<0.001
Ear axis (°)	Earlobe width (cm)	0.270	<0.001
Antihelix angle (°)	Ear width b (cm)	0.168	0.020
Ear length (cm)	Ear width a (cm)	0.153	0.034
Ear length (cm)	Ear width b (cm)	0.660	<0.001
Ear length (cm)	Earlobe length (cm)	0.603	<0.001
Ear length (cm)	Earlobe width (cm)	0.286	<0.001
Ear width b (cm)	Earlobe length (cm)	0.361	<0.001
Ear width b (cm)	Earlobe width (cm)	0.530	<0.001
Earlobe length (cm)	Earlobe width (cm)	0.437	<0.001

cm: Centimeters, r: Correlation coefficient

Discussion

Knowing about the morphological properties and normal anatomical dimensions of the auricle is important in the diagnosis and surgical planning of congenital and acquired malformations [5]. The objectives of ear surgery include basing the ratios of an aesthetically pleasing ear on not the personal aesthetical views of surgeons but evidence-based data. Therefore, it is important to create standard measurements. Human auricles have a unique shape and are a well-known part of our auditory system. The shape of the outer ear is far from random, and it has developed to allow spatial localization of sounds. As it performs shape-specific filtering, it mediates monoaural cues, while it mediates binaural cues due to the bilateral localizations of the right and left ears [9]. The distance of the ear to the lateral orbital edge is approximately the same as the height of the ear [6]. The apex of the ear should be on the level of the eyebrows. The auriculocephalic angle is ideally between 25 and 35 degrees, while angles of larger than 45 degrees are considered too high. A scapha-conchal angle of lower than 90 degrees is ideal, and an angle larger than 90 degrees leads to a less aesthetical appearance by causing the scapha and fossa triangularis to protrude anteriorly rather than laterally. The helical edge needs to protrude from the head by 15 to 20 mm [1].

According to published reports, the average length of an ear is 55 to 65 mm, and the average width is 55% of the length [1]. Moreover, it is known that the morphology of the ear differs between genders [2,3]. In their study which investigated the dimensions of the auricle based on the factor of gender, Verma et al. [5] found that the two ears were symmetrical, and measurements (upper-tragus ear length, lower-tragus ear length, ear width, concha length, concha width, lobular height, lobular width) were higher among men than women [5]. In our study with healthy Turkish volunteers between the ages of 18-25 years, similar to previous studies, the ear axis, ear length and ear width were larger in the males than females. On the other hand, Senthil Kumar and Selvi [3] found that, although the total ear length was larger in men, the lobule length and width were almost the same between men and women [3]. In our study, the lobule length and width were significantly larger in males than females. It is possible that this significant finding could have been caused by the differences in ethnic groups and ages. However, it should still be kept in mind looking at our findings that the difference between the genders was larger in terms of the ear length and ear width a. As it was previously reported that there is no significant relationship between head size (height /width) and ear size (length / width) [2], our study did not assess head dimensions.

Previous studies have observed that the antihelix angle does not vary based on the ethnic group, but there is a statistically significant reduction by increasing age in both men and women. It is thought that the elongation of the ear might affect this [2]. The results of our study also showed that difference in genders does not create a significant difference in terms of the antihelix angle. Not finding a significant difference between ethnic groups and gender in this parameter may be related to the fact that the antihelix angle shows a large variation among individuals. Consequently, the data suggest that the antihelix angle plays an exceedingly small role in defining a normal ear. In addition to this, another significant aspect of the shape of the outer ear is its uniqueness from one person to another on the level seen in fingerprints and facial properties [9]. Considering that, in the embryonic period, the antihelix and concha develop from different tissue elevations than the tragus, helix and antitragus [6], we recommend the necessity to investigate the place of the antihelix in more detail in terms of the significance of the ear in identification in forensic cases. The correlation between the ear axis and the antihelix suggests that antihelix characteristics may be also important for the function of sound localization.

The auricle grows based on age. The auricle grows fast in the first 3 years of life and reaches approximately 85% of the adult size at ages 6 to 8 and 95% at ages 8 to 10 [1]. The auricle reaches its adult size at the age of 13 in men and 12 in women [3]. In the last few years, ear dimensions in different ethnic groups have been investigated in various studies where direct and indirect anthropometrics and photography were used [10]. Although there are ethnic differences, all these studies have reported that the auricle's dimensions significantly increase by age in both men and women due to changes in elastic fibers after adulthood (even after reaching skeletal maturity) [3,10]. Previous studies showed that age-related dimensional changes are not the same for all variables; the ear length continues to increase faster and for a longer time in comparison to the ear width [10]. While our study provides findings on young adults, considering this continuing development of the ear, it will be important to collect data from different age groups to create a broad guide for Turkish plastic surgery. Our study showed a correlation between ear length and ear width. The further increase in the ear length in further years than the ear width may reduce this correlation.

The RoB 2 tool (22 August 2019 version) was used to estimate potential bias. Analysis showed low risk for randomization process, deviations from intended interventions, missing outcome data and some concerns for measurement of the outcome. The low risk for overall bias can be counted among the strengths of this study.

Limitations

The auricle reaches its adult size at the age of 12-13 [3]. However, the ear length and width continue to increase by age [10]. In our study, measurements were made only in a certain age group, and the lack of age-related comparisons are an important limitation. Besides, body mass index, which is an indicator of body fat level, was associated with soft tissue thickness and positively correlated with ear length and width [11]. Body mass index of the volunteers was not calculated in this study. This prevents the study from providing more extensive information. Furthermore, the contribution of the outer ear to the aesthetic perception is not limited to its own metric properties. The distance of the outer ear to the eyes, the location on the head, the auriculocephalic angle, scapha-conchal angle are also critical parameters for aesthetic perception. Although our data give clues about aesthetic appearance, we do not deal with all aspects of aesthetic perception in the absence of this information.

If future studies are designed to overcome the limitations of our study in more comprehensive groups, it will be possible to create a more consistent and useful atlas for ear surgeries. In addition, there is a need of literature for studies examining the contribution of the outer ear shape to hearing function. The morphology of the external auditory canal has previously been studied radiologically [12]. The evaluation of the features of the outer ear shape and the outer ear canal can be an interesting and unexpected study.

Conclusions

Studies on the ears usually aim at treatment of congenital deformities and development of surgical techniques for reconstruction of ears that are traumatically injured. Every individual wants to have ears that look normal and aesthetically pleasing, and this demand is the highest among individuals with congenital or acquired deformities of the ear. Achievement of good functional and aesthetical rehabilitation does not only increase the self-confidence of the person, but it also means better social acceptance. The dimensions of the outer ear and its various parts vary in different ethnic groups, and this requires surgeons to base their reconstructions on data collected from each ethnic group. In this sense, we believe our study includes noteworthy data regarding the young adult Turkish population.

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Management of resistant de Quervain tenosynovitis with local anesthetic (neural therapy): A case report

Dirençli de Quervain tenosinovitinin lokal anestezik ile tedavisi (nöralterapi): Olgu sunumu

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Abstract

De Quervain tenosynovitis is the most common reason of lateral wrist pain. Treatment consists of splinting, non-steroid anti-inflammatory drugs, and corticosteroid injections. Neural therapy (NT) is a treatment modality using injections with local anesthetics for diagnosis and treatment. Musculoskeletal disorders can be cured by NT. We herein present the management of resistant de Quervain tenosynovitis by neural therapy in a 45-year-old male patient, who was referred to our outpatient clinic with the complaint of right wrist pain lasting over 2 years. His pain was 7/10 based on visual analog scale which had gradually increased. The patient also stated that he could not lift bags and had experienced neck pain 2 years ago. He was engaged in the neural therapy program with the diagnosis of cervical discopathy and tenosynovitis. After 3 sessions he had improvement in functional outcome and pain. In the treatment of resistant de Quervain tenosynovitis accompanying cervical discopathy, neural therapy is an effective and safe method.

Keywords: De Quervain tenosynovitis, Local anesthtetic, Neuraltherapy

Öz

De Quervain tenosinoviti lateral el bilek ağrısının en sık nedenidir. Tenosinovitin tedavisinde splintleme, non-steroid anti inflamatuar ilaçlar ve kortikosteroid enjeksiyonları kullanılır. Nöralterapi (NT), lokal anestezikler kullanılarak yapılan bir tanı ve tedavi yöntemidir. Kas iskelet sistemi bozuklukları NT yaklaşımıyla tedavi edilebilir. Bu vaka sunumunda dirençli de Quervain tenosinovitinin nöralterapi yaklaşımıyla yönetimi sunulmuştur.45 yaşında masabaşı işe sahip erkek hasta polikliniğimize 2 yıldan uzun süredir devam eden sağ el bilek ağrısı şikayetiyle başvurdu. Vizüel analog skalaya göre hastanın ağrısı 7/10 idi ve günden güne ağrısının arttığını ve çanta taşımada sorun yaşadığından şikayetçi idi. Hikayesinde 2 yıl önce boyun ağrısı mevcuttu. Nöralterapi programına servikal diskopati ve tenosinovit tanılarıyla alındı. 3 seans sonra hastanın fonksiyonel son durumu ve ağrısında iyileşme saptandı. Servikal diskopati ile beraber dirençli de Quervain tenosinovitinin tedavisinde nöral terapi efektif ve güvenli bir method olarak uygulanabilir.

Anahtar kelimeler: De Quervain tenosinoviti, Lokal anestezik, Nöralterapi

Introduction

De Quervain tenosynovitis, which was identified by Fritz de Quervain in 1895, occurs by stenosing abductor pollicis longus and extensor pollicis brevis tendons in the first dorsal extensor compartment of the wrist. Being the most common reason of lateral wrist pain, it is more frequently seen in the middle-aged women's dominant hand. Symptoms exacerbate with repeated ulnar deviation and thumb extension [1].

While its etiology is unclear, mixoid degeneration, fibrose tissue deposits and increased vascularity seems responsible in the acute inflammation of the synovial sheath. Tendon sheath thickening due to fibrose deposits in dorsal extensor compartment is blamed for stenosis [2]. It is diagnosed by physical examination: Pain in the wrist is present in Finkelstein test, which involves ulnar deviation. Plain radiography may be helpful in the absence of clinical findings [1,2]. Treatment of the tenosynovitis consists of splinting, non-steroid anti-inflammatory drugs and corticosteroid injections. Clinical symptoms may regress without any intervention. Surgery is required when the patient does not respond to medical treatment and injections [2].

Neural therapy (NT) is a treatment modality involving injections of local anesthetics for diagnosis and therapy. Its indications include functional disorders, inflammatory diseases, and acute or chronic pain [3-5]. NT can be divided into local (ex. Infiltration of trigger points) and segmental therapy (ex. sympathetic ganglia, nerve roots, and peripheral nerves) [6-8].

We herein present the management of resistant de Quervain tenosynovitis by neural therapy.

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Case presentation

A 45-year-old male patient with a desk job was referred to our outpatient clinic with the complaint of right wrist pain lasting over 2 years. He stated that his pain had increased, and he was unable to lift bags recently. Prolonged computer use on his desk lead to pain in his right wrist, which was 7/10 on visual analog scale (VAS). 2 years ago, he underwent cervical magnetic resonance imaging due to neck pain, which revealed C5-6 and C6-7 protrusions without root compression. Medical treatment reduced his neck pain.

He had no history of any chronic diseases or surgery. He did not have obesity or intestinal problems, but he led a sedentary life. In addition, he underwent treatment in his tooth number 46.

In physical examination, Finkelstein test was positive on his right wrist. Bilaterally C2 and right C3 transverse process sensitivity was present on palpation. Increased skin turgor and hyperalgesia were detected on the right C6-7 segments. Motor and sensory examination were normal. Right rotation of lower cervical vertebrae was limited, and while there was no limitation in neck flexion, it was painful. Investigation of trigger points on flexor and extensor muscles of forearm was negative. Although he had received physical therapy, medical treatment, corticosteroid injection and used splints before, there had been no significant decrease in pain or improvement in function.

He was engaged in the neural therapy program with the diagnosis of cervical discopathy, tenosynovitis and interference field (teeth). First session included tendon sheath and segmental intradermal injections (C5-6-7-8) along with T1-8 intradermal injections to regulate the sympathetic nervous system that innervates the upper extremity. His symptoms substantially decreased following the first session, but he had discomfort in using his hand in daily activities. Lower cervical vertebral limitation persisted. Injection of interference field (teeth), facet joints of C5-6-7-8 vertebras and tendon sheath was performed in the second session of the therapy. After the third session, his symptoms and sensitivity with palpation of the transverse processes showed significant improvement. Informed consent was obtained from the patient.

Discussion

De Quervain tenosynovitis is a stenosing tenosynovitis which occurs with repeated ulnar deviation and thumb extension. Diagnosis can be made with physical examination. Splinting, non-steroid anti-inflammatory drugs, physical therapy modalities and corticosteroid injections can be used for treatment [1]. Recently, it has been shown that de Quervain tenosynovitis involves tissue inflammation [9]. Local anesthetics have anti-inflammatory effects around the tendons in the fibro-osseous canal. This anti-inflammatory effect may arise from the injection of local anesthetics. Additionally, segmental intradermal therapy involving the C5-6-7-8 facet joints may help decrease sympathetic activity and pathological signs in supra-spinal levels. Sympathetic nervous system is known to play a role in chronic musculoskeletal pain due to the memory of its neurons. Local anesthetics also may cancel this memory [5,10].

Interference fields are regions that lead to increased sympathetic system activation, sending pathological signals to distant body areas [7]. The most prominent example of the interference field is non-living teeth. Karakan et al. [11] showed the importance of interference field in cervical pathologies from a holistic perspective. In our case there was just one non-living teeth which may lead to chronic and resistant musculoskeletal pain.

In cases which do not resolve with local injections, contributing cervical discopathy should be kept in mind. The patient described neck pain 2 years ago but since that time he has had only wrist pain, which may be the leading reason of missing the cervical pathology. Tenosynovitis can be assessed individually, however, co-existence of two processes resulted in resistance of symptoms.

Previously, Rankin et al. [12] showed positive effects of corticosteroid/local anesthetic injections on de Quervain tenosynovitis, but there is need for further studies which evaluate the effect of local anesthetic injections.

Conclusion

In the treatment of resistant de Quervain tenosynovitis accompanying cervical discopathy, neural therapy may be an effective and safe method.

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Shock requiring thoracotomy after penetrating thoracic trauma: A case report

Penetran toraks travması sonrası torakotomi gerektiren şok kliniği: Olgu sunumu

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Abstract
Thoracic trauma is one of the leading causes of 25-50% of all traumatic injuries and death in the entire population. The main problem in thoracic traumas is the disruption of respiratory and hemodynamic functions. We aimed to investigate emergency thoracotomy performed in thoracic injury and its effect on patient mortality. In this case, we examined the time from the arrival of a 41-year-old woman with penetrating multiple injuries to the thorax to the decision to perform an emergency thoracotomy. Although the shock approach and resuscitation protocols were properly applied, an emergency thoracotomy was decided on, since there was no improvement in the patient's clinical condition and active bleeding was observed in FAST ultrasonography. The patient, whose vital values improved after thoracotomy, was discharged from the hospital after 1 week of intensive care and service follow-up. It should not be forgotten that performing an emergency thoracotomy in intrathoracic penetrating injuries is a key point in the patient's survival.
Keywords: Thorax, Trauma, Penetrating injuries

Öz
Toraks travması tüm travmatik yaralanmaların %25-50'sinin ve tüm yaş grubunda ölümün önde gelen sebeplerinden biridir. Toraks travmalarında ana sorun, solunumun ve hemodinamik fonksiyonların bozulmasıdır. Biz bu çalışmada acil servise ulaştığında yaşamsal değerleri bozulmuş ve resüsitasyona cevap vermeyen bir toraks yaralanmasında yapılan acil torakotomiyi sunmayı amaçladık. Bu vakada toraksa penetre multipl yaralanmaları olan 41 yaşında bir kadın olgunun hastaneye gelişinden acil torakotomi kararı alınmasına kadar olan süreyi inceledik. Şok yaklaşımının ve resüsitasyon protokollerinin uygun biçimde uygulanmasına rağmen hastanın klinik durumunda iyileşme olmaması ve yapılan FAST ultrasonografisinde aktif kanama görülmesi üzerine hastaya acil torakotomi kararı alındı. Torakotomi sonrası yaşamsal değerlerinde düzelme görülen hasta 1 haftalık yoğun bakım ve servis takibinin ardından ayaktan taburcu edildi. Şok yaklaşımı doğru bir şekilde uygulanmış olmasına rağmen, toraks içi penetran yaralanmalara acil torakotomi endikasyonu kararının alınmasının ve uygulanmasının hastanın mortalitesinde kilit bir nokta olduğu unutulmamalıdır.
Anahtar kelimeler: Toraks, Travma, Penetran yaralanma

Introduction

One of the significant causes of mortality among young adults is multiple traumas, reason mostly being accompanying solid organ injuries [1]. Eighty-five percent of the thoracic traumas are blunt traumas [2]. In their study on 34120 trauma cases between 1993 and 2002, Demetriades et al. [3] reported 65% blunt and 35% penetrating thoracal traumas [3]. Among all thoracic traumas (including blunt or penetrating), approximately 10% require surgical intervention [4].

The main problem in thoracic traumas is the disruption of respiratory and hemodynamic functions. The first group of patients die at the scene of accident; in most cases the cause is cardiovascular injuries. The second group of patients are lost within the first hour, because of uncontrolled bleeding and respiratory failure. The third group of patients die due to late complications such as infection, myocardial damage, and pulmonary embolism. In this case, we aimed to examine the importance of emergency thoracotomy in the management of uncontrolled bleeding in patients included in the first and second groups.

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Case presentation

A 41-year-old female patient with no known diseases was stabbed in many places in front of her apartment and brought to the hospital by the ambulance. When the patient was found, she had many penetrating injuries, the majority of which were on the thorax. Her Glasgow coma scale score was 8. The patient was fixed with a trauma board and a neck collar by the first-response team, and fluid resuscitation was started during transport. When the patient arrived at our hospital, her Glasgow coma scale score had dropped to 7. Her blood pressure was 69/25 mmHg, oxygen saturation at room air, 100%, and pulse was 105 beats/min. On physical examination, there was a stab wound about 10 cm-long, involving the skin, subcutaneous tissue, and the platysma muscle in the lower 1/3 half of the neck, from which there was no active bleeding. There was a 2-cm-long stab incision at the level of the 3rd costa on the sternum, which was actively bleeding. Additionally, there were two 7-cm-long incisions on the left scapula, one 8 cm-long incision on the right forearm, one 4-cm incision on the first and second fingers in the right hand, one 10-cm-long incision lateral to the left humerus, and numerous about 3-cm-long incisions in the distal interphalangeal joints on palmar aspect of all fingers of the left hand. The patient, who was unconscious and had difficulty breathing, was considered to have stage 4 shock, and intubated. She was administered 1000 cc 0.9% NaCl intravenously within 20 minutes, 2 units of non-specific 0 Rh-erythrocyte suspension in 20 minutes, and 1 gram of tranexamic acid in 100 cc of 0.9% NaCl in 10 minutes.

FAST ultrasonography performed at the bedside revealed fluid in the right upper quadrant in the Morrison space and B line in the left lung. Her hemoglobin value was 8 g/dL, platelet count was 224 000/mm^3 and leukocyte count was 13,300/µl at presentation. Biochemistry results were as follows: ALT (Alanine Aminotransferase): 11 U/l, AST (Aspartate Aminotransferase): 21 U/l, creatinine 1.12. mg/dl, BUN (blood urea nitrogen): 32.1 mg/dl, K: 3.5 mEq/l, Na: 131 mEq/l. After administration of erythrocyte suspension, her hemoglobin value was 6.7 g/dl in blood gas. Massive hemothorax was detected in the left lung (Figure 1), and there was pulsatile hemorrhage from the left scapular and left mammarian incisions. The thoracic surgery team was notified.

The patient, whose vascular injuries, lung parenchymal incisions and diaphragmatic incisions were repaired during the operation, was taken to the intensive care unit postoperatively (Figure 2). After the operation, the patient's hemoglobin value was 8.2 g/dl, platelet and leucocyte counts were 98.000/mm^3 and 16,400/µl, respectively. Biochemistry analysis of the blood sample revealed the following results: ALT: 13U/l, AST: 39 U/l, BUN: 27.82 mg/dl, creatinine: 0.63mg/dl, K: 4.1 mEq/l, Na: 144 mEq/l. The patient's troponin value after cardiopulmonary resuscitation was 1.527 ng/ml. The patient, whose clinical and laboratory values improved after 1 week of intensive care follow-up, was transported to the ward, and 10 days later, she was discharged. During discharge, her hemoglobin value was 9.7 g/dl ALT: 44 U/l, AST: 56 U/l, BUN: 12.4 mg/dl, creatinine 0.56 mg/dl, Na: 137mEq/l, and K: 3.7 mEq/l. She was followed-up uneventfully.

Figure 1: Chest x-ray at the presentation of the patient

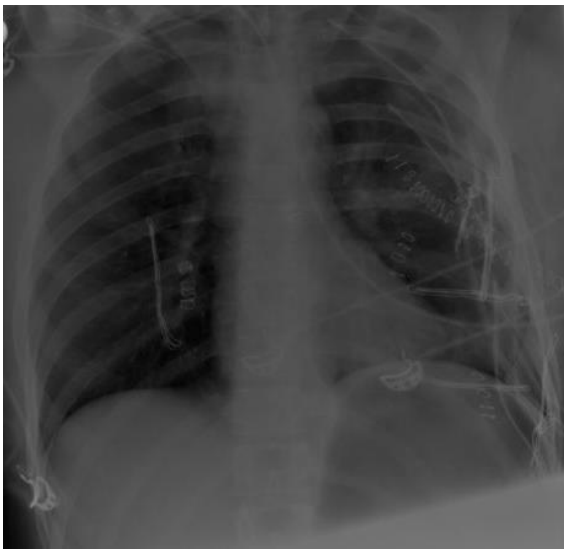

Figure 2: Chest x-ray after thoracotomy

Discussion

The form and time of trauma is highly significant in a patient with thorax trauma. If the patient is conscious, anamnesis should be obtained from the patient and eyewitnesses of the event in detail and quickly. Meanwhile breathing and circulation should be checked. It should be remembered that cervical spine injury may occur during evaluation of the head and neck region for airway obstruction. In case of unconsciousness, airway obstruction can easily occur due to tongue obstructing posteriorly, blood, vomit, secretion, foreign body aspiration, and crushing of the larynx and trachea. During inspiration, chest movements or paradoxical movements that do not participate in breathing should be evaluated by monitoring chest movements. Pulse and skin color should be checked to monitor circulation. With palpation, pain, irregularities and crepitations in the chest wall can be detected. Percussion may reveal hyper or hyporesonance in case of pneumothorax or hemothorax. The presence and characteristics of respiratory sounds should be evaluated with auscultation. Depending on the severity of the trauma, the patient may present with shock. Our patient was in stage-4 shock at presentation [1-4].

Emergency thoracotomy is performed on patients who are faced with death due to trauma in emergency conditions. 10-15% of all thorax traumas require emergency thoracotomy.

These cases usually progress with massive hemothorax, cardiac tamponade, extensive thoracic injury, or major thoracic vascular injury. Rarely, tracheobronchial or esophageal injuries occur. In the remaining 85-90% cases, chest tube insertion, pain control and observation are sufficient. Thoracotomy performed from the 4^{th} or 5^{th} intercostal space is best for penetrating cardiac injuries. Clamshell incision on the left should be preferred in the event of a right hemithorax injury. The survival chances of patients who are emergency thoracotomy candidates increase with appropriate pre-hospital intervention and rapid transport. ET is still a life-saving attempt in a small patient population. Limited injuries to the chest wall rarely require surgical intervention. In this case, there were multiple isolated injuries to the chest wall, as well as penetration to the thoracic cavity. If not within the thorax, wounds can be sutured after bleeding control. Intercostal vascular injuries and hemothorax-causing injuries such as those to the internal mammarian artery can be detected. These injuries can be controlled by cauterization or ligation [5].

Hemothorax is the presence of blood in the thoracic cavity. Depending on the location, duration, and amount of bleeding, it can be followed up only by tube thoracostomy, or emergency thoracotomy may be required. FAST ultrasonography performed in our patient detected massive hemothorax in the left lung and a decision for a thoracotomy was made. Traumatic diaphragmatic rupture is seen in 4.5-6% of trauma cases. Although it usually occurs with penetrating traumas, blunt traumas may also be the cause. Possible diaphragmatic, thoracic, and abdominal joint injuries should be considered in penetrating injuries of the thoracic region below the nipple line. In our case, a penetrating injury was present in the midclavicular line at the left 2^{nd}-3^{rd} ribs, and FAST USG showed pulsatile hemorrhage in the internal mammarian artery. The defect in penetrating diaphragmatic injuries was smaller than those which occur with blunt trauma. Rupture is usually observed in the left diaphragmatic leaf (80-90%) [6].

Our patient was classified as stage 4 shock at the time of arrival at the hospital, a blood transfusion protocol was initiated, the patient was intubated, and surgical teams were informed. Blood transfusion in stage 3-4 shock patients is not the first option and indicated if the patient is unresponsive to intubation and fluid resuscitation. It should be taken into consideration that active bleeding may continue in the patient and physical examination and imaging should be further expanded. Emergency thoracotomy in patients with penetrating thoracic trauma is a key point in the patient's survival.

Conclusion

Even if shock is managed appropriately, it should not be forgotten that performing an emergency thoracotomy in intrathoracic penetrating injuries is a key point in the patient's survival.

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Case report
Olgu sunumu

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Primary retroperitoneal hydatid cyst in pancreatic head region

Pankreas başında primer retroperitoneal hidatik kist

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Abstract
A hydatid cyst in retroperitoneal space is uncommon and one in the pancreatic head region is rare. We hereby report a case of a 20-year-old male presenting with a retroperitoneal hydatid cyst of the pancreatic head region. Investigations revealed no hydatid cysts in other organs of the body. The diagnosis was confirmed at laparotomy and partial pericystectomy was performed. Hydatid cyst should be considered in the differential diagnosis of cystic lesions of retroperitoneal area.
Keywords: Retroperitoneal cyst, Hydatid disease, Echinococcosis, Abdominal mass, Cystectomy

Öz
Hidatik kistler genel olarak retroperitoneal boşlukta görülmez, pankreas başı bölgesinde ise oldukça nadir saptanır. Bu vaka raporunda, pankreas başı bölgesinde retroperitoneal hidatik kist ile başvuran 20 yaşında bir erkek olguyu sunmaktayız. Araştırmalar vücudun diğer organlarında hidatik kist olmadığını ortaya çıkardı. Tanı laparotomide doğrulandı ve parsiyel perikistektomi yapıldı. Retroperitoneal alandaki kistik lezyonların ayırıcı tanısında hidatik kist düşünülmelidir.
Anahtar kelimeler: Retroperitoneal kist, Hidatik hastalık, Ekinokokkoz, Abdominal kitle, Kistektomi

Introduction

Hydatid disease (HD) is an anthropozoonosis that is present endemically in the grassland or temperate regions of the world, particularly the Mediterranean region, South America, and Australia. However, due to increased migration, hydatid disease is becoming a worldwide health problem [1].

HD is caused by the infection of the larval stage of *Echinococcus granulosus* parasite belonging to family Taeniidae of the Cestode class [3].

In 85-95% of the cases, the liver and/or the lungs are involved and in only 5-15% of patients, the cyst occurs at other sites [2]. Hydatid cyst (HC) developing in retroperitoneal space without accompanied lesion in other organs is rare, and one in the pancreatic head region is extremely rare. To the best of our knowledge, no such case of HC developing in retroperitoneal region in close proximity to the pancreatic head, without its involvement, has been reported. Rarity of this entity prompted us to report the case.

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Case presentation

A healthy looking, 20-year old male visited the outpatient clinic of General Surgery with complaints of early satiety, a feeling of fatigue and fullness in the upper abdomen for three months. He had no history of trauma, nausea, vomiting, anorexia, yellowish discoloration of eyes or alteration of bowel habits. His medical history was not significant. He had no history of prior surgery.

On examination, his vital signs were within normal limits. A cystic lump measuring approximately 15 cm x 12 cm was palpated over the epigastrium, right hypochondrium and part of the left hypochondrium. The lump was spherical, well-defined, had a normal surface temperature, and non-tender. It did not move with respiration and was not contiguous with liver dullness. On examining the patient in the knee-elbow position the lump did not fall forward, signifying retroperitoneal location of the swelling. Hemogram revealed a hemoglobin of 11.2 g/dl, total leukocyte count of 14,900/cu.mm and differential count revealed 10% eosinophilia. His biochemical investigations including liver function test and renal function tests, coagulation profile and serum amylase and lipase levels were within normal limits. Contrast enhanced computed tomogram (CECT) of abdomen revealed thin walled, decreased attenuating lesions with multiple thin walled septations, measuring around 94 x 98 mm in longest dimensions (Figure 1). Focal posterior wall calcification was seen in the pancreatic head region. The mass displaced and compressed the common bile duct posterolaterally and the gall bladder posteriorly, with mild dilatation of intra hepatic biliary tract. It medially abutted the superior mesenteric artery (SMA) and vein and posteriorly abutted the right kidney and right renal vessels (Figure 2). Pancreas was mildly displaced. Investigations revealed no other cyst in liver, lungs or other organs.

Written informed consent was obtained from the patient for the surgery, photography and for publication of photographs. Under general anesthesia, laparoscopic surgical exploration was planned. Cyst was approached via the intraperitoneal route. It was adherent to the medial wall of duodenum, pancreas and SMA. It was decided to convert to open laparotomy. Abdomen was opened in upper midline. The lesser sac was entered by taking the omentum off the transverse colon and the attachments of the posterior gastric wall to the anterior surface of the pancreas. The large cyst was seen nested in the retroperitoneal tissue in duodenal C-curvature. The cyst was isolated from the abdominal cavity and other structures by four 20% hypertonic saline soaked mops. After placing stay sutures, a stab incision was performed in the cyst wall, cyst fluid was aspirated and hypertonic saline was poured in the cavity, which was re-aspirated after fifteen minutes. Due to thick adhesions with the SMA, partial pericystectomy with cauterization of the residual endocyst was performed. There was no communication with the pancreatic duct. A drain was placed and the abdomen was closed in three layers.

The drain showed minimal output. The patient, who recovered uneventfully, was discharged after three days on oral albendazole. The drain was removed on day seven. Sutures healed well and were removed on day 10. Histopathological examination of the aspirate from the cyst and tissue from cyst wall confirmed the diagnosis. The patient is in our follow-up for more than a year now and has no recurrence.

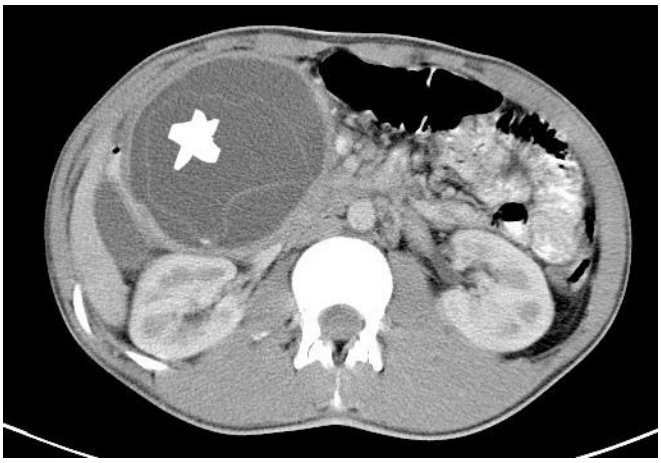

Figure 1: CT of abdomen showing thin walled decreased attenuating lesion (indicated by star) having multiple thin walled septations, measuring approximately 94 x 98 mm in longest dimensions.

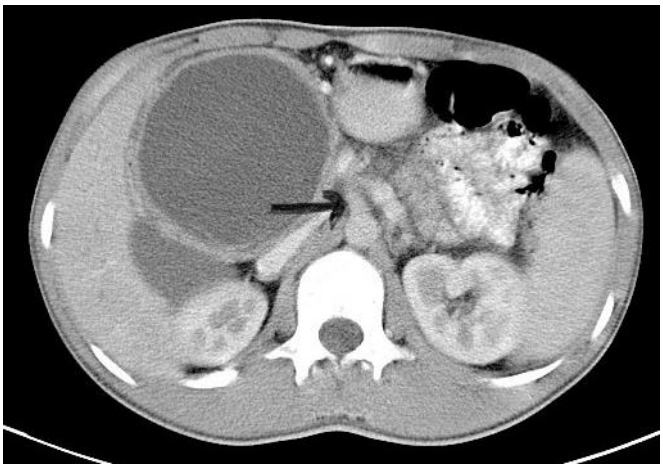

Figure 2: CT of abdomen showing Superior Mesenteric Artery (SMA) arising from the aorta. (indicated by arrow) Superior Mesenteric Vein is to the right of the SMA. SMA and SMV are adjacent to the cyst.

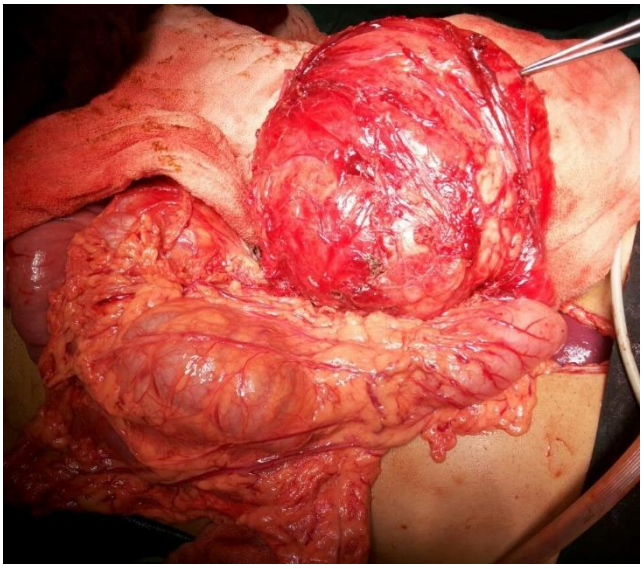

Figure 3: The transverse colon is reflected inferiorly, and mops are placed to cover the duodenum and liver. The forceps holds the pancreatic tissue. The pancreas head is stretched over the large cyst.

Discussion

Adult E. Granulosus lives in the intestinal tract of infected dogs. The parasite is transmitted to humans by the accidental consumption of soil, water, or food contaminated by the fecal matter of an infected dog. Echinococcus eggs deposited

in soil can remain viable for up to a year. In the stomach, the outer capsule of the egg gets digested and the freed larva (oncosphere) penetrate the duodenal/jejunal mucosa, enter the mesenteric venules and portal vein and reach the liver [3]. Larvae with diameters less than 0.3 mm pass through the sinus capillaries of liver into the vena cava and right side of heart and reach the lungs, where they are entrapped by pulmonary capillaries. Larvae that escape the lung may then pass to any organ of the body via arterial circulation.

Thus, the liver and lung account for the highest percentage of involvement. Isolated HC of the retroperitoneum is extremely rare [4]. A primary retroperitoneal HC without other organ involvement was first reported by Lockhart and Sapinza in 1958 and till 1973, only 9 cases had been reported in the literature [5,6]. Various modes of spread have been suggested to explain the escape of liver and lung involvement via lymphatics from the intestinal vessels to the thoracic duct or via veno-venous shunts within the liver and in the space of Retzius [7-9]

The larvae form cysts within the infected organs. The HC is a fluid-filled, spherical, unilocular cyst that consists of an inner germinal layer of cells (endocyst) and acellular laminated membrane. The outer layer, pericyst, forms due to the host response to the parasite and consists of modified host cells, fibroblasts, giant cells, and eosinophils [10].

Symptoms are usually due to compression as cysts increase in size [11]. When there are complications such as rupture and secondary infection, acute symptoms arise [5,7]. Rupture of the HC is the most common complication (about 15% of all cases). It may occur in the biliary tree causing acute cholangitis, or into the free peritoneal cavity with seeding daughter cysts in the peritoneum [1,2].

The differential diagnosis of a cystic retroperitoneal mass includes cystic lymphangioma, abscess, chronic hematoma, necrotic malignant soft tissue tumor, pancreatic cyst and hydronephrosis [12,13]. The establishment of diagnosis is based on the combination of clinical findings, imaging modalities, laboratory data and cytological information.

Abdominal ultrasonography is a sensitive tool for diagnosing HC with characteristic findings like floating membranes, hydatid sand and daughter cysts [14]. Presence of an undulating membrane and multiple daughter cysts within a mother cyst can suggest the diagnosis on CT and Magnetic Resonance Imaging [4,15]. The characteristic radiological findings described for hydatid cysts are often not present, as in our case.

Chemical tests include Casoni's test which is accurate in 90% of cases and Ghedini-Weinberg test which is accurate in 80% cases [16]. However, neither test is specific for this disease. Recently, many serological methods have replaced Casoni skin test to diagnose human hydatidosis. These methods include latex agglutination, indirect hemagglutination, counter immune-electrophoresis, enzyme-linked immunosorbent assay (ELISA) with whole hydatid fluid and with antigen 5 [17]. Indirect hemagglutination and ELISA are the most sensitive tests. Eosinophilia is detected in 20-50% of patients. [16,18,19]. Thus, serological tests are of limited value. A definite pre-operative diagnosis without histological examination is often difficult [20]. Delayed diagnosis and misdiagnosis increase the risk of impairment, recurrence, and sepsis.

Surgery is the cornerstone for treatment of HD [16,21]. Total cystectomy without contamination of the field is the procedure of choice. If total cystectomy is not possible, because of dense adhesions to important anatomical structures, partial cystectomy should be done [22]. A careful search for other abdominal and liver hydatid cysts should be made because secondary retroperitoneal hydatids far outnumber primary retroperitoneal HC.

Chemotherapy is effective when used in conjunction with surgery. A course of albendazole administered prior to surgery facilitates surgical manipulation of the cysts by inactivating protoscoleces, altering the integrity of the cystic membranes, and reducing the turgidity of the cysts [23].

Conclusion

Due to varied and vague symptomology, suspicion helps in the diagnosis of the HD. HC should be ruled out in cystic retroperitoneal lesions. HC can masquerade as more common lesions of the retroperitoneum. Surgical exploration with histopathological examination is the gold standard treatment. Total cyst excision must be aimed. Precautions should be taken to prevent catastrophic anaphylaxis.

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Sebaceous carcinoma of scalp with parietal bone destruction: A rare case presentation

Parietal kemik yıkımlı saçlı derinin sebasöz karsinomu: Nadir bir olgunun sunumu

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Abstract
Sebaceous carcinoma is a rare malignant tumor of the skin appendages, which occurs in the elderly. The most commonly involved site is the orbital region and it is rarely seen in the extra-orbital sites. We report a rare case of extra-orbital sebaceous carcinoma of the scalp with parietal bone destruction in a 45-year-old male. He was treated with wide local excision of the tumor with no regional or distant metastases. The patient received adjuvant chemo-radiation therapy, with no evidence of any local recurrence after one year of follow-up period. It is imperative to diagnose sebaceous carcinoma at an early stage to execute the primary treatment i.e., wide local excision and prevent recurrence of the tumor.
Keywords: Scalp, Sebaceous carcinoma, Bone destruction, Histopathology

Öz
Sebasöz karsinom, yaşlılarda ortaya çıkan, deri eklerinin nadir görülen kötü huylu tümörüdür. En sık tutulan bölge orbita bölgesidir ve orbita dışı bölgelerde nadiren görülür. 45 yaşında bir erkekte pariyetal kemik yıkımı ile ilerleyen, kafa derisinde orbita dışı sebasöz karsinomlu nadir bir olguyu sunuyoruz. Bölgesel veya uzak metastaz olmaksızın, tümörün geniş lokal eksizyonu ile tedavi edildi. Hasta, bir yıllık takip süresinden sonra herhangi bir lokal nüks olmaksızın adjuvan kemo-radyasyon tedavisi aldı. Birincil tedaviyi, yani geniş lokal eksizyonu gerçekleştirmek ve tümörün nüksetmesini önlemek için sebasöz karsinomu erken aşamada teşhis etmek zorunludur.
Anahtar kelimeler: Saçlı deri, Sebasöz karsinom, Kemik yıkımı, Histopatoloji

Introduction

Sebaceous carcinoma is a rare aggressive malignant tumor derived from the adnexal epithelium of sebaceous glands, seen frequently in the Asian population [1,2]. It commonly occurs in the peri-ocular region. Extra orbital sebaceous cell carcinoma is extremely rare, occurs on head and scalp due to the presence of abundant sebaceous glands [3]. Most sebaceous carcinomas have no obvious etiology, but few are associated with Muir-Torre syndrome and thought to arise from sebaceous glands in the skin [4].

Sebaceous carcinoma is classified into 2 groups, those arising from the ocular adnexa, particularly the Meibomian glands and glands of Zeiss, and those arising in extra ocular sites [4]. Ocular sebaceous carcinomas comprise 1% to 5.5% of all eyelid malignancies [5]. These tumors have a high incidence of local recurrence and regional metastasis. Early diagnosis is crucial in reducing the morbidity and mortality associated with the tumor [6]. We report a case of sebaceous carcinoma of the scalp with parietal bone destruction in a 45-year-old male, who presented with a painful gradually increasing scalp swelling over the parietal bone for the last 4 months.

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Case presentation

A 45-year-old male presented to the surgical outpatient clinic with a painful, gradually increasing scalp swelling over the parietal bone for the last 4 months. There was no discharge, fever, or any family history of malignancy. On examination, a solitary ill-defined tender erythematous mass measuring 4x2 cm was observed over the left parietal bone. The mass was mobile and firm to cystic in consistency. No regional lymph nodes were palpable and systemic examination was unremarkable. His routine blood investigations were within normal limits. Skull X-ray showed lysis of the parietal bone. CT scan of the head, neck, thorax, and abdomen was performed, which showed no evidence of distant metastasis, but destruction of the parietal bone. Magnetic resonance imaging of the brain revealed a small focal area of altered signal within the scalp in left posterior parietal region with cortical destruction of the underlying bone.

A wide local excision of the scalp swelling with local template flap was performed. Macroscopically, a polypoidal skin covered mass measuring 4x3 cm was seen. The cut section showed lobulated solid to cystic grey-white mass containing gelatinous material. Microscopically, the tumor comprised large round to polygonal cells arranged in trabeculae, nests, and cords in a hyalinized stroma, with abundant clear cytoplasm and oval hyperchromatic nuclei with distinct nucleoli (Figure 1 and 2) PAS stain showed strong positivity (Figure 3). On immunohistochemistry, the tumor cells showed cytoplasmic positivity for cytokeratin (Figure 4) and focal positivity for epithelial membrane antigen (EMA). The microscopic features demonstrated a malignant skin appendageal tumor compatible with sebaceous carcinoma. With the intent of decreasing the chances of local recurrence, adjuvant radiotherapy in the dose of 50 Gy in 20 fractions was delivered over 4 weeks using electron beam therapy. Currently, he has completed a follow-up period of one year after therapy, with no evidence of disease.

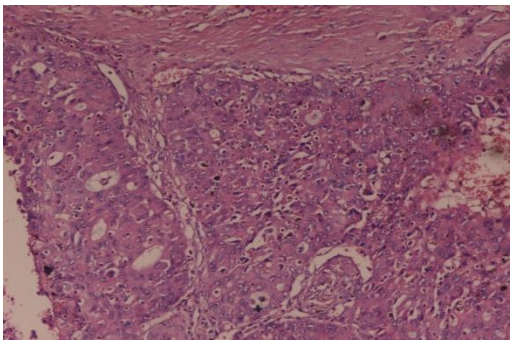

Figure 1: Microscopically, the tumor showed large round to polygonal cells arranged in trabeculae, nests, and cords in a hyalinized stroma, with abundant clear cytoplasm and oval hyperchromatic nuclei with distinct nucleoli. Hematoxylin and Eosin x 10X.

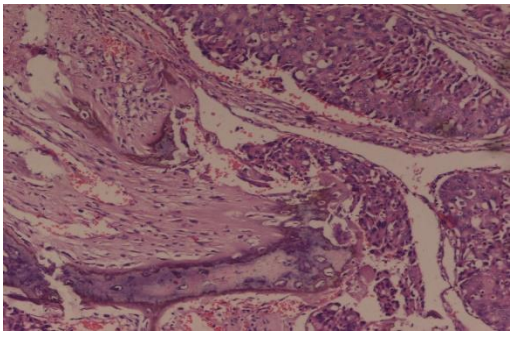

Figure 2: Section shows malignant cells in distinct lobules with strip of lysed bone. Hematoxylin and Eosin x 40X.

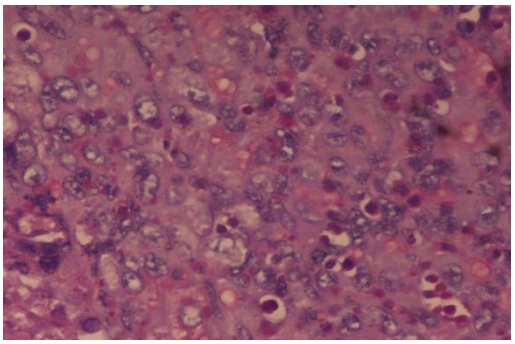

Figure 3: Section showed strong cytoplasmic PAS positivity. PAS stain x 40X.

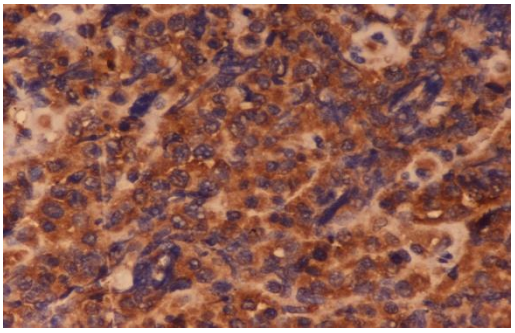

Figure 4: Immunohistochemistry showed strong cytoplasmic positivity for cytokeratin. IHC Cytokeratin x 40X.

Discussion

Sebaceous gland carcinoma is a rare aggressive cutaneous tumor, which occurs in the elderly [1]. The most frequent extra-orbital site for this tumor is skin in the head and neck region wherein sebaceous glands are most abundant [1]. Peri-orbital sebaceous carcinoma is three-times more common than the extra-orbital carcinoma. Extra-orbital tumors are known to show rapid growth with distant metastases [5].

Sebaceous carcinoma may occur in pre-existing dermatoses like naevus sebaceous and actinic keratosis or post radiation therapy for some cancerous diseases [6]. It has been associated with Muir-Torre syndrome which is an autosomal dominant dermatosis consisting of sebaceous neoplasms like sebaceous adenoma and sebaceous carcinoma, with associated visceral malignancy in the same individual, without any precipitating cause such as radiotherapy or AIDS [7]. Our patient was screened for Muir Torre syndrome with negative colonoscopy, ultrasonography of abdomen and chest and routine and microscopic urine examination findings.

Sebaceous carcinoma presents as a solitary, erythematous or pale yellow-colored, firm to hard, slowly growing nodule, with ulceration. It is seen with an increased frequency in the Asian population [2]. The gender predisposition of extraocular sebaceous carcinoma is equal in males and females, with mean occurrence age of 63 years [3]. This malignancy occurred in our patient at an early age of 45 years.

The four common histological patterns reported are lobular, comedo-carcinoma, papillary and mixed. The main histological picture is the lobular architecture, with cells showing marked nuclear pleomorphism and foamy vacuolated cytoplasm [4]. Some mature cells may show multiple cytoplasmic vacuoles with scalloped nuclei. Fat stains on frozen sections demonstrate fine lipid globules. Necrosis may be also present in the center of the tumor [8]. Siddhi et al reported local recurrence rates of 29.0%, regional nodal metastasis in 15%, and a disease-related

mortality of 20.0% in 91 cases with extra-ocular sebaceous carcinoma [4]. Adverse prognostic factors include poor differentiation, infiltrative growth pattern, multicentric origin of the tumor and size of the tumor more than 10 mm. Samarasinghe et al. have reported a case of sebaceous carcinoma of scalp with nodal metastasis [2].

The tumors of sebaceous glands are separated into three major categories: Sebaceous adenoma, basal cell carcinoma with sebaceous differentiation and sebaceous carcinoma [1]. Sebaceous carcinoma cells are large and may show squamous changes, and it should be differentiated from squamous cell carcinoma by hydropic changes in the cell cytoplasm. Tumor cells may show basaloid differentiation with presence of inconspicuous lipid vacuoles, and hence the tumor must be distinguished from basal cell carcinoma with sebaceous differentiation [9]. Immunohistochemical staining for EMA can differentiate sebaceous carcinoma from basal cell carcinoma and squamous cell carcinoma [10].

Complete surgical excision is the treatment of choice [11]. Sebaceous carcinomas tend to show 9 to 36% local recurrence within 5 years [12]. Metastasis to liver, lungs, bones, and brain have been reported in 14-25% of the patients [13]. Radiation therapy and chemotherapy have been used for regional and metastatic disease, with varying degrees of response. Only a few studies have shown satisfactory results of adjuvant chemotherapy in the treatment of sebaceous carcinoma with metastasis. There is one such report of complete response to systemic chemotherapy in metastatic sweat gland carcinoma to pleura, pericardium, and chest wall with 5‑fluorouracil after 3 months of follow up period [3].

Conclusions

Sebaceous carcinoma needs to be considered as a differential diagnosis for the cutaneous malignancies in all age groups. The timely recognition enables execution of the primary treatment i.e., wide local excision. Adjuvant radiotherapy may be considered to improve the clinical outcome of recurrent tumors.

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Case report
Olgu sunumu

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A rare case of cardiac tumor: Malignant fibrous histiocytoma

Nadir bir kardiyak tümör olgusu: Malign fibröz histiyositoma

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Abstract
Cardiac tumors are generally benign; however, they can rarely be malignant. Malignant fibrous histiocytoma is a type of sarcoma. Cardiac malignant fibrous histiocytomas are clinically and histologically confused with atrial myxomas. In this case report, we present a patient who was administered to the hospital with non-specific complaints, determined to have an intracardiac mass and subsequently diagnosed with malignant fibrous histiocytoma, which shortly recurred in the form of intracardiac masses after postoperative chemotherapy.
Keywords: Cardiac tumor, Malignant fibrous histiocytoma, Operative therapy, Chemotherapy, Recurrence

Öz
Kardiyak tümörler genellikle benign karakterdedir, fakat nadir de olsa malign karakterde seyredebilir. Malign fibröz histosiyoma bir sarkom türüdür, klinik ve histolojik açıdan atrial miksoma ile karışır. Biz bu vaka takdiminde, non-spesifik şikayetlerle başvuran bir hastada intrakardiyak kitle tespit edilmesinin sonrasında Malign Fibröz Histiyositoma tanısı alan ve cerrahi sonrası kemoterapi altında kısa sürede intrakardiyak kitleler şeklinde nüks yaşanan olguyu sunuyoruz.
Anahtar kelimeler: Kardiyak tümör, Malign fibröz histiyositoma, Cerrahi tedavi, Kemoterapi, Nüks

Introduction

Cardiac tumors are more easily diagnosed with developing imaging techniques. They are generally benign; however, they can rarely be malignant. Primary cardiac tumors are quite rare with an incidence around 0.0017–0.019%, and secondary heart tumors are significantly more common [1,2]. These cardiac masses can be asymptomatic or cause a wide range of symptoms that may even result in sudden death [3]. In this case report, we present a patient who was administered to the hospital with non-specific complaints, determined to have an intracardiac mass and subsequently diagnosed with malignant fibrous histiocytoma, which shortly recurred in the form of intracardiac masses after postoperative chemotherapy.

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Case presentation

A 61-year-old female patient who did not suffer from any chronic disease presented to the cardiology department of a medical center with the complaints of back pain, chest tightness, and palpitations which started following an upper respiratory tract infection. Echocardiography revealed moderate mitral insufficiency and a hyperechogenic mass (25x22 mm) in the posterior leaflet of the mitral valve, after which the patient was referred to our clinic. The physical examination did not reveal any pathology other than 2/6 mitral regurgitation murmur at the mitral focus. The echocardiography indicated the maximum pulmonary artery systolic pressure was 45 mmHg with moderate mitral and tricuspid regurgitation. We determined a hyperechoic mass (28x15 mm) adhering to the posterior leaflet of the mitral valve. Furthermore, we determined a mean diastolic pulmonary gradient of 17 mmHg which we attributed to the mitral stenosis caused by the mass on the mitral valve. We planned a transesophageal echocardiography (TEE) to more clearly evaluate the mass. The TEE revealed a mass (42x22 mm) in the left atrium adhering to the posterior region that extended towards the mitral valve, suggestive of a myxoma (Figure 1). There was moderate mitral insufficiency, but the myxoma was thought to affect mitral valve functions and cause mitral regurgitation. After the evaluation of the heart team, the patient was decided to undergo tumor resection and mitral valve replacement. The patient was preoperatively evaluated with a PET/CT scan to determine any other primary tumor or metastases. There only was focal pathological 18F-FDG retention in the right atrioventricular region as per the initial findings. The pathological examination of the excised surgery material confirmed the malignant fibrous histiocytoma diagnosis. Medical oncologists decided on chemotherapy after relevant examinations. The patient underwent a follow-up PET/CT scan to evaluate tumoral activity after the fourth round of chemotherapy. This examination revealed increased focal FDG retention similar to the metallic hyperdensity in the left atrium adjacent to the pulmonary trunk, and increased FDG retention in multiple hypodense mass lesions in the liver. The patient was subsequently referred to our clinic for cardiac evaluation. The apical 4-chamber (A4C) view of the echocardiogram showed a solid mass (25x20 mm) in the left ventricle that infiltrated the septum with thin pedicles. Also, there was a solid mass (20x17 mm) extending over the right ventricular tricuspid lateral valve (Figure 2). The image also revealed the functional prosthetic metal valve at the position of the mitral valve. The patient underwent cardiac MRI to confirm the solid lesions. The MRI results affirmed the masses that were detected by echocardiography (Figure 3). The patient was evaluated by the cardiovascular department once more. The mass was evaluated as malignant due to rapid progression. It was decided that the patient should be closely followed up with medical treatment, and reevaluated in case of impaired cardiac function. The patient's consent was obtained for the clinical presentation.

Figure 1: Transesophageal echocardiogram showing mass (42x22 mm) in the left atrium adhering to the posterior region that extended towards the mitral valve, suggestive of a myxoma

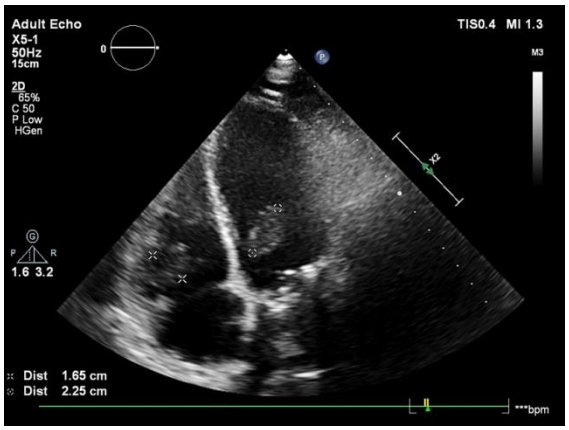

Figure 2: The apical 4-chamber view of the echocardiogram showing a solid mass (25x20 mm) in the left ventricle that infiltrated the septum with thin pedicles and a solid mass (20x17 mm) extending over the right ventricular tricuspid lateral valve

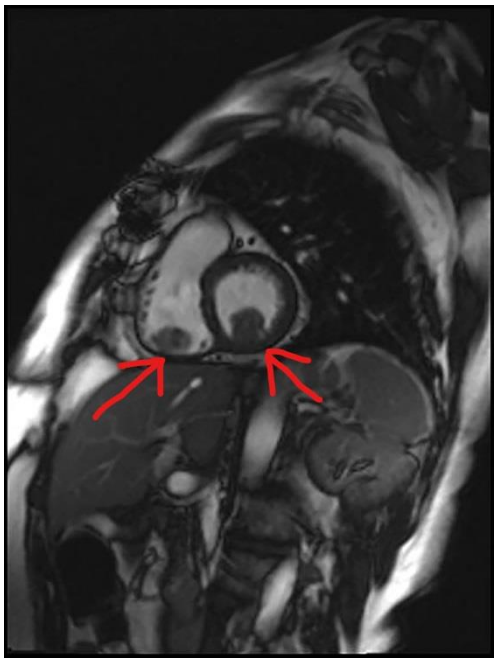

Figure 3: MRI showing masses in the left and right ventricle

Discussion

Malignant fibrous histiocytoma is a type of sarcoma that typically occurs in the extremities and the trunk. There are less than 100 reported cases of primary cardiac malignant fibrous histiocytomas in the literature [4]. The reported patients are aged between 14 and 77 years [5]. Cardiac malignant fibrous histiocytomas are clinically and histologically confused with atrial myxomas [6,7]. The first cardiac malignant fibrous histiocytoma case was reported in 1978 [8]. The majority of the

recently reported cases were associated with rapid prognosis in the form of recurrence, local infiltration, and distant metastasis, and eventual death. Complete surgical excision is the only treatment that has been shown to prolong survival [9]. However, even with complete resection, the recurrence is common in most patients with different sources reporting a median survival of 6 to 12 months [10]. Adriamycin and doxorubicin have been shown to improve survival outcomes compared to other drugs [11]. Radiation significantly reduces the incidence of local recurrence [12,13]. One study analyzed 42 cardiac sarcoma patients who received treatment between 1988 and 2013, and found that a multimodal therapy (any combination of surgery, radiotherapy and chemotherapy) was associated with better survival than surgery alone [14]. Patients with a cardiac mass should be examined in detail to determine surgical requirements. Patients with postoperative recurrence should be evaluated in terms of cardiac functions instead of mass involvement. In addition, the physician should consider medical follow-up together with surgical intervention.

Conclusion

In this case study, we report a rare case of malignant fibrous histiocytoma. We conclude that these cases must be carefully monitored for recurrence and metastasis. A multidisciplinary approach including cardiovascular and oncology specialists is crucial for determining the optimal treatment.

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