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Erakıncı G. Searching for antibodies against parasites in donors. İzmir: Ege University Health Sciences Institute. 1997.
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Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) l995 Jan-Mar (cited 1996 June 5): 1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlElD/cid.htm.

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MIDDLE BLACK SEA JOURNAL OF HEALTH SCIENCE

DECEMBER 2020 VOLUME 6 ISSUE 3

CONTENTS

EDITORIAL

As 2020 with Covid-19 ends,

We are completing a very painful year of days with Covid-19. We are proud that healthcare workmen face all kinds of difficulties under their heavy burden. I am grateful to all my colleagues who have not withheld their academic publications and services to humanity amidst all these problems throughout the year. We are very happy for the trust and intense interest in our magazine.

We hope to publish 2021 issue of our journal on beautiful days.

PhD, Assoc. Prof. Ülkü KARAMAN

Editor

Middle Black Sea Journal of Health Science December 2020; 6(3):281-287

RESEARCH ARTICLE

Stopping Ultrafiltration Related Arterial Pressure Changes in Hemodialysis Patients

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Abstract

Objective: The present study inquired the effects of stopping ultrafiltration on arterial pressure in hemodialysis patients.

Methods: Our study was performed in 92 hemodialysis patients. Ultrafiltration was stopped after the 3rd hour of hemodialysis. Arterial pressure was measured in the supine position at 0, 5, and 10 minutes after ultrafiltration was stopped.

Results: Systolic arterial pressure increased by a mean of 4 mm Hg and diastolic arterial pressure increased by a mean of 2 mmHg at 10 minutes after ultrafiltration was stopped. With regard to the difference between mean arterial pressure measured before dialysis and just after stopping ultrafiltration (0. minute), systolic arterial pressure increased by a means of 5 mmHg and diastolic arterial pressure increased by a mean of 2 mmHg at 10 minutes after ultrafiltration was stopped in the patients with a mean arterial pressure decrease of ≥ 10 mmHg. However, stopping ultrafiltration caused no significant changes in the systolic arterial pressure or diastolic arterial pressure of the patients with a mean arterial pressure decrease of < 10 mmHg. An important correlation was determined between systolic arterial pressure elevation after stopping ultrafiltration and age, ultrafiltration rate, duration of hemodialysis, gender in the patients with a mean arterial pressure decrease of ≥ 10 mmHg. Age and gender were the independent variables, which affected the systolic arterial pressure elevation after stopping ultrafiltration.

Conclusion: In patients with a mean arterial pressure decrease of ≥ 10 mmHg, stopping ultrafiltration increases arterial pressure but this is a limited elevation. Stopping ultrafiltration related systolic arterial pressure elevation is more evident in females and in the elderly.

Key words: Arterial pressure, hemodialysis, hypotension, ultrafiltration

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Introduction

Hypotension is one of the most common and critical problems in hemodialysis patients (K/DOQI Workgroup, 2005). Hypotension during hemodialysis is strongly associated with ultrafiltration. In hemodialysis, patients, extracellular fluid volume increases owing to weight gain between two dialysis sessions. Too much extracellular fluid is made away with by ultrafiltration during hemodialysis (Kooman et al., 2007). Ultrafiltration rate would be high by virtue of high fluid intake between two dialysis sessions and may cause to be intradialytic hypotension (Saran et al., 2006). Excessive

ultrafiltration through error evaluation of the patient's dry weight as well may bring about hypotension (Palmer et.al.,2008). The risk of hypotension in the course of hemodialysis is increased in some conditions such as cardiac disorders, diabetes mellitus (DM), agedness, and nitrate usage (K/DOQI Workgroup, 2005; Kooman et al., 2007).

Intradialytic hypotension has been described differently in different studies in the literature. Nonetheless, the European Best Practice Guideline and Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines have defined intradialytic hypotension as a ≥ 20 mmHg decrease in systolic arterial pressure or a drop off in mean arterial pressure by 10 mmHg and the presence of concomitant symptoms (K/DOQI Workgroup 2005; Kooman et al., 2007). In accordance with European Best Practice Guideline on hemodynamic instability advices, ultrafiltration should be stopped for the treatment of intradialytic hypotension. Stopping ultrafiltration prevents a further fall in blood volume and allow refill of blood volume from the interstitial compartment, by this way hypotension may be improved (Kooman et al., 2007). Although European Best Practice Guideline recommends ultrafiltration should be stopped for hemodialysis hypotension, the effects of stopping ultrafiltration on arterial pressure is indefinite. The present study investigated how arterial pressure was affected by stopping ultrafiltration in hemodialysis patients.

Methods

Study design and patients

This present study was confirmed by the Ordu University Clinical Research and Ethics Committee. (Date: 01/11/2018, issue number: 2018/224) Informed consent form was received from the subjects included in the study. All study procedures were performed according to the Declaration of Helsinki. Our study was conducted between April 2019-February 2020.Our study was multicenter. Data collection was done in two places Ordu University Training and Research Hospital hemodialysis center and Samsun D-Med hemodialysis center.

Our study population included 92 hemodialysis patients. Our study was conducted with all patients who agreed to participate in the study in two hemodialysis centers. The patients were above 18 years old and had hemodialysis treatment for at least 3 months. Patients received bicarbonate hemodialysis treatment 3 times a week. The dialysate flow rate was 500 ml / min. The blood flow rate was between 250-400 ml / min. Patients with cardiac dysrhythmia, acute-chronic bleeding, acute infection and hospitalized were not included the study.

Co-morbid conditions of the patients were investigated. The patients were questioned about the presence of hypertension [patients receiving antihypertensive drugs either occasionally or regularly], DM [patients receiving oral antidiabetic and/or insulin] and cardiovascular diseases (CVD) [coronary artery disease, congestive heart failure, cardiac valve replacement, cardiac pacemaker, peripheral vascular disease]. On physical examination, all patients were euvolemic. The dry weight of the patients was recorded, and their systolic arterial pressure and diastolic arterial pressure were measured prior to dialysis in the supine position. Mean arterial pressure was calculated as diastolic arterial pressure plus one-third of (systolic arterial pressure– diastolic arterial pressure) (Abdelfatah et al., 2001). The amount of ultrafiltration was recorded.

Ultrafiltration was stopped at the 3rd hour of hemodialysis and arterial pressure was measured 0, 5 and 10 minutes after ultrafiltration was stopped during the patients were in supine position. The difference between mean arterial pressure evaluated at the starting of hemodialysis and mean arterial pressure measured at the 3rd hour of hemodialysis [just after stopping ultrafiltration (0. minute)] was calculated. In hemodialysis patients, blood pressure drops towards the end of hemodialysis due to ultrafiltration. Coll et al. stopped ultrafiltration in their study after the 1st and 3rd hour of hemodialysis and found a blood volume increase of 2% and 2.3% respectively (Coll E at al.,2004). In our study, we stopped ultrafiltration at the the 3rd hour of hemodialysis. The patients who were symptomatic due to intradialytic hypotension and patients who were given saline infusion were excluded from the study. We analyzed the patients by dividing them into two groups according to the decline in the mean arterial pressure value (those with a mean arterial pressure decrease of ≥ 10 mmHg and those with a mean arterial pressure decrease of < 10 mm Hg). It was calculated how much arterial pressure increased after 5 and 10 minutes after ultrafiltration was stopped. All arterial pressure measurements were applied using the same automated arterial pressure apparatus (Omron M3 Intellisense, Omron Healthcare, Kyoto, Japan) (Akpolat T et al.,2012).

Statistical analysis

The SPSS 16 statistics software was used to evaluate the data in our study. The Kolmogorov-Smirnov test is used to determine whether continuous variables were normally distributed, while descriptive

analyses were presented as averages and standard deviations for variables with normal distribution. Median and interquartile range (25%-75%) were used for variables not distributed normally. The difference between the 0, 5 and 10-minute measurements was evaluated by repeated measures ANOVA. In cases in which was a significant difference between the groups was found, pairwise comparisons were made and evaluated using the Bonferroni correction. Normally distributed variables were compared using the paired Student's t test. For correlation analysis, Pearson test was used for variables with normal distribution, Spearman test for variables with at least one non-normal distribution, or sequential variables. Multivariate analysis was carried out using the significant factors identified in univariate analysis. Multiple linear regression analysis was carried out detect the independent predictors that affected the systolic arterial pressure elevation as a result of stopping ultrafiltration. Logarithmic conversion was carried out for the variables that did not show a normal distribution for the multiple linear regression analysis. A p value of < 0.05 was considered statistically significant.

Results

Baseline characteristics of the patients are shown in Table 1. Systolic arterial pressure was increased by a mean of 4 mm Hg ($p<0.001$) and diastolic arterial pressure increased by a mean of 2 mmHg ($p<0.001$) at 10 minutes after stopping ultrafiltration. Mean arterial pressure rised by a mean of 2 mmHg ($p<0.001$) at 10 minutes after stopping ultrafiltration (Table 2).

The patients were dichotomized in regard to the difference between the mean arterial pressure values measured before dialysis and just after stopping ultrafiltration (0th minute) (those with a mean arterial pressure reduce of ≥ 10 mmHg and those with a mean arterial pressure decrease of <10 mmHg). Systolic arterial pressure increased by a mean of 5 mmHg ($p<0.001$) and diastolic arterial pressure raised by a mean of 2 mmHg ($p=0.001$) at 10 minutes after stopping ultrafiltration in the patients with a mean arterial pressure decrease of ≥ 10 mmHg. Stopping ultrafiltration caused no prominent changes in the systolic arterial pressure or diastolic arterial pressure of the patients with a mean arterial pressure decrease of <10 mmHg ($p=0.919$ for systolic arterial pressure; $p=0.297$ for diastolic arterial pressure) (Table 3).

Table 1. Baseline characteristics of the patients

	Patients (n=92)
Age, years	62.5 (53-72)
Gender	
Male	44 (47.8%)
Female	48 (52.2%)
Duration of hemodialysis, months	63 (21-101)
Predialysis sistolic arterial pressure, mmHg	135±19
Predialysis diastolic arterial pressure, mmHg	77±11
Predialysis mean arterial pressure, mmHg	97±12
Cause of End Stage Renal Disease	
Hypertensive nephrosclerosis	32 (34.8%)
Diabetic nephropathy	17 (18.5%)
Amyloidosis	5 (5.4%)
Glomerulonephritis	4 (4.3%)
Polycystic kidney disease	4 (4.3%)
Vesicoureteral reflux	2 (2.2%)
Nephrolithiasis	2 (2.2%)
Unknown	26 (28.3%)
Comorbid conditions	
Hypertension	65 (70.7%)
Diabetes mellitus	20 (21.7%)
Cardiovascular disease	40 (43.4%)
Chronic Obstructive Pulmonary Disease	9 (9.8%)

Correlation analysis was fulfilled to inquire the factors associated with arterial pressure elevation as a result of stopping ultrafiltration in the patients with a mean arterial pressure decrease of ≥ 10 mmHg. An important correlation was determined between systolic arterial pressure elevation 10 minutes after stopping ultrafiltration and age ($r=0.3$; $p=0.012$), ultrafiltration rate ($r= -0.302$; $p=0.012$), duration of hemodialysis ($r= -0.270$; $p = 0.025$), gender ($r= -0.426$; $p<0.0001$). There was no significant correlation between stopping ultrafiltration related systolic arterial pressure elevation and the level of predialysis systolic arterial pressure reduction during hemodialysis ($r= 0.49$; $p = 0.692$), DM ($r= 0.120$; $p = 0.328$), HT ($r= 0.29$; $p= 0.813$), cardiovascular disease ($r= 0.139$; $p= 0.255$). In the same patient group, there was no significant correlation between the elevation in diastolic arterial pressure 10 minutes after stopping ultrafiltration and age ($r= 0.047$; $p=0.701$), ultrafiltration rate ($r= -0.237$; $p = 0.05$), duration of hemodialysis ($r = -0.145$; $p = 0.236$),

gender (r= -0.126; p=0.301), level of predialysis diastolic arterial pressure reduction during hemodialysis (r= -0.121; p=0.323), DM (=0.42; p=0.729), HT (r= -0.044; p=0.719), cardiovascular disease (r= -0.006; p=0.961).

Systolic arterial pressure (8.55 ± 7.80 vs. 1.82 ± 6.78 mmHg; p < 0.001) elevation 10 minutes after stopping ultrafiltration was more evident in females compared to males in the patients a mean arterial pressure decrease of ≥ 10 mmHg. Diastolic arterial pressure (2.29 ± 5.12 vs. 1.54 ± 4.33 mmHg; p = 0.513) increased similarly in both genders.

Multiple linear regression analysis was carried out for determination of the variables that affected the stopping ultrafiltration related arterial pressure elevation. Age and gender were found to be the independent variables that affected the stopping ultrafiltration related systolic arterial pressure elevation (Table 4).

Table 2. The values of arterial pressure at 0^{th}, 5^{th} and 10^{th} minutes after stopping ultrafiltration (n=92)

	0^{th} minute mean±SD	5^{th} minute mean±SD	10^{th} minute mean±SD
Sistolic arterial pressure, mmHg	105.23±19.81	107.48±20.31 *	109.07±19.36 *,†
Diastolicarterial pressure, mmHg	62.33±10.29	63.12±10.47	63.58±10.58*
Mean arterial pressure, mmHg	76.63±12.31	77.91±12.41 *	78.74±12.20 *,†

* p< 0.05 as compared to 0^{th} minute.
† p< 0.05 as compared to 5^{th} minute;

Table 3. The values of arterial pressure at 0^{th}, 5^{th} and 10^{th} minutes after stopping ultrafiltration according to the decrease in mean arterial pressure

	Mean arterial pressure decrease by ≥ 10 mmHg (n=69)			Mean arterial pressure decrease by <10 mmHg (n=23)		
	0^{th} minute mean±SD	5^{th} minute mean±SD	10^{th} minute mean±SD	0^{th} minute mean±SD	5^{th} minute mean±SD	10^{th} minute mean±SD
Systolic arterial pressure, mmHg	101.57±18.27	104.36±19.48*	106.71±18.82 *,†	116.22±20.56	116.83±20.29	116.13±19.67
Diastolic arterial pressure, mmHg	59.58±9.10	60.96±10.07	61.49±9.81*	70.60±9.30	69.60±8.99	69.82±10.52
Mean arterial pressure, mmHg	73.57±10.97	75.42±11.84*	76.56±11.36*	85.81±11.76	85.34±11.27	85.26±12.53

* p< 0.05 as compared to 0^{th} minute;
† p< 0.05 as compared to 5^{th} minute;

Table 4. Independent variables affecting the systolic arterial pressure elevation (multiple linear regression analysis)

Variables	β	Standardized β	95% CI		p value
			lower	upper	
Age	25.9	0.281	5.613	46.188	0.013
Gender	-5.892	-0.371	-9.256	-2.528	<0.001
Ultrafiltration rate	-0.245	-0.106	-0.769	0.279	0.354
Duration of hemodialysis	-2.073	-0.137	-5.246	1.099	0.196

CI=Confidence interval

Discussion

Hypotension is a serious problem in hemodialysis patients. European Best Practice Guideline on hemodynamic instability recommended placing the patient in Trendelenburg position and stopping ultrafiltration for the management of intradialytic hypotension and infusing isotonic saline as long as hypotension is improved with these procedures (Kooman et al., 2007). We have demonstrated that the arterial pressure increased with stopping ultrafiltration in the patients with a mean arterial pressure decrease of ≥ 10 mmHg compared to predialysis values; in addition to, this was a limited elevation. The systolic arterial pressure elevation after stopping ultrafiltration was more evident in females and in the elderly. Presence of DM, HT or cardiovascular disease did not have an effect on systolic arterial pressure elevation. The degree of the decrease in predialysis systolic arterial pressure values during hemodialysis did not affect the stopping ultrafiltration related systolic arterial pressure elevation. No significant changes happen in arterial pressure with stopping ultrafiltration in patients with a mean arterial pressure decrease of < 10 mmHg. Excessive fluid gained between two dialysis sessions is removed by ultrafiltration. Blood volume decreases with the removal of excess fluid during ultrafiltration, and this cause a decrease in arterial pressure. Once the blood volume is reduced, the body tries to maintain the arterial pressure within logical limits using

compensatory mechanisms. When the blood volume decreases, arterial constriction occurs, total peripheral resistance increases, and the arterial pressure increases. Vasoconstriction occurs in large vessels and blood is transferred to the central circulation resulting in cardiac contractility and cardiac output uplift. Moreover, direct autonomic stimulation causes an increase in heart rate and myocardial contraction, and cardiac output is maintained. Hypotension occurs when these recompense mechanisms fail (Kooman et al.,2007; Schneditz et al., 1992; Van der Sande et al.,2000; Thijssen et al., 2013) Compensatory mechanisms for keeping the arterial pressure within exact limits show variation among patients. Hypotension is more widespread in patients over the age of 65 years, patients with low systolic arterial pressure at the beginning of dialysis, diabetic patients, patients with hypoalbuminemia, uremic neuropathy, autonomic dysfunction, cardiovascular problems or severe anemia, and in patients requiring high volume ultrafiltration (K/DOQI Workgroup,2005).

Ultrafiltration is one of the most substantial factors in the development of hypotension in hemodialysis patients. Hypotension rarely occurs in patients that do not undergo ultrafiltration (Barth C et al.,2003; Thijssen et al., 2013). Ultrafiltration decreases blood volume and inadequate refilling leads to hypovolemia which is suspected to be a major cause for hemodialysis related hypotension (Schneditz et al., 1992; Thijssen et al., 2013). Stopping ultrafiltration increases the plasma volume of the patient, restrains a farther decline in blood volume and may ease refill of blood volume from the interstitial compartment (Kooman et al., 2007). Coll et al. demonstrated that pause of ultrafiltration at the end of the first and third hours of hemodialysis ensure a blood volume increase of 2% and 2.3%, in order of (Coll E et al., 2004). In the present study, we as well evidenced that arterial pressure increases with stopping ultrafiltration in patients with a mean arterial pressure decrease of ≥ 10 mmHg .

Hemodynamic instability European Best Practice Guideline is described as: intradialytic hypotension systolic arterial pressure ≥ 20 mmHg or a 10 mmHg reduction in mean arterial pressure and clinical symptoms that require nursing intervention (Kooman et al.,2007).

When the patients were divided into two groups as regards the decrease in mean arterial pressure, we observed that systolic arterial pressure increased by a mean of 5 mmHg 10 minutes after stopping ultrafiltration in the patients with a mean arterial pressure decrease of ≥ 10 mmHg; but no significant change was observed in systolic arterial pressure or diastolic arterial pressure in the patients with a mean arterial pressure decrease of < 10 mmHg. Normal healthy subjects can tolerate a volume loss up to 20% without developing hypotension; nevertheless, dialysis patients may improve hypotension even with far less loss in blood volume (Van der Sande et al.,2000; Kooman et al., 2007). The critical blood volume loss at which intradialytic hypotension occurs varies between 2% and 29% in hemodialysis patients with a large intra-individual variation. Whilst some hemodialysis patients cannot tolerate small volumes of blood loss, some can tolerate loss up to 29% (Barth et al., 2003; Kooman et al., 2007). The patients with a mean arterial pressure decrease of < 10 mmHg were able to tolerate blood loss due to ultrafiltration without developing hypotension; therefore , no increase was determined in arterial pressure by stopping ultrafiltration, whereas, as the patients with a mean arterial pressure decrease of ≥ 10 mmHg were less tolerable to fluid removal by ultrafiltration, arterial pressure was decreased by ultrafiltration. Stopping ultrafiltration increased the arterial pressure in such patients as fluid removal was discontinued by cessation of ultrafiltration. Stopping ultrafiltration related arterial pressure elevation has been investigated in other studies. In an earlier study, ultrafiltration was stopped when the patients were in the passive leg raising position (Erdem, 2016). Passive leg lifting was defined as flat passive lifting of the legs above the heart level while the patient was in a supine position (Geerts et al., 2012, Erdem, 2016). In patients with intradialytic hypotension, stopping ultrafiltration at passive leg raising position produced a mean increase of 3 mmHg in systolic arterial pressure and a mean of 1 mmHg increase in diastolic arterial pressure (Erdem, 2016). Different from the above-mentioned study, we stopped ultrafiltration when the patients were in supine position. Passive leg raising as well causes rise in arterial pressure (Erdem, 2016). The reason for a more remarkable increase in arterial pressure with stopping ultrafiltration in the present study is cessation of ultrafiltration in the supine position instead of passive leg raising position. Bradshaw et al. demonstrated a rise in mean arterial pressure by pausing ultrafiltration in the patients with decreased mean arterial pressure during hemodialysis. Ultrafiltration was paused for 10 minutes if the patient's mean arterial pressure was ≤ 70 mmHg or decreased by ≥ 30 mmHg as compared to the values before dialysis. Mean arterial pressure recovered to > 70 mmHg within 10 minutes in 24.6% cases (Bradshaw et al., 2011). The authors have reported

that short term interruption of ultrafiltration would lead to vascular refilling and an increase in mean arterial pressure (Bradshaw et al., 2011, Bradshaw et al., 2015).

In our study, the stopping ultrafiltration related systolic arterial pressure elevation was more notable in the elderly and in females. Dialysis-induced hypotension develops when the ultrafiltration related blood volume reduction is greater than the vascular refilling rate. Fluid transmission between interstitial space and vascular space depends on many factors such as capillary hydrostatic pressure, plasma oncotic pressure, capillary permeability, or lymphatic drainage (Thijssen et al., 2013). For this reason, the decrease in blood volume may widely vary among patients even if a similar ultrafiltration rate is applied (Santoro et al.,1998; Thijssen et al., 2013). The vascular space refilling rate may also be highly variable depending on these factors (Sulowicz et al., 2006). More evident arterial pressure improvement with stopping ultrafiltration in the elderly may be related to vascular permeability. Vascular permeability increases in advanced age (Oakley et al., 2014). This may lie behind a more rapid fluid transmission from the interstitial space to the vascular space when the vascular volume decreases and may bring about an elevation in blood pressure. A study investigated the acute influence of drinking water on arterial pressure in healthy participants. Whilst an acute systolic arterial pressure elevation developed in the elderly, systolic arterial pressure elevation did not occur in the young due to drinking water. A more obvious arterial pressure elevation may occur in the elderly with the same amount of fluid (Jordan et al., 2000). Vascular permeability was shown to increase due to estradiol in females (Hox et al., 2015). Hence, stopping ultrafiltration related arterial pressure elevation could have been more evident in females in whom the vascular volume decreased compared to males. There are studies existent indicating that intradialytic hypotension is more frequent in the elderly (K/DOQI Workgroup, 2005; Sands et al., 2014;) and in females (Shoji et al., 2004; Sands et al., 2014). Increased vascular permeability may have a duty in the development of both intradialytic hypotension and stopping ultrafiltration related arterial pressure elevation in females and in the elderly. Further studies are required to inquire this issue.

Conclusion

In conclusion, no significant change occurs in systolic arterial pressure or diastolic arterial pressure by stopping ultrafiltration in the patients with a mean arterial pressure decrease of < 10 mmHg. There is an increase in arterial pressure by stopping ultrafiltration in hemodialysis patients with a mean arterial pressure decrease of ≥10 mmHg but this is a limited elevation. Stopping ultrafiltration related systolic arterial pressure elevation is more evident in females and in the elderly. Stopping ultrafiltration may come across the treatment of patients that improve hypotension while hemodialysis.

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RESEARCH ARTICLE

Our Surgical Outcomes for Congenital Penile Curvature

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Abstract

Objective: Patients with congenital penile curvature (CPC) frequently require surgical treatment. However, patients cannot access the treatment required everywhere. The common reason for this is the insufficient information and experience of the people offering treatment. This study was planned to attract attention to the topic and present our 5-year experience.

Methods: The outcomes for 17 patients with tunical plication due to CPC were retrospectively analyzed. During attendance, ages and complaints were recorded. Data about the curvature angle, satisfactory straightening, and residual curvature in the process of surgery and after surgery were analyzed.

Results: Data from 17 CPC patients abiding by the criteria were used. The mean age of cases was 18.06±4.54 years. Mean curvature angle was identified as 55.8±17.8°. None of the patients had known trauma history or pain at attendance (0/17, 0%). All patients perceived this disease as a problem (17/17, 100%). During mean 9.4±3.5 (6-15) month follow-up, 15 of 17 patients (88.2%) were identified to have satisfactory penile correction. Clinically significant residual curvature (>20°) was identified in 2 of 17 patients (11.8%). Two of the 17 patients (11.8%) reported mild, insignificant, and not uncomfortable (<20°) curvature. Additional surgical procedures were not required for residual curvature.

Conclusion: Surgical correction is frequently unavoidable for treatment of this disease. As seen in our study, this surgical procedure is a simple, reliable, and effective treatment choice. However, many people offering treatment are known to avoid these patients or these surgical treatments. Though there are many reasons for this, according to our experience, the most important cause is lack of sufficient knowledge and experience. It is a very difficult situation for urologists to avoid curvature surgery, commonly found among urological diseases. We think it will be beneficial to provide the necessary information and experience for dealing with these patients during or after specialization training.

Key words: Congenital penile curvature, penile plication, surgical repair.

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Introduction

Congenital penile curvature (CPC) is bending of the penis during erection frequently in lateral or ventral direction. The definite incidence in society is not fully known. However, it is estimated to affect 0.5-10% of men (Kramer et al., 1982; Yachia et al., 1993; Montag and Palmer, 2011; Ziegelmann et al., 2019). As this curvature does not cause discomfort for some patients or they accept it as normal, they do not attend doctors, so it is probable there are many patients who are not diagnosed. Diagnosis remains silent until functional limitations occur during sexual relations.

This disease may be confused with Peyronie disease where the curvature is variable, and which generally occurs at adult ages. Peyronie disease has different underlying pathology and the fibrotic disease is related more to the tunic albuginea (Al-Thakafi and Al-Hathal, 2016). In Peyronie disease the patient is frequently sexually active, and their history includes new onset of curvature and sexual disorder. Physical examination finds palpable plaque (tunical thickening) and this plaque limits penile elasticity. The etiology of this disease has not been fully explained. It is thought that microtraumas occurring during sexual relations begin an inflammatory process resulting in fibrosis and this causes plaque development (Al-Thakafi and Al-Hathal, 2016; Jiang et al., 2018). It may be easily distinguished from CPC with detailed assessment.

Treatment of curvature frequently requires surgical treatment. The aim of surgery is to ensure correction to allow penetration of the penis. For successful surgery, serious training and experience is mandatory. However, according to our experience, curvature surgery has not found its rightful place among routine urologic surgical procedures. As a result, people offering treatment who do not see themselves as sufficient about the topic avoid these patients and surgical procedures as much as possible. This study was designed to draw attention to this topic.

The aim of this study is to present a 17-case CPC series and to share our experience about this topic to motivate people or clinics who are new to this procedure.

Methods

Study design and patients

Patient information was obtained from retrospective screening of records.

Data from 17 CPC patients attending our clinic from August 2014 to 2019 with information accessed were used.

Patients with hypospadias, Peyronie disease, and urethral surgery history were excluded from the study.

Demographic characteristics, history and physical examination findings, and preoperative and postoperative results were reviewed.

Clinical Assessment

All patients were evaluated preoperatively with detailed history and physical examination including sexual history, trauma, medication use, time of curvature onset and progression. The penile shaft was examined carefully in terms of pathologies that may be confused with CPC such as Peyronie disease. Pictures taken by patients of their erect penis were examined. If necessary, cases had intracavernosal injection performed and advanced tests were used to assess penile curvature or penile hemodynamics. Only cases who were stable in terms of curvature were taken for surgery.

After surgery, success was defined as satisfactory penile straightening as stated by the patient, while failure was the inverse. Continuation of curvature while patients remained satisfied or could maintain sexual life was defined as residual curvature.

Surgical Technique

The surgical procedure was completed under general anesthesia for all cases. At the start of surgery, artificial erection was induced in every case to assess curvature. Later, the penis was degloved with an incision on the circumcision line. The Buck fascia and neurovascular bundle (NVB) were carefully removed or lifted from the tunica albuginea. Later penile erection was induced and the tunica albuginea was held with Allis clamps on the opposite side to the curvature with the aim of straightening the penis. Later the Allis clamps were removed. The two marks with nearly 5 mm length left on the tunica albuginea by the clamp were used as plication suture sites. Two plication sutures were made with 2-0 unabsorbable sutures so the knots remained inside. The distance between the Allis clamps was adjusted according to the severity and location of curvature. After the procedure was completed, erection was induced again, and curvature was checked. If there was continuing curvature, the procedure was repeated with additional plication. After the desired straightness was obtained, the layers were anatomically closed, and the penis had compression bandaging with koban bandage.

For 2 weeks postoperative, a penile rehabilitation regime was recommended inducing penis traction with penile massage and the hand to prevent development of contraction and to initiate rapid healing. After patients were discharged, they were called for check-up 10 days later. Later they were called for check-ups every 3 months for the first year and then annually after that.

Statistical Analyses

Normal distribution of continuous data was checked with the Shapiro-Wilk test, while homogeneity of group variance was checked with Levene test. Comparison of variables abiding by assumptions was performed in two groups with the student t test and data are expressed as mean ± standard deviation. Variables not abiding by assumptions were compared in two groups with the Mann-Whitney U test and data are expressed as median [interquartile range (IQR)]. Categoric variables are expressed as frequency and analyzed with Pearson chi-square analysis. All calculations were performed with SPSS v.25 (IBM corp, Chicago, IL, USA) statistical program. Statistical significance used $p<0.05$.

Results

There were 17 CPC patients who abided by the criteria. Mean age at attendance was 18.06±4.54 years. Patients did not describe trauma history or pain (0/17, 0%). The whole group perceived penile curvature as a frustrating problem (17/17, 100%) (Table 1).

Table 1: Patient complaints with CPC

Complaints	n (%)
Penile Pain	0 (0%)
Changes in curvature	0 (0%)
Psychological stress	17 (100%)
Trauma history	0 (0%)

Examination of patients identified mean curvature angle of 55.8±17.8°. In 9 of the 17 patients (42.9%) curvature was towards ventral, while in 5 (23.8%) it was dorsal and in 12 (57.1%) it was lateral. During the surgery, the number of points held by Allis clamps were 2.8±1.2 (1-5) and the number of sutures was identified as 5.65±2.5 (Table 2).

Table 2: Examination findings for patients

Cases undergoing surgery	n (%)
Primary curvature angle (mean±std)	55.88 ±17.8 (40-90)
Primary curvature direction	
Ventral n (%)	
Dorsal n (%)	9 (42.9%)
Lateral n (%)	5 (23.8%)
Number of points held with Allis clamp (mean±std)	12 (57.1%) 2.8±1.2

With mean 9.4±3.5 (6-15) months of follow up, 15 of 17 patients (88.2%) were identified to have satisfactory penile correction. Clinically significant residual curvature (>20°) was identified in 2 of 17 patients (11.8%). In 2 of 17 patients, mild, insignificant curvature (<20°) that was not a source of discomfort was reported (Table 3). Two patients described uncomfortable curvature in the early postoperative period (2/17); however, this problem was resolved during check-ups (6 months). No patient required additional surgical procedure for residual curvature. In the postoperative period, no problem was encountered that could not be resolved in the short term with simple precautions. There was no problem encountered related to the surgical field or to feeling sutures.

Table 3: Surgical outcomes

Postoperative outcomes	n (%)
Satisfactory correction (n, %)	15/17 (88.2%)
Residual curvature (n, %)	3/17 (17.6%)
Re-surgery for residual curvature (n, %)	0/17(0%)
Complication requiring re-surgery (n, %)	0/17(0%)

Discussion

CPC is a commonly observed urologic pathology. The underlying cause of this disease is not fully known. Causes that have received most focus include asymmetric corporal length, fibrosis of the Buck or dartos fascia, and congenitally shortened urethra (Donnahoo, 1998). Frequently noticed in the childhood period or in the sexually-active period, the search for treatment for curvature or functional problems begins (Ebbehoj and Metz, 1987; Zahran et al., 2012). This process may be very frustrating and uncomfortable for both patient and parents. Psychological problems like loss of self-confidence, introversion, disrupted social relationships, distancing from the opposite sex, anxiety and depression are frequently seen in this period. A study showed that these people even avoid marriage (Paulson, 1995).

The most frequent reason for attending hospital among our patients was curvature and problems developing linked to this curvature, in accordance with the literature. We observed that the traumatizing effect on patients increased in cases who became aware of the problem during sexual relations especially (penetration or functional disorder). People involved in treating this disease should be aware that these patients require more interest and time compared to other diseases.

For diagnosis of this disease, detailed medical and sexual history is generally sufficient. In some situations, self-portraits taken during erection or imaging after intracavernosal injection may be required, especially for differential diagnosis (Kızılay et al., 2017). In our clinic, we see these images as an inseparable part of diagnosis. Self-portraits are very beneficial for recording the disease, identifying the degree of curvature and for planning treatment. For identification of curvature levels, patient statements may be misleading (Liguori et al., 2018).

Generally, 30 – 45º curvature is used as the threshold value for treatment of these patients (Walsh et al., 2013). When the literature about CPC is examined, though many treatment methods have been described, the actual treatment is surgical correction. Though the area of use is limited, some noninvasive methods have been described. However, most of these are methods used after surgery (Bella et al., 2018). Procedures during surgery are in the form of lengthening the short edge using a variety of material (vein grafts, synthetic materials) or shortening the long edge. This shortening may be in the form of plication or removing elliptical pieces from the tunica (Gunlusoy et al., 2003). The Nespit method and a few different plication techniques are the most commonly used surgical methods (Lee et al., 2004).

The plication technique is the most commonly chosen method. The reason for this includes significant advantages like being less invasive and simple, adjustable, less hemorrhage risk, low postoperative erectile dysfunction risk and easy learning curve (Salem, 2018). We chose this technique due to our experience in our training clinic, ease of learning and implementation, and having very effective outcomes.

When the literature is examined, the success rates for surgery performed for curvature is reported as 83-100% independent of method. The reason for this broad interval is due to differences in the success criteria used in studies. In our study, in accordance with the literature, we identified the satisfactory correction rate as 88.2%. Ziegelmann et al. published outcomes from 35 CPC patients. They reported success rate of 90% defined as satisfactory correction as a result of the study (Ziegelmann et al., 2019). A study from Turkey published the outcomes for 50 CPC patients. The success rate in this study was reported as 72% (Kizilay et al., 2017). Another study reported the success for curvature surgery was generally 88% (Gunlusoy et al., 2003).

Patients attending with residual curvature continuing after surgery should be carefully evaluated. Assessment of correction is a very variable or subjective situation. For people with active sexual lives, the critical point required for success is whether the penis is functional or not. Residual curvature may not be significant if it does not affect penis function. Some authors have recommended a classification of success as full straightening or residual curvature without discomfort (<20-30°). Especially for patients with insignificant residue, the term functional straight penis may be beneficial (Nehra et al., 2015). Ziegelmann et al. reported their insignificant residual curvature rate as 20% (Ziegelmann et al., 2019). In our study, this was identified in 2 of 17 patients (11.8%) and no additional surgical procedure was required.

In some residual curvature patients, correction with additional surgeries is unavoidable. This situation is a frustrating event for both patient and doctor. There may be more than one reason for this, with possible causes including asymmetric scar, differences in erection induced during surgery and erection levels at home, surgical experience and complicated cases (Cordon et al., 2017). When the literature is examined, the re-surgery rates for residual curvature vary from 0-3% (Kuehhas and Egydio, 2012). Surgeries to correct residual curvature are more difficult compared to primary surgery. As a result, patients need to be informed as necessary about the potential risks of re-surgery. Additionally, corrective sutures may cause shortening of the penis or unnecessary corrections.

In our study, no patient was observed to have curvature requiring re-surgery. We think it is necessary to avoid surgical procedures for patients with insignificant residual curvature (<20º-30º) or who do not have problems during sexual relations in relation to this topic. When informed as necessary, most patients do not feel they require surgery for curvature without clinical significance. The problem after another surgery is pain during erection or sutures being felt. In some studies, the use of unabsorbable sutures is reported to be associated with some problems like irritation during erection or related to knots (Poulsen and Kirkeby, 1995; Baskin and Lue, 1998). A study reported discomfort related to knots or

painful erection at rates of 12% and 11%. In our patients we used unabsorbable sutures. Our patients were not observed to have any problems related to knots or pain after the surgery.

As seen in the literature and from our study results, curvature surgery is a very effective and reliable treatment method. However, most patients cannot access this treatment at every health center. In our study, most patients described attending more than one hospital or doctor. We do not know the definite reason for this. Among probable causes are interest in other fields during training (laparoscopy, robot, oncology, etc.) or inability to access sufficient information and experience due to this surgery not being performed in training clinics, legal problems, and potential complications involved in the procedure. Especially problems related to malpractice in recent times may make people providing treatment right in avoiding procedures related to the penis, a matter of self for men. However, as urologists all surgical procedures we perform carry at least if not more risk than curvature surgery. As a result, we think this very reliable and simple surgical procedure should gain its rightful place in specialization training programs. For a variety of reasons, it is unavoidable that some surgical procedures remain for the period after training (Cirakoglu and Benli, 2017 and Benli et al., 2018).

There are some limitations to this study. The main limitations are that the study presents outcomes from a single center, is retrospective and the outcomes of people living with this problem in society are not known. At this point, the use of patient statements to assess postoperative success may cause errors in some cases.

Conclusion

Congenital penile curvature is a very frustrating situation. Treatment frequently requires surgical correction. We have very reliable, simple and effective treatment choices. Among these techniques, the plication technique we frequently use is very effective with very low complication rates and high patient satisfaction after surgery.

However, many people offering treatment avoid these patients or surgical treatments. The reason for this may be not gaining the necessary experience during specialization training. As a result, necessary information and experience for management of this disease should definitely be obtained during specialization training. However, it is not over for people who do not access sufficient experience during training. Necessary training and course programs can resolve this deficiency with one-on-one live surgeries in centers where this procedure is performed. We think it is necessary to gain the necessary information and experience to manage these patients during or after specialization training.

Ethics Committee Approval: Ethics committee approval was received for this study from Clinical Research Ethics Committee of Ordu University (2020/05).

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RESEARCH ARTICLE

Clinical Results of Harms Technique in Atlantoaxial Instability Treatment

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Abstract

Objective: The aim of this study is to present the clinical experience and results in the application of atlantoaxial stabilization performed with Harms technique to contribute to the literature.

Methods: Archive files of adult patients who underwent C1-2 stabilization using Harms technique with the diagnosis of atlantoaxial instability for 2015-2020 were examined. Clinical and radiological findings of 15 patients with at least 6 months of follow-up were evaluated. Preoperative clinical and radiological records, preoperative observations, postoperative complications, and clinical responses were evaluated.

Results: 15 patients included in the study; 10 were men and 5 were women. The age range was 25-82 (mean: 58.7). There were 6 patients (40.0%) who had Anderson and D'Alanzo classification type 2 odontoid fracture 2 patients (13.3%) with Jefferson fracture, 2 patients (13.3%) with C2 extension type tear drop fracture, 2 patients (13.3%) with narrowing in the level of craniocervical junction, 1 patient (6.7%) with upper cervical region tumor and 2 patients (13.3%) was in the form of hangmans fracture. Screw malposition was not observed in the postoperative period. Bone fusion developed in all patients after surgery. No vertebral artery damage or neurological damage was observed. Wound infection was not observed in any of these patients. Visual analog scale (VAS) reduction and Japanese orthopedic (JOA) scores were increased in all postoperative patients.

Conclusion: Surgery of atlantoaxial instability is a pathology requiring adequate surgical experience due to the complicated anatomical structure. Using the Harms technique, sufficient stability is provided with a low complication rate. With this method, improvement in the clinical findings of the patients and high bone fusion were obtained.

Key words: C1-2 screw fixation, cervical trauma, odontoid fracture.

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Introduction

The level of C1 (Atlas) and C2 (Axis) vertebrae, called upper cervical vertebrae, have a unique anatomical structure. There is no corpus, pedicle and spinous process on C1 vertebrae. In addition, there is odontoid process on C2 vertebrae different from other vertebras. Vertebral arteries traverse through the transverse vertebral foramen into the cranium through the posterior arch of C1 vertebrae. The axial load of the weight of skull is transferred from the occipital condyles to the masses of the C1 vertebra, and from there to the C1-2 facet joints and the C2 lareal masses. The load is then distributed to the subaxial region with the disc and facet joints of C 2-3. The atlantoaxial joint consists of 4 synovial joints. The first one is between the back of the anterior arch of C1 vertebra and the dens and the second one is between the odontoid process and the transverse ligament. Two of them are between the facet joints on both sides (Chen et al., 2020). The atlantoaxial joint is the most mobile region of the spine and makes 38.9% of the axial rotation movement (Badhiwala et al., 2017). It also performs a small amount of flexion-extension and lateral bending motion.

Approximately 25-35% of cervical fractures in an adult concern the first three cervical vertebrae. In these fractures, 45-60% neurological deficits can be encountered (Anderson and D'Alanzo, 1974- Çağlar et al., 2005). Due to upper cervical traumas (traffic accidents, falls from height, diving, etc.), instability may develop in the atlantoaxial joint. According to the classification made by Anderson and D'Alanzo, type 2 odontoid fractures are considered unstable (Anderson and D'Alanzo, 1974). In addition, it has been reported that 25% of patients with rheumatoid arthritis may have instability due to chronic inflammation (Kim and Hilibrand, 2005). It has also been reported that instability may develop with Marfan syndrome and Grisel's syndrome (Dagtekin et al., 2011). Regardless of the cause, atlantoaxial instability becomes an important mortality and morbidity problem (Isik et all., 2018). Neurological findings, radiological findings showing pressure and instability on neuronal structures, additional diseases and age that will affect morbidity are important in the planning of treatment. The purpose of treatment is to provide adequate neuronal decompression, providing stability, preservation of sagittal alignment and formation of bone fusion.

The aim of this study is to present the clinical experience and results in the application of atlantoaxial stabilization performed with Harms technique to contribute to the literature

Methods

This study was conducted with the approval of Ordu University Clinical Research Ethics Committee number 129.

Between January 2016 and January 2020, patients who were diagnosed with atlantoaxial instability in our clinic regardless of their etiology and applied screw fixation with Harm's technique were scanned and file data were obtained. All patients were evaluated in terms of complaints, diagnosis, preoperative and postoperative images, complications and fusion. Average follow up period is 24.6 months (6-48 months).

Patients with C1-2 screw fixation using the Harms technique and clinical follow-up data of at least 6 months were included in the study. Anterior route stabilization applications and patients with clinical follow-up less than 6 months were excluded from the study.

According to the clinical complaints, a suitable neck collar was worn to the patients who applied for trauma. Then all patients underwent cervical radiography, cervical computed tomography and cervical MRI examination. Angiography examination for the position of the vertebral artery was made in the preoperative period.

Surgical Procedure

Under general anesthesia, the prone position was taken to the operation with head holder. After cleaning and covering the surgical field; the skin was opened with a midline skin incision from the inion to the required cervical segment, then the paravertebral muscles were lateralized. C1 lateral mass and C2 pedicle screw were placed in accordance with the harm's technique with intraoperative fluoroscopy. Lateral mass screw was placed according to the Magerl technique planned to extend stabilization according to the level of lesion. Then, the system was stabilized with the help of cervical lordotic inclined rods.

Bone grafts were placed after the posterior elements were decorticated with the aid of a drill for fusion purposes, and the layers were closed anatomically.

All patients were evaluated for screw malposition and cervical alignment by pulling cervical CT on Day 1 after the operation. Preoperative Visual pain score (VAS) and Japanese Orthopedic Score (JOA) at 6th postoperative month were compared for clinical evaluation. Bone fusion was evaluated by dynamic radiographs and coronal sagittal plane CT examination at 6th postoperative month.

Results

Ten (66.7%) of the 15 patients included in the study were male and 5 (33.3%) were female. The average age was found to be 58.7 (25-82). There were 6 patients (40.0%) who had type 2 odontoid fracture according to Anderson and D'Alanzo classification, 2 patients (13.3%) with Jefferson fracture, 2 patients (13.3%) with C2 extension type tear drop fracture, 2 patients (13.3%) with narrowing in the level of craniocervical junction, 1 patient (6.7%) with upper cervical region tumor and 2 patient (13.3%) was in the form of hangmans fracture. Patient distributions are given in Table 1. Two of our patients (13.3%) had preoperative myelomalacia. Other patients did not have preoperative myelomalacia. Preoperative average JOA scores were 16.4 and average VAS scores were 7.2. There was no postoperative complication in all patients. No screw malposition was observed in the tomography examination performed in the postoperative period. Clinical worsening was not observed in any of our patients. It was observed in the postoperative 6th month follow-up that the JOA score increased by 17.8 and the VAS score decreased to 1.2. None of our patients had vertebral artery injuries and wound infection was not developed.

Case Illustration (Case 13)

Type 2 odontoid fracture was observed in the 81-year-old female patient due to a traffic accident. In his neurological examination, the Glasgow coma scale was 15 points. There were no motor and sensory deficits. The patient underwent posterior C1-3 stabilization. No postoperative complications were seen. During the follow-up, the patient was discharged without any neurological disorders (Figure 1).

Table 1. Patient distributions

Case No	Age	Sex	Follow Up	Application Reason	Diagnosis	Stabilized Segments
1	72	Male	15	Falling from high	C2 extension type tear drop fracture Left C2 lamina fracture	C1-3
2	80	Female	44	Falling from high	Type 2 odontoid fracture	C1-4
3	25	Male	40	Firearm injury	Type 2 odontoid fracture	C1-2
4	45	Female	42	Neck pain	Recurrent cervical meningioma	C1-3
5	64	Male	36	Traffic accident	Jefferson fracture	C1-2
6	49	Male	24	Traffic accident	Jefferson fracture	C1-2
7	33	Male	48	Traffic accident	C2 extension type tear drop fracture Right C1 lateral mass fracture	C1-3
8	47	Female	36	Neck pain	Os odontoideum	C1-2
9	71	Male	10	Falling from high	Hangman fracture C1 anterior arch fracture C2 cervical contusion	C1-4
10	81	Male	11	Falling from high	Type 2 odontoid fracture C1 anterior & posterior arch fracture	C1-3
11	82	Male	13	Traffic accident	Type 2 odontoid fracture	C1-2
12	73	Male	7	Traffic accident	Type 2 odontoid fracture C5-6 spinous process fracture C5-6 cervical contusion	C1-7
13	81	Female	12	Falling from high	Type 2 odontoid fracture	C1-3
14	43	Female	25	Neck pain	Narrowing of the craniocervical junction, Ankylosing spondylitis	C1-5
15	40	Male	6	Falling from high	Hangman Fracture C3 corpus fracture	C1-4

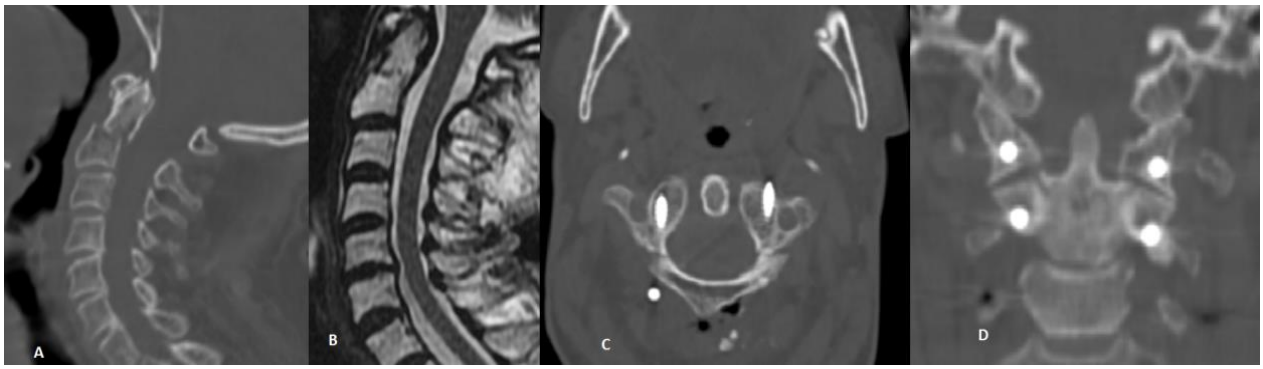

Figure 1: A: Sagittal CT image of Type 2 odontoid fracture, B: Preoperative T2 Cervical MR image, C: C1 lateral mass screw image on postoperative cervical CT axial plane, D: C1-2 lateral mass screw image on postoperative cervical CT coronal plane.

Discussion

Due to the complicated anatomical structure of the Atlas and axis and the location of the vertebral artery in this region, it makes the surgical treatment of the instability of the region difficult. Wiring fixation of C1-2, defined by Hadra in 1981, was used with various modifications (Gallie, 1939; Brooks et al.,1978; Coyne et al., 1995; Dickman et al., 1998). In order to reduce the neurological complications that may occur during wiring, interlaminary clamping known as halifax technique has been defined and developed as an apofix method by Honess and Back (Holness et al., 1984). However, it was observed that it was not sufficient especially in rotational stability (Huang et al., 2015). The C1-2 transarticular screw fixation technique defined by Magerl and Seeman in 1987 solved the fusion problem (Magerl and Seemann, 1987; Low and Redfern, 2002). However, it has been reported that spinal cord injury, vertebral artery injury, and hypoglossal nerve injury are observed in relation to this method (Dobran et al., 2016; Rajinda et al., 2017). This situation prompted researchers to develop methods with lower complication rates and higher fusion rates. Therefore, Goel and Laheri were first described as segmental screw flexion in 1994. In addition to the high fusion rate with this method, the risk of vertebral artery injury decreases, however, C2 root must be sacrificed during C1 lateral mass screw application (Goel and Lahari, 1994). Harms and Melcher showed that the root does not need to be sacrificed during screw application (Harms and Melcher, 2001). In this study, we used Harms technique to treat atlantoaxial instability of all our cases. In a study that conducted by Rajinda et al., in a series of 60 patients operated with C1 lateral mass and C2 pedicle screw fixation, 97% fusion rate and significant improvement in VAS and JOA scores were reported (Rajinda et al., 2017). C2 ganglion was not required to be sacrificed in any of our patients. Neurological complications or vertebral artery injuries due to this method were not observed in any of our patients. Bone fusion in all our patients developed at 6 months. No neurological damage, vertebral or internal carotid artery injury were not observed due to 30 C1 lateral mass, 30 C2 pedicle screws, 36 C3-C6 lateral mass and 2 C7 pedicle screws that we used in the stabilization of our cases. Significant decrease in all VAS scores and increase in JOA scores was observed.

This study is conducted by a single neurosurgeon to contribute to the literature by using Harm's technique.

Limitation

This study is limited in several ways. The most significant limitation was the fact that the population of the study was a small group because upper cervical traumas are rarely seen incidents. This study is conducted by single surgeon and this is also another reason of the above mentioned limitation. In addition, there was no comparison with other techniques that defined to treat atlantoaxial instability.

Conclusion

Surgery of atlantoaxial instability is a pathology requiring adequate surgical experience due to the complicated anatomical structure. Using the Harms technique, sufficient stability is provided with a low complication rate. With this method, improvement in the clinical findings of the patients and high bone fusion are obtained.

Ethics Committee Approval: This study was conducted with the approval of Ordu University Clinical Research Ethics Committee number 129.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept- DOK, Design- DOK, Supervision- DOK, Analysis and/or Interpretation- DOK, Literature Review- DOK, Writing- DOK, Critical Review- DOK.
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RESEARCH ARTICLE

Indicators of Isotretinoin-Induced Myopathy: Neutrophil/Lymphocyte Ratio, Cobb Angle of Spine

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Abstract

Objective: There are many side effects of isotretinoin on the musculoskeletal system, liver, nervous system and dermatological side effects. To investigate usage and side effects of isotretinoin (13-cis retinoic acid), which is popularly recommended by dermatologists for the treatment of acne vulgaris, on young patients admitted to the hospital with severe low back and neck pains.

Methods: We evaluated 61 patients who, using isotretinoin for the treatment of acne vulgaris for an average of eight months, experienced cervical and lumbar pain between 2017-2019. The age range of patients was between 16 and 38 years, there were 45 female and 16 male patients. These patients used isotretinoin at a dose of 0.5-0.8 mg/kg/day for the treatment of acne vulgaris for about eight months. The patients were questioned about cervical and lower back pain, joint pain, muscle weakness, myoglobinuria, creatine phospo-kinase (CPK), Visual Analog Scale (VAS), inflammation myopathy, neutrophil/lymphocyte ratio (Neu/Lymp ratio), and Cobb angle of the spine during monthly controls.

Results: The VAS and Neu/Lymp ratio, cervical and lumbar Cobb angles of the patients were statistically analyzed and the relationship between them was shown.

Conclusion: The Neu/Lymp ratio and Cobb angle of the cervical and lumbar spine should be considered as an alternative or additional parameter to diagnose drug-induced myopathy.

Key words: Cobb angle, Inflammation, Myopathy, Neu/Lymp ratio, Pain

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Introduction

Isotretinoin (13-cis retinoic acid) is a synthetic vitamin A analog used in the treatment of resistant cystic acne that is not responsive to conventional treatments and isotretinoin shows its effectiveness by suppressing sebaceous glands (Layton, 2009). There are many side effects of isotretinoin on the musculoskeletal system, liver, nervous system and dermatological side effects (Scuderi et al, 1993; Nesher and Zuckner, 1995). Musculoskeletal side effects were reported as 15–20% in the literature (Mclane, 2001). Since musculoskeletal side effects are not very common, cervical and lumbosacral myalgia complaints are not considered or neglected by clinicians; most of musculoskeletal side effects

disappear shortly after the drug is released (Cengiz et al., 2018). There are a few reports in the literature that isotretinoin is associated with inflammatory rheumatologic symptoms; for example, sacroiliitis and inflammatory myopathic back pain (Elias et al., 1991; Fiallo and Tagliapietra, 1996; Dincer et al., 2008).

Muscles constitute 45% of total body mass and skeletal muscles are responsible for 80% of total glucose uptake and over 30% of resting metabolic rate (Sameem and Semira, 2016). Because of these properties, muscles are vulnerable to the toxic effects of circulating drugs including isotretinoin.

In this study, new parameters with easy applicability and accessibility and auxiliary radiological examinations that can be used in the diagnosis and follow-up of cervical and lumbar myalgia caused by drug-induced myopathy were investigated.

Methods

We evaluated 61 patients who used isotretinoin for the treatment of acne vulgaris for about eight months and complained of lumbar and cervical pain between 2017 and 2019 retrospectively. 45 of 61 patients were female, 16 were male and the age range was between 16-38 years. These patients used isotretinoin at a dose of 0.5-0.8 mg/kg/day for about eight months to treat acne vulgaris. Liver and kidney function tests, complete blood count, creatine phospo-kinase (CPK), sedimentation and C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), anti-nuclear anticor (ANA), and rheumatoid factor (RF) values were examined in monthly controls. Patients with a rheumatological disease such as sacroiliitis, seronegative arthritis, degenerative spinal disease such as cervical and lumbar disc hernias or operated on, for this reason, traumatic spinal injuries, malignancy, renal and liver failure, HIV-infected, endocrinopathy were excluded from this study. Patients were questioned about other drug usage inducing myopathic reactions such as statins, immune-suppressive agents, and antiviral agents during monthly follow-up periods, and patients using these drugs were excluded from the study. Neurological examination and spinal magnetic resonance imaging (MRI) of the patients included in the study were within normal limits.

Patients using isotretinoin experienced cervical and lumbar pain admitted to the neurosurgery clinic. We preferred to discontinue the isotretinoin treatment and follow up complaints of patients and no other medications such as non-steroidal anti-inflammatory drugs were given for the treatment of pain.

After the discontinuation of isotretinoin, complaints of the patients gradually decreased and disappeared at the end of the third month of the follow-up period. Visual Analog Scale (VAS), Complete blood count, liver and kidney function tests, CPK, and neutrophil/lymphocyte ratio examined during monthly control of the patients.

Cobb angles of the cervical and lumbar spine of the patients were made on lateral roentgenography at the admission to neurosurgery clinic and at the end of the third month after discontinuation of the drug, and obtained data were analyzed statistically.

Statistical analysis

Data analysis was performed using SPSS for Windows, version 20.0 (IBM Corp., Armonk, NY, USA), if the parametric test assumptions are not met in the evaluation of the data, the Kolmogorov-Smirnov test, Wilcoxon signed rank test, and Spearman correlation coefficient will be calculated and the level of error is 0.05 as received.

Results

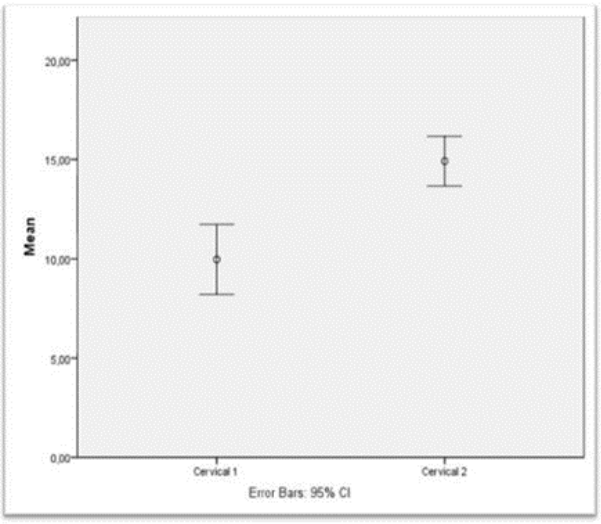
The relationship between the variables was tested with the Spearman correlation test: according to this; as lymphocyte (Lymp) increases, VAS decreases with a probability of 60.4%, as neutrophil (Neu) increases with a probability of 44.2%, VAS increases with a probability of 72.3%.

There was no significant relationship between creatine and VAS values. However, a significant positive correlation was found between Neu/Lymp and VAS values ($p<0.05$, r: 0,723), as a result; the Neu/Lymp value increases, the VAS score increases, and the patient's symptoms increase (Table 1). There was a statistically significant difference between cervical and lumbar Cobb angle measurements (Wilcoxon signed rank test $p<0,05$) performed on the day the patients applied to the clinic and at the end of the third month after isotretinoin discontinuation (graph 1,2).

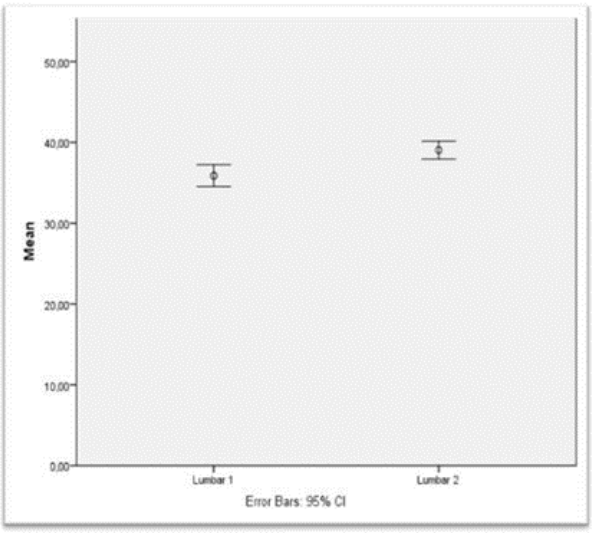
Table 1: Spearman correlation test results of data and VAS scores of the patients show a positive correlation between the VAS and the Neu/Lymp ratio

Variables	Max.	Min.	Mean	SD	Statistics	VAS
Creatine	1,18	0,51	0,76	0,141	r	0,051
					p	0,350
Lymp	4,12	0,83	2,39	0,6601	r	-,604**
					p	<0,001
Neu	8,2	1,86	4,08	1,378	r	,442**
					p	<0,001
Neu/ Lymp	5,75	0,56	1,85	0,923	r	,723**
					p	<0,001

****** There was a significant correlation between values (r), and there is a significant relationship between the two variables p<0,05



Graph 1. Cervical 1 and lumbar 1: Cobb angles of cervical and lumbar spine at the admission day. (Wilcoxon signed rank test



Graph 2. Cervical 2 and lumbar 2: Cobb angles of cervical and lumbar spine at the end of third month. (Wilcoxon signed rank test)

There were statistically significant differences between Cobb angles of spine (Cervical 1 versus Cervical 2, and Lumbar 1 versus Lumbar 2) p<0,05.

Discussion

Drug-induced myopathy is defined as a manifestation of myopathic symptoms such as muscle weakness, myalgia, creatine kinase (CK) elevation, or myoglobinuria that can occur in patients, who have not muscle disease, using specific drugs (Dalakas, 2009). There are many myotoxic drugs such as immunosupressive agents (glucocorticoids), cholesterol-lowering drugs (statins), antivirals (interferons, clevudine), rheumatologic agents (antimalarials), and in this study, we investigated dermatologic agents (isotretinoin).

Isotretinoin induced musculoskeletal side effects can include myalgia, sacroiliitis, back pain, diffuse idiopathic skeletal hyperostosis, ligament and tendon calcifications, bone resorption, and attenuated collagen synthesis (Penniston and Tanumihardjo, 2006; DiGiovanna, 2001). Symptoms in patients may occur such as mild muscle pain and cramps to severe muscle weakness, resulting in rhabdomyolysis, renal failure, and death (Sameem and Semira, 2016). Myalgia and muscle stiffness were reported in 16-51% of patients with acne vulgaris treated with isotretinoin, and serum Creatine Kinase (CK) levels were found to be increased in 41% of these patients (Dicken, 1984; Heudes and Laroche, 1998; Janati, 2014). It is reported in the literature that exercise can increase serum CK levels in patients who use isotretinoin, as well as in all people (McBurney and Rosen, 1984), and also serum CK levels are normal in many patients with muscle pain and symptoms using isotretinoin (Fiallo and Tagliapietra, 1996; Hodak et al., 1986; Karagun 2019). Drug-induced myotoxicity is explained as multifactorial: brunt may be on muscle organelles, for example, mitochondria, lysosomes, and myofibrillar proteins; muscle antigens can be altered leading to inflammation or

immunologic reaction; nutritional and electrolyte imbalances may occur resulting in muscle dysfunction (Valiyil and Christopher-Stine, 2010). Isotretinoin-induced myalgia may be related to TRAIL-mediated muscle cell apoptosis (Bodo C. Melnik, 2017) (Figure 1). The nuclear FoxOs transcription factor can create an artificial starvation state on muscle metabolism and cause hemostasis to transform into catabolic events in the muscle cell, which may open the isotretinoin-induced myalgia mechanism (Melnik 2011) (Figure 2).

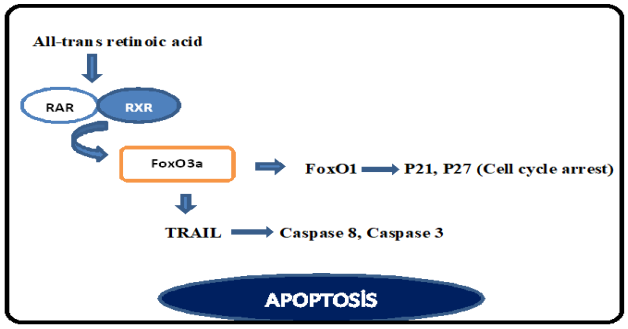


Figure 1. Mechanism of Isotretinoin–induced myopathy (apoptosis).

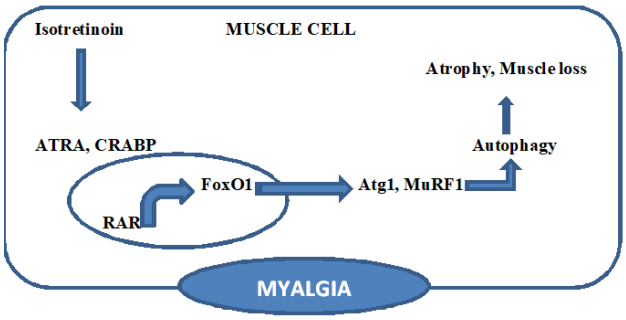


Figure 2. Mechanism of Isotretinoin–induced myopathy (myalgia)

Isotretinoin initiates an inflammatory cascade especially in the synovial membrane of joints like sacroiliac joint causing sacroiliitis reported by Aydog E et al., Dincer et al., Levinson et al. (Dincer et al., 2008; Levinson et al., 2012; Aydog et al., 2019). Many hypotheses suggest it affects immunomodulation and starts the inflammatory process by various mechanisms such as isotretinoin and cytokine balance alteration; the detergent-like effect of isotretinoin causes changes in lysosomal membrane structures, resulting in degeneration of synovial cells (Dincer et al., 2008). Levinson et al. (Levinson et al., 2012) indicated that retinoic acid can activate matrix metalloproteinase 2 (MMP-2), causing synovial membrane degradation in joints. In our study, patients using isotretinoin complained of cervical and lumbar pain because of myalgia, and no evidence or examination of synovial membrane inflammation such as sacroiliitis, spondylarthritis, or facet joint hypertrophy was observed. Radicular pain examinations of our patients did not yield a positive result; besides, the pain was alleviated or completely disappeared in the follow-up periods after discontinuation of the drug.

Cases similar to our study, pain caused by isotretinoin are in the literature such as Alkan S. et al. in 2015 reported isotretinoin related spondyloarthropathy series that most common SpA symptoms were inflammatory back pain (Alkan et al., 2015). In a series of four cases reported by Pehlivan et al., isotretinoin-related inflammatory low back pain present and symptoms disappeared completely after drug discontinuation (Pehlivan et al., 2011). In these studies, lower back pain caused by the inflammatory process that could occur in the lower back muscles was emphasized.

In our study, patients using isotretinoin experienced cervical and lumbar pain caused by an inflammatory myopathic process in spinal muscles were reported, and none of our patients had concomitant sacroiliitis. Neurological examinations of the patients were within normal limits and no radicular pain was detected and there was a significant direct correlation between the Neu/Lymp ratio and the severity of myalgia. Inflammatory responses secondary to isotretinoin usage led to myalgia, causing cervical and lumbar pain. In contrast to the literature, myalgia because of isotretinoin was evaluated with neutrophil/lymphocyte ratio instead of CPK level which shows a myopathic inflammatory process and may show false positivity. In this study, we detected a relation between VAS of cervical and lumbar myalgia and Neu/Lymp ratio. After discontinuation of isotretinoin, the decrease of the inflammatory myopathic process occurred simultaneously with the decrease of the Neu/Lymp ratio.

Cobb angles of the cervical and lumbar spine of the patients showed a statistically significant difference between admission to the clinic and the end of the treatment. There was a decrease in lordosis of the cervical and lumbar spine according to normal limits on lateral roentgenography on the admission day, but there was an increase in lordosis of the cervical and lumbar spine and approaching normal limits on lateral roentgenography at the end of 3rd month after discontinuation of isotretinoin. While drug-induced myopathy is the main mechanism responsible for myalgia in the low back and neck, decreasing lordosis of the cervical and lumbar spine are another mechanism to produce pain in that area.

Myopathy related muscle weakness decreasing normal lordosis of cervical and lumbar spine could cause pain in the neck and lower back regions. There was a significant difference in the Cobb angles of the cervical and lumbar spine of the patients between admission day and the end of the third month after discontinuation of the drug. While the mean Cobb angle of the cervical spine was 9,96+/- 6,82 degrees on the first day, the mean Cobb angle of the cervical spine was 14,91+/- 4,84 at the end of the third month. The same event is seen on the lumbar spine, while the mean Cobb angle was 35,89+/- 5,20 at first, the mean Cobb angle was 39,05+/- 4,30 after discontinuation of the drug.

The differential diagnosis for toxic myopathies can be quite broad. Elevated CPK levels and muscle weakness and pain may indicate toxic myopathy, but endocrine disorders such as hypo/hyperthyroidism, hyperparathyroidism, muscular dystrophies such as limb-girdle muscular dystrophy, Becker's and Duchenne's muscular dystrophies, metabolic disorders such as glycogen or lipid storage diseases, mitochondrial myopathies, and exercise intolerance can elevate CPK levels and cause muscle weakness and pain mimicking drug-inducing myopathy (Valiyil and Christopher-Stine, 2010). Isotretinoin-induced myopathies can manifest as muscle weakness, increased CPK levels, myalgia, myoglobinuria, EMG, histologic changes and we want to add Neu/Lymp ratio as a new indicator for isotretinoin induced myopathy to the literature by this article. Because many metabolic disorders, endocrinologic diseases, and severe exercise can elevate CPK levels, to be more precise diagnose the isotretinoin-related myopathy, we want to discuss the efficiency of Neu/Lymp ratio in facilitating the diagnosing of isotretinoin induced myopathy causing cervical and lumbar pain.

Limitations in our article, evaluating isotretinoin as a meta-analysis in a larger number of patients, will enable us to get clearer results. The mechanism of the side effects of isotretinoin on the muscle is still unclear.

Conclusion

Isotretinoin causes severe low back and cervical pain. Patients should be well informed about the side effects of isotretinoin commonly used in the treatment of acne vulgaris and clinicians should be aware of side effect during follow-up periods.

In cases of cervical and lumbar pain seen as a side effect, inflammatory myopathic processes secondary to drug usage should be questioned before interventional procedures and radiological evaluation of the patients. The Neu/Lymp ratio and Cobb angle of the lumbar and cervical spine should be considered as an alternative or additional parameter due to its ability to be applied and accessed as an alternative or additional parameter to muscle biopsy and CPK measurements performed for diagnosis and follow-up in drug-induced myopathy cases.

Ethics Committee Approval: This study was conducted with the approval of Cumhuriyet University Clinical Research Ethics Committee number 2019-02/22.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept- RG, DA, Design- DA, Supervision- RG, DA, Analysis and/or Interpretation- RG, DA, Literature Review- DA, Writing- DA, Critical Review- DA.
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RESEARCH ARTICLE

Evaluation of the Frequency of Suicidal Thoughts and Attempts and Related Factors in Female Adolescents with Anorexia Nervosa

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Abstract

Objective: Although anorexia nervosa (AN) has been associated with increased suicidal attempts, clinical variables that that influence this relationship still remains to be elucidated. The aim of this study is to examine the frequency of suicide attempts in females with AN, and the general psychopathology and associated clinical variables in patients with anorexia nervosa who do and do not attempt suicide.

Methods: In this study, archive files and reports of 43 females with AN admitted to the department of child and adolescent psychiatry between 2015 and 2020 were analyzed retrospectively. Participants' socio-demographic variables (age, peer relationships, psychiatric comorbidity, abuse history, history of suicidal thought and/or plan, family history of AN, etc.) and clinical (subtypes of AN, clinical features, response to treatment, the presence of suicidal ideation/attempts, etc.) characteristics were investigated. Also, the Children's Depression Inventory (CDI) and the State-Trait Anxiety Inventory (STAI) were used.

Results: Our results revealed that 18.8% of patients with restricting AN, 81.3% of patients with purging or binging/purging AN, and 37.2% of the entire sample had at least one suicidal attempt, and 39.5% of the patients engaged in nonsuicidal self-injury behaviors. Further, binge-eating/purging AN type, more severe forms of AN, treatment resistance and poor insight or lack of insight, the presence of physical and emotional abuse, domestic violence, and the existence of psychiatric comorbidity markedly elevated the risk of suicide.

Conclusion: The present study shows that patients with AN should be investigated not only for problems with eating and weight but also for possible non-suicidal self-harm behaviors, suicidal attempts.

Key words: Anorexia nervosa, suicide, suicide attempt, adolescent, eating disorders.

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Introduction

Eating disorders are serious diseases causing bodily and psychosocial dysfunctions and may sometimes result in death (Smith et al. 2019). Anorexia Nervosa (AN), which is a form of eating disorder, is defined with the DSM-5 (Diagnostic and Statistical Manual of Mental Health, Fifth Edition) criteria as having low body weight, fear of gaining weight, and doing behaviors that prevent weight-gain by limiting the energy received compared to body requirements (American psychiatric association 2013). Although the lifetime prevalence in adolescent girls is between 0.3% and 2.6%, it is stated in studies that it rates from 0.1% to 0.3% in boys (Swanson et al. 2011, Smink et al. 2014, Keski-Rahkonen and Silén 2019).

Suicide is a devastating act of death that is committed by individuals with the intention of open or implicit death. When this self-harming behavior does not result in death, it is called a suicide attempt (Bridge et al. 2006). According to the World Health Organization, suicide ranks the second among the causes of death among young people between the ages of 10 and 24, and suicide attempts are 20 times more common than completed suicide (World Health Organization). In a metaanalysis study evaluating the suicide rates and causes in psychiatric disorders, it was emphasized that suicide rates were higher in all psychiatric diseases than in normal population; and that borderline personality disorder, anorexia nervosa, depression and bipolar disorder had the highest risk of suicide (Chesney et al. 2014).

Anorexia Nervosa has a high risk of mortality in adolescents who are between the ages of 15 and 24 (Hoang et al. 2014). The high mortality rate in patients with anorexia was previously associated with to hunger and secondary complications of hunger; however, recent studies show that deaths associated with suicide contribute to this high rate (Franko et al. 2004). According to a meta-analysis of Keshaviah et al., individuals with AN have an 18.1 times higher risk of mortality from suicide than the 15- to 34-year-old female population (Keshaviah et al. 2014). In this study, the purpose was to evaluate the frequency of suicidal thoughts/attempts and associated sociodemographic features and clinical factors in female adolescents with AN diagnosis in the light of the relevant literature. In this way, it was also targeted to identify the risk factors for suicide in AN.

Methods

Study Design and Sampling Selection

The study was designed in retrospective design, and received local ethics committee approval (No: 2020/1129), including the data of 43 patients who were followed up and treated with AN in line with the DSM-5 criteria in Department of Child and Adolescent Psychiatry of Inonu University between 2015 and 2020. The sociodemographic characteristics, history of abuse (all of the cases with a history of sexual abuse had forensic reports), subset of the disease, clinical characteristics, response to treatment, whether there was suicidal thoughts/attempts, the number/method of suicide attempts, peer relationships, the presence of comorbid psychiatric conditions, family history of AN, family history of suicide, the Children's Depression Inventory (CDI) and the State-Trait Anxiety Inventory of the patients were evaluated in detail. Patients with incomplete data were excluded from the study.

Children's Depression Inventory (CDI): It was developed by Kovacs in 1992 to determine the severity of depression in children and in young people (Kovacs 1981) and was adapted into Turkish by Öy in 1990 (Öy 1991). CDI is a self-assessment scale and is filled by reading to children or reading to the child by him/herself. Based on a total of 27 items, responses are given scores ranging from 0-2; and on 19, the highest score that may be received is 54, and higher scores show a higher level of depression.

State-Trait Anxiety Inventory for Children (STAI-C): The scale was developed by Spielberg et al., and has two separate subgroups as the state anxiety scale and trait anxiety scale each of which consists of 20 items (Gaudry et al. 1975). The scale was adapted into Turkish by Ozusta (1995). In trait anxiety scale, the child is often asked to rate how s/he feels, while in state anxiety scale s/he is asked to assess how s/he feels in that moment.

Statistical Analysis

IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Compliance of the data to normal distribution was determined by the one-sample Kolmogorov-Smirnov test. The numerical and categorical data were presented as number (n), median (min-max), percentage (%), and mean±standard deviation (SD) whenever appropriate. The Chi-square Test and Mann-Whitney-U-Test were used to for statistical

analysis. Also, to evaluate the predictor value of some main clinical variables on the frequency of suicidality, the Binary Logistic Regression Analysis (stepwise) were performed. p <0.05 was considered statistically significant.

Results

Demographic characteristics of the sample

The study population consisted of forty-three adolescent girls with AN between 12 and 17 years of age (mean age:15.16±1.17 years). Twenty-seven (62.8) of the participants were from the urban area and 21 (48.8%) were from a low economic level. Most of the cases (n=30, 69.8%) had problematic or poor peer relationships. 41.9% (n=18) of the participants were smoking, 9.3% (n=4) were using alcohol/substance. Sixteen participants (37.2%) reported physical abuse, seven participants (16.3%) sexual abuse, and twenty-two participants (51.2%) emotional abuse. Domestic violence was present in 22 cases (51.2%), 6 (14%) of whom were only emotional abuse, while 16 (37.2%) were both physical and emotional abuse. Regarding the psychiatric comorbidity, more than half of the participants (n=27, 62.8%) were diagnosed with at least one psychiatric comorbid disorder. With respect to their primary diagnoses, the most common diagnosis was depression (n=13, %30.2), this was followed obsessive-compulsive disorder (n=7, %16.3), post-traumatic stress disorder (n=5, %11.6) and disruptive behavior disorders (n=2, %4.7) followed. None of the patients had a chronic disease. 23.3% (n=10) of the patients had a positive family history of suicide and 20.9% (n = 9) had a positive AN family history. The sociodemographic and familial characteristics of the participants are shown in Table 1.

Table 1. Demographic characteristics of the sample

Variables	Number (n)	Percentage (%)
Place of residence		
Urban	27	62.8
Rural	16	37.2
Family income level		
The minimum wage/less than minimum wage	21	48.8
Above the minimum wage	22	51.2
Peer relationships		
Good or average	13	30.2
Problematic or poor	30	69.8
Smoking	18	41.9
Use of alcohol/substance	4	9.3
Physical abuse	16	37.2
Sexual abuse	7	16.3
Emotional abuse	22	51.2
Domestic violence		
No	21	48.8
Emotional only	6	14
Physical and emotional	16	37.2
Psychiatric comorbidity	27	62.8
Comorbid psychiatric disorders		
Depressive disorders	13	30.2
Post-traumatic stress disorder	5	11.6
Obsessive-compulsive disorder	7	16.3
Disruptive behavior disorders	2	4.7
Family history of suicide	10	23.3
Family history of anorexia nervosa	9	20.9

Clinical features of anorexia nervosa

The mean age of onset of anorexia was 13.67±0.96 years. Participants' mean "body mass index" value was 15.89±0.62. 62.8% (n=27) of the patients were diagnosed with restricting type AN, 37.2% (n=16) binge-eating/purging type AN. The severity of AN was distributed as mild (n=18, 41.9%), moderate (n=14, 32.6%), severe (n=8, 18.6%) and extreme

(n=3, 7%). Regarding the clinical features of anorexia, while 18 patients (41.9%) had self-induced vomiting, 8 patients (18.6) had amenorrhea. 14 patients (32.6%) were doing exercise excessively. Binge eating was present in 18 patients (41.9%). There were no patients who misused laxatives, diuretics, or enemas. With regard to the motives of AN, 27 patients (62.8%) reported the "trying to look like their friends" as the factor that triggered their symptoms, while sixteen patients (37.2%) defined the "feedback about being overweight" as the reason. Twenty patients (60.5%) had previously received treatment for AN or were under treatment, and 21 patients (48.8%) had treatment resistance and poor insight or lack of insight. The clinical features of anorexia are described in Table 2.

Table 2. Clinical features of anorexia nervosa

	Number (n)	Percentage (%)
Anorexia nervosa subtypes		
Restricting type	27	62.8
Binge-eating/purging type	16	37.2
Severity of AN		
Mild	18	41.9
Moderate	14	32.6
Severe	8	18.6
Extreme	3	7
Self-induced vomiting	18	41.9
Absence of menstruation	8	18.6
Exercising excessively	14	32.6
Binge eating	15	34.9
Motives of AN		
Trying to look like friends	27	62.8
Feedback about being overweight	16	37.2
Previous treatment for AN (in patient)	26	60.5
Treatment resistance and poor insight or lack of insight	21	48.8

Abbreviations: AN, anorexia nervosa

Evaluation of nonsuicidal self-harm behaviors, and suicidal thought, plan, and attempts

Nonsuicidal self-harm behaviors were detected in 39.5% (n=17) of the participants. Self-cutting (n=17, 39.5%), self-burning (n=9, 20.9%) and skin damage by other methods (n=9, 20.9%) were determined as the nonsuicidal self-harm methods. While the frequency of suicidal thought and/or plan before AN were 53.5% (n=23), the frequency of suicidal attempt was 34.9% (n=15) before AN. As for method(s) of suicidal thought, plan or attempts before AN, drug intake in 15 patients (34.9%), drug intake+use of other methods in 7 patients (16.3%) and jumping from a height in 1 patient (2.3%) were found. The frequency of suicidal thought and/or plan after AN was 58.1% (n=25), while the frequency of suicidal attempt after AN was 37.2% (n=16). Table 3 displays the data on features of nonsuicidal self-harm behaviors, and suicidal thought, plan, and attempts.

Table 3. Features of nonsuicidal self-harm behaviors, and suicidal thought, plan, and attempts

	Number (n)	Percentage (%)
Nonsuicidal self-harm behaviors	17	39.5
Methods of nonsuicidal self-harm		
Self-cutting	17	39.5
Self-burning	9	20.9
Skin damage by other methods	9	20.9
Suicidal thought and/or plan before AN	23	53.5
Suicidal attempt(s) before AN	15	34.9
Method(s) of suicidal thought, plan or attempts before AN		
Drug intake	15	34.9
Drug intake + Other method(s)	7	16.3
Jumping from height	1	2.3
Suicidal thought and/or plan after AN	25	58.1
Suicidal attempt(s) after AN	16	37.2
Method(s) of suicidal thought, plan or attempts after AN		
Drug intake	9	20.9
Drug intake + Other method(s)	9	20.9
Jumping from height	7	16.3

Abbreviations: AN, anorexia nervosa

Comparison of clinical variables of patients with and without suicidal attempt(s) after AN

The mean age of those who had attempted suicidal attempts after AN was significantly higher than those who did not (p 0.004), but the mean age of onset of AN did not reach a significant value (p=0.566). AN subtype differed significantly between the two groups (p<0.001), accordingly, those who had suicidal attempt(s) had a higher rate of binge-eating/purging AN type than those who did not (81.3% vs. 11.1, respectively). The two groups also significantly differed in terms of the severity of AN (p<0.001); all of those who had attempted suicide had moderate or other serious types, this rate was 33.3% in those who did not. In contrast, average body mass index scores were not different between the two groups (p=0.241). Treatment resistance and poor insight or lack of insight rates of those who had attempted suicide after AN were significantly higher than those who did not attempt suicide after AN (93.8% vs. 22.6%, respectively, p<0.001) (Table 4).

While psychiatric comorbidity was present in all those who had attempted suicide, this rate was 40.7% in those who did not, and the difference was statistically significant (p<0.001). Smoking rates (93.8% vs. 11.1%, respectively, p <0.001) and alcohol-substance use rates (25% vs. 0%, respectively, p = 0.015) were significantly higher in those who had attempted suicide compared to those who did not. In terms of the frequency of non-suicidal self-harm behaviors, a significant difference was observed between the groups (p<0.001), accordingly, while all of those who had attempted suicide after AN had previously engaged in self-injurious behavior, only 1 patient (3.7%) among those who did not attempt suicide had previously engaged in self-injurious behavior. The rates of suicidal thought and/or plan before AN (100% vs. 25.9%, respectively), suicidal attempt(s) before AN (100% vs. 0%, respectively), and suicidal thought and/or plan after AN (100% vs. 33.3%, respectively) of those who had attempted suicide after AN were significantly higher than those of those who did not (all p-values <0.001). Moreover, our findings showed that the positive family history of suicide was significantly higher in those who had attempted suicide after AN than those who did not (p=0.001), whereas the family history of AN did not differ (p=0.06) (Table 4).

The frequency of physical abuse (68.8% vs. 18.5%, respectively, p=0.001), emotional abuse (87.5% vs. 29.6%, respectively, p<0.001), and domestic violence (87.5% vs. 29.6%, respectively, p<0.001) among those who had attempted suicide were significantly higher compared to those who did not. However, there was no significant difference between the two groups in terms of sexual abuse (p=0.082). Regarding peer relationships, it was observed that those who had attempted suicide had more problematic or poorer peer relationships than those who did not, and the difference was statistically

significant (87.5% vs. 55.6%, respectively, p=0.031) (Table 4).

As for the scale scores, the mean CDI scores (40.0±5.35 vs. 28.59±7.04, respectively, p<0.001) and the mean STAI-trait (33.62±6.31 vs. 30.41±6.30, respectively, p=0.029) scores of those who had attempted suicide were significantly higher than those of those who did not. However, the mean STAI-state scores were not different between groups (p=0.087). The comparisons of clinical variables of patients with and without suicidal attempt(s) after AN is given in Table 4.

Table 4. Clinical variables of patients with and without suicidal attempt(s) after AN. Data were given as mean±standard deviation or number (percent %)

	Suicidal attempt(s) after AN		
	Yes (n=16)	**No (n=27)**	**p-value[a]**
	mean±SD	**mean±SD**	
Age (years)	15.81±0.65	14.78±1.25	**0.004***
Age of onset of AN (years)	13.56±0.81	13.74±1.05	0.566
CDI score	40.0±5.35	28.59±7.04	**<0.001****
STAI-state score	31.94±6.70	28.74±5.13	0.087
STAI-trait score	33.62±6.31	30.41±6.30	**0.029***
Body Mass Index (mean±SD)	16.02±0.62	15.81±0.61	0.241
	Number (%)	**Number (%)**	
Anorexia nervosa subtypes			
Restricting type	3 (18.8)	24 (88.9)	**<0.001****
Binge-eating/purging type	13 (81.3)	3 (11.1)	
Severity of AN			
Mild	0 (0)	18 (66.7)	**<0.001****
Moderate or other serious types	16 (100)	9 (33.3)	
Treatment resistance and poor insight or lack of insight	15 (93.8)	6 (22.2)	**<0.001****
Psychiatric comorbidity	16 (100)	11 (40.7)	**<0.001****
Nonsuicidal self-harm behaviors	16 (100)	1 (3.7)	**<0.001****
Suicidal thought and/or plan before AN	16 (100)	7 (25.9)	**<0.001****
Suicidal attempt(s) before AN	15 (93.8)	0 (0)	**<0.001****
Suicidal thought and/or plan after AN	16 (100)	9 (33.3)	**<0.001****
Family history of suicide	9 (56.3)	1 (3.7)	**0.001***
Family history of AN	6 (37.5)	3 (11.1)	0.06
Smoking	15 (93.8)	3 (11.1)	**<0.001****
Use of alcohol/substance	4 (25)	0 (0)	**0.015***
Abuse history			
Physical abuse	11 (68.8)	5 (18.5)	**0.001***
Sexual abuse	5 (31.3)	2 (7.4)	0.082
Emotional abuse	14 (87.5)	8 (29.6)	**<0.001****
Domestic violence	14 (87.5)	8 (29.6)	**<0.001****
Peer relationships			
Good or average	2 (12.5)	12 (44.4)	**0.031***
Problematic or poor	14 (87.5)	15 (55.6)	

Abbreviations: AN, anorexia nervosa, CDI, Children's Depression Inventory, STAI, State-Trait Anxiety Inventory.
[a]The chi-square test and Fisher's exact test (as appropriate) for categorical variables and the Mann–Whitney U test for continuous variables were used to test group differences.
*: p<0.05, **: p<0.001

Logistic regression results for suicide attempt(s)

In the multiple logistic regression analysis performed for suicide attempt after AN; among the sociodemographic variables, the patient's age, age at diagnosis of AN, family income level, place of residence, alcohol-substance use, domestic violence, physical/sexual/emotional abuse and neglect history did not affect suicide attempt risk (p>0.05 for all variables). Regression analysis according to the mental illness of the patient and his family did not reveal the presence of comorbid psychiatric illness, a history of nonsuicidal self-harm behavior, a history of suicide or AN in the family, and a history of suicidal ideation/plan/attempt in the patient before AN on the risk of suicide attempt (for all variables. p> 0.05). When analyzed in terms of AN properties; the effect of vomiting-amenorrhea, exercising, condition that causes AN and treatment resistance (low insight) on suicide attempt risk was not determined (p> 0.05 for all values). The binge-eating/purging subtype of AN increased the risk of suicide attempt 32 times (p=0.006) compared to the restrictive subtype, and the group with severe AN increased 16 times (p=0.011) compared to mild and moderate severity. In regression analysis based on scale scores, while STAI-state and STAI-trait scale scores did not have an increasing effect on suicide attempt risk, a 1-unit increase in depression scale score increased the risk of suicide attempt 1.2 times (p<0.001). The results of binary logistic regression analysis (stepwise) for suicide attempt were given in Table 5.

Table 5. Results of Binary logistic regression analysis (stepwise) for suicide attempt

Sociodemographic variables	**Reference category**	**Other category**	**Beta**	**OR (%95 Cl)**	**p value**
Smoking	Yes	No	4,689	108,768 (8.242-1435,331)	**0,000****
Physical abuse	Yes	No			0,090
Features of mental status	**Reference category**	**Other category**	**Beta**	**OR (%95 Cl)**	**p value**
Nonsuicidal self-harm behaviors	Yes	No			0.097
Suicidal attempt(s) before AN	Yes	No			0.998
Family history of anorexia nervosa	Yes	No			0.997
Clinical features of AN	**Reference category**	**Other category**	**Beta**	**OR (%95 Cl)**	**p value**
Severity of AN	Severe-extreme	Mild-Moderate	2.781	16,141(1.895-137.451)	**0.011***
Anorexia nervosa subtypes	Binge-eating/purging type	Restricting type	3.471	32.166 (2.699-383.321)	**0.006***
Scale scores	**Reference category**	**Other category**	**Beta**	**OR (%95 Cl)**	**p value**
CDI	-	-	0.248	1.282 (1.112-1.506)	**0.000****

OR: Odds ratio, CI: Confidence interval, CDI: Child depression inventory, AN: Anorexia nervosa, STAI: State-Trait anxiety inventory for children, *: p<0.05, **p<0.001

Discussion

In this study, we examined the frequency of nonsuicidal self-harm and suicide attempts in females with AN, and the general psychopathology and associated clinical variables in patients with AN who do and do not attempt suicide. Our results established that AN is associated with an increased likelihood of suicidality (a variable of varying severity from transient or persistent thoughts, plans to attempt), and depressive symptoms and symptoms of higher anxiety mediate this relationship. We determined that 39.5% of the patients engaged in nonsuicidal self-harm behaviors, and 37.2% attempted suicide at least once. Further, binge-eating/purging AN type, moderate or other serious AN forms, treatment resistance and poor insight or lack of insight, the presence of physical and emotional abuse, domestic violence, the existence of psychiatric comorbidity, and problematic or poor peer relationships elevated the risk of suicide.

Previous studies have reported that AN patients have elevated rates of suicide attempts compared to the general healthy population and suicide contributes to excessive mortality rates in AN patients (Pompili

et al. 2006, Bulik et al. 2008, Forcano et al. 2009, Forcano et al. 2011, Crow et al. 2014, Wade et el. 2015). It has been found that a significant proportion of patients with eating disorders, and AN in particular, have suicidal suicidal ideation at any time during the course of their illness and lifetime. The frequency of suicidal thoughts is given at the rate of one quarter to one-third (Swanson et al. 2011, Carano et al. 2012). Although the prevalence of suicidal attempts varies significantly among studies due to methodological differences including study design, the severity of the disorder, and demographic characteristics such as age and population composition, regarding the suicidal attempts, almost similar rates were also determined (Franko and Keel 2006, Crow et al. 2014). It has been reported that the risk of suicide in patients with AN is 6-10 times higher than in the general population (Mendolicchio et al. 2014). A prior study has found a frequency of suicidal attempts in 8.65% of outpatients with restricting AN and in 25.0% outpatients of purging AN (Forcano et al. 2009). In another study, it was found that 20% of anorexic patients attempted suicide, and the rate of successful ones was 5% (Franko et al. 2004). We found a higher rate of suicidal attempts than this study reported. Our results revealed that 11.1% of patients with restricting AN, 81.3% of patients with purging or binging/purging AN, and 37.2% of the entire sample had at least one suicidal attempt. Our high rates may be due to our sampling strategy because most of the cases in our sample had moderate or other severe forms and a significant portion of the participants were recruited from the inpatient service. In addition, it has been shown that 40.8% of adolescents with eating disorders exhibit self-harming behaviors (Peebles et al. 2011). According to the types of eating disorders, the prevalence of self-injurious behavior is 26-55.2% in bulimia nervosa, 27.8-68.1% in purging or binging/purging AN, and 13.6-42.1% in restricting AN (Svirko and Hawton, 2007). We also found similar rates of nonsuicidal self-harming behaviors in this population.

With regard to underlying mechanisms or dynamics, a number of theories have been proposed to explain the increased suicidality in individuals with eating disorders. In general, asserted theories have argued that eating disorders themselves bring about suicidal behavior or that they contribute to increased suicidality by they co-occur with other factors that give rise to suicidal behavior1. It is emphasized that AN and psychopathological conditions that lead to suicidal behavior share common genetic and environmental risk factors (Koutek et al. 2016). Accordingly, some authors have suggested that high comorbidity rates with other psychiatric disorders related to increased suicidality may make the patients more prone to suicide (Blinder et al. 2006). In parallel with this, it has been shown that the risk of suicidal attempts increases in the presence of comorbidity with conditions such as mood disorders, posttraumatic stress disorder, various impulse-control disturbances, and substance use, each of which is an independent risk factor for suicide (Franko et al. 2004, Bulik et al. 2008, Davico et al. 2019). There have even been reports that eating disorders are not substantially increasing suicidal propensity after adjusting for comorbidities (Forrest et al. 2016). In our study, the rate of psychiatric comorbidity was quite high with 62.8%, and the most common diagnoses were disorders associated with a great risk of suicide such as depression, PTSD and OCD (Auerbach et al. 2015, Chou et al. 2020, Agne et al. 2020). Moreover, we found that psychiatric comorbidity is very strongly associated with suicidal attempts. In addition, we found that alcohol-substance use, and especially smoking, are important risk factors for suicidal attempts among individuals with AN. Our results support the literature information (Franko et al. 2004, Auerbach et al. 2015, Lian et al. 2017, Chou et al. 2020, Agne et al. 2020). Eating disorders show comorbidity with 40-50% depression, 60-70% anxiety disorders, as well as other psychological disorders such as alcohol-substance abuse and personality disorders (Swanson et al. 2011). Studies have also found that individuals with AN have a high risk of depression and that that suicide attempts in these patients are modified by depression (Favaro and Santonastaso et al. 1997, Koutek et al. 2016, Lian et al. 2017).

Apart from psychopathology, studies have indicated that purging behavior (Favaro and Santonastaso 1997, Franko and Keel 2006), low BMI (Favaro and Santonastaso 1997), earlier onset (Franko et al. 2004), longer disease duration (Favaro and Santonastaso 1997, Stein et al. 2004), history of physical and/or sexual abuse (Favaro and Santonastaso 1997), and worse prognosis (Steinhausen 2009) increase the risk of suicidality in patients diagnosed with AN. We could not assess the prognosis due to the design of our study, but all other clinical variables except BMI were associated with increased suicidality rates. Furthermore, we also detected that positive family history of suicide, a history of nonsuicidal self-harm behaviors, and the presence of suicidal thoughts, plans, and/or attempts before AN increase the risk of subsequent suicide.

Although evidence is limited to a few studies that controlled for whether there is a difference in the incidences of suicidal attempts of two AN subtypes, research shows that patients who suffered from restricting AN have lower percentages of suicidal attempts (Favaro and Santonastaso 1997, Franko et al. 2004, Youssef et al. 2004). Similarly, we have also found higher frequency of suicide attempts in purging or binging/purging AN. Our results are consistent with the results of other studies showing that the presence of purging symptoms is more common in patients who have attempted suicide (Franko et al. 2004, Forcano et al. 2011). This finding has been attributed to the fact that "purging" behaviors are associated with greater psychopathology and impulsivity, and poorer emotional regulation, especially anger (Krug et al. 2008) each of which may increase the suicide risk.

More importantly, the outcomes of our study yielded that more severe forms of AN and rates of treatment resistance and poor insight or lack of insight are more frequent in cases who attempted suicide, suggesting the dose-response relationship between the severity of AN and suicidal attempts. Our findings support data from a recent study showing that patients with more severe AN have an elevated risk of suicidality (Fennig and Hadas 2010; Lian et al. 2017).

Other striking findings of this study are that AN case who attempted suicide have more physical and emotional abuse and domestic violence experiences and more problems in peer relationships. The most likely explanation for these findings may be that such stressful life events indirectly predispose to disorders that are robustly associated with suicidality, such as depression and post-traumatic stress disorder. However, there is insufficient data on whether these variables are predictive values for suicidality in patients with AN (Favaro and Santonastaso 1997). Therefore, further studies are needed to determine whether these variables contribute to the increased risk of suicidality in this population.

This study was subject to several limitations. First, the design of our study was retrospective. Second, our sample lacked a control group and consisted of a female group with AN only, hence, our sample is not representative for all anorexic patients. Third, our sample size did not allow us to evaluate the relationship between some clinical variables and suicidality risk. These weaknesses occlude the generalization of our results. Therefore, future longitudinal studies with large sample size including both a healthy control group and a male group with AN would be considerably beneficial to elucidate the existing knowledge further.

Conclusion

To summarize, the current study demonstrates that the severity, type, and certain clinical variables of AN affect the relationship between AN and suicidality, and comorbid psychopathological conditions, in particular, depressive symptoms and symptoms of higher anxiety, mediate this relationship. Also, our results suggest that clinicians should be particularly aware of the great risk of suicide if there are conditions including binge-eating/purging AN type, treatment resistance and poor insight or lack of insight, the presence of physical and emotional abuse, domestic violence, and problematic or poor peer relationships. If there are these adverse states, possible nonsuicidal self-harm behaviors, suicidal thoughts, plans, and/or attempts of these patients must be investigated.

Ethics Committee Approval: Ethics committee approval was received for this study from the Inonu University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision No: 2020-1129).
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RESEARCH ARTICLE

The Role of Wikipedia in Providing Information on Coronavirus to Societies during the COVID-19 Pandemic

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Abstract

Objective: The coronavirus, which had first appeared in late 2019, turned into a pandemic spreading all over the world in a short time. People used internet resources to get information during the pandemic process. Wikipedia is one of the popular sources of internet preferred for accessing information in diseases and previous outbreaks. This study, the use of Wikipedia as an internet source in the coronavirus pandemic process was evaluated. The societies access to the articles on Wikipedia has been analyzed in detail.

Methods: In the study, among the articles related to coronavirus on Wikipedia, the articles with a high number of views, which are displayed between January 20, 2020, and May 20, 2020, containing information in all languages were determined. 4 articles with the highest number of views matching these items were selected. These articles were evaluated in terms of views and updates. Searched topics on Wikipedia by societies during to pandemic process were determined.

Results: The number of Wikipedia searches in search engines increased significantly in the period of 20 January 2020 - 20 May 2020 compared to the period of 20 January 2019 - 20 May 2019 ($p<0.001$). During the Coronavirus pandemic, "Wikipedia" was searched more in search engines. 4 articles reached over 130 million page views in total. Societies have researched past outbreaks and measures against coronavirus on Wikipedia.

Conclusion: Wikipedia has been an important source of internet for societies during the coronavirus pandemic process. Wikipedia data can be applied to predicting and modeling trends in societies.

Key words: Coronavirus, Wikipedia, Information, Internet.

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Introduction

In late December 2019, a new case of coronavirus, which can be transmitted to humans in Wuhan, China, was reported (Chen et al., 2020). The new Coronavirus spread rapidly among humans. Coronavirus was detected in many people within a short time period in Wuhan. In late January, coronavirus cases were reported in many parts of China. Cases of coronavirus were reported in other surrounding countries. Coronavirus spread to distant countries in a short time. The World Health Organization (WHO) declared an "emergency" for the new coronavirus (2019-nCov) on January 30, 2020 (Sohrabi et al., 2020). Coronavirus spread to many countries in the world in February. WHO named the new disease COVID-19 (WHO, 2020). Coronavirus was observed in many countries in Europe, America, and Africa. The speed of the coronavirus spread is quite high. Coronavirus spread to many countries of the world in March. WHO announced the COVID-19 outbreak as a pandemic on 11 March (WHO, 2020). As of May 20, approximately 5,085,000 cases and 329,000 deaths have been reported worldwide (Worldometers, 2020).

The coronavirus outbreak affected the whole world in a short time. Pandemic has been the most important agenda topic worldwide. Coronavirus caused great anxiety and panic. Country governments implemented different measures to prevent the spread of coronavirus. Country administrations carried out many applications such as quarantine implementation, curfew, travel restriction, continuing education of students online, postponing sports, and organizations. Apart from the social effects of the coronavirus pandemic in society, there were also psychological effects (Roy et al., 2020).

Pandemics are special situations, which societies rarely experience within a century. Therefore, societies do not have experience against pandemics. Societies aren't acquainted with the new coronavirus. Societies needed information to fight against coronavirus pandemic. Societies met their information needs about coronavirus from different sources.

Providing individual measures in terms of public health is at the forefront of the main preventive practices. Access to valid information resources in all societies is important for individual measures to be taken. The Internet has created a powerful alternative to traditional information resources such as TV, radio, and newspaper in terms of providing access to information in the society. The Internet has provided quick access to information. Stack of information on a large scale has come into being on the internet. Not all of the information on the internet environment can be reliable and accurate. It is possible to reach the desired information in every field with the internet. The Internet has been one of the most influential resources of information in the 21st century. Wikipedia is an internet encyclopedia with open access, the content of which is developed by users and which contains information about many articles (http://wikipedia.org). Wikipedia provides information to people in many languages. There are millions of articles on Wikipedia (2020). Wikipedia is an internet encyclopedia that is constantly growing and updated by users. Over time, Wikipedia has become a powerful source of information for users (Viegas et al., 2020).

Related Works

Many websites contain reliable and accurate information in the field of health. There is a lot of information about health on Wikipedia. There has been a lot of research on the reliability and usability of the information available on Wikipedia. In their study, Del Valle et al. (2018) compared the information on diseases on Wikipedia articles with the information on Pubmed. As a result, they stated that the information on Wikipedia is similar to the information in PubMed. They stated that Wikipedia is a reliable source of information on diseases. Wikipedia is one of the frequently used information sources for information about diseases. Brigo et al. (2018) investigated how multiple sclerosis patients learned about the disease from Wikipedia. Moccia et al. (2016) stated that Wikipedia is one of the information resources that multiple sclerosis patients frequently access. Brigo et al. (2018) conducted research to obtain information about the attitudes and behaviors of epilepsy patients in Italy while accessing information. Jabaley et al. (2019) evaluated articles on asthma on Wikipedia to test awareness about asthma in their studies. Wikipedia is preferred as a source of information on issues related to epidemics. In their studies, Al tamime et al. (2018), evaluated the change in the number of articles and updates on Wikipedia about epidemics. In their studies, Priedhorsky et al. (2017), made an evaluation through Wikipedia to see the effects of the diseases that cause a global epidemic in society.

In this study, detailed research was conducted on the use of Wikipedia as a source of internet about coronavirus. Articles related to coronavirus on Wikipedia were examined. People’s access to information on coronavirus was evaluated on Wikipedia.

Methods

In the study, Wikipedia's articles about coronavirus, which were displayed between January 20, 2020, and May 20, 2020, were taken into consideration. There are many articles about coronavirus on Wikipedia. Articles with the highest number of pageviews and information about coronavirus in multiple languages are included in the study. The articles "Coronavirus," "Severe acute respiratory syndrome coronavirus 2", "COVID-19 pandemic" and "Coronavirus Disease 2019" on Wikipedia were evaluated within the scope of the study. The distribution of references in the articles is examined by their categories. Table 1 shows the categories of references. Pageviews of the articles for accessing information sources were taken into consideration. In the evaluation of the up-to-dateness of the information, the update numbers of the articles were taken into consideration. In terms of determining what kind of information societies access most, the pageviews of the articles by languages were compared. The data set of the study was obtained from Wikipedia's pageviews analysis tool (https://pageviews.toolforge.org). Article update numbers and article views were obtained from the pageviews analysis tool (https://pageviews.toolforge.org). Search rates of Wikipedia's on search engines are accessed through the Google trends tool (Google Trends, 2020).

Statistical Analysis

The conformity of the data to the normal distribution was examined with the Kolmogorov-Smirnov test. A paired t-test was used for repeated measurement in variables with a normal distribution. The statistical significance was accepted as $p<0.05$. The data were evaluated with IBM SPSS for Windows version 22 (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States).

Results

People researched information from different sources during the coronavirus pandemic process. In this process, the search rates of 20 January 2020 - 20 May 2020 and 20 January 2019 - 20 May 2019 were compared to determine the change on Wikipedia search rates on internet search engines. Comparison results are given in table 1. Between January 20, 2020, and May 20, 2020, Wikipedia search rates in internet search engines increased significantly ($p<0.001$). Figure 1 shows the change in search rates over time. As of April, in the pandemic process, there was a significant increase on Wikipedia search rates on internet search engine compared to the previous year.

Table 1. Comparison of search rates of Wikipedia on internet search engines

	20 January 2019 - 20 May 2019	20 January 2020 - 20 May 2020	p
Search Ratio of Wikipedia on Search Engine, Mean±SD	73,90±4,43	76,33±4,76	**p<0.001***

Paired t test; α:0.05; *Statistical significance

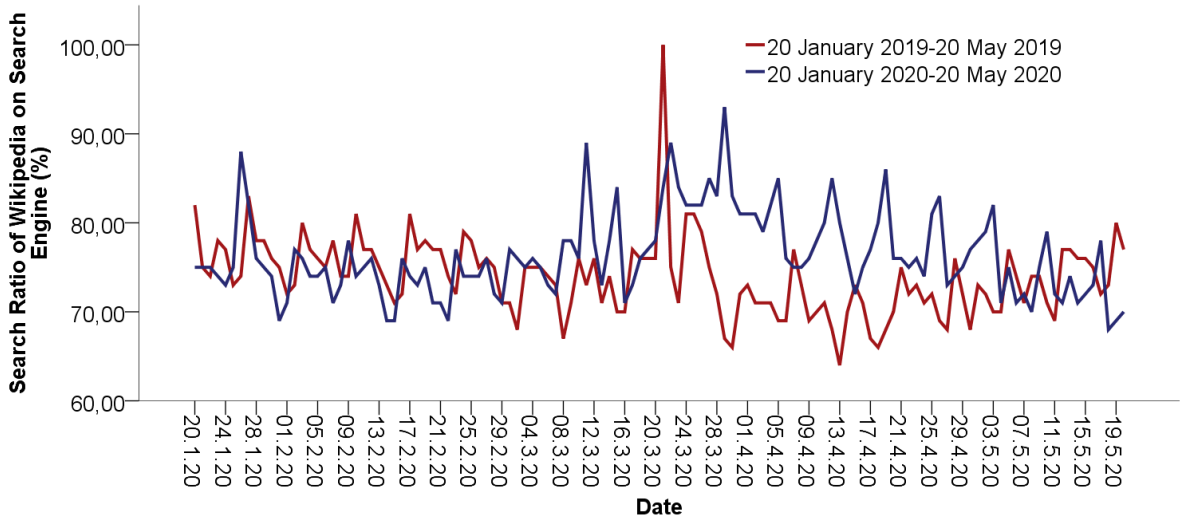

Figure 1. Search rates of Wikipedia on internet search engines according to time

Table 2. Updating article titles on Wikipedia according to time

Date	Article titles on Wikipedia			
	Coronavirus	**Severe acute respiratory syndrome coronavirus 2**	**Coronavirus Disease 2019**	**COVID-19 pandemic**
January 2020	Coronavirus	Novel coronavirus (2019-nCoV)	-	2019–20 outbreak of novel coronavirus (2019-nCoV)
February 2020	Coronavirus	Novel coronavirus (2019-nCoV)	Coronavirus disease 2019	2019–20 coronavirus outbreak
March 2020	Coronavirus	Severe acute respiratory syndrome coronavirus 2	Coronavirus disease 2019	2019–20 coronavirus pandemic
April 2020	Coronavirus	Severe acute respiratory syndrome coronavirus 2	Coronavirus disease 2019	2019–20 coronavirus pandemic
1-20 May 2020	Coronavirus	Severe acute respiratory syndrome coronavirus 2	Coronavirus disease 2019	COVID-19 pandemic

The content of articles related to coronavirus on Wikipedia was updated as new information about coronavirus came out. Article titles related to coronavirus on Wikipedia also changed as the information was updated. The change and updating of the article titles by months are given in table 2. During the Coronavirus pandemic process, new information was continuously obtained. The change in the number of times the article contents of Wikipedia are updated over time is shown in figure 2. The article that received the most updates was "COVID-19 Pandemic". The change in the number of updates in the articles revealed that new information about the pandemic was obtained. New information on coronavirus was obtained mostly in late January and in March. The number of times the articles about coronavirus on Wikipedia are displayed according to time is shown in Figure 3. It was observed that the most viewed article was "Coronavirus". The total number of updates and pageviews of the articles are given in table 3.

Table 3. Views and updated numbers of articles about Coronavirus on Wikipedia

	Numbers of View	**Numbers of Update**
Coronavirus	50.929.853	1.001
COVID-19 pandemic	37.434.046	20.323
Coronavirus Disease 2019	28.357.359	4.708
Severe acute respiratory syndrome coronavirus 2	15.591.762	3.223

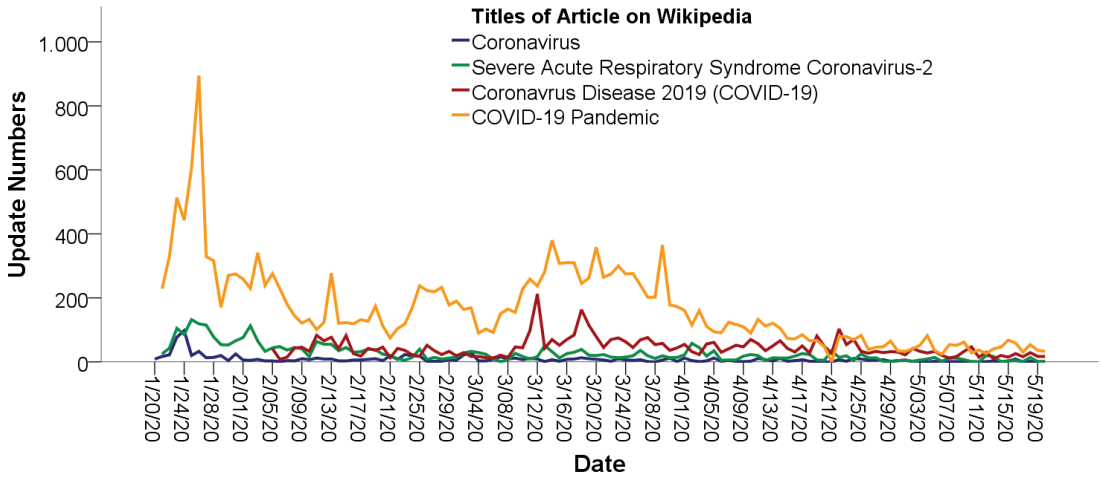

Figure 2. Update numbers of articles on Wikipedia according to time

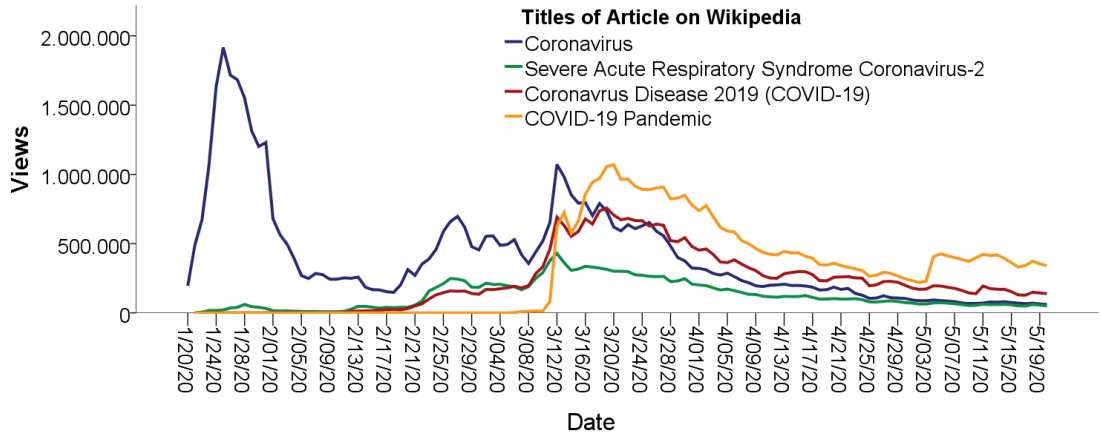

Figure 3. View numbers of articles on Wikipedia according to time

The pageviews of Wikipedia says a lot about people's access to information. The spelling languages of the items displayed on Wikipedia provide an idea about the access of societies to information. The number of pageviews in different languages on 4 articles on Wikipedia between January 20, 2020, and May 20, 2020, were evaluated. The most frequently viewed language is English. In terms of pageviews, Spanish, Russian, German, French, and Chinese are the most viewed languages after English. The "Coronavirus" article was viewed the most in societies using English, French, Polish and Portuguese languages. In societies using Spanish, German, Chinese, Italian, and Russian languages, the article "COVID-19 pandemic" was displayed mostly. In societies using the Japanese language, "Severe acute respiratory syndrome coronavirus 2" article was displayed mostly. View numbers of articles on Wikipedia according to languages are displayed in Figure 4.

The most researched title of pages related to the Coronavirus on Wikipedia are determined for different languages between January 20, 2020 and May 20, 2020. The most researched title of pages differs according to the societies. Societies have generally researched past outbreaks on Wikipedia in order to understand coronavirus. In addition, societies have examined the measures to be taken against coronavirus on Wikipedia. Most searched title of pages related to Coronavirus on Wikipedia according to languages are given in table 4.

In combating the COVID-19 pandemic, it is very important for people to comply with the measures taken against the Coronavirus. The use of masks, social distance and hand hygiene are the most important measures for Coronavirus. In Figure 5, the numbers of views for masks, social distance and hand washing titles of pages on Wikipedia is showed. It is observed that societies are mostly researching the use of masks.

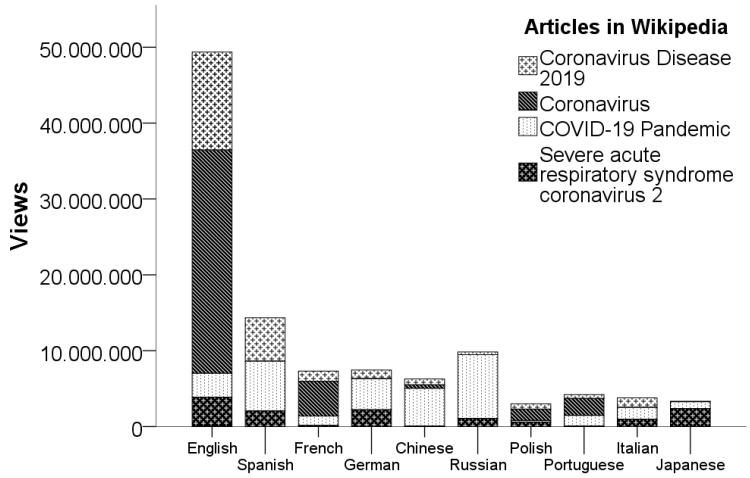

Figure 4. View numbers of articles on Wikipedia according to languages

Table 4. Most searched titles of Article related to Coronavirus on Wikipedia according to languages

Languages	**Titles of Article on Wikipedia**				
English	Deaths in 2020	Spanish Flu	WHO	COVID-19 Testing	Swine Influenza
Spanish	Quarantine	State of alarm	N95	1918 flu pandemic	Wuhan
French	FFP Mask	1918 Influenza	Ebola	Body temperature	Malaria
German	Paracetamol	Ebola	Short time work	Hantavirus	Body temperature
Chinese	Etanol	Italy	WHO	Black Death	H1N1 Influenza
Russian	Pneumonia	Black Death	BCG Vaccine	Hand antiseptic	Mask
Polish	State of emergency	Iran	Cholera	China	SARS
Portuguese	Bubonic plague	70% Alcohol	Asymptomatic	Avian Influeza	WHO
Italian	Herd immunity	Lombardia	Infection	Wuhan	Ebola
Japanese	SARS	MERS	Spanish Flu	BCG Vaccine	State of emergency

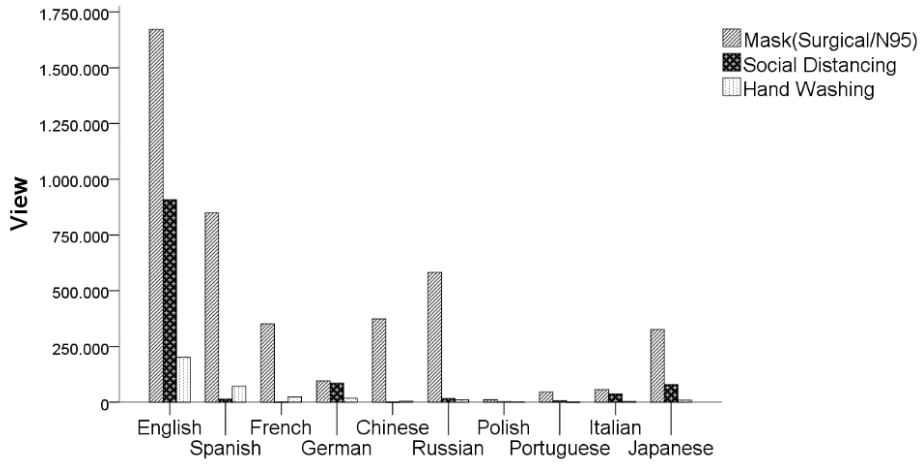

Figure 5. View numbers of articles on coronavirus measures according to languages

Discussion

Coronavirus pandemic caused great anxiety in societies. One of the biggest reasons for this anxiety was that people had little information about the coronavirus. Humans needed more information about the disease to take action against coronavirus. During this process, people often used internet sources to learn about coronavirus. Many websites contain information about coronavirus. People used more internet sources during the pandemic process than in previous years. Khatri et al. (2020) conducted a research on the use of YouTube as a source of information during the coronavirus pandemic process. They stated that Youtube had higher viewing rates during the coronavirus pandemic than the previous outbreaks. Wikipedia is one of the popular websites containing information about coronavirus. In our study, it was determined that Wikipedia was displayed more in the coronavirus pandemic period compared to previous years. This result we obtained supports the literature. Wikipedia is one of the preferred sources of information during the pandemic.

The change of article titles on Wikipedia over time was examined. The articles "Coronavirus" and "Coronavirus Disease 2019" on Wikipedia did not change over time. The titles "COVID-19 pandemic" and "Severe acute respiratory syndrome coronavirus 2" on Wikipedia changed over time. The main reason for the change of these titles on Wikipedia is the announcement of the pandemic in March. In addition to the change of article titles on Wikipedia, the article contents are also frequently updated. Georgescu et al. (2013) stated that on Wikipedia, many users can update the content of the articles. The change in the number of updates is an important sign to show that there are new findings about the article, that the content has been improved and that new information has been obtained. The findings of our study showed that there were many updates in four articles on Wikipedia. The most frequent updates were made in the article "COVID-19 pandemic". A lot of new information was obtained during the pandemic. The periods, in which the most information updates are made, are in the middle of March and as of the second half of January. The first case was reported in the United States on January 20 (Omer et al., 2020). The first cases were reported in Europe on 24 January (Stoecklin et al., 2020). WHO announced coronavirus pandemic worldwide on 11 March Cucinotta and Vanelli, 2020).

The number of pageviews on the websites is considered a behavioral measure of the search for information in society (Tausczik et al., 2012). In the study, the number of pageviews on Wikipedia was determined to show the public's search for information about coronavirus pandemic. The highest number of pageviews was observed in the article "Coronavirus" (number of pageviews: 50.929.853). In other articles, it was observed that the number of pageviews was quite high (number of pageviews range: 37.434.046-15.591.762). Coronavirus articles have reached very high page views in a short time. These findings show that societies are intensely seeking information about coronavirus.

The number of page views of the article "Coronavirus" increased significantly in the second half of January. The reason for this is that the coronavirus outbreak spread to America and Europe in the second half of January. Another period, in which the number of page views increased in mid-March. In March, WHO announced the coronavirus as a global pandemic (Cucinotta and Vanelli, 2020). At the same time, the coronavirus outbreak spread to many countries around the world in March. The Coronavirus outbreak became one of the most important issues in the world in March. In their study, Tizzoni et al. (2020) investigated the number of Wikipedia page views of articles related to the Zika virus. The number of page views of Coronavirus articles was higher than the number of page views of Zika virus articles. The Coronavirus outbreak has led to more information seeking in societies than happened in the world before.

Examining the information researched by societies is an important criterion in determining the behavioral differences of societies. In our study, it is observed that societies using English, French, Polish, and Portuguese language mostly view the article "Coronavirus". The article "Coronavirus" contains general information about the virus. Societies using Spanish, Russian, German, and Chinese languages mostly viewed the article "COVID-19 pandemic". The article "COVID-19 Pandemic" gives information about the developments during the pandemic. Societies using the Italian language mostly viewed the article "Coronavirus Disease 2019". The article "Coronavirus Disease 2019" contains information about the disease. Finally, societies using the Japanese language mostly viewed the article "Severe acute respiratory syndrome coronavirus 2". The article "Severe acute respiratory syndrome coronavirus 2" contains information about the biological structure of the virus.

During the pandemic process, the topics related to the coronavirus most viewed on Wikipedia have been specified according to Societies. Societies using the Russian language have often sought measures against

coronavirus. Other societies have frequently investigated past outbreaks, WHO, the social effects of the pandemic, and similar viruses. Societies have researched measures against coronavirus on Wikipedia. Societies have researched measures against coronavirus on Wikipedia.

Limitations

There are some limitations to this study. Wikipedia is a dynamic internet encyclopedia that is constantly updated and displayed. The data and information on Wikipedia can change constantly. Coronavirus pandemic is still ongoing. Therefore, the findings we obtained from the study cover between January 20, 2020, and May 20, 2020. Since Coronavirus emerged since January 2020, there was no chance to compare the study findings with previous years. Similarly, it could not be compared to a different outbreak or disease. There are many articles about coronavirus on Wikipedia. However, many articles were excluded because they were written only in a specific language or the scope of the article was for a specific region. Quantitative methods could not be evaluated because there is no quantitative measurement tool for the title of articles on Wikipedia. In terms of some languages, data cannot be found in every articles on Wikipedia's pageview analysis tool (https://pageviews.toolforge.org). Therefore, some languages could not be included in the study. Wikipedia's pageview analysis tool does not provide data on for country. For this reason, the languages used by societies were included in the study.

Conclusion

As a result, Wikipedia has been observed to be a frequently used source of internet that societies prefer to read during the coronavirus pandemic. Wikipedia has been identified as a popular source of internet for coronavirus. Wikipedia can provide information about trends in societies. Wikipedia can be applied to research based on prediction and modeling about societies should have more access to Wikipedia.

Ethics Committee Approval: We did not evaluate any human participants or animals in this study. Internet data that anyone can access were evaluated. Therefore, there was no need for approval of the ethics committee for this study.
Peer-review: Externally peer-reviewed.
Author Contributions: Concept -A.D; Design- A.D; Supervision- A.D; Materials- A.D; Data Collection and/or Processing- A.D; Analysis and/or Interpretation- A.D; Literature Review- A.D; Writing- A.D; Critical Review- A.D.
Conflict of Interest: No conflict of interest was declared by the author.
Financial Disclosure: The author declared that this study hasn't received no financial support.

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Middle Black Sea Journal of Health Science December 2020; 6(3):325-332

RESEARCH ARTICLE

Classification of Prostate Cancer and Determination of Related Factors with Different Artificial Neural Network

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Abstract

Objective: In this study, it is aimed to classify prostate cancer, compare the predictions of these two models and determine the factors associated with the disease by applying Multilayer Perceptron Neural Network (MLPNN) and Radial-Based Function Neural Network (RBFNN) methods on the open access Prostate cancer dataset.

Methods: In this study, the dataset named "Prostate Cancer Data Set" was used by obtaining from https://www.kaggle.com/sajidsaifi/prostate-cancer address. To classify prostate cancer, MLPNN and RBFNN methods, which are artificial neural network models, is used. The classification performance of the models was evaluated with the sensitivity, specificity, accuracy, negative predictive value and positive predictive value, which are among the classification performance metrics. Prostate cancer related factors were estimated by using MLPNN and RBFNN models.

Results: With the applied MLPNN model, performance metric values were obtained as AUC 0.937, Sensitivity 100%, accuracy 92.5%, Selectivity 84.6%, Positive predictive value 87.5% and Negative predictive value 100%. With the RBFNN model, the performance metric values were obtained as AUC 0.921, Sensitivity 83.3%, accuracy 86.6%, Selectivity 91.6%, Positive predictive value 93.7% and Negative predictive value 78.5%. When the effects of variables in the dataset in this study on prostate cancer are examined; The three most important variables for the MLPNN model were obtained as perimeter, area and compactness, respectively. For the RBFNN model, the three most important variables were obtained as perimeter, area and compactness, respectively.

Conclusion: It was seen that MLPNN and RBFNN models used in this study gave successful predictions in the classification of prostate cancer. In addition, estimating the significance values of factors associated with the disease with these classification models made it different from similar studies with the same dataset.

Key words: Prostate cancer, Multilayer perceptron neural network, Radial-based function neural network, Classification.

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Introduction

The prostate is a small walnut-shaped gland that produces seminal fluid that nourishes and carries sperm in men. Prostate cancer is a type of cancer that occurs in the prostate (Ah 2012). Prostate cancer occurs when cells in the prostate gland begin to grow uncontrollably, and it is a heterogeneous and often multifocal disease that often occurs as adenocarcinoma (Foster et al. 2000). Prostate cancer is the most common urological cancer. Since the prostate is a gland found only in men, prostate cancer is a type of cancer that occurs only in men. Prostate cancer is a disease that significantly affects the health of men and the quality of life due to the problems it causes, and its incidence increases with age. Unlike other organ cancers, early-stage prostate cancer usually develops slowly (Badger et al. 2011). Prostate cancer ranks second among the most common cancers in men worldwide. Prostate Cancer ranks sixth in cancer-related deaths, with approximately 1,600,000 cases and 366,000 deaths annually. Despite this high incidence, information on the etiology and risk factors of prostate cancer is limited. For this reason, mortality and morbidity caused by prostate cancer constitute important health expenses worldwide (Siegel, Miller and Jemal 2019, King et al. 2015).

Artificial neural networks (ANN) are computer systems designed to automatically apply skills such as the ability to obtain new information, create and discover new information through education, which are one of the features of the human brain without any help (Elmas 2016). Similar to the characteristics of the human brain, ANN is applied in areas such as learning, association, classification, generalization, feature determination and optimization with the information obtained from samples (Yildirim 2020). Technically, the most basic task of ANN is to determine a result that can correspond to the examples shown to it. In order to do this, the artificial neural network is trained with examples and gained the ability to generalize. With this generalization, output sets corresponding to similar events are determined (Oztemel 2003). While designing a model in ANN, input and output sets are used. Thus, ANN is able to generate solutions at certain limit ranges for previously unseen, unrecognized, unlearned and unapplied examples by learning all linear and nonlinear relationships between inputs and outputs, and previously acquired past situations. Due to the non-linear feature of ANN, it has many advantages such as its ability to work quickly, learning ability, ability to generalize, adaptable to different problems easily and requiring less information, so it is used in solving different problems in many areas (Oztemel 2003).

The multilayer perceptron neural network (MLPNN) consists of three layers the input layer where neural network information is entered, hidden layers and output layer. Information's is introduced to the network from the input layer, reaches the output layer from the hidden layers and is transferred from the output layer to the outside world (Haykin 2007). MLPNN is a non-parametric artificial neural network technique that performs many detection and prediction processes (Orhan, Hekim and Ozer 2010). There are transitions called forward and back propagation between layers in MLPNN. Purpose of MLPNN learning method; It is to make the error between the desired output and the output produced by the network minimum. In the forward propagation phase, the output of the network and the error value are calculated. In the back-propagation phase, the connection weight values between the layers are updated to minimize the calculated error value (Arı and Berberler 2017).

The Radial Basis Function neural network (RBFNN) consists of a three-layer structure: an input layer, a single hidden layer using radial functions that give the network its name, and an output layer. The working principle of RBFNN is the process of determining RBFNNs with appropriate width and center values in the hidden layer depending on the input data, creating linear combinations of the outputs produced by these functions in the output layer and determining the relationship between input-output (Kaynar et al. 2016). Radial-based networks are similar in structure to back propagation networks, the difference in RBFNN is that the radial-based activation function (gauss, exponential) in the intermediate layer transforms the inputs. There is also a linear activation function in the output layer (Gemici, Ardiclioglu and Kocabas 2013).

In this study, it was aimed to compare the classification success of prostate cancer and determine the risk factors related to prostate cancer by applying MLPNN and RBFNN methods on the open access prostate cancer dataset.

Methods

Dataset

In the study, an open access dataset named "Prostat Cancer Data Set" was obtained from https://www.kaggle.com/sajidsaifi/prostate-cancer to examine the working principles of MLPNN and RBFNN methods and to determine risk factors. There are 100 patients diagnosed with prostate cancer in this

open access dataset. Of the patients diagnosed with cancer, 38 (38%) were diagnosed as benign, and 62 (62%) were diagnosed as malignant. The variables and the descriptive properties of the variables in the relevant dataset are given in Table 1.

Table 1. Variables in the dataset and their descriptive properties

Variable	Variable Explanation	Variable type	Variable role
Diagnosis	The diagnosis of breast tissues (M = malignant, B = benign)	Qualitative	Dependent/ Target
Radius	Mean distances from the center to perimeter points	Quantitative	Independent/ Predictor
Texture	The standard deviation of gray-scale values	Quantitative	Independent/ Predictor
Perimeter	Mean size of the core tumor	Quantitative	Independent/ Predictor
Area	-	Quantitative	Independent/ Predictor
Smoothness	Mean of local variation in radius lengths	Quantitative	Independent/ Predictor
Compactness	(mean of perimeter)^2 / (area - 1)	Quantitative	Independent/ Predictor
Symmetry	-	Quantitative	Independent/ Predictor
Fractal dimension	mean for "coastline approximation" - 1	Quantitative	Independent/ Predictor

Multilayer Perceptron Neural Network (MLPNN)

Multilayer Perceptron Neural Network (MLPNN) is known as the back propagation model of a feed forward neural network developed by Rumelhart, Hinton and Williams (Rumelhart, Hinton and Williams 1986). MLPNN is an artificial neural network model with a feed forward structure consisting of the input layer, the output layer and the hidden layer(s) between these two layers. The inputs to the neurons in the hidden layer are collected and transmitted to the output layer by multiplying the connection weights between the hidden layer and the output layer in the same way. Neurons in the output layer collect these inputs and produce an output accordingly (Efe and Kaynak 2000).

The main purpose of the MLPNN method is to minimize the error between the expected output of the network and the output it produces. During the training, both the inputs and the (expected) outputs that should be produced against those inputs are shown in these networks (Soylemez 2020). Samples are applied to the input layer, processed in hidden layers, and outputs are obtained from the output layer (Selcuk 2020). According to the training algorithm used, the error between the output of the network and the desired output is spread backwards again and the weight of the network is changed until the error is minimized (Kayna, Tastan and Demirkoparan 2010).

Radial Based Function Neural Network (RBFNN)

The concept of Radial-Based Functions was introduced into the artificial neural networks literature by Broomhead and Lowe in 1988. The artificial neural network model based on Radial Based Functions is inspired by local impulse-response behaviors seen in neurons (nerve cells) in the human nervous system (Poggio and Girosi 1990). RBFNN is a feed forward network consisting of a three-layer structure consisting of an input layer, a single hidden layer using radial functions that give the network its name as a transfer function, and an output layer. While the inputs of this network are not linear, its output is linear (Kim and Kim 2004).

The input layer consists of source nodes and provides the network's connection with the environment. The second layer, the only hidden layer in the network, makes nonlinear conversion from the input area to the hidden area. The transformation from the input layer to the hidden layer is a nonlinear constant transformation with radial based transfer functions (Yildiz, Tasova and Polatci 2020). The output layer is linear and responds to the network, which is the transfer signal applied to the input layer. An adaptive and linear transformation is performed from the hidden layer to the output layer. Thus, the output layer, which provides the response of the network to the transfer signal applied to the input, has the feature of linearity (Haykin 1999).

Performance evaluation metrics

In the performance evaluation of the radial-based artificial neural network and multilayer artificial neural network models, which were created to predict the factors that may be associated with prostate cancer, the performance metrics obtained by using the classification matrix (Table 2) given below were used.

Table 2. Classification matrix for calculating performance metrics

		Real		
		Positive	**Negative**	**Total**
Predicted	**Positive**	True positive (TP)	False negative (FN)	**TP+FN**
	Negative	False positive (FP)	True negative (TN)	**FP+TN**
	Total	**TP+FP**	**FN+TN**	**TP+TN+FP+FN**

The performance metrics to be used in the performance evaluation of the models in this study are given below.
Sensitivity = TP/(TP+FP)
Specificity = TN/(TN+FN)
Accuracy = (TP+TN)/(TP+TN+FP+FN)
Negative predictive value =TN/(TN+FP)
Positive predictive value = TP/(TP+FN)

Statistical Analyses

Quantitative data were expressed as mean ± standard deviation, median (minimum-maximum), and qualitative data as number (percentage). Conformity to normal distribution was evaluated using the Shapiro-Wilk test. Whether there is a statistically significant difference between the "Bening" and "Malignant" groups, which are the categories of dependent / target variable (prostate cancer) in terms of independent variables, was examined using the Mann-Whitney U test and the independent samples t test. Values of $p < 0.05$ were considered statistically significant. IBM SPSS Statistics 26.0 package program was used for all analyzes.

For the validity of the model, a 10-fold cross-validation method was used. In the 10-fold cross-validation method, all data is divided into 10 equal parts. One part is used as a test set and the remaining 9 parts are used as a training data set and this process is repeated 10 times.

Results

Descriptive statistics for the independent variables examined in this study are given in Table 3. There is a statistically significant difference between the dependent / target variable groups in terms of perimeter, area, compactness, symmetry, smoothness variables ($p<0.05$).

Table 3. Descriptive statistics for quantitative independent variables

Variables	Diagnosis				p-value
	Benign		Malign		
	Median(min-max)	Mean± Standard deviation	Median(min-max)	Mean± Standard deviation	
Radius	18 (9-25)	-	16 (9-25)	-	0.090*
Texture	17 (11-27)	-	18 (11-27)	-	0.450*
Perimeter	78.5 (52-133)	-	104 (72-172)	-	**<0.001***
Area	458.5 (202-1326)	-	790.5 (371-1878)	-	**<0.001***
Compactness	0.0785 (0.038-0.246)	-	0.1405 (0.051-0.345)	-	**<0.001***
Symmetry	0.182 (0.135-0.274)	-	0.193 (0.153-0.304)	-	**0.013***
Fractal_Dimension	0.0635 (0.053-0.09)	-	0.063 (0.053-0.097)	-	0.963*
Smoothness		0.099±0.015		0.105±0.014	**0.049****

*: Mann Whitney U test, **: Independent samples t-test

Classification matrix of MLPNN and RBFNN models are given in Table 4 and Table 5, respectively.

Table 4. Classification matrix of MLPNN model

Real / Predicted	Malign	Benign	Total
Malign	14	2	16
Benign	0	11	11
Total	14	13	27

Table 5. Classification matrix of the RBFNN model

Real / Predicted	Malign	Benign	Total
Malign	15	1	16
Benign	3	11	14
Total	18	12	30

In Table 6, the values of performance metric calculated from the models created to classify prostate cancer in the test stage are given below.

Table 6. Performance metric values calculated from created models in the testing stage

Model / Performance Metrics	MLPNN Value	RBFNN Value
Accuracy (%)	92.5	86.6
Specificity (%)	84.6	91.6
AUC	0.937	0.921
Sensitivity (%)	100	83.3
Positive predictive value (%)	87.5	93.7
Negative predictive value (%)	100	78.5

AUC: Area under the ROC curve; MLPNN: Multilayer perceptron neural network; RBFNN: Radial-based function neural network

In Figure 1, values of performance metric obtained from MLPNN and RBFNN models are plotted.

In this study, while the significance values of the factors associated with prostate cancer are given in Table 7, the values for these significance percentages are shown in Figure 2.

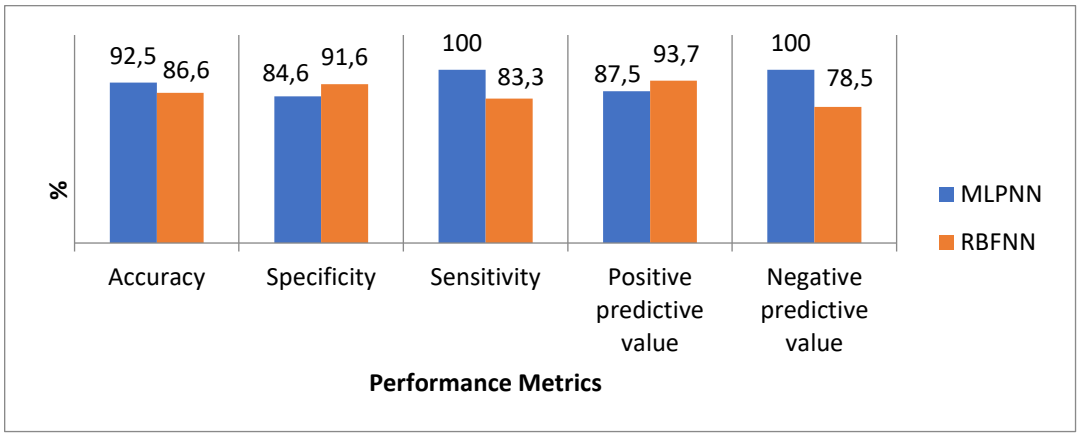

Figure 1. Performance metric values obtained from MLPNN and RBFNN models in the testing stage

Table 7. Importance values of explanatory variables according to MLPNN and RBFNN models

Explanatory Variables	MLPNN	RBFNN
radius	0.042	0.027
texture	0.054	0.036
perimeter	0.279	0.233
area	0.198	0.210
smoothness	0.087	0.106
compactness	0.189	0.187
symmetry	0.083	0.113
fractal_dimension	0.068	0.088
Total	1	1

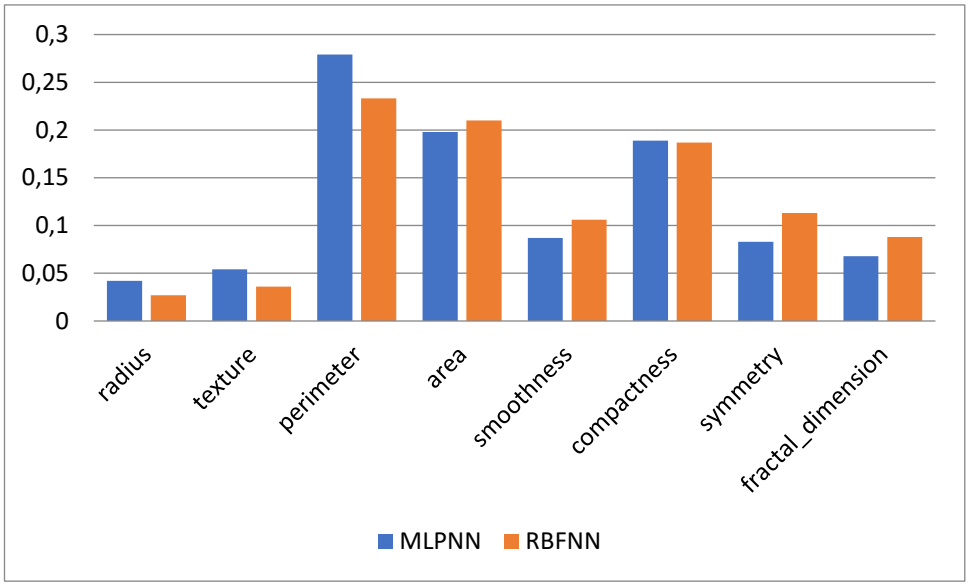

Figure 2. The importance values for possible risk factors

Discussion

Prostate cancer, in the world as of 2018 and is the second most common cancer in men in Turkey. The increase in the prevalence due to the aging of the population will bring along an increase in health expenditures. Considering its potential impact on health expenditures, it has become necessary to evaluate factors related to prostate cancer (Arslan and Esatoglu, 2018).

Artificial neural networks is a model that have the ability to obtain solutions for large and complex datasets, have no distribution requirements, can be applied to multivariate nonlinear problems, can detect complex nonlinear relationships between dependent and independent variables, can detect all possible interactions between predictive variables (Etikan et al. 2009). First, artificial neural networks perform training on the determined dataset. Second, the model examined is validated to determine the classification of a new dataset. The performance of the created models is evaluated using different metrics (Nasser and Abu-Naser, 2019).

In this study, multilayer artificial neural network and radial-based artificial neural network models, which are among the artificial neural network models, were applied on an open access prostate cancer dataset and it was aimed to compare the classification estimates of these two models. In this context, different factors (explanatory variables) that may be associated with prostate cancer (dependent variable) have been estimated with multilayer artificial neural network and radial based artificial neural network models. Thus, it has been shown that artificial intelligence models can be used in the classification problem. In addition, significance levels of factors that may be associated with prostate cancer were obtained from these models for use in preventive medicine practices.

In this study, the MLPNN model gave better predictive results than the RBFNN model in the

classification of prostate cancer according to the performance criteria AUC, negative predictive value, and accuracy results used to compare classification performances. However, considering the positive predictive value and specificity criteria, the RBFNN model gave better predictive results than the MLPNN model. The three most important risk factors that may be associated with prostate cancer were obtained as perimeter, area and compactness according to MLPNN model. In the RBFNN model, the three most important risk factors that may be associated with prostate cancer were estimated as perimeter, area and compactness.

In a study using the same dataset, the accuracy results obtained with different machine learning methods were compared. According to the results of the current study, the highest accuracy was obtained as 0.80 with the k-Nearest Neighbor and Naive Bayes Classification models. In this study, an accuracy of 0.9 was obtained, and the rules related to the disease were also obtained (https://www.kaggle.com/alihantabak/prostate-cancer-predictions-with-ml-and-dl-methods).

Conclusion

In conclusion, considering the findings of this study, it was seen that classification of prostate cancer diagnosis gave successful predictions. At the same time, estimating the significance values of factors associated with the disease with the classification models used in this study made it different from similar studies with the same dataset.

Ethics Committee Approval: We did not evaluate any human participants or animals in this study. Therefore, there was no need for approval of the ethics committee for this study.
Peer-review: Externally peer-reviewed.
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RESEARCH ARTICLE

Evaluation of Anxiety and Depression in Idiopathic Pulmonary Fibrosis

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Abstract

Objective: Depression and anxiety are the comorbid diseases of Idiopathic Pulmonary Fibrosis (IPF) and these diseases are more frequently in patients with serious progressive types of IPF. The aim of this study was to use the Hospital Anxiety and Depression Scale (HADS) to evaluate the levels of depression and anxiety in IPF patients.

Methods: A total of 27 patients were included to the study. Demographic characteristics, pulmonary function tests, GAP indexes (gender, age, and physiology), 6-minute walk test (MWT) values were recorded from the patient files. To measure the levels of anxiety and depression in patients with IPF, the validated Turkish version of the HADS, including 14 questions, was used.

Results: Anxiety was determined in 33.3% of the patients and depression was detected in 37% of the patients. The patients' avearage anxiety score was 5.5 and the mean depression score was 6.2. Desaturation in patients with anxiety was significantly higher ($p<0.05$) and was found to be higher in patients with depression ($p<0.05$). DLCO levels were detected to be lower in patients with depression ($p <0.05$).

Conclusion: The quality of life of patients diagnosed with IPF can be improved by psychiatric assessment and adequate supportive care, including antidepressant medication and psychological therapy.

Key words: Anxiety, depression, Idiopathic Pulmonary Fibrosis

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, incurable disease with unexplained etiology. It is characterized with a gradual and permanent decrease in lung capacity and is mostly seen in elderly men with a mean life span of 2.5-3.5 years (Raghu et al., 2018). It is characterized by severe fibrosis and lung transplantation is still the most common treatment in appropriate patients. IPF has a severe impact on quality of life and its incidence is increasing. The presence of progressive dyspnea and dry cough that deteriorates the quality of life of IPF patients, the development of hypoxia with the progression of the

disease, and the lack of definitive treatment of the disease cause an increased tendency to anxiety and depression. In patients with chronic illnesses, depression is 1.5-7 times more common than in the population overall (Zheng et al.,1997; Solano et al., 2006; Moussavi et al., 2007). Mechanisms of the relationship between depression and IPF and the long-term effect of depression on IPF have not been identified. The prevalence of depression is 21-49% and the prevalence of anxiety in IPF patients is 27-31%. (Ryerson et al., 2011; Ryerson et al., 2012; Akhtar et al., 2013; Holland et al., 2014).

Anxiety and depression are more commonly identified in serious and progressive forms of IPF, (Pink K et al., 2014). Psychological problems, which are the secondary consequences of chronic lung diseases, are often ignored. Dyspne, dry resistant cough, loss of independence, feelings of social isolation and insufficient sleep are among the leading causes of psychological distress (Akhtar et al., 2013). There is a mutual interaction of dyspnea and depression. While dyspne can cause depressive symptoms, on the contrary, depression can exacerbate the perception of respiratory symptoms (Ryerson et al., 2012).

Depression and anxiety should be regularly scanned in patients with IPF, and proper supportive managements, including antidepressants and anxiolytics. Psychological support and pulmonary rehabilitation were suggested to manage anxiety and depression and to improve the quality of life (Yalnız E et al., 2019).

The relationship between anxiety and depression with severity and progression of IPF disease, the effect of these diseases on clinical outcomes of IPF and the effects of treatment of anxiety and depression on pulmonary function tests are not fully clarified in the literature.

We aimed to evaluate the levels of depression and anxiety in IPF and to examine whether the functional severity of the illness was associated with the depression and anxiety score in this study.

Methods

A single-center, retrospective research was conducted on patients with IPF, followed up and treated in the 8th clinic of our hospital. A total of 27 IPF patients were evaluated in this study. Patients who didn't fully answer the questions and had depression/anxiety before the diagnosis of IPF, had malignancy or an unstable medical condition or had missing data were excluded from the study. Informed consents based on institutional guidelines were taken from all patients. Approval for the study was granted by the medical training board of our hospital. (Approval number and date: 615 / 23.01.2019). Diagnosis of all patients was made clinically, radiologically, or pathologically based on the American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/The Latin American Thoracic Association (ALAT) statement (Raghu et al., 2018). Demographic characteristics, pulmonary function tests, DLCO (Diffusing capasity of the lungs for carbon monoxide), GAP (gender, age, and physiology) indexes, 6-minute walk test (MWT) values, treatment information were recorded from the patient files. The staging of IPF patients were evaluated according to the symptoms, findings from high resolution computed tomography (HRCT) and pulmonary function test (PFT). Desaturation was defined as a decrease of 4% or more in the O2 saturation in the 6-MWT which was applied at the last visit of the IPF patients. To measure the levels of anxiety and depression in IPF, the validated Turkish version of the HADS (Hospital Anxiety and Depression Scale) including 14 questions was used. The test was carried out at the last hospital visit, so that each patient was at different follow-up periods of the disease. Seven items for depression (HADS-D) and seven items for anxiety (HADS-A) are included in the HADS, in addition there are scores between 0 to 21 points in each subscale. (Aydemir et al., 1997). The scores ≥8 on both HADS-D and HADS-A, respectively, show clinically relevant depression and anxiety. Although there is no diagnostic scale, patients with violence above these scores are candidates for clinical evaluation

Statistical Analyses

The Statistical Package for the Social Sciences (SPSS) version 22 was used for the statistical analyses. The mean, standard deviation, median, minimum, maximum, frequency and ratio values were utilized in the presentation of the descriptive data of the study. The distribution of variables was measured with the kolmogorov simirnov test. Mann-Whitney u test was used to analyze quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and fischer test was used when chi-square test conditions were not met. A value of $p<0.05$ was considered statistically significant.

Results

Twenty seven patients diagnosed with IPF were investigated in this study. Twenty six patients were male, and 1 patient was female. The average age of the patients was 65. 6 ± 7. 6 years. The General characteristics of the patients are demonstrated in table 1.

Table 1. The general characteristics of the patients

		n	%
Gender			
	Female	1	3.7%
	Male	26	96.3%
Comorbitdiy		14	51.9%
	Lung cancer	1	3.7%
	OSAS	7	25.9%
	GERD	12	44.4%
	Respiratory failure	10	37.0%
Smoking			
	Never	5	18.5%
	Exsmoker	18	66.7%
	Smoker	4	14.8%
Desaturation			
	No	1	3.7%
	Mild	16	59.3%
	Moderate	3	11.1%
	Severe	7	25.9%
Stage			
	Low	16	59.3%
	Mild	5	18.5%
	Severe	16	22.2%
Medicine			
	Nintedanib	2	7.4%
	Pirfenidon	25	92.6%

OSAS: Obstructif Sleep Apne Syndrome, GERD: Gastroesophageal Reflux Disease

The average GAP index was 3 and the assessment of the functional condition of IPF patients is demonstrated in table 2.

Table 2. Evaluation of the functional status of IPF patients

	mean±sd
GAP index	3.9±1.7
6MWT/m	407.2±108.7
DLCO	57.0±19.4
DLCO/VA	85.8±27.5
FVC	67.8±15.5
FEV_1	72.9±16.5
FEV_1/FVC	84.3±5.3
SPO_2	93.1±4.5

GAP: Gender-Age-Physiology, 6- (MWT): 6-minute walk test, FEV1: Forced Expiratory Volume in one second, FVC: Forced vital capacity, SPO2: Saturation of Peripheral Oxygen, DLCO: Diffusing capacity of the lungs for carbon monoxide

All patients were having antifibrotic treatment. The mean anxiety score of the patients was 5.5 and the mean depression score was 6.2. Anxiety was found in 33.3% of the patients and depression was determined in 37% of the patients (Table 3).

Table 3. The results of HADS

	n	%
HADS-A	5.5±5.7 (mean±sd)	
Anxiety		
(-)	18	66.7%
(+)	9	33.3%
HADS-D	6.2±5.7 (mean±sd)	
Depression		
(-)	17	63.0%
(+)	10	37.0%
Total score	11.7±11.0 (mean±sd)	

HADS-A: Hospital Anxiety and Depression Scale-Anxiety; HADS-D: Hospital Anxiety and Depression Scale-Depression

The comparison between patients with and without anxiety is shown in table 4 and the comparison between patients with and without depression is shown in table 5, based on the GAP Index values (score and stage), the results of 6-MWT, DLCO and PFT, $SP0_2$, desaturation and stage. DLCO levels were found to be lower in the depression group than in the non-depression group ($p<0.05$), they didn't vary significantly in the anxiety and non-anxiety group ($p> 0.05$). Desaturation rates in the patients with anxiety/depression were found to be significantly higher than in the non-anxiety/non depression population ($p <0.05$).

Table 4. The comparison between patients with and without anxiety

		Anxiety(-)			Anxiety(+)			p
			Mean ±sd/n-%	Median (%25-%75)		Mean ±sd/n-%	Median (%25-%75)	
GAP Index			4.0±1.645	3.5		3.56±2.007	3	0.432[m]
GAP	Stage I	9	50.0%		5	55.6%		0.785[x2]
	Stage II	5	27.8%		1	11.1%		
	Stage III	4	22.2%		3	33. 3%		
6MWT (m)			423.4±121.6	480.0		376.7±75.5	360.0	0.160[m]
DLCO			61.9±18.5	65.0		48.8±19.18	46.0	0.114[m]
DLCO/VA			93.1±23.66	84.0		73.4±30.42	85.0	0.221[m]
FEV1			74.0±15.85	74.0		70.6±18.61	73.0	0.681[m]
FVC			69.1±14.8	72.5		66.2±17.36	67.0	0.571[m]
FEV_1/FVC			83.9±5,624	83.5		85.2±4.684	86.0	0.518[m]
SPO_2			93.8±2.915	95.0		91.7±6.745	94.0	0.658[m]
Desaturation	None	1	5.6 %		0	0.0%		0.024[x2]
	Mild	13	72.2%		3	33.3%		
	Moderate	1	5.6 %		2	22.2%		
	Severe	3	16.7%		4	44.4%		
Stage	Mild	13	72.2%		3	3.33%		0.053 [x2]
	Moderate	3	16.7%		2	2.22%		
	Severe	2	11.1%		4	4.44%		

[m] Mann -Whitney U Test / [x2]Chi Square Test

Data are presented as n, mean ± SD., GAP: Gender-Age-Physiology, 6- (MWT): 6-minute walk test, FEV1: Forced Expiratory Volume in one second, FVC: Forced vital capacity, SPO2: Saturation of Peripheral Oxygen, DLCO: Diffusing capacity of the lungs for carbon monoxide,

Table 5. The Comparison between patients with and without depression

		Depression (-)			Depression (+)			p
			Mean ±sd/n-%	Median		Mean ±sd/n-%	Median	
GAP Index			3.9±1.6	3.0		3.7±2.1	3.5	0.645[m]
GAP	Stage I	9	52.9%		5	50.0%		0.883 [x2]
	Stage II	4	23.5%		1	10.0%		
	Stage III	4	23.5%		3	30.0%		
6MWT(m)			424.9±114.8	460.0		379±96,9	370.0	0.178[m]
DLCO			63.0±18.83	67.0		48.5±17.8	48.5	0.046[m]
DLCO/VA			93.6±26.09	90.0		74.7±26.8	80.5	0.121[m]
FEV_1			76.0±14.31	77.0		67.5±19.4	62.5	0.269[m]
FVC			70.9±13.34	74.0		62.6±18.1	59.5	0.228[m]
FEV_1/FVC			83.8±5.855	84.0		85.2±4.3	85.5	0.480[m]
SPO_2			93.9±3.569	95.0		918±5.8	93.5	0.309[m]
Desaturation	None	1	5.9%		0	0.0%		0.007 [x2]
	Mild	13	76.5%		3	30.0%		
	Moderate	2	11.8%		1	10.0%		
	Severe	1	5.9 %		6	60.0%		
Stage	Mild	12	70.6%		4	40.0%		0.118[x2]
	Moderate	3	17.6%		2	20.0%		
	Severe	2	11.8%		4	40.0%		

[m] Mann -Whitney U Test / [x2]Chi Square Test

Data are presented as n, mean ± SD., GAP: Gender-Age-Physiology, 6- (MWT): 6-minute walk test, FEV1: Forced Expiratory Volume in one second, FVC: Forced vital capacity, SPO2: Saturation of Peripheral Oxygen, DLCO: Diffusing capacity of the lungs for carbon monoxide,

Discussion

One of the leading causes of increased impairment and reduced quality of life in older adults is psychological disorders. In particular, in patients with chronic respiratory problems, severe depression, dysthymias (chronic depressive symptoms of moderate severity) and anxiety disorders are widespread (Ng et al., 2007; Maurer et al., 2008; Xu et al., 2008; Schneider et al., 2010).

Anxiety was found in 33.3% of patients and depression was found in 37% of the patients with IPF in this research. The patients' average anxiety score was 5.5 and the mean depression score was 5.5 and the mean depression score was 6.2. In patients with anxiety and depression, the desaturation rates were significantly higher and DLCO levels were found to be lower in patients with depression. In our study it was found that hypoxia emerged in IPF significantly contributed to progressing anxiety and depression. In a study (Schneider et al., 2010) involving 35000 patients with chronic obstructive pulmonary disease (COPD), the incidence of depression was almost twice as much in the COPD group, compared to the patients without COPD. And severity of COPD was related developing depression those with COPD (Atlantis et al.,2013).

Findings for IPF are worser than COPD. Some studies have pointed out that depression prevalence varies from 24.3% to 49.2% in IPF. (Ryerson et al., 2011; Amin et al., 2014). Severity of disease in IPF is strongly related to depression (Schneider et al., 2010). Dyspnea, pulmonary dysfunction and cough are more related than other variables (Ng et al., 2007; Xu et al., 2008) and are considered to be significant health-related quality of life determinants in IPF (Xu et al., 2008).

The findings of present study, which showed that DLCO levels were lower and desaturation rates were higher in depression group, are similar with findings aforementioned. Despite these findings were not correlated some previous studies, this might result from the differences of severity of disease (Lee et al., 2017). The prevalence of anxiety is 13-46% in COPD outpatients (Willgoss et al., 2013). In addition, patients with comorbid anxiety disorders in COPD are twice as likely as those without anxiety symptoms to have self-reported functional disabilities and a higher incidence of acute exacerbations. Indeed, anxiety disorders are debilating and they may become chronic and raise the risk of hospitalization unless properly treated (Maurer et al., 2008; Atlantis et al., 2013; Holland et al., 2014).

The prevalence of anxiety was found to be 31–60% in many studies that measured anxiety in patients with IPF (Schneider et al., 2010; Lee et al., 2017). These findings are similar to the results of current study. Possible mechanism of anxiety in patients with chronic pulmonary problems is the relation between respiration and fear. Subjective difficulty on respiration is one of the main somatic symptoms of anxiety disorders, but also this can be a cause in patients with chronic pulmonary problems. Depression is substantially related to a greater risk of exacerbations and hospitalizations in COPD. (Willgoss et al., 2013; Amin et al., 2014; Lee et al., 2017). This is possibly because there is no successful treatment to relieve IPF symptoms unlike with COPD. Therefore, inadequate compliance with recommended medical care because of depression is unlikely to impact treatment results. In researchs examining the quality of life status of these patients, there are several arguments for the increased frequency of depressive symptoms in IPF, (Vries et al., 2001, Xu et al., 2008). There is, however, a substantial lack of major prospective research examining the diagnosis and its impact on the health status of these people.

This study has many limitations. It is a small, observational, retrospective study with no control group. Although HADS is a well-validated depression screening tool, it is not a diagnostic test but based on self-reported questionnaires rather than a complete psychiatric examination. To our knowledge there is no study that determines and compares the level of anxiety and depression in patients with IPF using the HADS scale in our country. Although the number of patients is small, we think that our study will contribute to the literature.

Conclusion

Anxiety and depression are comorbid diseases related to IPF. The quality of life of patients diagnosed with IPF can be improved by a good psychiatric assessment and adequate supportive care, including antidepressant medication and psychological therapy.

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RESEARCH ARTICLE

Radiologic analysis of correlations between sinonasal anatomical variations in patients with nasal septal deviation

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Abstract

Objective: This study aims to analyze the sinonasal anatomical variations accompanying the nasal septal deviation, the correlations between these variations, and their relationship with the septal deviation angle.

Methods: In this retrospective study, preoperative paranasal computed tomography (CT) scans of 206 patients who underwent septoplasty between January 2015 and December 2019 were examined. In CT scans, different nasal septal deviation types, Keros classification, optic nerve type, ethmoid air cell variants, nasal concha variants, paranasal sinus pneumatization variants, and the correlation between accessory pneumatization variants and their relationship with the septal deviation angle were analyzed.

Results: In patients with nasal septal deviation, supraorbital ethmoid cell, anterior clinoid process pneumatization and onodi cell were more frequent compared to the literature. Any significant correlation between the nasal septal deviation angle and the presence of sinonasal variants was not detected ($p > 0.05$). Correlations were significant between the presence of Frontal sinus hypoplasia and Haller cell ($\phi = -0.142$, $p = 0.042$), Supraorbital Ethmoid cell ($\phi = -0.173$, $p = 0.013$) and Paradoxal middle concha ($\phi = 0.152$, $p = 0.029$).

Conclusion: Careful examination of paranasal CTs before craniomaxillofacial surgeries is important to determine sinonasal anatomic variants, to determine the appropriate treatment plan and to prevent possible complications peroperatively.

Key words: Nasal septal deviation, Paranasal computerized tomography, Anatomic variation, Supraorbital ethmoid cell, Anterior clinoid process

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Introduction

Nasal septal deviation (NSD) is one of the major causes of nasal obstruction. Paranasal sinus (PNS) computed tomography (CT) is a widespread method to assess the paranasal anatomy (Wuister et al., 2014). Nasal anatomy and accompanying sinonasal pathologies can be evaluated with preoperative PNS CT in patients undergoing septoplasty (Akoglu et al., 2007). There are many sinonasal variants, and the identification of sinonasal anatomic variants in paranasal CT scans before craniomaxillofacial surgeries are important to prevent complications. The most common sinonasal anatomical variations are Agger nasi cells, infraorbital ethmoidal cells (Haller), sphenoethmoidal cells (Onodi), NSD and concha bullosa (Kantarci et al., 2004; Alkire and Bhattacharyya, 2010). Sinonasal anatomical variants as upper concha bullosa, lower concha bullosa, uncinate bulla, supraorbital ethmoid cell, anterior clinoid process pneumatization (ACPP) are less rarely seen (Fadda et al., 2012).

According to Mladina's classification, NSD was categorized into seven types. Type 1, unilateral vertical crest up to nasal valve; Type 2, unilateral vertical crest reaching to nasal valve; Type 3, unilateral vertical crest at the level of middle nasal concha; Type 4, the combination of Type 1 defined as S type septal deviation or Type 2 combined with Type 3; Type 5, unilateral horizontal crest in touch with the lateral nasal wall; Type 6, bilateral horizontal crest, and Type 7, NSDs with combinations of all these types.

Delano classification was used to determine the relationship of the optic nerve to the sphenoid sinus (SS) (DeLano et al., 1996). According to this classification, there is no recess into the Type 1 SS wall. Type 2 has a recess in the SS wall that does not come into contact with the posterior ethmoid cell. There is a protrusion to the SS wall in Type 3. Type 4 extends into the SS and posterior ethmoid cells.

The olfactory fossa depth was calculated by Keros classification. Accordingly, the length of the vertical line drawn from the horizontal line connecting the infraorbital nerves perpendicularly to the medial point of the ethmoid roof was determined as the height of the medial ethmoid roof. The length of the vertical line drawn from the horizontal line connecting the infraorbital nerves perpendicularly to the lamina cribrosa was determined as the height of the cribriform plate. The difference between the two heights was accepted as the height of the lamina lateralis, and the depths of olfactory fossa ranging between 1-3 mm, 4-7 mm, and 8-16 mm were graded as Keros Types 1, 2, and 3.

The frequency of coexistence of NSD and concha bullous has been explored many times before (Koo et al., 2017; El-Taher et al., 2019). There are limited number of studies investigating the relationship between NSD and other sinonasal anatomical variations (Koo et al., 2017; Yazici, 2019).

This study aims to analyze the sinonasal anatomical variations accompanying the nasal septal deviation, the correlations between these variations, and their relationship with the septal deviation angle.

Methods

In our study, age, gender, and preoperative PNS CTs of 206 patients who underwent septoplasty between January 2015 and December 2019 were retrospectively analyzed. Patients younger than 18 years old, patients who had undergone septum or paranasal sinus surgery, patients with acute or chronic sinusitis, and patients with sinonasal polyposis or tumor were excluded from the study.

CT scans were obtained in the supine position using routine PNS CT imaging without contrast or sedation. CT examinations were performed by using a 64-channel multidetector CT unit (Revolution CT GE Healthcare, Milwaukee, WI, USA). The imaging parameters were KvP: 100, mAs: 90, a slice thickness 0.625 mm, a reconstruction increment 1,5 mm, a scan field of view of 20 cm, and a matrix of 512 × 512 with the high-resolution bone algorithm.

CT scans were examined by a single experienced radiologist using PACS (Picture Archiving and Communicating System). Different NSD types, Keros classification, optic nerve type, ethmoid cell variants as Agger nasi cell, Onodi cell, Haller cell, supraorbital ethmoid cell, also nasal concha variants as superior concha bullosa middle concha bullosa, paradoxal middle concha, paranasal sinus pneumatization variants as frontal sinus hypoplasia and maxillary sinus hypoplasia; accessory pneumatization variants, as uncinate bulla in paranasal CTs; prevalence of ACPP and their in-between correlations with NSD angle were evaluated.

In CT scans, two different classifications defined by Elahi et al. and Mladina were used to determine the type of septum deviation of patients (Elahi et al., 1997; Mladina et al., 2008). NSD was classified in 3 types as mild (< 9°), medium (9° - 15°), advanced (> 15°) according to the septal deviation angle (SDA rating system of Elahi et al. (Elahi et al., 1997)

Statistical Analyses

The variables were summarized with median (Interquartile range) and frequency (percentage). Comparative statistical tests between groups were performed using the Kruskal–Wallis, Mann Whitney U, Pearson's chi-square or Fisher's exact tests, where appropriate. The ϕ (phi) correlation coefficient was used to estimate the degree of association between the anatomical variations. Statistical significance was set at $p < 0.05$ and the Statistical Package for Social Sciences 25.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for conducting the analysis.

Results

A total of 206 patients [62.1 % males and 37.9 % females] between the ages of 18-67, were included in the study. The effects of demographic data of patients, NSD type, Keros classification, prevalence rates of optic nerve type; as ethmoid air cell variants Agger nasi cell, Onoid cell (Figure 1), Haller cell, supraorbital ethmoid cell (figure 2); as nasal concha variants superior concha bullosa, middle concha bullosa (Figure 3), paradoxal middle concha; as paranasal sinus pneumatization variants frontal and maxillary sinus hypoplasia; and accessory pneumatization variants, uncinate bulla (Figure 4), ACPP (Figure 5), and gender on the distribution of these variants are shown in Table 1.

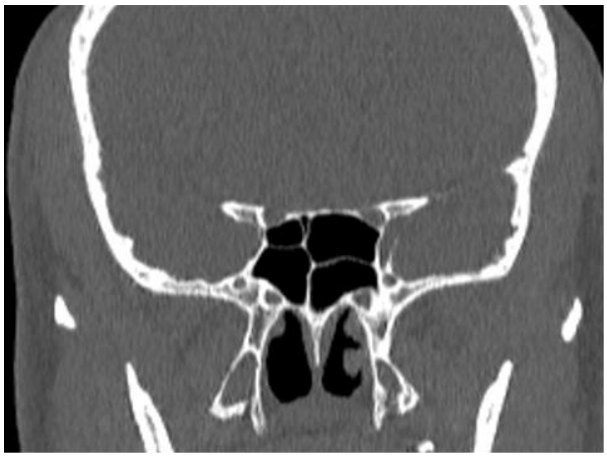

Figure 1. Coronal paranasal CT image of 38-year-old man with bilateral onodi cell (arrows).

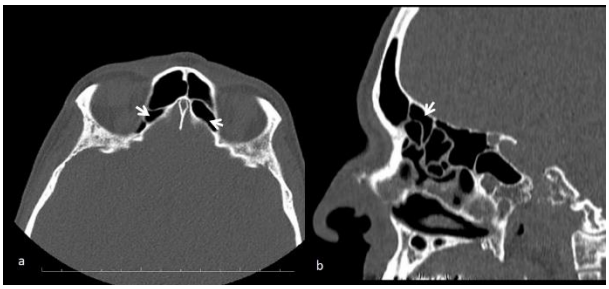

Figure 2. 55-year-old man with bilateral supraorbital ethmoid cell. a, bilateral supraorbital ethmoid cell on paranasal BT (arrows): axial view b, left supraorbital ethmoid cell on paranasal CT (arrow): sagittal view.

Figure 3. Coronal paranasal CT image of 20-year-old man with mladina type 4 nasal septal deviation and bilateral middle concha bulloza (arrows).

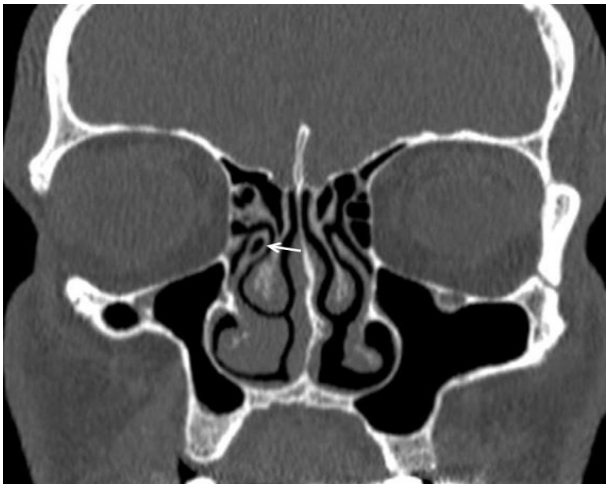

Figure 4. 35-year-old man with right uncinat bulla. The arrow marks the uncinate bulla on paranasal CT: coronal view.

Figure 5. Coronal paranasal CT image of a 30-year- old women with ACPP. a, Coronal CT section showing DELANO TYPE 2 Optic nerve canal (thick arrow). b, Coronal CT section showing ACPP (thin arrow).

Agger nasi was the most frequently paranasal anatomical variation (56.8 %), followed by middle concha bullosa (53.9 %) and ACPP (35.0 %) (Table 1)

The most frequently Keros type was Type 2 (67 %) and the most frequently seen optic nerve type was Type 1 (48.1 %), according to Delano classification. When we look at the effect of gender on Keros and Delano classifications, we saw that there was no significant difference between them ($p = 0.349$, $p = 0.077$) (Table 1). The prevalence of NSD types as per Mladina is significant between males and females ($p = 0.036$). Among males, Type 4 is the most common nasal septum deformity (19.5 %) (Figure 3), whereas Type 7 has the highest prevalence among female patients (23.1 %). The presence of supraorbital ethmoid is significantly higher in males compared to female patients [21.1 % vs. 6.4 %] ($p = 0.005$) (Table 1).

There is no significant difference was found between NSD types as per angle classification in terms of the sinonasal variation ($p > 0.05$) (Table 2).

The analysis of correlations between the sinonasal anatomical variations accompanying the septum deviation is shown in Table 3. A significant positive correlation between the presence of Haller cell and onodi cells was observed ($\phi = 0.154$, $p = 0.027$). Correlations were also significant between the presence of Frontal sinus hypoplasia and Haller cell ($\phi = -0.142$, $p = 0.042$), Supraorbital Ethmoid cell ($\phi = -0.173$, $p = 0.013$) and Paradoxal middle concha ($\phi = 0.152$, $p = 0.029$). Supraorbital Ethmoid cell was also positively correlated with Uncinate bulla ($\phi = 0.152$, $p = 0.041$) (Table 3).

Table 1. Demographic and clinical characteristics of the sample (n=206).

Patient Characteristics	Total	Gender		
	median (IQR) or n (%)	Males (n=128)	Females (n=78)	p
Demographic variables				
Age	27.0 (17.8)	29.0 (18.0)	27.0 (17.8)	0.292[a]
NSD type as per Mladina's classification				**0.036**[b]
Type 1	20 (9.7%)	12 (9.4%)	8 (10.3%)	
Type 2	22 (10.7%)	14 (10.9%)	8 (10.3%)	
Type 3	30 (14.6%)	13 (10.2%)	17 (21.8%)	
Type 4	30 (14.6%)	25 (19.5%)	5 (6.4%)	
Type 5	32 (15.5%)	22 (17.2%)	10 (12.8%)	
Type 6	36 (17.5%)	24 (18.8%)	12 (15.4%)	
Type 7	36 (17.5%)	18 (14.1%)	18 (23.1%)	
NSD type as per angle classification				0.117[b]
Type 1	35 (17.0%)	18 (14.1%)	17 (21.8%)	
Type 2	100 (48.5%)	69 (53.9%)	31 (39.7%)	
Type 3	71 (34.5%)	41 (32.0%)	30 (38.5%)	
Variation of ethmoid air cell				
Agger nasi cell	117 (56.8%)	67 (52.3%)	50 (64.1%)	0.098[b]
Onodi cell	40 (19.4%)	26 (20.3%)	14 (17.9%)	0.677[b]
Haller cell	63 (30.6%)	44 (34.4%)	19 (24.4%)	0.130[b]
Supraorbital Ethmoid cell	32 (15.5%)	27 (21.1%)	5 (6.4%)	**0.005**[b]
Variation of nasal turbinate				
Sup. concha bulloza	4 (1.9%)	4 (3.1%)	0 (0.0%)	0.300[c]
Middle concha bulloza	111 (53.9%)	63 (49.2%)	48 (61.5%)	0.085[b]
Paradoxal middle concha	38 (18.4%)	26 (20.3%)	12 (15.4%)	0.376[b]
Paranasal sinus pneumatization variations				
Frontal sinus hypoplasia	48 (23.3%)	30 (23.4%)	18 (23.1%)	0.953[b]
Maxillary sinus hypoplasia	7 (3.4%)	6 (4.7%)	1 (1.3%)	0.257[c]
Accessory pneumatization variations				
Uncinate bulla	18 (8.7%)	10 (7.8%)	8 (10.3%)	0.547[b]
Anterior Clinoid Process pneumatization	72 (35.0%)	49 (38.3%)	23 (29.5%)	0.199[b]
Delano Classification				0.077[b]
Type 1	99 (48.1%)	53 (41.4%)	46 (59.0%)	
Type 2	73 (35.4%)	51 (39.8%)	22 (28.2%)	
Type 3	16 (7.8%)	10 (7.8%)	6 (7.7%)	
Type 4	18 (8.7%)	14 (10.9%)	4 (5.1%)	
Keros Classification				0.349[b]
Type 1	39 (18.9%)	27 (21.1%)	12 (15.4%)	
Type 2	138 (67.0%)	81 (63.3%)	57 (73.1%)	
Type 3	29 (14.1%)	20 (15.6%)	9 (11.5%)	

Data summarized as median (IQR) or frequency (%). [a] Mann Whitney U test [b]Pearson's chi-square test [c]Fisher's exact test. Bold p-values indicate statistical significance at α=0.05. IQR: Interquartile range.

Table 2. Comparison of variables between NSD type as per angle classification

	Tip 1 (n=35)	Tip 2 (n=100)	Tip 3 (n=71)	p
Demographic variables				
Age	25.5 (17.3)	30.5 (17.8)	27.0 (18.0)	0.575[a]
Gender				0.117[b]
Male	18 (51.4%)	69 (69.0%)	41 (57.7%)	
Female	17 (48.6%)	31 (31.0%)	30 (42.3%)	
Variation of ethmoid air cell				
Agger nasi cell	19 (54.3%)	56 (56.0%)	42 (59.2%)	0.871[a]
Onodi cell	7 (20.0%)	23 (23.0%)	10 (14.1%)	0.347[a]
Haller cell	9 (25.7%)	34 (34.0%)	20 (28.2%)	0.567[a]
Supraorbital Ethmoid cell	8 (22.9%)	15 (15.0%)	9 (12.7%)	0.388[a]
Variation of nasal turbinate				
Sup. concha bulloza	0 (0.0%)	4 (4.0%)	0 (0.0%)	0.171[c]
Middle concha bulloza	16 (45.7%)	55 (55.0%)	40 (56.3%)	0.559[b]
Paradoxal middle concha	5 (14.3%)	14 (14.0%)	19 (26.8%)	0.083[b]
Paranasal sinus pneumatization variations				
Frontal sinus hypoplasia	8 (22.9%)	20 (20.0%)	20 (28.2%)	0.460[b]
Maxillary sinus hypoplasia	0 (0.0%)	4 (4.0%)	3 (4.2%)	0.679[c]
Accessory pneumatization variations				
Uncinate bulla	5 (14.3%)	5 (5.0%)	8 (11.3%)	0.159[b]
Anterior Clinoid Process pneumatization	15 (42.9)	30 (30.0)	27 (38.0)	0.311[b]
Delano Classification				0.801[b]
Type 1	14 (40.0%)	52 (52.0%)	33 (46.5%)	
Type 2	14 (40.0%)	31 (31.0%)	28 (39.4%)	
Type 3	4 (11.4%)	7 (7.0%)	5 (7.0%)	
Type 4	3 (8.6%)	10 (10.0%)	5 (7.0%)	
Keros Classification				0.059[b]
Type 1	4 (11.4%)	14 (14.0%)	21 (29.6%)	
Type 2	24 (68.6%)	73 (73.0%)	41 (57.7%)	
Type 3	7 (20.0%)	13 (13.0%)	9 (12.7%)	

Data summarized as median (IQR) or frequency (%). [a] Kruskal-Wallis test [b]Pearson's chi-square test [c]Fisher's exact test. Bold p-values indicate statistical significance at α=0.05. IQR: Interquartile range.

Table 3. Correlations between anatomic variants

	Agger nasi			**Onodi**			**Haller**			**Supraorbital Ethmoid**		
	Yes	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**
Agger nasi cell	-	-	-	21 (17.9%)	96 (82.1%)	0.541	38 (32.5)	79 (67.5)	0.498	18 (15.4%)	99 (84.6%)	0.946
				(ϕ=-0.043)			(ϕ=0.047)			(ϕ=-0.005)		
Onodi cell	21 (52.5%)	19 (47.5%)	0.541	-	-	-	18 (45.0%)	22 (55.0%)	**0.027**	5 (12.5%)	35 (87.5%)	0.555
	(ϕ =0.043)						(ϕ=0.154)			(ϕ=-0.041)		
Haller cell	38 (60.3%)	25 (39.7%)	0.498	18 (28.6%)	45 (71.4%)	**0.027**	-	-	-	12 (19.0%)	51 (81.0%)	0.355
	(ϕ=0.047)			(ϕ=0.154)						(ϕ=0.064)		
Supraorbital Ethmoid cell	18 (56.3%)	14 (43.7%)	0.946	5 (15.6%)	27 (84.4%)	0.555	12 (37.5%)	20 (62.5%)	0.355	-	-	-
	(ϕ=-0.005)			(ϕ=-0.041)			(ϕ=0.064)					
Sup. concha bullosa	3 (75.0%)	1 (25.0%)	0.635	1 (25.5%)	3 (75.0%)	1	2 (50.0%)	2 (50.0%)	0.587	1 (25.0%)	3 (75.0%)	1
	(ϕ=0.052)			(ϕ=0.020)			(ϕ=0.059)			(ϕ=0.037)		
Middle concha bullosa	63 (56.8%)	48 (43.2%)	0.99	24 (21.6%)	87 (78.4%)	0.387	33 (29.7%)	78 (70.3%)	0.774	17 (15.3%)	94 (84.7%)	0.925
	(ϕ=-0.001)			(ϕ=0.060)			(ϕ=-0.020)			(ϕ=-0.007)		
Paradoxal middle concha	25 (65.8%)	13 (34.2%)	0.215	9 (23.7%)	29 (76.3%)	0.462	12 (31.6%)	26 (68.4%)	0.883	4 (10.5%)	34 (89.5%)	0.345
	(ϕ=0.086)			(ϕ=0.051)			(ϕ=0.010)			(ϕ=-0.066)		
Frontal sinus hypoplasia	33 (68.8%)	15 (31.3%)	0.056	9 (18.8%)	39 (81.3%)	0.894	9 (18.8%)	39 (81.3%)	**0.042**	2 (4.2%)	46 (95.8%)	**0.013**
	(ϕ=0.133)			(ϕ=-0.009)			(ϕ=-0.142)			(ϕ=-0.173)		
Maxillary sinus hypoplasia	3 (42.9%)	4 (57.1%)	0.701	0 (0.0%)	7 (100.0%)	0.35	0 (0.0%)	7 (100.0%)	0.103	1 (14.3%)	6 (85.7%)	1
	(ϕ=-0.053)			(ϕ=-0.092)			(ϕ=-0.124)			(ϕ=-0.006)		
Uncinate bulla	8 (44.4%)	10 (55.6%)	0.268	3 (16.7%)	15 (83.3%)	1	6 (33.3%)	12 (66.7%)	0.791	6 (33.3%)	12 (66.7%)	**0.041**
	(ϕ=-0.077)			(ϕ=-0.022)			(ϕ=0.018)			(ϕ=0.152)		
Anterior Clinoid Process pneumatization	41 (56.9%)	31 (43.1%)	0.975	15 (20.8%)	57 (79.2%)	0.706	24 (33.3%)	48 (66.7%)	0.53	16 (22.2%)	57 (77.8%)	0.052
	(ϕ=0.002)			(ϕ=0.026)			(ϕ=0.044)			(ϕ=0.135)		

P-values are calculated from Pearson's chi-square or Fisher's exact test. ϕ: Phi correlation coefficient. Bold p-values indicate statistically significant correlation at α=0.05.

Table 3. (cont). Correlations between anatomic variants.

	Sup. Concha bulloza			**Middle concha bulloza**			**Paradoxal middle concha**			**Frontal sinus hypoplasia**		
	Yes	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**
Agger nasi cell	3 (2.6%)	114 (97.4%)	0.635	63 (53.8%)	54 (46.2%)	0.99	25 (21.4%)	92 (78.6%)	0.215	33 (28.2%)	84 (71.8%)	0.056
	(ϕ=0.052)			(ϕ=-0.001)			(ϕ=0.086)			(ϕ=0.133)		
Onodi cell	1 (2.5%)	39 (97.5%)	1	24 (60.0%)	16 (40.0%)	0.387	9 (22.5%)	31 (77.5%)	0.462	9 (22.5%)	31 (77.5%)	0.894
	(ϕ=0.020)			(ϕ=0.060)			(ϕ=0.051)			(ϕ=-0.009)		
Haller cell	2 (3.2%)	61 (96.8%)	0.587	33 (52.4%)	30 (47.6%)	0.774	12 (19.0%)	51 (81.0%)	0.883	9 (14.3%)	54 (85.7%)	**0.042**
	(ϕ=0.059)			(ϕ=-0.020)			(ϕ=0.010)			(ϕ=-0.142)		
Supraorbital Ethmoid cell	1 (3.1%)	31 (96.9%)	1	17 (53.1%)	15 (46.9%)	0.925	4 (12.5%)	28 (87.5%)	0.345	2 (6.3%)	30 (93.8%)	**0.013**
	(ϕ=0.037)			(ϕ=-0.007)			(ϕ=-0.066)			(ϕ=-0.173)		
Sup. concha bullosa	-	-	-	2 (50.0%)	2 (50.0%)	1	0 (0.0%)	4 (100.0%)	1	1 (25.0%)	3 (75.0%)	1
				(ϕ=-0.011)			(ϕ=-0.067)			(ϕ=0.006)		
Middle concha bulloza	2 (1.8%)	109 (98.2%)	1	-	-	-	23 (20.7%)	88 (79.3%)	0.363	23 (20.7%)	88 (79.3%)	0.344
	(ϕ=-0.011)						(ϕ=0.063)			(ϕ=-0.066)		
Paradoxal middle concha	0 (0.0%)	38 (100.0%)	1	23 (60.5%)	15 (39.5%)	0.363	-	-	-	14 (36.8%)	24 (63.2%)	**0.029**
	(ϕ=-0.067)			(ϕ=0.063)						(ϕ=0.152)		
Frontal sinus hypoplasia	1 (2.1%)	47 (97.9%)	1	23 (47.9%)	25 (52.1%)	0.344	14 (29.2%)	34 (70.8%)	**0.029**	-	-	-
	(ϕ=0.006)			(ϕ=-0.066)			(ϕ=0.152)					
Maxillary sinus hypoplasia	0 (0.0%)	7 (100.0%)	1	4 (57.1%)	3 (42.9%)	1	1 (14.3%)	6 (85.7%)	1	2 (28.6%)	5 (71.4%)	0.666
	(ϕ=-0.026)			(ϕ=0.012)			(ϕ=-0.020)			(ϕ=0.023)		
Uncinate bulla	0 (0.0%)	18 (100.0%)	1	10 (55.6%)	8 (44.4%)	0.882	2 (11.1%)	16 (88.9%)	0.536	3 (16.7%)	15 (83.3%)	0.77
	(ϕ=-0.044)			(ϕ=0.010)			(ϕ=-0.059)			(ϕ=-0.049)		
Anterior Clinoid Process pneumatization	0 (0.0%)	72 (100.0%)	0.3	36 (50.0%)	36 (50.0%)	0.412	14 (19.4%)	58 (80.6%)	0.787	12 (16.7%)	60 (83.3%)	0.099
	(ϕ=-0.103)			(ϕ=-0.057)			(ϕ=0.019)			(ϕ=-0.115)		

P-values are calculated from Pearson's chi-square or Fisher's exact test. ϕ: Phi correlation coefficient. Bold p-values indicate statistically significant correlation at α=0.05

Table 3 (cont). Correlations between anatomic variants.

	Maxillary sinus hypoplasia			Uncinate bulla			Anterior Clinoid Process		
	Yes	**No**	**p**	**Yes**	**No**	**p**	**Yes**	**No**	**p**
Agger nasi cell	3 (2.6%)	114 (97.4%)	0.701	8 (6.8%)	10 (93.2%)	0.268	41 (35.0%)	76 (65.0%)	0.975
	(ϕ=-0.053)			(ϕ=-0.077)			(ϕ=0.002)		
Onodi cell	0 (0.0%)	40 (100.0%)	0.35	3 (7.5%)	37 (92.5%)	1	15 (37.5%)	25 (62.5%)	0.706
	(ϕ=-0.092)			(ϕ=-0.022)			(ϕ=0.026)		
Haller cell	0 (0.0%)	63 (100.0%)	0.103	6 (9.5%)	57 (90.5%)	0.791	24 (38.1%)	39 (61.9%)	0.53
	(ϕ=-0.124)			(ϕ=0.018)			(ϕ=0.044)		
Supraorbital Ethmoid cell	1 (3.1%)	31 (96.9%)	1	6 (18.7%)	26 (81.3%)	**0.041**	16 (50.0%)	16 (50.0%)	0.052
	(ϕ=-0.006)			(ϕ=0.152)			(ϕ=0.135)		
Sup. concha bulloza cell	0 (0.0%)	4 (100.0%)	1	0 (0.0%)	4 (100.0%)	1	0 (0.0%)	4 (100.0%)	0.3
	(ϕ=-0.026)			(ϕ=-0.044)			(ϕ=-0.103)		
Middle concha bulloza	4 (3.6%)	107 (96.4%)	1	10 (9.0%)	101 (91.0%)	0.882	36 (32.4%)	75 (67.6%)	0.412
	(ϕ=0.012)			(ϕ=0.010)			(ϕ=-0.057)		
Paradoxal middle concha	1 (2.6%)	37 (97.4%)	1	2 (5.3%)	36 (94.7%)	0.536	14 (36.8%)	24 (63.2%)	0.787
	(ϕ=-0.020)			(ϕ=-0.059)			(ϕ=0.019)		
Frontal sinus hypoplasia	2 (4.2%)	46 (95.8%)	0.666	3 (6.3%)	45 (93.8%)	0.77	12 (25.0%)	36 (75.0%)	0.099
	(ϕ=0.023)			(ϕ=-0.049)			(ϕ=-0.115)		
Maxillary sinus hypoplasia	-	-	-	0 (0.0%)	7 (100.0%)	1	1 (14.3%)	6 (85.7%)	0.425
				(ϕ=-0.058)			(ϕ=-0.081)		
Uncinate bulla	0 (0.0%)	40 (100.0%)	0.35	3 (7.5%)	37 (92.5%)	1	15 (37.5%)	25 (62.5%)	0.706
	(ϕ=-0.092)			(ϕ=-0.022)			(ϕ=0.026)		
Anterior Clinoid Process pneumatization	0 (0.0%)	63 (100.0%)	0.103	6 (9.5%)	57 (90.5%)	0.791	24 (38.1%)	39 (61.9%)	0.53
	(ϕ=-0.124)			(ϕ=0.018)			(ϕ=0.044)		

P-values are calculated from Pearson's chi-square or Fisher's exact test. ϕ: Phi correlation coefficient. Bold p-values indicate statistically significant correlation at α=0.05.

There is no significant correlation between the presence of onodi cell and ACPP (ϕ = 0.026, p = 0.706) (Figure 6).

A significant association was observed between Delano classification and presence of ACPP (p < 0.001) (Figure 7). While the majority of the patients with ACPP have Type 2 Delano classification (n = 34, 47.2 %) (Figure 5), ACPP was present in all patients in the type 3 Delano group (Figure 7).

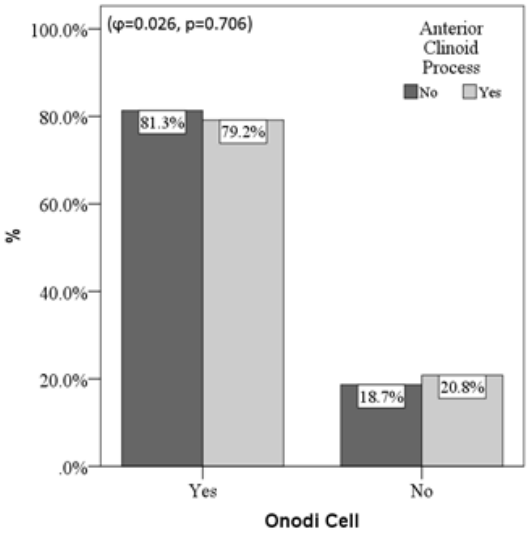

Figure 6. Association between the presence of onodi cell and Anterior Clinoid Process pneumatization

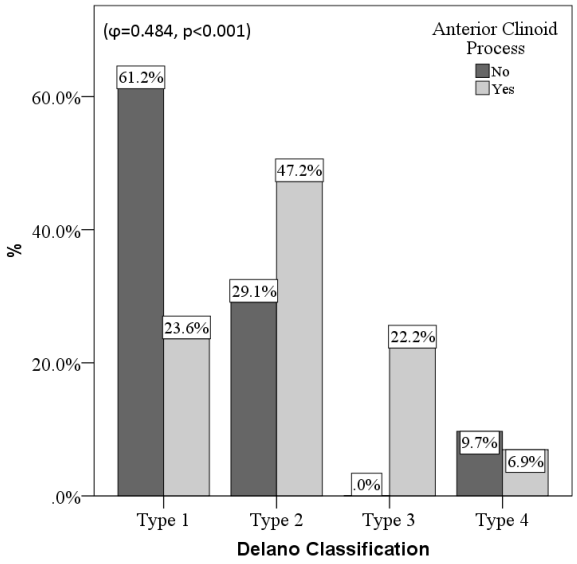

Figure 7. Association between Delano classification and presence of Anterior Clinoid Process Pneumatization.

Discussion

Various classification systems have been defined for typing NSD in the literature. Mladina et al. (Mladina et al., 2008) defined the Mladina classification for NSD typing and reported that the most frequently type was type 3. Haytoglu et al. (Haytoglu et al., 2017) reported that type 2 is the most frequently type in patients with septoplasty. In our study, unlike the literature findings, the most frequently NSD type was type 4 in men and type 7 in women. These differences in the literature may result from differences of geographic regions.

Based on the literature, many studies have investigated the frequency of concurrence of concha bullosa with septum deviation, which is one of the sinonasal anatomical variations (Koo et al., 2017; El-Taher et al., 2019). The various incidence rates of concha bullosa with septal deviation have been reported (Yigit et al, 2010) 45.34 %, Yazici et al. (Yazici, 2019) 45.3 %, Koo et al. (Koo et al., 2017) 52.4 %). In our study, the incidence of concha bullosa was 53.9 % by these studies previous studies showing that the NSD angle is related to the concha bullosa (Uygur et al., 2003; El-Taher et al., 2019). Contrary to these findings, any relationship between the NSD angle, and concha bullosa was not found in our study.

The incidence of paradoxal middle turbinates, which is one of the anatomical variations of turbinates, ranges from 3 to 40 % in the literature (Bolger et al., 1991; Ozcan et al., 2008). In our study, paradoxal middle turbinate incidence was 18.4 % and this rate was compatible with the literature.

The prevalence of the Haller cell, which is one of the ethmoid air cell variants, varies between 2.7 – 45.1 % in the literature (Bolger et al., 1991; Yazici, 2019). Shokri et al. (Shokri et al., 2019) found a correlation between Haller cell and NSD. In our study, the incidence of the Haller cell was 30.6 %. We found a significant correlation between Haller cell and Onodi cell and frontal sinus hypoplasia. The presence of sinonasal anatomical variants and correlations between them are important in order to establish a diagnosis and treatment plan and to prevent possible surgical complications.

The prevalence of supraorbital ethmoid cell, which is important for safe dissection of the frontal ostium, varies in the literature by ethnic origin (Zhang et al., 2007). The incidence of supraorbital ethmoid cell has been reported as 5.3 % and its association with the anterior ethmoid artery has been shown (Zhang et al., 2007). In our study, the incidence of supraorbital ethmoid cells was 15.5 % and it was significantly higher in men compared to women [27 (21.1 %) vs. 5 (6.4 %)]. We also found a significant correlation between supraorbital cell, paradoxal middle turbinate and uncinate bulla. The prevalence of uncinate bulla, which is a rare anatomic variant that can lead to narrowing of the infundibulum, varies between 0.4-13 % in the literature (Fadda et al., 2012; Yazici, 2019). In our study, the incidence of uncinate bulla was 8.7 % and it were in concordance with the literature.

In order to prevent vital complications that may occur during transsphenoidal and skull base surgery, it is essential to identify anatomic variations associated with the SS preoperatively. Removal of the ACPP during skull base surgery carries the risk of cerebrospinal fluid rhinorrhea and associated sepsis (Nandapalan et al., 1996; Sirikci et al., 2000). Prior to skull base surgery, the risk of this complication is reduced by identifying ACPP in paranasal CT and preferring extradural approach (Noguchi et al., 2005). In the literature, the prevalence rates of ACPP, and Onodi cell were reported to range between 13.3 – 16 %, and 0 - 18 %, respectively (17,23,25) (Bolger et al., 1991; Sirikci et al., 2000; Unal et al., 2006). In a study of patients with NSD, Onodi cells, and ACPP were seen in 2 %, and 29.3 % of the patients respectively. In our study, Onodi cells and ACPP were seen in 19.4 %, and 35 % of the patients, respectively which were higher when compared with the literature findings. In NSD patients, changes in the turbulence of airflow through the nasal cavity or genetic mechanisms may be associated with pneumatization anomalies. Pneumatization of the anterior clinoid process may cause the optic nerve to medialize into the SS during the development process. Studies have reported that ACPP is

associated with optic nerve protrusion (Sapci et al., 2004; Itagi et al., 2017). In our study, we identified a positive correlation between ACPP and Delano type 2 and 3, where the optic nerve protrudes into the SS. Especially in patients with NSD, the identification of ACPP by examining paranasal CTs in detail before transsphenoidal and skull base surgery reduces the risks of complications that may occur.

A limitation of the present study is that it was retrospective and not having a control group of patients without septum deviation. Further studies including large numbers of case-control studies are necessary to evaluate the relationship of septal deviation with sinonasal anatomic variants.

Conclusion

In our study, the incidence of onodi cell, supraorbital ethmoid cell, anterior clinoid process pneumatization were more frequent in patients with nasal septal deviation compared to the literature. However, there is no significant difference was found between NSD types as per angle classification in terms of the presence of sinonasal variation. Careful examination of paranasal CTs before craniomaxillofacial surgeries is important to determine sinonasal anatomic variants, to determine the appropriate treatment plan and to prevent possible complications preoperatively.

Ethics Committee Approval: This retrospective study was performed after approval of the Abant Izzet Baysal University ethics committee in accordance with the Helsinki declaration (07.03. 2019 2019/63).
Peer-review: Externally peer-reviewed.
Author Contributions: Concept -E.K A.G E.D Design E.K E.D Z.C; Audit E.K E.D A.G AU.; Materials – E.K E.D Z.C Data Collection and / or Processing – E.K O.K A.U Analysis and / or Interpretation – E.K O.K A.G Z.C ; Literature review – E.K A.G E.D Z.C.; Text – E.K E.D O.K; Critical Review – E.K A.U O.K
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RESEARCH ARTICLE

Investigation of a Possible Association Between Dynamic Thiol/Disulfide Homeostasis and Pain in Knee Arthroplasty Patients

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Abstract

Objective: Dynamic thiol/disulfide homeostasis plays a pivotal role in many physiologic mechanisms. In the present study, we aimed to elucidate the relationship between postoperative pain and thiol/disulfide homeostasis in patients who underwent primary total knee arthroplasty for primary knee osteoarthritis.

Methods: This prospective uncontrolled study included 28 patients (10 male, 18 female) with a diagnosis of primary gonarthrosis who underwent primary total knee arthroplasty and met the study inclusion criteria. Venous blood samples were taken from the patients and pain values were recorded simultaneously using the visual analog scale (VAS) preoperatively and at the 4th postoperative week. Thiol/disulfide hemostasis levels were measured using a new fully-automated and spectrophotometric method developed by Erel and Neselioglu.

Results: The average age of the patients participating in the study was 66.25 ± 8.29 years and 18 (64.3%) of the patients were female. B values for preoperative native/total thiol (+7,652), preoperative disulfide/native thiol (+10,550), and postoperative total thiol (+128), positively affected the difference in VAS values. B values for preoperative disulfide (-219), postoperative disulfide (-1,297), postoperative native/total thiol (-4,238), and postoperative disulfide/native thiol (-3,316) negatively affected the difference in VAS values.

Conclusion: The disulfide level, an oxidized form in thiol/disulfide homeostasis, appears to be a valuable marker for evaluating the effect of oxidative stress on postoperative pain.

Key words: Thiol/disulfide homeostasis, oxidative stress, pain, osteoarthritis, knee arthroplasty

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Introduction

Osteoarthritis (OA), the most well-known form of arthritis, is defined by degeneration of the articular cartilage. As life expectancy has increased, OA has become a common disease in the elderly. Oxidative stress, described as an imbalance between increased free radical load and cellular clearance mechanisms is an important part of OA pathogenesis (Ziskoven et al., 2010).

Total knee arthroplasty (TKA) is a surgical procedure applied to patients with severe knee OA to obtain a painless functional joint and increase their

quality of life. Pain that occurs after TKA is a major concern for patients and may directly affect functional results. It has been shown that oxidative stress may lead to hyperalgesia by causing peripheral sensitization and inflammation (Nashed, Balenko, & Singh, 2014; Ergonenc & Beyaz, 2019).

Thiols, organic molecules including sulfhydryl groups, are the basis of the oxidant/antioxidant balance in the body. When thiols (the reduced state) undergoes an oxidative reaction, they turn into disulfide groups (the oxidized state). Disulfide groups can be degraded back to thiol groups increasing thiol reserves. Dynamic thiol/disulfide homeostasis is provided because of these reactions at the cellular level. Dynamic thiol/disulfide homeostasis plays an essential role in antioxidant guard, detoxification, cell signaling and transcription, apoptosis, and regulation of enzymatic activity. Studies have revealed that in thiol/disulfide homeostasis, an increase in the balance towards thiols leads to proliferation, while an increase towards disulfides leads to apoptosis (Nar & Calis, 2018). Disulfide levels were found to be higher in patients with degenerative states such as smoking, diabetes, obesity, and OA, and lower in patients with proliferative conditions such as multiple myeloma and cancers. Erel and Neselioglu described a new method to determine dynamic thiol/disulfide homeostasis which allowed them to evaluate native and total thiol concentrations simultaneously. The oxidant-antioxidant balance can be assessed together with disulfide parameters calculated handling native thiol and total thiol levels (Erel & Neselioglu, 2014).

In the current study, we proposed to elucidate the correlation between postoperative pain and thiol/disulfide homeostasis in patients who underwent primary TKA for primary knee OA. There is no previous study investigating the relationship between pain and thiol/disulfide homeostasis after TKA.

Methods

Study design

This prospective cohort study was carried out with the approval of the Ahi Evran University Clinical Research Ethics Committee (2019-05/61). This study was supported by the Kırsehir Ahi Evran University Scientific Research Project Unit (TIP.A4.19.002) and prepared in accordance with the Helsinki Declaration of Principles. This study has not been presented as a poster or oral presentation previously.

The present study included 28 patients (10 males, 18 females) with a diagnosis of primary gonarthrosis who underwent primary TKA between April 2019 and March 2020 at the Kırsehir Ahi Evran University Medical Faculty Orthopedics and Traumatology Clinic and met the inclusion criteria. Patients with comorbidities such as diabetes mellitus, cardiovascular disease, acute or chronic renal failure, hyperlipidemia, depression, chronic lung disease, inflammatory disease, malignancy, or infection were not included in the study. In addition, individuals using any medication (steroidal or non-steroidal anti-inflammatory drugs, antioxidants, vitamin supplements) during the 4 weeks before venous blood sampling were also excluded. Study patients also did not smoke or consume alcohol.

All surgical procedures were performed under spinal anesthesia by the same surgeon experienced in the field, using the same surgical technique and medial parapatellar approach. In all cases, a lower extremity pneumatic tourniquet was adjusted to a pressure of 300 mmHg during the operation. The same brand and type of cemented posterior-stabilized primary knee prosthesis (Vanguard Rotating Platform High Flex; Biomet, Warsaw, IN, USA) was applied for all 28 patients. Patellofemoral surface change was not applied, and desensitization was performed around the patella with electrocautery. A drainage tube was not used in the operation. The same drug protocol routinely used after knee arthroplasty in our clinic was applied for 5 days (paracetamol 3x1 gr iv, cefazolin 3x1 gr iv, tramadol 3x100 mg iv, pantoprazole 1x40 mg iv, enoxaparin 1x0.4 ml sc). Steroidal or non-steroidal anti-inflammatory drug treatment was not used. The patients were mobilized by placing full weight at the 24th postoperative hour and the same rehabilitation program was applied for all patients in the presence of a physiotherapist.

At 24 hours preoperatively and during the 4th postoperative week, after fasting overnight, 3 ml of venous blood was taken from the patients and transferred to ethylenediaminetetraacetic acid (EDTA) containing tubes. The collected samples were centrifuged at 4°C and 1500 × g for 10 minutes. The plasma samples were kept frozen at -80°C until the thiol/disulfide homeostasis analysis tests were conducted at which time all samples were thawed and analyzed simultaneously.

The pain values of the patients were recorded simultaneously with the preoperative and postoperative venous blood samples, using the visual analog scale (VAS) scale. VAS is a widely used scale for evaluating pain severity. The scale ranges from 0 to 10, with 0 indicating no pain and a value of 10 meaning unbearable pain (Karcioglu, Topacoglu, Dikme, & Dikme, 2018).

Biochemical Analysis

Thiol/disulfide hemostasis levels were calculated using the spectrophotometric method developed by Erel and Neselioglu(Erel & Neselioglu, 2014). A Shimadzu UV-1800 spectrophotometer with a temperature-controlled cuvette holder and Cobas c501 automatic analyzer (Roche) were used.

After defining the native and total thiol levels, the disulfide concentration was determined using the following formula:

Disulfide = (total thiol–native thiol)/2

Disulfide/total thiol (%), disulfide/native thiol (%), and native thiol/total thiol (%) ratios were calculated using previously determined disulfide, native thiol, and total thiol concentrations (Erel, 2005).

Statistical Analyses

The skewness and kurtosis values between -3 and +3, sufficient for normal distribution and parametric methods, were used to evaluate the results of the study. The relationship of variables was evaluated using t-tests and parametric tests. The interaction between dependent (VAS score) and independent variables (native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native thiol/total thiol) was investigated using the multiple linear regression method. $p < 0.05$ was noted statistically significant. SPSS version 22 for Windows (SPSS Inc., Chicago, IL, USA) was used to evaluate the results.

Results

The average age of the patients participating in the study was 66.25 ± 8.29 years and 18 (64.3%) of the patients were female. All of the 28 cases involved TKA performed due to primary OA. No local or systemic complications were observed in the patients during the postoperative period. No peri-operative blood transfusions were required. While the preoperative mean C-reactive protein (CRP) value was 0.4 ± 0.4, the postoperative 4th week CRP mean value increased to 1.4 ± 1.1, which was a statistically significant difference between the preoperative and postoperative CRP measurements ($p < 0.05$).

Pre- and postoperative patient VAS, native thiol, total thiol, disulfide, disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol values are given in Table1. The difference between the pre- and postoperative VAS measurements is statistically significant ($p < 0.05$) (Table 2). Linear regression analysis was applied to examine the parameters affecting this difference between the pre- and postoperative VAS measurements (Table 3). According to this analysis method, among the independent variables it was found that the rates of preoperative native/total thiol, preoperative disulfide/native thiol, and postoperative total thiol, positively affected the VAS difference (B values: +7,652, +10,550, and +128, respectively) whereas preoperative disulfide, postoperative disulfide, postoperative native/total thiol, and postoperative disulfide/native thiol ratios negatively affected the difference in VAS scores (B values: -219, -1,297, -4,238, and -3,316, respectively) (Table 3). In other words, lower preoperative disulfide, postoperative disulfide values, and postoperative native/total thiol, and postoperative disulfide/native thiol ratios correlated with lower patient postoperative VAS scores

Table 1. Pre- and postoperative patient variables

	Preoperative Mean±SD	Postoperative Mean±SD
VAS	7.6±2.1	3.2±0.9
Native Thiol (µmol/L)	218.0±53.0	223.6±38.7
Total Thiol (µmol/L)	261.8±59.5	264.6±40.7
Disulfide (µmol/L)	21.9±4.6	20.5±5.4
Disulfide/Native Thiol (%)	10.3±1.8	9.4±2.7
Disulfide/Total Thiol (%)	8.5±1.3	7.8±1.9
Native Thiol/Total Thiol (%)	83.0±2.5	84.3±3.9

Table 2. Pre and postoperative VAS scores

	Preoperative Mean±SD	**Postoperative** Mean±SD	p
VAS	7.6±2.1	3.2±0.9	.000*

*p<0.05 is considered statistically significant.

Table 3. Linear regression analysis of variables

Dependent Variable	Independent Variable	B	p	R^2
Pre-op-Post-op VAS Gap	Pre-op Disulfide	-.219	.016*	.668
	Pre-op Native/Total Thiol (%)	7,652	.006*	
	Pre-op Disulfide/Native Thiol (%)	10,550	.006*	
	Post-op Total Thiol	.128	.029*	
	Post-op Disulfide	-1,297	.050*	
	Post-op Native/Total Thiol (%)	-4,238	.042*	
	Post-op Disulfide/Native Thiol (%)	-3,316	.094	

*p<0.05 is considered statistically significant.

Discussion

In the present study, it was observed that patients with low levels of disulfide, which is an indicator of oxidative stress levels, had lower postoperative VAS scores; that is, they felt less pain. There are several publications in the literature describing the pathophysiological connection between oxidative stress levels and pain. One study indicated that oxidative stress could trigger pain pathways through glutamatergic signaling and activation of inflammatory reactions, as well as by directly affecting nociceptive centers in the brain (Perrone et al., 2017). In another study, it was mentioned that oxidative stress may cause peripheral sensitization; that is, it can change nociception that may cause hyperalgesia (Nashed et al., 2014). Therefore, it has been recommended that a reduction of oxidative stress by antioxidants may reduce peripheral inflammation and stimulation of nociceptive receptors and alleviate pain. In support of this mechanism, Payal et al. (2009) showed that antioxidant supplementation reduced oxidative stress levels and alleviated pain levels in patients with chronic pancreatitis. Bellieni et al. (2009) observed a positive correlation between high pain levels and high oxidative stress levels in newborns. In another study conducted with ankylosing spondylitis patients, it was reported that native and total thiol levels negatively correlated with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and VAS scores (Dogru et al., 2016). Ayhan Tuzcu et al.(Tuzcu et al., 2019) examined thiol/disulfide homeostasis in patients with fibromyalgia syndrome (FMS) and found that native thiol and native thiol/total thiol levels were significantly lower in FMS cases compared to healthy individuals; however, disulfide levels in FMS patients were significantly higher than in healthy individuals. They also found a positive correlation between disulfide levels and pain and the number of sensitive points (Tuzcu et al., 2019).

In current study, similar to other studies in the literature, a significant relationship was found between low levels of disulfide and low VAS scores. In support of this relationship statistically, the preoperative native/total thiol ratio positively affected the pre- and postoperative VAS score difference. However, contrary to expectations, the postoperative native/total thiol ratio negatively affected the pre- and postoperative VAS score difference. According to the literature, this is not an expected result. Similarly, many articles in the literature on oxidative stress have shown conflicting data. Inanir et al. (Inanır, Sogut, Ayan, & Inanır, 2013), in their study to evaluate the relationship between pain level and oxidative stress levels in patients with acute and chronic inflammatory or non-inflammatory low back pain, observed that there was no relationship between oxidative stress levels and pain intensity and pain level.

As in the present study, other authors have attempted to set a link between oxidative stress and disease pathophysiology. It is hard to evaluate oxidative stress and the response of the human body to this stress because there is no single biomarker that can objectively measure oxidative stress (Grune & Berger, 2007). In addition, there is no biomarker showing the tissue oxidative stress level in peripheral blood (Arsalani-Zadeh, Ullah, Khan, & MacFie, 2011). It has been shown that oxidative damage can appear at the tissue level without a measurable change in peripheral blood (Kerkweg et al., 2010). Also, blood and tissue biomarkers of oxidative stress may not follow the same pattern of change (Arguelles, Garcia, Maldonado, Machado, & Ayala, 2004). In the current study, we found that the preoperative native/total thiol ratio positively affected the pre- and postoperative VAS score difference, but contrary to

what was expected, the postoperative native/total thiol ratio negatively affected the pre- and postoperative VAS score difference, which may be explained by that situation. In light of the data obtained, we think that the disulfide level, an oxidized form, is a more valuable marker than postoperative native/total thiol ratio in evaluating the effect of oxidative stress on postoperative pain.

Due to the large number of exclusion criteria, the low number of patients meeting the inclusion criteria is one of the most prominent limitations of the current study. Randomized controlled studies with large patient populations are required to obtain statistically significant data. In addition to the absence of an ideal method for measuring oxidative stress, the unknown clinical significance of oxidative stress changes can be considered as the main limitation of oxidative stress measurement studies in general.

Conclusion

We think that the disulfide level, an oxidized form, is a more valuable marker than other independent variables evaluating the effect of oxidative stress on both postoperative and preoperative pain

Ethics Committee Approval: This study was approved by the Ethics Committee of the Ahi Evran University Clinical Research Ethics Committee (Ethical approval number: Protocol Number 2019-05/61) and prepared in accordance with the Helsinki
Peer-review: Externally peer-reviewed.
Author Contributions: Concept -HS, BI; Design-HS,BI; Supervision-HS; Materials – HS, BI; Data Collection and/or Processing -HS.; Analysis and/or Interpretation -HS, BI; Literature Review -HS; Writing - HS; Critical Review – HS, BI.
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RESEARCH ARTICLE

Microorganisms that Reproduce in Wound Cultures in Rize Region and Their Antimicrobial Susceptibility

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Abstract

Objective: Among nosocomial infections, wound infections are one of the important factors causing mortality and morbidity after urinary tract infections. In this study, it was aimed to guide the empirical treatment and to contribute to epidemiological data by determining the microorganism and antimicrobial susceptibility which have been isolated from cultures of wounds and abscesses, which came from outpatient clinics, services and intensive care units, that grow in wound site and abscess cultures that comes from outpatient clinics, services and intensive care units.

Methods: This study was conducted on the basis of cultures in which at least one microorganism grew in the wound site and abscess samples from the polyclinic, service and intensive care units during routine application at the Recep Tayyip Erdoğan University Training and Research Hospital Microbiology Laboratory, between January 2011 and December 2016. Samples were taken with two sterile swabs in the form of superficial swabs or deep aspiration and delivered to the laboratory with transport medium as soon as possible. Gram staining preparation was prepared and inoculated on 5% sheep blood agar, eosin-methylene-blue agar, chocolate agar and sabouraud dextrose agar. The gram-stained preparation was evaluated by Q scoring. Evaluation of the culture and antibiogram susceptibility were made according to the Clinical and Laboratory Standards Institute (CLSI) criteria.

Results: A total of 2202 samples were received, and reproduction was observed in 930 samples. Among the 793 wound and 137 abscess samples, the most common microorganism was *Staphylococcus aureus* (224 cultures) and the second was *Escherichia coli* (135 cultures).

Conclusion: Surgery clinics, especially orthopedics, provided the most common wound infections, from which *S. aureus* was the most isolated microorganism. The fact that bacterial, most notably *S. aureus*, propagation occurred from surgery samples indicates that surgical site infections are generally caused by endogenous flora. It has, thus, become apparent in our study that patients and hospital staff should pay more attention to hygiene, especially hand washing. Due to the changing of the distribution and resistance patterns of microorganisms that are frequently seen in hospitals at certain time intervals, their antibiotic susceptibility will be a guide in the rational use of antibiotics. Thus, specific treatment will contribute to the saving on the cost and reduce mortality.

Key words: Abscess, antimicrobial susceptibility, microorganism, wound culture

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Introduction

The physical integrity of the skin is the most important barrier that prevents colonization and preventing infection by pathogenic microorganism in the skin and underlying tissues (Atiyeh et al., 2002). Breaching of this barrier by pathogens may result in infection (Broughton et al., 2006).

Infection development may also result if pathogenic microorganism colonization's occur other than normal flora members (Schultz et al., 2003). Since wound colonization is mostly polymicrobial, the wound is likely to become infected (Akinjogunla et al., 2009). Infections of the skin and subdermal tissue occur when the microorganisms settle, proliferate, and spread in the wound and also overcome the immune system by virulence factors (Yurtseven et al., 2009).

Wound infections are the second source of nosocomial infections after urinary tract infections and are among important causes of mortality and morbidity (Owens et al., 2008). Wound infection factors vary depending on the infected area, its clinical characteristics and the underlying disease of the person (Sesli et al., 2006).

Although different microorganisms are among the infectious agents, the most common are gram positive bacteria, which are also found in normal flora. (Citil et al., 2015). The correct identification of the microorganism and antimicrobial susceptibility will increase the success of the treatment, increase the quality of life of the person, decrease the costs by shortening the duration of hospital stay, and reduce the use of unnecessary antibiotics, in addition the development of antimicrobial resistance will be minimized (Cirit et al., 2014).

In this study, it was aimed to guide symptomatic treatment and contribute to epidemiological data by identifying the microorganism species and antimicrobial susceptibilities isolated from wound site and abscess samples sent to our laboratory from outpatient clinics, services, and intensive care units of our hospital, retrospectively.

Methods

This study was carried out retrospectively scanning the wound and abscess cultures from the outpatient, wards, and intensive care units during routine referral to the Microbiology Laboratory of the Training and Research Hospital (Faculty of Medicine, Recep Tayyip Erdogan University) between January 2011 and December 2016. The cultures in which at least one microorganism grew were evaluated. Samples were taken in the form of superficial swab or deep aspiration with sterile eucvyon rod and delivered to the laboratory as soon as possible with the transport medium. All samples were inoculated to 5% sheep bloody agar, eosin-methylene-blue (EMB) and sabourand dextrose agar and chocolate agar media then under aerobic conditions incubated at 37°C for 24-48 hours. Gram-stained preparats were prepared simultaneously from wound samples. Morphologies of leukocyte, epithelium and microorganisms were evaluated using x100 magnification. At the end of the 48th hour, the plaques were examined together with gram-stained results. The Gram stained preparat was evaluated in terms of epithelial cells, leukocytes and microorganisms by Q scoring. In the microscopic examination, if there is little / no epithelium as well as leukocytes, the samples were evaluated as quality samples. It was decided whether the microorganisms in the reproductive plaques were causative or contaminant, based on direct microscopic examination. Conventional methods and the automated system VITEK 2 (BioMérieux / France) were used for the assessment of the culture and determination of antimicrobial susceptibilities. Evaluation of the culture and antimicrobial susceptibilities were made according to the Clinical and Laboratory Standards Institute (CLSI) criteria (CLSI; 2011-2016). TMC-ADTS Restricted Notification Table was used in the evaluation.

Ethics committee approval was obtained from the Recep Tayyip Erdoğan University Non-Interventional Ethics Committee (Approval no: 40465587-140).

Statistical data were evaluated using the SPSS 21.0 program.

Results

A total of 2202 wound, and abscess samples were sent from the outpatient, wards and intensive care units between January 2011 and December 2016 during routine referral to the Microbiology Laboratory. 856 samples were reported as "no growth", 348 were "evaluated as contamination with skin flora members", 68 samples were reported as "normal flora members have grown", 930 samples were reported as "growth detected".

Of 930 samples with growth, 793 were wound site and 137 were abscess samples. Of the 930 samples, 523 (56.2%) were derived from males and 407 (43.8%) from females. Of the microorganisms grown, 435 (46.8%) were Gram positive bacteria, 484 (52.1%) were Gram negative bacteria, while 11 (1.1%) were fungal agents. *Staphylococcus aureus (S. aureus)* was the most common microorganism isolated (224 specimens), followed by *Escherichia coli (E. coli)* isolated (135 specimens). The rest were

Pseudomonas aeruginosa (P. aeruginosa), Coagulase negative staphylococci (CNS), *Acinetobacter baumannii (A. baumannii)*, *Streptococcus* spp. *Candida* spp. and others. (Table I)

Tablo 1. Clinical Distribution of Microorganisms

Microorganism/Unit	Outpatient 390(%41.9)	Service 445(%47.9)	Intensive care 95(%10.2)	Total 930(%100)
S. aureus	135(%14.5)	83(%8.9)	6 (%0.6)	224 (% 24)
E. coli	38 (%4.1)	83(%8.9)	14(%1.5)	135 (% 14.5)
CNS	58 (%6.3)	49(% 5.3)	13 (% 1.4)	120 (% 13)
A. baumannii	11(%1.1)	36(%4)	35(3.9)	82 (% 9)
P. aeruginosa	61 (%6.6)	55(%6)	7(%0.7)	123 (%13.3)
Proteus spp.	14 (%1.5)	25(%2.7)	2(%0.2)	41 (% 4.4)
Enterococcus spp.	6 (% 0.6)	26(% 2.8)	7(%0.7)	39 (% 4.1)
Candida albicans	5(%0.5)	5(%0.5)	0 (%0)	10 (% 1)
Non-*Candida albicans* yeast	0 (%0)	0 (%0)	1 (%0.1)	1 (% 0.1)
Klebsiella spp.	31(%3.3)	39(%4.2)	8(%0.8)	78 (% 8.3)
Streptococcus spp.	18 (%1.9)	34 (%3.7)	0 (%0)	52 (%5.6)
Enterobacter spp.	13 (%1.4)	10 (%1.1)	2 (%0.2)	25 (% 2.7)

Methicillin resistance was 26.3% in *S. aureus*, while it was 69.6% in CNS. ESBL (+) positivity was 41.7% among the agents in the Enterobacteriaceae family; In terms of organisms, it was found as 59.7% in *E. coli*, 44.2% in *Klebsiella* spp. 14.3% in Proteus spp. and 16.7% in *Enterobacter* spp. Antifungal susceptibility tests were not performed on fungi. 390 (41.9%) of the wound cultures with reproduction outpatient clinic patients, 445 (47.9%) are service patients and 95 (10.2%) intensive care patients. When the distribution of reproductive specimens by clinics was examined, the orthopedics polyclinic had the largest share with 11.3%. By grouping microorganisms, antibiotic sensitivities are shown in Table II, III and IV.).

Table 2. Antimicrobial resistance rate in Gram-positive bacteria

Microorganism	**p**	**amp**	**fox**	**van**	**tec**	**lzd**	**gn**	**ak**	**cıp**	**hlgn**	**f**	**sxt**
Enterococcus spp.	-	18,9	-	0	0	0	-	-	60	15	8,3	-
CNS	90,4	60	69,6	0	0	0	31,1	25	57,3	-	50	44,4
Stafhyilococcus aureus	90,2	80	26,3	0	0	0	4,4	0	16,8	-	1,4	33,3
Streptococcus spp.	8,3	5,9	-	0	0	0	-	-	8,3	-	-	0

P: Penicillin, AMP: Ampicillin, FOX: Cefoxitin, VAN: Vancomycin, TEC: Teicoplanin, LZD: Linezolid, GN: Gentamycin, AK: Amikacin, CIP: Ciprofloxacin, HLGN: High Level Gentamicin, F: Nitrofurantoin, SXT: Trimethoprim/sulfamethoxazole

Table 3. Antimicrobial resistance rate in Gram-negative bacteria

Microorganism	**amp**	**amc**	**pip**	**tzp**	**caz**	**cro**	**fep**	**atm**	**mem**	**ıpm**	**fox**	**gn**	**ak**	**cıp**	**f**	**sxt**
E. coli	83,2	40,2	72,5	22,4	39,2	59,7	36,8	53,3	0,8	0,8	3,6	27,9	2,4	41,2	8,8	53,8
Klebsiella spp.	100	50	100	16,7	36,4	42,6	15,4	44,2	0	0	33,3	25,4	0	31,1	25	47,9
Proteus spp.	78,9	42,5	16,7	0	5,7	14,3	0	6,5	0	5,6	-	10,5	0	12,8	100	48,7
Enterobacter spp.	100	100	23,1	14,3	16,7	4,5	0	10,5	0	0	100	0	0	4	33,3	60

AMP: Ampicillin, AMC: Amoxicillin / clavulanic acid, PIP: Piperacillin, TZP: Piperacillin / tazobactam,CAZ: Ceftazidime, CRO: Ceftriaxone, FEP: Cefepime, ATM: Aztreonam, MEM: Meropenem, IPM: Imipenem, FOX :Cefoxitin, GN: Gentamicin, AK: Amikacin, CIP: Ciprofloxacin F: Nitrofurantoin, SXT: Trimethoprim / sulfamethoxazole

Table 4. Resistance rate in Gram-negative non-fermentative bacteria

Microorganism	pip	tzp	caz	fep	ıpm	mem	gn	ak	cıp	sxt	tg
P.aeruginosae	26,7	13,9	13	12,1	17,3	19,8	7,1	3,3	14,7	-	-
A. baumannii	97,2	92,3	88,9	92,3	87,2	86,5	65,9	65,9	88,9	80,5	7,3

PIP: Piperacillin, TZP: Piperacillin / tazobactam, CAZ: Ceftazidime, FEP: Cefepime, IPM: Imipenem, MEM: Meropenem, GN: Gentamicin, AK: Amikacin, CIP: Ciprofloxacin, SXT: Trimetoprim / sulphametoxazole, TG: Tigecycline

Discussion

Correct determination of microorganisms in wound infections and accurate reporting of theirantibiograms are the key points in both reducing the duration of hospital stay and health costs (Dogan et al., 2010).

Misuse of antimicrobials can cause significant side effects and lead to the development and spread of antimicrobial resistance (Wong et al., 2015). Considering the fact that microorganisms can be transmitted from own flora or the environment, paying attention to the personal hygiene and healthcare personnel will help reduce the infection rates (Copeland-Halperin et al., 2016). The importance of this is that wound-site infections tend to be polymicrobial (Espejo et al., 2018).

Isolates in wound site cultures vary in studies depending on region. In our study, Gram-negative bacteria isolation rate was 52.1%, Gram positive 46.8%. In a similar study conducted in İzmir, 21.8% of the isolates were Gram positive bacteria and 78.2% were Gram negative bacteria (Yurtsever et al., 2009). In another study conducted in Duzce, it was reported that 46.4% of the microorganisms isolated were Gram positive bacteria, 53% Gram negative bacteria and 0.6% were fungi (Candida albicans) (Avcioglu et al., 2019). In another study by Turhanoglu et al. (2018) 52.5% of the isolates were Gram positive bacteria, 42.8% Gram negative bacteria and 4.61% fungal agents. Similarly, in a study conducted in Erzincan city, the rates were found to be 67.6% Gram positive, 32.4% Gram negative bacteria (Gundem et al., 2012).

When microorganisms isolated in wound culture are examined, while Avcioglu et al. determined S. aureus as the most common 21%, CNS as the second most frequent 16%, *E. coli* as the third 15%; Gundem et al. *S. aureus* 32.4%, CNS 25.3%, *E. coli* 11.3%, *Klebsiella* spp. 9.9% *Streptococcus* spp. 9.9%, *P. aeruginosa* 7% and *Acinetobacter* spp. 4.2% (Gundem et al., 2012; Avcioglu et al., 2019). In their retrospective study spanning study six years, found CNS 58.5%, *S. aureus* 41.4%, *Pseudomonas* spp. 18.2%, *E. coli* 13.1%, *Klebsiella* spp. 5.48%, Enterobacter cloacae complex 4.9% and *Acinetobacter* spp. 4.3%. *E. coli* and *S. aureus* are the most frequently isolated organisms from wound infections in the study of Davarci et al. (2018). A few wound infection reports from different parts of the world have shown that *S. aureus* and *E. coli* are the most common agents (Bhatt et. al., 2006 and Mulu et al., 2012). Schnuriger et al. (2010) reported *E. coli* especially in wound infections that develop after surgery. In our study, the most frequently isolated agent was *S. aureus* with a rate of 23.5%, followed by *E. coli* with a rate of 14.1%, P. aeruginosa with a rate of 12.8%, CNS with a rate of 12.5%, and *A. baumannii* with a rate of 8.6%.

In studies examining the distribution of species, S. aureus and CNS draw attention in terms of rates and have a large share in hospital infections especially in the presence of methicillin resistance (Cirit et al., 2014). In studies investigating methicillin resistance in *S.aureus* and CNS in wound cultures, methicillin resistance was found as follows: Dogan et al. 18.3%, 54.5%; Avcioglu et al. 16.7%, 58.8%, Gundem et al. 21.8%, 33.3%; Turhanoglu et al. 35.8%, 71,1%. In our study, while 26.3% methicillin resistance was detected in *S. aureus* and 69.6% in CNS, no glycopeptide resistance was found in *S. aureus* isolate as in many previous studies (Dogan et al., 2010; Gundem et al., 2012; Turhanoglu et al., 2018; Avcioglu et al., 2019). Ozturk et al. (2020) also did not find glycopeptide resistance in their study. In our study, resistance to antibiotics such as Linezolid, Vancomycin and Teicoplanin was not observed in Gram positive bacteria.

The fact that the isolated agents are strains producing ESBL (Expanded Spectrum Beta-Lactamase) causes limitations in antibiotics to be used for treatment, resulting in serious economic losses due to increased mortality and high costs (Cirit et al., 2014). Cirit et. al. (2014) found ESBL positivity in *E. coli* and *Klebsiella pneumoniae* strains, respectively, 55% and 39% and Turhanoglu et al. (2018). Found 63.3% and 72.2% for the same agents. In this study, ESBL positivity was 41.7% for the Enterobacteriaceae family and 59.7% in *E. coli*, 44.2% in *Klebsiella* spp. 14.3% in *Proteus* spp. and *Enterobacter* spp. 16.7%. Davarci et al. (2018) found that colistin is the most effective antimicrobial against Gram negative in their study. In addition, they found that 86.9% of *E. coli* strains were resistant to

ampicillin, 60.7% to ceftriaxone, 60% to cefepime, 54.1% to trimethoprim/ sulfamethoxazole and 0.6% to imipenem. Bessa et al. (2015) found ampicillin resistance 94.1%, ceftazidime resistance 5.9%, cefepime resistance 11.8%, ciprofloxacin resistance 52.9% in *E. coli* strains. They also reported that all strains were susceptible to meropenem and ertapenem. In our study, ampicillin resistance was 83.2%, ceftazidime resistance was 39.2%, ciprofloxacin resistance was 41.2%, and carbapenem resistance was 0.8% in *E. coli* strains. Fosfomycin/trometamol resistance was found around 3%, making it one of the antimicrobials with the least resistance. Our results are like other studies.

In a worldwide study piperacillin/tazobactam resistance was 52.2%, ciprofloxacin resistance 45.6%, meropenem resistance 30.4%, and ceftazidime resistance 50% in Pseudomonas spp. strains (Bessa et al, 2015). In our study, the resistance in *P. aerigosae* was determined as 13.9% for piperacillin/tazobactam, 14.7% for ciprofloxacin, 19.8% for meropenem, 13% for ceftazidime. The resistance profile of *A. baumannii* strains was determined to be higher. Piperacillin and piperacillin/tazobactam resistance is over 90%, carbapenem resistance is over 80%. Tigecycline resistance was found to be 7.3%.

Many studies found that surgical clinics constitute the largest group in the distribution of cultures with reproduction according to clinics (Yurtsever et al., 2009; Dogan et al., 2010; Altan et al., 2017). Similarly, in our study, it was observed that surgical clinics constituted the largest group, especially the orthopedic clinic.

Conclusion

In conclusion, in our study, it was determined that the clinics that wound infection is most common are surgical clinics, especially orthopedics clinics, and *S. aureus* was the most frequently isolated from wound cultures. The fact that surgical clinics are the most common units may be an indicator of post-traumatic development. At the same time, since the area where the sample is taken is a region with flora, it is important that both the patient and the person taking the sample pay attention to the hygiene rules in defining the correct factor. It is very important to determine infectious agents and susceptibilities through regular surveillance studies conducted at regular intervals, and to contribute to the rational use of antibiotics with the information obtained

The data determine the resistance rates and will contribute both to infection control and management strategies which will be carried out in our institution and also to national and international epidemiological data.

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RESEARCH ARTICLE

The Effect of Perforation Size and Site on Graft Success and Hearing in Cartilage Tympanoplasty with Mastoidectomy

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Abstract

Objective: Chronic otitis media (COM) treatment aims to obtain a dry middle ear mucosa as much as possible with medical treatment and to closure the perforation in the tympanic membrane with the help of various graft materials after the eradication of the disease. In the presence of perforation, the surface area of the tympanic membrane is decreases, which causes a decrease in the sound pressure in the middle ear and adversely affect hearing. At present, there is no globally accepted standardization of factors affecting anatomical success of the graft and hearing outcomes. In this study, the effect of perforation size and site in the tympanic membrane on anatomic success and hearing was investigated in cases where autogenic composite tragal cartilage graft material was used.

Methods: The patients were classified in groups with respect to the perforation site (central or marginal) and size (large if the perforation comprised more than 50% of the membrane area, and small if it comprised less) in the tympanic membrane. Anatomical success and preoperative–postoperative mean air bone gap pure tone average (ABG PTA) values of the graft were separately calculated for each group, and the ratios were compared.

Results: In 69 patients who underwent Type 1 tympanoplasty with mastoidectomy, 48 tympanic membrane perforations were central, 21 were marginal, 46 were small, and 23 were large. Graft anatomic success rates were 91.7% in the central group, 66.7% in the marginal group, 89.1% in the small group, and 73.9% in the large group. The anatomical success of the central group was found to be significantly higher than that of the marginal group. No difference was found between the small and large groups. When the effect on hearing was calculated, the postoperative hearing levels were significantly better in the central group.

Conclusion: Perforation size had no effect on the anatomical success and hearing level of the graft, while the perforation site affected both the anatomical success of the graft and the hearing level.

Key words: Tympanoplasty, cartilage, hearing, tympanic membrane perforation, mastoidectomy.

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Introduction

Chronic otitis media (COM) is an important clinical condition characterized by inflamation of the middle ear and mastoid air cells, manifested by tympanic membrane perforation, recurrent otorrhea, and hearing loss. In the presence of perforation in the tympanic membrane, the membrane surface area decreases; this causes a decrease in the sound pressure passing to the middle ear, thus adversely affecting hearing (Jalali et al., 2017). If active infection is found in the middle ear and mastoid cells, it should first be contained with medical treatment, and then, after obtaining as dry middle ear mucosa as possible, the perforation should be closed with the help of various graft materials (Kamath et al., 2013).

Type 1 tympanoplasty is the closure of the perforation in the tympanic membrane using autogenous graft materials in cases with intact and mobile ossicular chains. The cause, size, and site of the perforation, the experience of the surgeon, and the applied surgical method can affect the success of autografts to varying degrees (Westerberg et al., 2011).

In this study, the effect of perforation size and site in the tympanic membrane on anatomic success and hearing was investigated in cases where autogenic composite tragal cartilage graft material was used.

Methods

A total of 69 patients (both male and female) over the age of 18 who underwent type 1 tympanoplasty with mastoidectomy using a composite graft prepared from autogenous tragal cartilage to repair the perforation in the tympanic membrane in the Department of Otorhinolaryngology (ENT) of a Tertiary Training and Research Hospital between January 2015 and December 2018 were retrospectively evaluated. Compliance of the study with the principles of the Helsinki Declaration was approved by the local ethics committee (Ethics Committee Approval dated July 25, 2019, numbered E-19-025) and informed consent was obtained from all patients before the surgery. Anamnesis, microscopic examination, and high-resolution computed tomography (HRCT) findings were reviewed. The patients were divided into groups based on whether the perforation in the tympanic membrane was in the central or posterior-dominated marginal location and whether the perforation was large, covering more than 50% of the membrane area, or small, covering less than 50% membrane area (Westerberg et al., 2011). Patients with other accompanying inner ear–middle ear pathologies, such as cholesteatoma, glomus tympanicum, traumatic–nontraumatic ossicular chain disorders, anatomical malformation, and congenital anomaly, patients with tympanosclerosis and adhesive otitis, patients who were operated for revision purposes, and patients who did not undergo mastoidectomy were excluded from the study.

Pure-tone speech audiometry measurements were performed at the preoperative and postoperative 12th month. Air conduction (AC) threshold was measured at frequencies of 250, 500, 1000, 2000, 4000, and 6000 Hz, and bone conduction (BC) threshold was measured at frequencies of 500, 1000, 2000, and 4000 Hz. Pure-tone averages (PTAs) were then determined based on the threshold values at 500, 1000, 2000 and 4000 Hz, and air bone gap (ABG) PTA values were calculated. For audiometric tests, AC 40 clinical audiometers (Interacuostic, Denmark) were used. Temporal bone HRCT was performed on all patients during the preoperative period. Following a scan with 0.5-mm axial and 1-mm coronal cross-sectional range using an Alexion multislice 16 CT scanner (Toshiba, Otawara City, Tochigi, Japan), 0.3-mm axial reconstruction was performed.

All operations were performed under general anesthesia, using a surgical microscope (Moller-Wedel Optical; Hamburg, Germany), under the supervision of surgeons with otologic surgical experience of at least 10 years, and using a retroauricular approach. The composite cartilage graft, which was prepared by elevating the unilateral perichondrium from the tragal cartilage without thinning, was placed with the underlay technique, with the perichondrum extended to the inferior wall of the external auditory canal. At postoperative 1st, 3rd, 6th, and 12th months, whether the tragal cartilage graft material was intact or perforated was evaluated with otoscopic and microscopic examinations. Anatomical success at the 12th month and preoperative–postoperative ABG PTA values were calculated for each group and the rates were compared among themselves.

Statistical analysis

Shapiro Wilk test was used to evaluate the distribution of data. Categorical data were expressed as percentage, and continuous data were expressed as mean and standard deviation. Categorical data were evaluated using the Chi-square test or Fisher's exact test. Differences between two independent groups were analyzed using the unpaired t-test or the Mann–Whitney U test. $P < 0.05$ was considered statistically significant. SPSS statistics software (SPSS for Windows version 21.0; SPSS Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

In the study, 37 (53.6%) of the 69 patients were male and 32 (46.4%) were female, and the mean age of the patients was 34.0 ± 12.6 years (range: 18–59).

Furthermore, 48 (69.6%) of the perforations in the tympanic membrane were central, 21 (30.4%) were marginal with posterior localization, 46 (66.7%) were small, and 23 (33.3%) were large. Gender and age distributions of all the groups were similar.

At the end of one year, the graft was intact and at its normal position (anatomical success) in 44 (91.7%) of the 48 patients in the central perforation group and in 14 (66.7%) of the 21 patients in the marginal perforation group. When preoperative–postoperative ABG PTA values and anatomic success rates were compared, we found that patients with central perforation had significantly better preoperative ($p = 0.019$) and postoperative hearing ($p < 0.001$) as well as anatomical success ($p = 0.027$) (Table 1).

Anatomical success was achieved in 41 (89.1%) of the 46 patients in the small perforation group and in 17 (73.9%) of the 23 patients in the large perforation group. Similarly, when preoperative–postoperative ABG PTA values ($p = 0.132$, $p = 0.115$) and anatomical success rates ($p = 0.161$) were compared, no significant difference was found (Table 2).

Table 1: Findings according to tympanic membrane perforation site

		Central Perforation (N = 48)	Marginal Perforation (N = 21)	p value
Age (years)		33.6 ± 11.7	34.9 ± 14.7	0.839
Gender	Male	25 (52.1%)	12 (57.1%)	0.698
	Female	23 (47.9%)	9 (42.9%)	
Graft	Successful	44 (91.7%)	14 (66.7%)	**0.027**
	Unsuccessful	4 (8.3%)	7 (33.3%)	
ABG PTA[1] (dB)		23.7 ± 7.6	29.6 ± 10.7	**0.019**
ABG PTA[2] (dB)		10.1 ± 4.2	20.2 ± 9.1	**<0.001**

The values indicate means and standard deviations, N: Number of ears, dB: Decibel
PTA: Pure Tone Average (500, 1000, 2000, and 4000 Hz), ABG: Air Bone Gap, ABG PTA[1]: Preoperative, ABG PTA[2]: Postoperative.

Table 2: Findings according to tympanic membrane perforation size

		Small Perforation (N = 46)	Large Perforation (N = 23)	p value
Age (years)		32.2 ± 12.0	37.6 ± 13.2	0.111
Gender	Male	26 (56.5%)	11 (47.8%)	0.732
	Female	20 (43.5%)	12 (52.2%)	
Graft	Successful	41 (89.1%)	17 (73.9%)	0.161
	Unsuccessful	5 (10.9%)	6 (26.1%)	
ABG PTA[1] (dB)		24.0 ± 8.9	27.5 ± 9.2	0.132
ABG PTA[2] (dB)		12.0 ± 6.7	15.6 ± 8.9	0.115

The values indicate means and standard deviations, N: Number of ears, dB: Decibel

Discussion

The objective of type 1 tympanoplasty is to repair the perforation in the tympanic membrane, prevent recurrent ear discharge, middle ear infections, and improve hearing loss. This operation can be performed with or without mastoidectomy, depending on the extent of the pathology in the middle ear and mastoid cells.

McGrew et al. evaluated the effectiveness of mastoidectomy on the repair of uncomplicated tympanic membrane perforations and found that persistent otological disease and the need for a secondary surgical intervention in the same ear were almost 50% less common in the group that underwent tympanoplasty in combination with mastoidectomy. In addition, even if there is no evidence of active disease, they recommended that tympanoplasty and mastoidectomy should be performed together during the repair of simple perforations and reported that their hearing results were also comparable (McGrew et al., 2004). In contrast, other studies have reported that tympanoplasty can be performed without mastoidectomy, and the anatomical success in the use of cartilage graft material is not affected by this

situation (Mishiro et al., 2001; Oz et al., 2018). We use both methods in our clinic; however, in the present study, patients who underwent tympanoplasty together with mastoidectomy were evaluated.

Temporal fascia, tragal–conchal cartilage, perichondrium, and adipose tissue can be used as autogenous graft material in perforation repair (Jalali et al., 2017). Cartilage and perichondrium are mesenchymal originated formations. The cartilage has various advantages, including being easy to manipulate and maintaining its vitality for a long time. Using a perichondrium-supported graft (composite graft) as the graft material makes an important contribution to epithelialization in the tympanic membrane in the postoperative period (Levinson 1987, Milewski 1993). Zhang et al. compared three different autogenous graft materials in a patient group comprising 75 small perforations and 42 large perforations and found that graft success was the highest in the group in which tragal cartilage–perichondrium composite grafts were used. Furthermore, they stated that the long-term benefits of this graft material, especially in the large perforation group, were better in terms of both hearing and tympanic membrane morphology (Zhang et al., 2011). Gamra et al. (2008) evaluated the anatomical and audiological results of type 1 cartilage tympanoplasty and stated that they achieved functional results similar to the temporal fascia. Moreover, they recommended the use of cartilage grafts as the first choice in tympanoplasty operations. In our clinic, in the last 5 years, cartilage graft materials are being used with an increasing frequency, especially in cases undergoing simultaneous mastoidectomy.

Karela et al. stated that both perforation site and size had no significant effect on graft success (Karela et al., 2008). In a different study reporting the results of type 1 tympanoplasty, graft success was 87.2% in cases with central perforation, 88.9% in cases with marginal perforation, 75.0% in the subtotal perforated group, and 50.0% in the total perforated group; in addition, it was reported that perforation site and size had no effect on anatomical success (Yilmaz et al., 2009). In the study of Westerberg et al., these rates were 98.5% in the central perforation group, 94.1% in the marginal perforation group, 92.0% in the small perforation (<25% perforation) group, 96.2% in the medium perforation group (25%–50% perforation), and 97.9% in the large perforation group (>50% perforation), and they concluded that neither the site nor the size of the perforation had a significant effect on the success of the operation (Westerberg et al., 2011). A different study investigating the correlation of anatomical and functional results with prognostic factors in tragal cartilage tympanoplasty reported that in cases where the perforation size was more than 50% of the tympanic membrane area, the graft anatomic success rate was significantly lower (Oz et al., 2018). In this study, perforation size had no effect on graft success, and marginal perforation localization significantly reduced the success rate.

Alsarhan et al. (2016) investigated the relationship between the degree of hearing loss and perforation size and site by forming groups of small, moderate, and large perforations and dividing perforation sites into anteroinferior, anterosuperior, posteroinferior, and posterosuperior quadrants. They stated that hearing worsened as the perforation size increased and that hearing was worse in perforations located in the posteroinferior quadrant compared to those located in the other quadrants. When the preoperative ABG PTA values of our cases were reviewed, we found that there was no relationship between perforation size and hearing, and hearing was worse in the marginal perforation group with predominantly posterior quadrant localization.

In another study where the effects of a successful operation, the size and site of the perforation, and other patient criteria on mean AC (AC PTA) and ABG PTA parameters were investigated, both perforation size and site had an effect on postoperative hearing gain, with the highest gain in subtotal perforated and big central perforated groups (Dawood, 2017). Wasson et al. reported that the postoperative mean airway hearing gain was positively correlated with preoperative perforation size (Wasson et al., 2009). A different study stated that hearing was worse in patients with large perforation before the operation, and the level of recovery in these cases following the operation (hearing gain) was better than the hearing gain of patients with small perforation (Kumar, 2015). Contrary to these studies, Rasha and Ahmed (2015) reported that the postoperative hearing gain of patients with small perforations was better than that of patients with a large preoperative perforation size and poor hearing. In the present study, preoperative and postoperative hearing levels of patients with central perforation were better than those of patients with marginal perforation. Contrary to our expectations, hearing levels in both the preoperative and postoperative periods did not differ significantly difference in the large perforation group, where the perforation covered more than 50% of the tympanic membrane.

Conclusion

In conclusion, we determined that perforation size had no effect on graft anatomic success and hearing level, while perforation site affected both. Following the calculation of surface area measurements of perforations in the tympanic membrane by endovision imaging systems, the results of the present study should be supported with larger case studies.

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RESEARCH ARTICLE

Gallbladder Polyp; When Surgical Treatment is Necessary?

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Abstract

Objective: Gallbladder polyps (GBP) are the lesions that are originated from the mucosa of the gallbladder and reach out to the lumen. The biological behaviours of GBP have still been uncertain, their follow-ups and treatments are controversial as they carry the risk of malignancy. Our aim is to present the results of patients who have been operated on with the diagnosis of GBP in this study.

Methods: This retrospective study was conducted at Department of General Surgery, Giresun University. Patients who underwent surgery for GBP were included between January 2015 and December 2019. The age, gender, symptoms, ultrasonography findings (numbers polyps, types and presence of polyp and stone), surgery method (open and laparoscopic), and histopathological examination results were analysed.

Results: A total of 1486 cholecystectomies, including 1388 laparoscopic cholecystectomy and 98 open cholecystectomies, were performed. One-hundred thirty-two (8.8%) of these patients were operated with the diagnosis of the GBP. One-hundred thirty of them were operated with the laparoscopic method and two of them with the open surgical method. Overall, fourty two (31.8%) of the patients were male and 90 (68.2%) were female. The average age was 48.7. One-hundred one (76.5%) patients were clinically symptomatic. Gallstones were analysed in 35 (26.5%) patients. Multipl polyps were detected in 34 (25.8%) patients. There were no polyps determined in 47 (35.6%) patients the histopathological examination. The most common polyp type was cholesterol polyps (%64.8). Cancer histopathology was not found in any patient.

Conclusion: It is difficult to differentiate premalign and/or malignant lesions of the gallbladder from benign lesions. Therefore, we believe that surgical treatment is the correct approach for all GBP, which are symptomatic, accompanying stones, and that have a risk of malignancy ultrasonographically.

Key words: Gallbladder, polyp, cholecystectomy

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Introduction

Gallbladder polyps (GBP) are defined as lesions that are mostly benign nature and originated from gallbladder mucosa reach out to the lumen. They are found in 0.3-12% of healthy individuals (Chaet al., 2011). The true prevalence is unknown yet. They usually diagnosed as a result of radiologic examination performed for other reason and appear without any symptom. GBP are divided into two categories as pseudopolyp and true polyps. Pseudopolyps consist of cholesterol polyps/cholesterolosis, adenomyoma, inflammatory

polyps, and hyperplastic polyps. All of them are benign lesions. True polyps are grouped as benign (adenoma), premalignant (dysplastic polyps), and malignant (adenocarcinoma) (Zielinski et al., 2009). The abdominal imaging techniques has caused a dramatic increase in the diagnosis of a polyp (Lin et al., 2008, Cairns et al., 2012, Marangoni et al., 2012, Xu et al., 2012). Adenomas constitute 10% of SKPs and are found in approximately 1% of cholecystectomy specimens (Sun et al., 2019). GBP is detected in 3-7% of people who undergo ultrasonography (US) and at the rate of 2-12% in cholecystectomy specimens (Yuksel et al. 2016). The disease is observed more commonly in the age of forties and in women (Dinc et al., 2013). GBP mostly consist of cholesterol polyps. Even though it is considered to have no potential for malignancy, the US images of polyps are like the early stages of gallbladder cancer. The risk of malignancy development increases especially in the presence of polyps with adenomatous features (Dinc et al., 2013) over 10 mm, and three or more polyps regardless of the diameter. It has been thought that gallbladder cancer occurs due to the malignant transformation of adenoma (adenoma- adenocarcinoma sequence) based on the diameter of polyp (Yuksel et al. 2016). Hence, the diagnosis and treatment of the polyp in the gallbladder become crucial in a way of detecting cancer in an early stage. In this study, the data of the patients, who were operated with the diagnosis of GBP were examined and the results were aimed to be discussed in the light of the literature.

Methods

The data of patients who were operated with the diagnosis of GBP between January 2015 and November 2019 at the Department of General Surgery of the Ministry of Health of Giresun University Prof. Dr. A. İlhan Özdemir Education and Research Hospital were analyzed through the hospital's electronic patient file archive. Patients whose preoperative examinations were performed in another hospital were not included in the study. All surgeries, radiological and pathological examinations were performed by specialist physicians in our hospital. The age, gender, presence of symptoms, US findings (the number of polyps, the dimension of the polyp, the presence of stone), surgery method (open or laparoscopic) the results of histopathological examination of patients were included to study after obtaining the necessary permissions. The diagnosis of polyp at US was established according to the criterias of projection of lesion to the lumen, inability to form an acoustic shadow, and inability to be replaced. According to histopathological findings, cholesterol polyps/cholesterolosis, hyperplastic polyps and polyps with adenomyomatosis were evaluated as non-neoplastic polyps, adenomas benign neoplastic polyps, and adenocarcinomas were examined as neoplastic polyps. Histopathological results are assessed by pathologist in hospital.

Statistical analysis

Statistical analysis was performed using the SPSS 23.0 software (IBM Corporation, Armonk, NY, USA). For the data analysis, SPSS package program version 23.0 was used. The descriptive statistics were given to define and to explore properties of sample units in the research. The agreement among pathology and US decisions for determining polyp stone has been measure by using Cross tables and kappa statistics. Moreover, the significances of the Kappa statistics were tested by using statistical hypothesis test. P-value <0.05 was considered as statistically significant.

Results

A total of 1486 cholecystectomies, including 1388 laparoscopic cholecystectomy and 98 open cholecystectomy, were performed. One-hundred thirty two (8.8%) of these patients were operated with the diagnosis of GBP. The cross-tabulation for these patients is given in Table 1. One-hundred thirty of them were operated with the laparoscopic method and two of them with the open surgical method. Overall, forty two (31.8%) of the patients were male and 90 (68.2%) of them were female. The average age was 48±13 years. The polyp-stone coexistence was determined for 18.2% of patients in both US and histopathologically examination. Both US and pathology have found that there was no polyp-stone coexistence for 56.1% of patients. The results of US and histopathology were coherent for 74.3% of patients in total. The kappa coefficient obtained for the compliance of US and histopathology in determining the polyp-stone coexistence was 0,447 and it shows moderate concordance. It was also concluded that this coefficient indicates a non-ignorable statistically significant compliance according to approximate significance value (p value) (Table-1).

Table-1. US Polyp-Stone, Pathology Polyp Stone Cross-tabulation

			Pathology Polyp Stone		
			Yes	No	Total
US Polyp-Stone	Yes	n	24	11	35
		% of Total	18.2	8.3	26.5
	No	n	12	74	86
		% of Total	9.1	56.1	65.2
	Undefined	n	4	7	11
		% of Total	3.0	5.3	8.3
Total		n	40	92	132
		% of Total	30.3	69.7	100.0
Kappa coefficient: 0.447		P=0.000			

The relationship between the number of polyps determined according to US and the number of polyps determined according to histopathology was investigated with the Kappa coefficient by creating a cross-tabulation (Table 2). While US was determining a single polyp for 23.5% of patients and multiple polyps for 12.1% of the patients, there is no polyp established as a result of histopathology. There whilst US was detecting a single polyp for 16.7% of patients and multiple polyps for 13.6% patients, the single polyp was determined as a result of the pathology of the same patients. While US was determining a single polyp in 8.3% of patients and multiple polyps in 25.8% of patients, the multiple polyps were identified in these patients in consequence of pathology. US was detecting a single polyp in 35.6% of patients whereas there is no polyp identified in the pathology results of the same patients. Kappa coefficient determining the compliance in the number of polyps between US and histopathology was obtained as 0.15 and showed a weak but statistically significant concordance since $p<0.01$ (Table-2).

Table-2. Numbers of polyp US, Number of polyp Pathology Cross-tabulation

			Number of Polyp Pathology			
			No	Single	Multiple	Total
Numbers of polyp US	Single	n	31	22	11	64
		% of Total	23.5	16.7	8.3	48,5
	Multiple	n	16	18	34	68
		% of Total	12.1	13.6	25.8	51,5
Total		n	47	40	45	132
		% of Total	35,6	30.3	34.1	100.0
Kappa coefficient: 0.150		p=0.004				

Table-3. Symptom, US Polyp-Stone Cross-tabulation

			US Polyp-Stone			
			Yes	No	Undefined	Total
Symptom	Yes	n	25	66	10	101
		% of Total	18.9	50.0	7.6	76.5
	No	nt	10	20	1	31
		% of Total	7.6	15.2	0.8	23.5
Total		nt	35	86	11	132
		% of Total	26.5	65.2	8.3	100.0
Kappa coefficient: -0.023		p=0.643				

One-hundred one (76.5%) patients were clinically symptomatic. Gallstones were found in 35 (26.5%) patients. Multiple polyps were present in 68 (51.5%) patients (on pathological examination) and 34 (25.8%) patients (on US examination). The Kappa coefficient obtained through the cross-tabulation (Table-3) which was created to identify the effect of presence or absence of symptoms for US to determine the polyp-stone coexistence shows that there is no statistically significant relation (Table-3).

Cholesterol polyps were the most frequently detected polyp types in this study. When all the operated patients were evaluated, this rate was found to be 64.4%. Pseudopiloric metaplasia in company with polyp was detected in one patient, xanthogranulomatous cholecystitis without polyp in one patient, and adenomyosis was determined in three patients. Neoplastic polyp and invasive cancer were not identified in any patients.

Discussion

The biological behaviors of GBP have still been uncertain (Yildirim et al., 2005). There are studies that report the gender distribution is equal or more frequent in females. The rate of incidence is after the age of forties (Yildirim et al., 2005). The average age of the patients in our study was 48±13 years and 68.2% of all patients were female.

Even though many of the polyps consist of benign cholesterol polyps, the risk of malignancy is still the biggest problem. Hence, the diagnosis, follow-up and treatment are crucial (Dincet al., 2013). It has been reported that the rate of incidental diagnosis of GBP is 7-20% and it is mostly asymptomatic. The most common symptom is right upper quadrant pain in symptomatic cases. In addition, hemobilia and obstructive jaundice have been indicated as symptoms (Yildirim et al., 2005). US examination is the most preferable tool in the diagnosis of GBP. In US, polyps are evaluated as lesions that are hyperechoic, are without posterior shadows, and cannot displace by position. The sensitivity of US for the GBP has been reported as between 32% and 90% in the literature (Yuksel et al. 2016). However, the most important restrictive factors are; dependency of US to the person, not being standardized and the factors that belong to the patient (obesity, accompanying gallstones etc.) affect the correct diagnosis (Yuksel et al. 2016). Although the sensitivity of conventional US is not high in the benign and malign differentiation of cases with GBP, the morphological appearance of the polyp can provide insight. Considering the studies, it has been reported that the imaging methods, except US, such as computerized tomography and endoscopic retrograde cholangiopancreatography have lower values for the diagnosis of polyps than US and have higher costs. Therefore, the most frequently used US examination has still been today (Yuksel et al. 2016). In our study, all diagnosis was established via US. After the histopathological examination polyps were detected in rate of 64.4% in patients with polyps that were determined through US in our study.

In a study with 194 patients that was conducted by Sun et al., it has been indicated that US was the most suitable diagnostic method for the diagnosis of the polyp and using computerized tomography (CT) was recommended for suspicious lesions (Sun et al., 2004). In a study that was conducted by Lou et al., it has been stated that CT was a sensitive and reliable technique in order to show the polyps of the gallbladder and the lesions up to 1.5 mm in length easily (Lou et al., 2004). Moreover, techniques such as endoscopic US (EUS), contrast EUS, and magnetic resonance imaging (MRI) are recommended in polyps with high-risk factors in terms of neoplastic features (Sun et al. 2019). In our study, the median of polyp diameters determined according to US was found five and the median of polyp diameters established according to pathology was found three. Therefore, it is concluded that the diameters that were identified according to US were higher.

The essential topic in patients with a polyp in the gallbladder is that how the follow-up and the treatment procedure will take place. Hereby, we have the risk of polyp malignancy. It has been reported in the studies that are conducted, the GBP are malignant at the rate of 3-8% (Goetze et al., 2010). Establishing an early diagnosis becomes crucial when the poor prognosis of gallbladder cancers is considered. The segregation between benign and malign cannot be performed with any of the preoperative imaging techniques (Kwon et al., 2009). Folded gallbladder, mucosal residues or stones that are impacted to the wall may have a role in the false-positive rate in US examination. In our study, US was determining a polyp for 35.6% of the patients while any kind of polyp could not be identified as a result of histopathology for the same patients. We believe this circumstance has occurred due to the folded gallbladder, mucosal residues, stones impacted to the wall, missing the small polyps with thin stems with the gall flow during the pathological examination, and the person who performed US.

In a prospective study that was conducted by Shinkai et al., (1998) the diameter of lesion and echogenicity remained the same in 93% of the patients who were following-up due to the polyp in

gallbladder. Furthermore, in a study that was done by Csendes et al., (2001) polyp diameters were constant for 50% of the patients while there was an increase detected in the polyp diameters for 25% of them for six years follow-up periods of 98 patients. The adenomatous polyp was detected in one patient among the patients who had an increase in polyp diameters and the rest of them were reported as cholesterol polyps (Dincet al., 2013). In the present study, due to the increase in the diameters and numbers of the polyp, the operation was decided for five patients in one year of follow-up and all of those patients were reported as cholesterol polyps.

Cholesterol polyps are the most common type of GBP. Histologically, they are formed by histiocytes including cholesterols covered by single-row epithelium. Their etiologies are not completely known. Directly storing the serum cholesterols in the gallbladder, aggregation of free sterols from gall or the transformation after cholesterol synthesis of the liver are the defended mechanisms in cholesterolysisetiology (Yildirim et al., 2005). True neoplastic polyps, on the other hand, show a broad spectrum and malignancy is more common in patients older than 50, in lesions that are single and larger than 10 mm, with gallstones or show ultrasonographic rapid grow in a short period of time even the ones smaller than 10 mm. The prevalence of neoplastic polyps has been stated as 5-10% (Jones-Monahan et al., 2000). There were no neoplastic polyps detected in our study.

Atypia and dysplasia have been reported in various ratios in adenomas. The development of metaplasia in polyp has a higher rate especially in patients who have stones in the gallbladder. This rate has been stated as 48% particularly in adenomatosis polyps (Yildirim et al., 2005). Polyps including atypia and dysplasia have not been identified in our study.

The treatment algorithm of GBP has still been controversial. Shinkai et al. (1998) have recommended for cholesterol polyps which are above 10 mm to be operated with laparoscopic cholecystectomy which is a minimally invasive method. Csendes et al. (2001) have suggested to apply cholecystectomy for lesions with over 10 mm polyp dimension and to perform open cholecystectomy when the risk of malignancy is taken into consideration. Lee et al. (2004) have stated to perform frozen section examination and to treat with open cholecystectomy for polyps' cases with over 20 mm dimension. In our study, 98.5% of the patients were operated with laparoscopy and 1.5% of them with open cholecystectomy. The decision to open surgery arisen from previous abdominal surgery.

Some of the risk factors have been stated for the malign GBP in the literature. Polyp size over 10 mm, patients older than the age of 50, being symptomatic, solitary and sessile polyp, accompanying gallstones are the risk factors that were identified (Sarkut et al., 2013).

The relationship between the symptoms and risk of malignancy is not clear.However, according to some research, there is a connection between the symptoms and malignancy (Sun et al. 2019) whereas some of them could not find any relationship (Albores-Saavedraet al., 2012). The mechanism underlying the malign transformation is unclear and is required more molecular research (Sun et al. 2019). The neoplastic polyp was not determined in our study. Additionally, the communications between the polyp and presence and/or absence of symptoms and between polyp-stone coexistence could not be formed.

Cholecystectomy is accepted in symptomatic cases regardless of the size. The surgical method should also be applied in cases that are not symptomatic but above the age of 50, that the polyp size is above 10 mm, in sessile morphology, with accompanying gallstones since malignancy cannot be excluded in those cases. In other cases, six months follow-up with US is recommended. During this period, if an extension is detected in polyp sizes or symptoms are developed, surgical treatment becomes a current issue. If the polyp disappears in the US during follow-up, it is recommended to remove those cases from follow-up (Yildirim et al., 2005). Cholecystectomy should be taken into consideration in GBP that shows the intra-lesional bloodstream regardless of the size by virtue of high risk for neoplastic polyp (Sun et al. 2019). In our study, all of the patients had one or more of the risk factors mentioned above, and operation was decided for those patients.

Sugiyama et al. have reported that they detected adenoma or cancer at the rate of 14% in polyps with a size of 6-10 mm in their study (Goetze et al., 2010). Zielinski et al. have indicated that the risk of neoplasia increases in polyp size $\geq$ 6 mm and cholecystectomy should be applied to those patients (Zielinski et al., 2009).

Some limitations of our study should be accepted. Firstly, despite a great number of cases, it was a retrospective, single-center. Secondly, there were no patients in the adenoma-cancer group. Thirdly, US is a device-dependent examination and shows variability between doctors. Fourthly, some factors such as polyp's growth rate, body mass index, eating

habits, family history, and occupations could not be analyzed.

Conclusion

Consequently, it is difficult to diagnose premalignant and malignant lesions and to differentiate them from benign lesions during preoperative period. The underlying transformation mechanism requires more molecular studies. We have the opinion that surgical treatment is the right approach for all GBP that are symptomatic, with accompanying stones, that have the ultrasonographic risk of malignancy.

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RESEARCH ARTICLE

Correlations between Arteriograph-Derived Augmentation Index and Disease Activity in Acromegaly Patients.

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Abstract

Objective: The high prevalence of cardiovascular diseases in acromegaly patients attracted attention to the association between the growth hormone and cardiovascular system. New markers such as the augmentation index (AIx) and central aortic pressure (CAP) have recently been introduced to the clinical practice for a variety of diagnostic and monitoring purposes in predicting arterial stiffness and associated endothelial dysfunction. In this present study, we aimed to determine the condition of the vascular system using the non-invasive arterial stiffness marker; AIx measured using by the Arteriograph device and to evaluate the relationship between these markers and the disease activity in acromegaly patients.

Methods: This was a cross-sectional study. The study included 53 acromegaly patients and 20 individuals age and sex matched as controls. The arterial stiffness was evaluated to estimate the AIx and CAP with a low-frequency suprasystolic waveform analysis in the occluded brachial artery, performed by using a Cardio Scope II Arteriograph device, which was adapted from a standard sphygmomanometer.

Results: The mean augmentation index was statistically significantly different between the three groups, being 98% in the active acromegaly (AA) group, 92% in controlled acromegaly (CA) and 79.5% in the control group (p=0.001). In the acromegaly group, the results of the regression analysis indicated a strong correlation of the arterial stiffness parameters with HbA1c and the platelet counts, however, the levels of IGF-1 and GH were not correlated

Conclusion: It might be thought that AIx may have an important role in predicting the cardiovascular risk in acromegaly.

Key words: Augmentation index; disease activity; acromegaly; arterial stiffness;

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Introduction

Acromegaly is a syndrome characterised by the secretion of growth hormone (GH) and insulin-like growth factor (IGF-1) (Colao et al. 2001). The long-term exposure of tissues to excessive GH in acromegaly leads to increases in the cardiovascular disease-associated morbidity and mortality by two- to three-folds. The coronary heart disease and hypertension are the most important causes of increased mortality and morbidity in acromegaly patients (Bengtsson et al. 1988).

The development of vascular abnormalities has been demonstrated in acromegaly patients even in the absence of cardiovascular risk factors. Studies have shown that the abnormal GH secretion may be associated with an increased risk of atherosclerosis in acromegaly (Bengtsson et al. 1988). In the liver, the GH stimulates the production of IGF-1, which mediates the GH activity in the peripheral tissues (Sowers, 1997). GH and IGF-1 have significant effects on the cardiovascular system (Celermajer et al. 1992, Neunteufl et al. 2000). In acromegaly, GH assume its effects on the endothelium via the endothelial IGF-1 receptors directly or via the lipid metabolism indirectly (Tan et al. 1997). It affects the IGF-1's regulating function on the vascular tonus, attenuating the vascular contractility and triggering the endothelial dysfunction (Walsh et al. 1996).

Endothelial dysfunction and arterial stiffness in acromegaly patients have received a considerable attention in recent years (Smith et al. 2003). Several parameters have recently been introduced to assess arterial stiffness and have proven to be the independent predictors of untoward cardiovascular outcomes. (Nichols, 2005, Laurent et al. 2006) Pulse wave analysis has been used in most studies to investigate arterial stiffness in acromegaly. (Smith, et al. 2003; Sakai et al. 2008; Paisley et al. 2011). Augmentation index (AIx) is the amplification ratio of the central arterial waveform pressure attributed to the reflected pulse pressure. Central AIx has been reported to be closely associated with several risk factors for atherosclerosis and future cardiovascular events (London et al. 2001; Izzo, 2004; Weber, et al. 2004) and in these studies AIx had measured by using applanation tonometry. However, in Yaron et al. (2016) study, there were no significant differences in Alx between acromegaly and control subjects. AIx can be estimated from the brachial artery waveform as peripheral AIx and can provide information on arterial stiffness, as it is closely related to the central aortic AIx (Manisty and Hughes, 2013).

While arterial stiffness can be measured in many different ways, few studies have focused on arterial stiffness in acromegaly using peripheral arteries (Matsuda, Kawate et al. 2013). The aim of our study was to investigate the brachial artery AIx as an arterial stiffness parameter by using arteriograph device in a group of acromegaly patients with active acromegaly (AA) controlled acromegaly (CA) compared with control group. Also, we want to demonstrate the correlation between the endothelial dysfunction and the disease activity in acromegaly patients.

Methods

Study population

The study included acromegaly patients presented to the endocrinology outpatient clinic of the internal medicine department of Uludag University between May 2015 and August 2015. In order to prevent any interferences with the cardiovascular assessments, the patients were excluded from the study if they had a previously known structural heart disease (congenital/rheumatic heart valve disease, arrhythmia, or heart failure), coronary artery disease, a diagnosis of cancer, renal or hepatic failure, an acute or chronic infectious disease, a diagnosis of autoimmune disease or had a history of undergoing a major surgery or trauma in the recent 3 months.

It was planned to include acromegaly patients who were followed up in the endocrinology outpatient clinic. During the endocrinology outpatient clinic application, the patients were asked to be included in the study and were evaluated. After the preliminary evaluation, 21 patients were excluded from the study for the reasons stated above. A total of 53 patients were included in the study.

A control group comprised the individuals with diabetes or hypertension at ages between 20 and 80 years, in whom the diagnosis of acromegaly was excluded. The individuals in the control group were matched with those in the patient group in terms of age and gender.

Assessment of Disease Activity

The diagnosis of acromegaly was made with the presence of classical clinical features, higher serum IGF-1 levels by age, and GH concentrations of 1 µg/L (ng/ml) or higher after a 75-gram OGTT.

The patients with acromegaly were assigned to two groups as active acromegaly (AA) and controlled acromegaly (CA) according to the disease activity and the consensus criteria for cure of acromegaly (Melmed et al. 2018) The patients with GH levels reduced below 1 µg/L (ng/ml) and the patients achieving IGF-1 levels within the age-adjusted limits

were included in the cured acromegaly group. A total of 32 patients in the study were included in this group meeting the criteria for cure. In the active acromegaly group, a total of 21 patients, who did not meet the criteria for cure were included. Of these 21 patients, four were newly diagnosed acromegaly patients and 10 were the patients who did not meet the cure criteria despite the ongoing hormone suppressor therapy.

All patients were questioned about the duration of symptoms before clinical diagnosis, the treatments they received, any systemic involvement in association with acromegaly, and the co-morbid systemic diseases. The following independent risk factors for cardiovascular diseases were evaluated, including diabetes mellitus (DM), hypertension (HT), hyperlipidemia, obesity, and smoking.

The height (cm) and body weight (kg) of the patients were recorded and their body mass indices (BMI) kg/m2 were calculated. The results of the laboratory tests performed at the routine outpatient control visits were recorded including the fasting plasma glucose, total cholesterol, triglycerides, HDL, LDL, GH, IGF-1, HbA1c, and hemoglobin levels and the platelet and leukocyte counts.

Measurement of Arterial Stiffness

Patients who were included in the study at the time of the endocrinology outpatient clinic admission were evaluated. At the same time, cardiac evaluation was performed. Our aim was to measure the central SBP, DBP and brachial AIx as the primary output variables. The patients had a rest for 15 minutes, staying away from external stimuli after the control visit in the endocrinology outpatient clinic. In this study, arterial stiffness was assessed with the blood pressure (BP) and the central blood pressure in the brachial artery in a non-invasive manner using the Cardio Scope II device. After completing the pressure measurements with the specified device, the cuff was inflated to a level above the current systolic pressure (at least 35 mmHg). This way, occlusion of the brachial artery was accomplished, stopping the blood flow during the measurement according to the procedure protocol (only 8-20 seconds, with a mean of 8 seconds). In this very specific condition (stop-flow condition), a membrane develops in the brachial artery at the level of the upper margin of the inflated cuff, where the blood flow was stopped. When the central pressure changes and early (direct P1) and late (reflected backwards; P2) systolic and diastolic waves reach the site of occlusion, they became detectable like the pulsating blood beating the membrane. Like a transferring medium, the upper arm tissue transfers the small but sensible changes, caused by the pressure of the flowing fluid, to the cuff along the skin and the border of the cuff, allowing them being generalized. The high-resolution pressure sensors of the arteriography are capable of detecting these small and weak changes in the pressure. Two components of the measured pulse wave, the pulse wave from the heart and the reflection wave at the periphery, were analyzed. The data were processed with a specific software developed for this purpose and the central SBP, DBP, and AIx values were recorded.

Statistical analyses

It was calculated that at least 38 patients should be included in the study for AIx 90% in acromegaly patients with an alpha value of 0.05 and a strength of 80% in the power analysis program. The SPSS 22.0 statistical package program (SPSS Inc., Illinois, USA) was used to perform all data analyses. The Kolmogorov–Smirnov test was used to analyze the distribution pattern. Normally distributed numerical variables were presented as mean ± standard deviation, whereas the ones not normally distributed were presented as median and interquartile range. Categorical variables were presented as number and percent (%). Basal characteristics were classified according to predefined subgroups and the parametric variables of the three independent groups were evaluated using analysis of variance with/without Bonferroni. The categorical variables were evaluated using the appropriate Chi-square test. The Kruskal–Wallis H test with/without Bonferroni correction was used while examining the three groups in the analysis of variables that do not fit the normal distribution. The Spearman rank test was performed to define the correlation of disease activity and arterial stiffness. The relationship coefficient was expressed as "r" and the significance value was expressed as "p".

Results

Based on the previously defined disease activity criteria; 21 active acromegaly (AA) and 32 controlled cured acromegaly (CA) patients were included in the study. Table 1 presents the comparison of the patient and control groups in terms of their demographic and basic clinical features and in terms of the risk factors for cardiovascular diseases. There were no statistically significant differences in gender or age between the control group and the two patient groups. Body mass index was higher in both AA and CA groups compared to the control group when all acromegaly patients were compared to the control group and also when AA and CA groups were

individually compared to the control group (p = 0.001).

There were no significant differences in terms of treatment duration or the history of surgery or radiotherapy between the active acromegaly and cure acromegaly groups. The medication use was higher in the AA group compared to the CA group (p = 0.001). DM rate was statistically significantly higher in the AA group compared to the CA and control groups (p=0.001). HT was found to be at similar rates in the CA and AA groups; however, the rates of HT in these groups were higher compared to the control group. The rates of HL and smoking were similar in all three groups. Obesity was observed at similar rates in the CA and AA groups; but these rates were higher than that of the control group.

Table 2 lists the biochemical parameters compared between the groups. The levels of growth hormone, IGF-1, glucose, and HbA1c were significantly higher in the AA group compared to the CA and control groups (p = 0.001). The levels of HDL, LDL, and haemoglobin; and the WBC counts were not different among the groups. TG levels were higher in the control group (p = 0.001). The platelet count was higher in the AA and CA groups compared to the control group (p = 0.001).

Arterial stiffness parameters measured with the arteriograph devices were presented in Table 3. In our study, the arterial stiffness parameters including AIx, central SBP, central DBP; and SBP and DBP were significantly higher in the AA group compared to both CA and control groups (p = 0.001). The AIx, central SBP and DBP were significantly higher in the CA group compared to the control group (p = 0.001).

Correlation analysis of AIx are presented in Table 4. In acromegaly patients, there was a positive and strong correlation of AIx with the HbA1c levels and the platelet count [respectively (r:0.699, p<0.01) (r:0.796, p<0.01)]. The correlation analysis showed a positive and strong correlation of AIx with APG, HbA1c, and BMI in the control group [respectively (r: 0.535, p<0.01) (r: 0.660, p<0.01) (r:0.796, p<0.01)].

Table 1. Clinical characteristics of acromegaly patients and healthy control

	AA (n=21)	CA (n=32)	Control(n=20)
Age, years	45.5 ±14.2	48.7± 12.7	47.5± 10.3
Gender, f/m	9/12	13/17	9/11
BMI, kg/m^2	29,3±4.1†	29,4±4.5*	24,5±3.6
Surgery, n	20	31	-
Drug use, n			
Somatostatin analogs	11	12	-
Dopamine agonist	3	1	-
GH receptor ant.	2	1	-
TOTAL, n (%)	16(%76) ‡	14(%46)	-
Radiotherapy, n (%)	4/21	6/32	
Treatment duration	7.8 ± 5.0	7.4± 3.9	
DM, n (%)	8 (%38) †‡	8(%25)	5(%25)
HT, n (%)	11 (%53) †	16 (%51) *	5(%25)
HL, n (%)	4(%19)	6 (%20)	3 (%15)
Obezite, n (%)	7 (%33) †	11 (%34) *	1 (%5)
Sigara, n (%)	5 (%19)	7 (%21)	4 (%20)

AA: active acromegaly; CA: Controlled acromegaly, F: female; M: male; BMI: body mass index; GH; growth hormone; DM: diabetes mellitus; HL: hyperlipidemia; HT: hypertension;
* P < 0.01 for controls versus KA
†P < 0.01 for controls versus AA
‡P < 0.01 for KA versus AA

Table 2. Biochemical measurements in acromegaly and control groups

	AA (n=21)	CA (n=32)	Control(n=20)
GH, ng/ml	2.37(1.1-40.0)†‡	0.46(0.060.99)	0.51(0.431.63)
IGF-1, ng/ml	265(91-982) †‡	206(49-417)*	157(121-203)
Glucose, mg/dl	120.4±23.7†‡	103.2±40.5	99.6±8.7
HDL, mg/dl	43.0±10.7	42.5±9.5	43.9±6.7
LDL, mg/dl	115(63-272)	114(51-292)	112(79-192)
TG, mg/dl	136(64-441) †‡	115(26-272) *	187(103-303)
Hemoglobin, mg/dl	13.3±1.44	13.6±1.3	13.5±1.1
WBC, 10^3/ul	7757±1400	8128±1209	7705±1059
PLT, 10^3/ul	286900±64100†	297000±48200*	235000±48200
HBA1c, mg/dl	6.1(5.1-12.5) †‡	5.6(5.0-9.5)	5.5(5.0-9.6)

AA: active acromegaly; CA: Controlled acromegaly, GH: growth hormone; IGF-1: insülin like growht factor-1; HDL: high density lipoprotein; LDL: low density lipoprotein; TG: triglyceride; WBC: White blood cell; PLT: platelet; HBA1c: hemoglobin A1c;

* P < 0.01 for controls versus KA
† P < 0.01 for controls versus AA
‡P < 0.01 for KA versus AA

Table 3. Arterial stiffness parameters acromegaly and control groups

	AA (n=21)	CA (n=32)	Control(n=20)
AIx, %	98(74-145) †‡	92(75-126)*	79.5(69-96)
SBP, mm/Hg	133.8±10.2†‡	129.9±9.5*	125.5±11.3
DBP, mm/Hg	84.4±8.2†‡	83.2±8.7*	77.3±10.7
Central SBP, mm/Hg	123.5±10.1†‡	119.6±9.2*	115.5±11.1
Central DBP, mm/Hg	88.5±9.5†‡	84.8±7.6*	78.5±10.8

AA: active acromegaly; CA: Controlled acromegaly; AIx: augmentation index; SBP: Systolic blood pressure; DKB: Diastolic blood pressure
* P < 0.01 for controls versus KA
†P < 0.01 for controls versus AA
‡P < 0.01 for KA versus AA

Tablo 4. Correlation analysis of Augmentation index

Parameters	Acromegaly (n=53)		Control (n=20)	
	r	p	r	p
GH	0.067	p>0.05	0.148	p>0.05
IGF-1	-0.331	p>0.05	0.074	p>0.05
Glucose	0.410	p>0.05	0.535	p<0.01
TG	-0.077	p>0.05	-0.066	p>0.05
PLT	0.796	p<0.01	-0.22	p>0.05
HBA1c	0.699	p<0.01	0.660	p<0.01
BMI	0.355	p>0.05	0.495	P<0.01

GH: growth hormone; IGF-1: insülin like growht factor-1; TG: triglyceride; PLT: platelet; HBA1c: hemoglobin A1c; BMI: body mass index

Discussion

Our study is the first, in which the augmentation index measured with the cardioscope device was used to determine the arterial stiffness in predicting the cardiovascular risk in acromegaly patients. AIx and the central aortic blood pressure were significantly increased in acromegaly patients compared to the controls. Arterial stiffness markers were found to be associated with the disease activity; however, there was not a significant correlation between the biochemical parameters.

High levels of GH and IGF-1 in the patients cause structural and functional changes in the heart and vascular system. These specific changes developing in the heart and the vascular bed in the absence of hypertension or diabetes mellitus occur starting from the early stages of the disease; however, the clinical symptoms become manifest in years (Morvan et al. 1991). This leads the cardiovascular involvement to progress without being noticed. Several studies have shown that cardiac dysfunction is alleviated with the curative treatment given in the early stages of cardiac

involvement (Parolin, Dassie et al. 2018). However, the regression of the vascular bed alterations was not satisfactory. For example, it was reported that the increase in the IMT persisted due to the high insulin levels in the patients including the cured ones (Colao et al. 2001). Endothelial dysfunction and arterial stiffness increase as a result of early pathophysiological and structural changes in the cardiovascular system.

In acromegaly patients, a method or a diagnostic test that can identify the cardiovascular involvement in the early asymptomatic phase will allow for making the diagnosis of cardiovascular diseases at earlier stages and taking necessary preventive measures before disease progression. Non-invasive methods, such as pulse wave velocity, flow-mediated vasodilation, cardio-ankle vascular index, and ambulatory arterial stiffness index, have been used in a variety of studies to identify the subclinical structural changes, leading to the development of arterial stiffness in acromegaly. (Davies and Struthers 2003, Baykan et al. 2009, Matsuda et al. 2013). Among these non-invasive methods, AIx receives attention as it is easy and fast to measure, therefore, AIx was used to detect arterial stiffness in different clinical conditions (Fischer-Rasokat et al. 2009, Eguchi et al. 2016, García-Ortiz et al. 2018). Aortic pressure wave comprises a forward propagating wave caused by the left ventricular ejection and the retrograde waves reflected back from the periphery. Therefore, the augmentation of the aortic pressure waveform is a manifestation of wave reflection. To make it clear, the augmentation pressure or the augmentation index (AIx) can be expressed as a percentage of the pulse pressure. Peripheral augmentation index (PAIx) is defined as the ratio of the systolic peaks and is considered as a measure of the arterial functions (Rosenbaum et al. 2013, Eguchi et al. 2016). A high PAIx causes an increased systemic vascular resistance resulting in an increased systolic load. Therefore, it indicates that the myocardial hypertrophy is increased (Izzo, 2014). Several studies have associated PAIx with cardiovascular morbidity and mortality and demonstrated that it predicts the untoward cardiac events independently. (Fischer-Rasokat et al. 2009). In this study, we selected to investigate PAIx as an indicator of arterial stiffness because our aim was to use an easily applicable practical method. Measurements were made using a Cardio Scope II device. This non-invasive and sphygmomanometer-based device is easy to use and provides highly precise and reproducible measurements of several parameters, including the (aortic) systolic and diastolic blood pressures, AIx, and the pulse waveform (Lin et al. 2012). The Cardio Scope uses the common upper arm cuff with conventional oscillometry in a fast, continuous, and simple manner without the need for additional training and without the requirement for additional sensors. In addition, it provides signal quality indices and data on the pulse rate variability.

In our study, one of our aims was to evaluate the correlation between the arterial stiffness parameters and disease markers. But the correlation analysis did not reveal any association of AIx with either GH or IGF-1. This might have occurred due to the low number of study patients and the heterogeneity of the parameters such as the duration of the disease. It may be suggested that the most important reason was the difficulties in performing OGGT, leading to an unsatisfactory reflection of the disease activity by IGF-1 and GH levels used in the diagnosis and follow-up of the disease. It is recommended that only IGF-1 should be measured in the patients receiving growth hormone receptor antagonists (Trainer et al. 2000). A multi-centre study has reported that 30% of the lowest GH levels after OGTT were inconsistent with the actual diagnosis (Pokrajac et al. 2007). There are several studies reporting that OGTT may not be needed if the levels of IGF-1 and GH are significantly higher. On the other hand, there are other studies indicating that the use of OGTT may not be appropriate to determine the disease activity in patients receiving medical treatment (Carmichael et al. 2009). Our study also included patients receiving radiotherapy. It has been reported that GH levels could be normal despite high levels of IGF-1 after radiotherapy, as radiotherapy ensures more stable levels of GH instead of a pulsatile secretion (Van Gelder et al. 2002).

The DM frequency was similar in the patient and control groups of our study; however, the mean HbA1c levels were higher in the AA group. Lee Shin et al. (2016) and Cavero-Redondo et al. (2018) demonstrated in their studies that there was a positive association between arterial stiffness and HbA1c levels. Similar to the previous studies, the correlation analysis in our study revealed a positive correlation between HbA1c and AIx in both the patient group and the control group.

Limitations

We recognise the limitations of our study. First, this is a single-centre study conducted with a relatively small number of patients. Further multi-centre studies with a larger patient population will be beneficial. The participants of our study did not have

overt cardiovascular diseases, however, some of them received antihypertensive, antidiabetic or statin medications with a potential to affect the measurement of AIx. The presence of a coronary heart disease could not be excluded completely as no invasive stress tests or angiographies have been performed; however, the presence of ischaemia was excluded by the clinical, electrocardiographic, or echocardiographic findings. A final possible limitation can be that an imaging of the arterial system of the upper extremities was not performed in the patients prior to the measurements, and that the potential presence of arterial stenoses might have affected the measurements.

Conclusion

In this study, AIx has been demonstrated as a parameter associated with arterial stiffness in predicting the cardiovascular risk in patients with acromegaly. As the use of Cardio Scope is simple and swift, it might be thought that AIx measured by using this device can be easy and economical in the prediction of arterial stiffness in patients with acromegaly, helping physicians identify the high-risk patients. Further prospective studies are required to investigate AIx in predicting arterial stiffness in a variety of clinical conditions in acromegaly as this parameter is practical to measure with a low-cost.

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RESEARCH ARTICLE

Student Opinions on the Importance and Detail of the Accumulation of Anatomy Knowledge Integrating General Surgery

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Abstract

Objective: The aim of the study is to create an original study that guides the anatomy and surgical branches and supports education within the framework of their opinions by raising awareness on this issue in medical faculty students.

Methods: The study was carried out on the fourth, fifth and sixth year medical students of Kafkas University Medicine Faculty in the 2019–2020 academic year. Data collection questions were prepared with a five-point Likert scale. The answers given by the students were automatically analyzed through the web system and the results were obtained through the software

Results: The participation of the students to the opinions of the questions 1, 2, 4, 8, 10 and 12 is quite high (73.2%, 74.6%, 56.3%, 67.6%, 52.1%, 62%). In general, the students want the integration of anatomy into clinical branches in a more up-to-date manner, apart from the traditional anatomy course.

Conclusion: This study was conducted for the importance and awareness of the integration of clinical and anatomy branches with each other. Student opinions were taken to emphasize the importance of the study. Anatomy basis is very important for surgical branches. Apart from classical anatomy education, anatomy education should keep up with technological developments and should be more integrated with clinical branches.

Key words: Anatomy education, Clinical anatomy, Five likert test

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Introduction

In anatomy education, cadaver has been an important object throughout history (McLachlan et al., 2004; Biasutto et al., 2005). In recent years, developing technology with 3D software programs, as well as cadaver, has shown itself in a very eye-catching way in the field of anatomy (Rizzolo and Stewart, 2006; Hoyek et al., 2014; Bahsi et al., 2020). Anatomy department in every faculty in the world and in our country has made its way, some of them are benefiting from digital platform, some of them continue their course flow with both digital and

cadaver, some cadaver and model, and some only with model (Older, 2004; Estai and Bunt, 2016;)

The quality of the anatomy education students receive significantly affects the success of the surgical courses and the training of qualified physicians and surgeons (Singh et al., 2015). When we examine this issue; Students love the anatomy education they receive and are interested in surgical lessons or the anatomy education they receive causes phobia in the students and decreases their interest in surgical lessons. The effect of anatomy education on students can determine two extreme situations, such as cooling the student from the medical school or, on the contrary, making the student a good physician (Kagan, 2002; Singh et al., 2015; Bahsi et al., 2017).

Unfortunately, an effective education cannot be provided in medical faculties when the basic sciences, which include the anatomy course, are not integrated with the surgical units. In addition to having a good anatomy education, the students should take the education together in anatomy and surgical branches so that the physician candidates can integrate the training they have basically received into the clinic (Fitzpatrick et al., 2001; Are et al., 2009; Ozcan et al., 2015)

When the basic sciences, which also include the anatomy course, are not integrated with surgical units, unfortunately, an effective education cannot be provided in medical faculties. In addition to having a good anatomy education, the students should take the education of anatomy and surgical branches together so that the physician candidates can integrate the training they have basically received into the clinic. For example, the better the branches such as histology, pharmacology, biochemistry can be integrated with the departments of pathology and internal medicine, the more rational and dynamic education progresses (Sugand et al., 2010; Heisler, 2011; Singh et al., 2015). Thus, physicians who know what they are doing and think rationally serve human health.

In this study, it was planned to conduct a data collection study that presents opinions about the compatibility of anatomy and surgery lessons. The aim of the study is to create an original study that guides the anatomy and surgical branches and supports education within the framework of their opinions by raising awareness on this issue in medical faculty students. In this way, education can be supported with integrated sessions that concern not only anatomy but all other branches, and student views can also be effective on this issue.

Methods

This study was approved by the ethics committee of Faculty of Health Sciences Kafkas University (Approval number: 2020/6/decision 01). The study was carried out on the fourth, fifth and sixth year medical students of Kafkas University Medicine Faculty in the 2019–2020 academic year. The data collection questionnaire was not sent to the first, second and third year students since they have not yet taken general surgery and other clinical courses. The questions asked in the data collection form were designed by literature review. The data collection forms used in the study were prepared on the web and sent to the students by e-mail. 71 students answered the questions in the data collection form. Data collection questions were prepared with a five-point Likert scale (totally agree, agree, undecided, disagree, totally disagree) (Gozil et al., 2006). The answers given by the students were automatically analyzed through the web system and the results were obtained through the software.

Statistical analysis

The fourth, fifth and sixth year medical students were compared according to the answers given by the students. Statistical analysis was carried out using SPSS 22.0 version software program for Windows. Descriptive statistics for categorical variables are expressed as frequency and percentage values. Data collection surveys were conducted with fourth, fifth and sixth grade students collectively. The questionnaires could not be applied separately because there is a great difference in the number of students in each class. Therefore, a comparative statistic could not be made.

Results

The answers given by the students to each question are shown in Table 1. In the first question; 73.2% of the students completely agreed, 25.4% only agreed, and 1.4% were indecisive. No one marked completely disagree and disagree in this question. In the second question; 74.6% of the students completely agreed, 21.1% only agreed, and 4.3% were indecisive. Again, in this question, no one marked completely disagree and disagree. In the third question; 42.3% of the students totally agreed, 38% only agreed, 11.3% were undecided, 5.6 did not agree totally and 2.4 did not agree. In the fourth question; 56.3% of the students totally agreed, 26.8 % only agreed, 8.4 % were undecided and 8.5 did not agree. No one marked completely disagree in this question. In the fifth question; 40.8% of the students totally agreed, 25.4% only agreed, 16,9% were undecided,

2,8 did not agree totally and 14,1 did not agree. In sixth question; 50.7% of the students totally agreed, 23.9% only agreed, 11.3% were undecided, 2,8 did not agree totally and 11.3 did not agree. In the seventh question; 50.7% of the students totally agreed, 28.2% only agreed, 14.1% were undecided, 4.3 did not agree totally and 2.7 did not agree. In the eighth question; 67.6% of the students totally agreed, 22.5% only agreed, 8.5% were undecided and 1.4 did not agree. No one marked completely disagree in this question. In the ninth question; 29.6% of the students totally agreed, 35.2% only agreed, 16.9% were undecided, 2.8 did not agree totally and 15.5 did not agree. In the tenth question; 52.1% of the students totally agreed, 25.5% only agreed, 12.7% were undecided, 1.4 did not agree totally and 11.3 did not agree. In the eleventh question; 28.2% of the students totally agreed, 47.9% only agreed, 12.7% were undecided, 2.7 did not agree totally and 8.5 did not agree. In twelfth question, 62% of the students totally agreed, 31% only agreed, 1.3% were undecided, 2.9 did not agree totally and 2.6 did not agree.

Table 1. Frequency (f) percentages of the first and second year students' answers to the questions

Medicine Faculty Students' 4th, 5th and 6th grade n:71	**ANSWERS**				
Questiones	**5**	**4**	**3**	**2**	**1**
1-A good anatomy education infrastructure is required for the general surgery branch.	73,2	25,4	1,4	-	-
2-For the general surgery course, I need topographic and three-dimensional anatomy rather than systematic anatomy.	74,6	21,1	4,3	-	-
3- I need a (theoretical) repetition of anatomy knowledge before the general surgery course.	42,3	38	11,3	5,6	2,4
4- I need (Practically) knowledge of anatomy.	56,3	26,8	8,4	-	8,5
5- Before the general surgery course, I need both theoretical and three-dimensional visual anatomy knowledge.	40,8	25,4	16,9	2,8	14,1
6- Anatomy education with models and three-dimensional digital visuals is ideal to lay the groundwork for upper classes of surgery.	50,7	23,9	11,3	2,8	11,3
7- Anatomy education with cadavers is ideal to prepare the ground for surgery lessons in higher classes.	50,7	28,2	14,1	4,3	2,7
8- The most ideal anatomy training is given by integrating cadavers, models and three-dimensional digital images to prepare the ground for surgical lessons in upper classes.	67,6	22,5	8,5	-	1,4
9- Anatomy education with models and digital images cannot complement the perception of reality encountered in surgical lessons.	29,6	35,2	16,9	2,8	15,5
10- It is seen that even cadaveric education is lacking in completing the perception of reality in surgical lessons, while anatomy education with only models and digital models will be insufficient in medical education.	52,1	25,5	12,7	1,4	11,3
11- Reality perception discovered and acquired in living tissue in the general surgery clinic is the enhanced version of the anatomy lesson.	28,2	47,9	12,7	2,7	8,5
12- two- and three-dimensional anatomy perception such as radiological anatomy, ultrasonographic anatomy and laparoscopic anatomy are needed in the general surgery clinic. In order to understand these, a good knowledge of anatomy and a good anatomy repetition before the lesson is required.	62	31	1,3	2,9	2,6

5: Totally agree (%), 4: Agree (%), 3: Undecided (%), 2: Totally Disagree (%). 1: Disagree (%)

Discussion

Anatomy is like the mother of medical education (Murgitroyd et al., 2015). Students grasp the importance and seriousness of medical school with the anatomy lesson, which is the first step to medicine (Cetkin et al., 2016). In addition, the foundation of surgical branches is based on anatomy education. Technological advances in recent years have brought many innovations to anatomy education. 3D digital software, plastination technique and 3d models have enabled the development of anatomy education (Gunderman and Wilson, 2005; Lewis et al., 2014). Examination of anatomy from different dimensions with the developing technology has increased the importance of the interaction of this branch of science with surgical branches (Fitzpatrick et al., 2001; Ozcan et al., 2015).

The aim of this study is to emphasize the importance of anatomy-surgery branches interaction awareness with student views. Almost all of the students (73.2%) agreed that a good anatomy foundation is necessary for general surgery. This situation has supported the importance of anatomy education in the literature as the basis of surgical branches. Before the general surgery course, instead of the classical systematic anatomy, which is taught theoretically, topographic and 3D anatomy practice lesson is a more preferred situation for students (56.3%). This can also be interpreted as follows; Instead of an intense anatomy course based on memorization, an anatomy training based on visual memory and practice, which includes the anatomical neighborhood of the organs and their interactions with other organs necessary for general surgery, can be considered. The students gave equal notice (50.7%) about learning anatomy with only cadavers or taking only 3-dimensional software and models. The reason for not adopting too much education in

which only cadaver is shown may be the exam anxiety in the cadaver or the feeling of anxiety towards the cadaver.

Most of the students want an integrated anatomy education model based on three-dimensional software, models and cadaver association in preparation for surgical lessons (67.6% totally agree, 22.5% agree). In addition to this view, most students agree that anatomy training with models and digital images cannot complement the perception of reality encountered in surgical lessons. But a small number of students disagree with this view. In other words, it can be thought that they agree with the view that three-dimensional software and visuals meet anatomy education before surgical lessons.

While it was observed that even cadaveric education was incomplete in completing the perception of reality in surgical lessons, almost all students agreed that anatomy education with only models and digital software will be insufficient in medical education. Those who disagree with the opinion in this question and undecided are very few. The conclusion to be drawn here is that touching, perceiving and manipulating the human body requires an enormous training. For the three-dimensional structure and mystery of the human body, the cadaver is a very important and precious lesson tool that is hard to find, even it is insufficient to meet the real tissue perception of reality.

The indispensable part of anatomy education for the sense of perception and reality is cadavers. The anatomy lesson, on the other hand, must renew itself in three-dimensional perception apart from the traditional systematic anatomy and be supported by technological innovations (Zumwalt et al., 2010). Because the basis of clinical anatomy such as ultrasonographic anatomy, radiological anatomy, laparoscopic anatomy and cross-sectional anatomy, which should be mastered in the surgical and clinical classes of medical education, is also very necessary for students (Sure et al., 2005; Orsbon et al., 2014). Students' opinions on this subject support this situation. In order for anatomy to develop itself and keep up with technology, clinical branches and anatomy branches should be integrated with each other (Morgan et al., 2017).

Conclusion

This study was conducted for the importance and awareness of the integration of clinical and anatomy branches with each other. Student opinions were taken to emphasize the importance of the study. As a result of these views, it was tried to be revealed with quantitative data both how anatomy education should be given and the importance of anatomy education in its interaction with surgical branches.

Ethics Committee Approval: The study was approved by the ethics committee of Faculty of Health Sciences Kars University (Approval number: 2020/6/decision 01). The study was performed following the aid of the ethical standards down in the 1964 Declaration of Helsinki and its later amendments.

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RESEARCH ARTICLE

Comparison of Videofluoroscopic Swallowing Study and Fiberoptic-Endoscopic Evaluation of Swallowing Findings in Pediatric Patients

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Abstract

Objective: This study is designed to determine the value and accuracy of Fiberoptic Endoscopic Evaluation of Swallowing (FEES) in the diagnosis of swallowing disorders as a diagnostic tool, in comparison with the widely accepted Videofluoroscopic Swallowing Study (VFSS) in pediatric patients.

Methods: Cross-sectional study in tertiary referral center. Fifty one children with swallowing difficulty due to various diseases were prospectively evaluated using both VFSS and FEES. The variables, early pharyngeal spillover, pharyngeal residues, laryngeal sensitivity-silent aspiration, laryngeal penetration and laryngeal aspiration were evaluated in all patients.

Results: Mean patient age was 29.8±17.8 (range 9-72) months. Six patients were younger than 13 months, 19 were between 13 and 24 months, and 26 patients were older than 2 years of age. There were 21 (42%) females and 30 (58%) males in the study group. Significant correlation in pharyngeal residues and laryngeal sensitivity-silent aspiration findings were found between FEES and VFSS data. No Significant dissimilarity in laryngeal aspiration and penetration evaluation was found.

Conclusion: Swallowing evaluation in children is more challenging than adults. Study findings showed that FEES outcomes correlate with VFSS data, especially in the diagnosis of laryngeal aspiration and FESS is a valuable tool in identifying swallowing disorders in pediatric patients.

Key words: Swallowing disorders, Fiberoptic endoscopic evaluation of swallowing, Dysphagia, Videofluoroscopic Swallowing Study, Laryngeal aspiration.

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Introduction

Genetic malformations, neurological and systemic diseases are frequently associated with pathologic feeding and swallowing in children. In these patient's gastro-esophageal reflux and aspiration pneumonia due to swallowing disorders can be seen frequently, causing significant mortality and morbidity (Darrow and Harley 1998).

Videofluoroscopic swallowing study (VFSS) which has long been viewed as the "gold standard"(Logeman 1983.; Langmore et al. 1988; Langmore 2017; Re et al. 2019) and fiberoptic endoscopic evaluation of swallowing (FEES) are the most commonly used methods for the diagnosis and follow-up of swallowing disorders. Both of these instrumental studies are utilized to determine the deficit in swallowing and feeding, causing airway contamination. Ability to observe all swallowing phases, including the oral preparatory, oral transit times, upper esophageal sphincter opening and esophageal transit time and assessing the position of hyoid-larynx complex are major superiorities of VFSS. On the other hand, radiation exposure is the main limitation of VFSS (Jones 1999; Bluestone 2003; Ko et al. 2019), especially in the pediatric population. Patients who have chronic diseases such as hypoxic ischemic encephalopathy may require multiple radiologic examinations which increase the cumulative radiation exposure. FEES have some advantages such as no radiation exposure, less cost, the opportunity of bedside evaluation, diagnostic power for anatomical features of the larynx and is performed routinely in the pediatric population by otolaryngologists to diagnose various concomitant pathologies. Briefly, these techniques cannot provide identical diagnostic information across all aspects of swallowing and both methods are known to be useful and complementary to each other. In adults, both methods have been shown to be equally effective by many studies (Kidder et al. 1994; Langmore et al.1988; Kaye et al. 1997; Wu et al. 1997; Colodny 2002; Giraldo-Cadavid et al. 2017). However, in the English language literature there are few studies including infants and children (Leder and Karas 2000; da Silva et al. 2010; Reynolds et al. 2016; Miller and Willging 2020) that compare the accuracy and reliability of these methods.

The aim of the present study is to investigate the place and accuracy of FEES in swallowing disorders in children by comparing FEES findings with the widely accepted VFSS in a pediatric population with swallowing dysfunction.

Methods

Subjects and Study Design

This study was approved by the Committee of Ethics of Hacettepe University, School of Medicine (Approval number: HEK 11/32-3). Children and guardians of patients were informed about the study and a signed consent form.

Fifty-one children referred to our clinic with dysfunctional swallowing or associated respiratory problems mainly from pediatric gastroenterology, pediatric neurology and pediatric pulmonology departments were prospectively evaluated using VFSS and FEES between April 2011 and November 2011 at Hacettepe University, School of Medicine, Otorhinolaryngology and Radiology departments. Diagnostic value of FEES was evaluated in comparison with VFSS as the gold standard method for dysphagia assessment.

Procedures and equipment

The basic FEES protocol was performed at the outpatient department, with the patient in sitting position either alone or held by one of the parents. All food used during the tests was dyed with methylene blue for better visualization. Approximately 5-mL boluses of food with purée consistency (yogurt with methylene blue) and 5-mL boluses of food with liquid consistency (milk or water with methylene blue) were given during FEES procedures. All FEES procedures were carried out by an experienced pediatric otolaryngologist and were videotaped. FEES was performed with a Storz 3.2 mm nasopharyngo-laryngoscope and Storz halogen light source (Karl Storz GmbH &Co., Germany). The captured images were transferred to a Sony video monitor and recorded onto a Sony videocassette (Sony Corp., Tokyo, Japan).

Videofluoroscopic swallowing evaluation was performed with food samples of the same quantity and consistency (puree and liquid). During the radiographic study, patients were seated and viewed in the lateral projection. The fluoroscopic tube was focused on the lips anteriorly, the cervical vertebrae posteriorly, the soft palate superiorly, and the cervical esophagus inferiorly (J.A. Pro-ed,1998: 169-185.)

The videofluoroscopic studies were recorded on a DVD.

Compared Swallowing Parameters

The following nine parameters were compared:

1- pharyngeal spillover,

2a- pharyngeal residue in the valleculae (purée),

2b- pharyngeal residue in the valleculae (liquid)

3a- pharyngeal residue in the pyriform sinuses (purée)

3b- pharyngeal residue in the pyriform sinuses (liquid)

4- velopharyngeal patency,

5- laryngeal sensitivity-silent aspiration,

6- laryngeal penetration (food or contrast residues above the vocal folds),

7- laryngeal aspiration (food or contrast residues below the vocal folds).

Laryngeal reflex assessment in FEES was used as an analogue to silent aspiration in VFSS. After larynx visualization was obtained with the endoscope, the tip of endoscope was brought in contact with either the epiglottis or arytenoids of the patient and response of the patient in terms of vocal cord adduction was observed and recorded. If there was an absence of response, the patient was noted to have no laryngeal reflex (who was considered a candidate for silent aspiration).

Statistical analysis

Analysis of all data was performed in PASW 18.0 (IBM Inc.) statistical package program McNemar test and Receiver Operating Characteristic (ROC) Curve was used for the assessment of statistical differences between FEES and VFSS. P values under 0.05 were considered statistically significant.

Results

Mean patient age was 29.8±17.8 (range 9-72) months. Six patients were younger than 13 months, 19 were between 13 and 24 months, and 26 patients were older than 2 years of age. There were 21 (42%) females and 30 (58%) males in the study group. The major cause for ENT referral was respiratory problems in 17 (%33), gastroesophageal reflux in 5 (%9.8), persistent vomiting in 3 (%5.8), genetic malformations in 11 (%21) and other causes (%9.8).

All previously explained parameters of swallowing dysfunction were compared for diagnostic agreement. If non-parametric testing indicated agreement between FEES and VFSS ($p>0.05$), ROC curves were also evaluated to further establish correlation for the first seven parameters. Diagnostic agreement was found between FEES and VFSS for pharyngeal spillover (1), pharyngeal residue in the valleculae (purée food) (2a), pharyngeal residue in the valleculae (liquid) (2b), pharyngeal residue in the pyriform sinuses (purée food) (3a), pharyngeal residue in the pyriform sinuses (liquid) (3b), laryngeal sensitivity-silent aspiration (5). No correlation was present regarding velopharyngeal patency (4) between the two methods. A concise summary of results regarding the first seven parameters is provided in table 1.

Laryngeal penetration and aspiration was evaluated for both purée food and liquids. While in 29 (57%) patients both FEES and VFSS indicated aspiration for liquid consistency, FEES could not detect 2 instances of penetration (4%) and 1 instance of aspiration (2%) that was detected by VFSS. Five patients (10%) had penetration according to FEES while according to VFSS these patients did not have penetration for liquid consistency. For purée food in 22 patients (42%) FEES and VFSS agreed on aspiration. FEES could not detect 4 cases of penetration (%8) and 2 cases of aspiration (4%) which were detected by VFSS. Three patients (6%) had penetration according to FEES while according to VFSS these patients were found normal. Cross-distribution tables for VFSS and FEES results regarding purée and liquid food consistencies can be seen in Table 2 and 3.

Sensitivity for detecting aspiration was 96% for liquids and 73% for purée food. Specificity for detecting aspiration was 95% for liquids and 85% for puree food. Sensitivity for detecting aspiration or penetration was 90% for liquid consistency and 81% for puree consistency. Specificity for detecting aspiration or penetration was 72% for liquid consistency and 84% for puree consistency. Sensitivity and specificity values for FEES can be seen in Table 4.

Table 1. Statistical analyses for early pharyngeal spillover, Residues for vallecula and pyriform sinuses, velopharyngeal patency and laryngeal sensitivity-silent aspiration

Compared parameter	p* values	Area Under Curve**
1-Early pharyngeal spillover	0.453	0.783
2a-Residues for vallecula (purée food)	0.990	0.887
2b-Residues for vallecula (liquid)	0.996	0.769
3a-Residues for pyriform sinuses (purée food)	0.219	0.863
3b-Residues for pyriform sinuses (liquid)	0.998	0.880
4-Velopharyngeal patency	0.012	
5-Laryngeal sensitivity (FEES)-Silent aspiration (VFSS)	0.754	0.785

* McNemar Test ** ROC curve

Table 2. Aspiration-Penetration cross- tabs for liquid consistency

		VFSS			Total
		Normal	**Penetration**	**Aspiration**	
FEES	Normal	13(%25)	2(%4)	1(%2)	16
	Penetration	5(%10)	0	0	5
	Aspiration	0	1(%2)	29(%57)	30
Total		18	3	30	51

(McNemar Test, P= 0.350 > 0.05)

Table 3. Aspiration-Penetration cross- tabs for puree consistency.

		VFSS			Total
		Normal	**Penetration**	**Aspiration**	
FEES	Normal	16(%32)	2(%4)	4(%8)	22
	Penetration	3(%6)	0	2(%4)	5
	Aspiration	0	2(%4)	22(%42)	24
Total		19	4	28	51

(McNemar Test, p= 0.241 > 0.05)

Table 4. Sensitivity and specificity values for FEES

Paramaters	Sensitivity (%)	Specificity (%)
Detection of aspiration		
Liquid	96%	95%
Puree	73%	85%
Detection of aspiration or penetration		
Liquid	90%	72%
Puree	81%	84%

Discussion

While the use of FEES is relatively well known for swallowing evaluation, there is a need to show the accuracy of this procedure in the pediatric patient population. In this study, we aimed to determine the reliability of FEES in the pediatric population by correlating this method with VFSS which is considered a gold standard evaluation for swallowing disorders. We found good correlation between FEES and VFSS to detect early pharyngeal spillover, residue in valleculae and pyriform sinuses, and laryngeal sensitivity-silent aspiration. Penetration and aspiration were also reliably determined with both methods.

There has been an interest in endoscopic evaluation of swallowing since Langmore et al.

(1983) described FEES in 1983. In 1991 Langmore et al (1991) published the first study comparing FEES and VFSS as the gold standard in adults and showed high levels of agreement in diagnosis for adult patients. Likewise, in children, VFSS is still regarded as the standard diagnostic method by several authors (Arvedson and Lefton-Greif 2007; Kramer and Eicher 1993; Newman et al. 1991). But in spite of the variety of studies on this subject conducted for adults (Kaye et al.1997; J.A. Pro-ed,1998: 169-185.) which compare FEES with VFSS, in the current literature there are only two prospective studies which evaluate the value of FEES in swallowing disorders in children (Leder and Karas 2000; da Silva et al. 2010). One of the mentioned studies includes only seven patients and evaluates only laryngeal aspiration and penetration. Sensitivity and specificity values seem different between two studies. Contradictory findings from these studies prompted both authors to recommend further investigation with larger sample sizes.

Leder and Karas (Langmore et al.1991) showed the value of FEES as a diagnostic tool beside VFSS in their study for the first time in 2000. In their study, 7 patients were tested with both VFSS and FEES and there was 100% agreement in detecting laryngeal penetration and aspiration between the two methods. No other parameters were compared in this study.

In 2010, Andréa P. da Silva at al. (2010) evaluated the diagnostic value of FEES performed by two independent observers against VFSS in 30 patients. In this study FEES yielded good interobserver agreement for all parameters which demonstrates that FEES is a method with reproducible results. On the other hand, consistency between FEES and VFSS results for both of the two observers have been found to be low, indicating less than ideal diagnostic agreement between the two methods. Detecting laryngeal penetration and aspiration yielded the highest specificity and positive predictive value when compared to VFSS. The pharyngeal residue parameters and early spillover parameters show moderate correlation in this study for the worse of the observers testing with liquids. For the better observer pharyngeal residue (Sensitivity: 83% and Specificity: 79%) and early spillover (Sensitivity: 44% and Specificity: 76%) shows better correlation for liquids. Similarly, in our study, early pharyngeal spillover demonstrated good correlation between the two methods according to ROC analyses (AUC: 0.783). Compared to this study, pharyngeal residues for both liquid and purée food also show better agreement.

Our specificity and sensitivity values for laryngeal aspiration and penetration seem similar with Leder and Karas's findings. While da Silva et al. shows better specificity (100%) for laryngeal aspiration with purée food than our study (%85), our results (Sensitivity:96% and Specificity:95%) are better than this study (Sensitivity: 27% and Specificity: 91%) for liquids. In addition, Langmore et al. (1991) also reported good results (Sensitivity:88% and Specificity:92%) for laryngeal aspiration in adults. Despite these optimistic results for detection of aspiration, we have six patients for purée food (12%) and 3 patients for liquids (6%) that were considered normal according to FEES while having aspiration or penetration in VFSS. In the pediatric population, 12% undetected aspiration is quite significant and larger samples are needed to discuss the weaknesses of FEES that might lead to misdiagnosis.

Laryngeal sensitivity can also be assessed by endoscopic examination; this is accomplished by directly stimulating various laryngeal areas with the tip of the endoscope. This evaluation can also be accomplished by the rhythmic administration of air in a sequence of pressures, to elicit laryngeal adduction and consequently establish the sensitivity threshold (Willging and Thompson 2005; Nacci et al. 2008). In our study we evaluate laryngeal sensitivity by direct stimulation of laryngeal mucosa by contact with the tip of the endoscope and we have considered absent response to stimulation as impaired laryngeal sensitivity. We observed impaired laryngeal sensitivity outcomes of FEES correlates well with silent aspiration in VFSS. Leder at al. (1998) used FEES for diagnosis of silent aspiration in their study. In our study we demonstrate the relationship between FEES findings of laryngeal sensitivity and silent aspiration of VFSS in pediatric population. This may suggest that silent aspiration may be predicted by laryngeal sensitivity testing in FEES and then patients can be referred to further evaluation by VFSS.

Transnasal flexible fiberoptic laryngoscopy is performed routinely in children and infants but using it for FEES is not common. Some of the limitations of VFSS, such as the need for cooperation of the patient during examination is also valid for FEES in the pediatric population. Additional care should be taken to avoid any airway problems for children with severe aspiration risk. Our study showed that FEES can be used in children to avoid the aforementioned limitations of VFSS as a relatively safe and easy procedure without major difficulties or complications. Using FEES will give general and pediatric otolaryngologists a more active role in dysphasia diagnosis and management.

Conclusion

Swallowing evaluation in children is more challenging than adults. The value of FEES, a well-accepted diagnostic test, has only been investigated twice in the literature. Results of these studies could not agree on the level of diagnostic reliability of FEES in children. In our study, good agreement levels between FEES and VFSS support the use of FEES as a valuable diagnostic method in pediatric patients with swallowing disorders.

Ethics Committee Approval: This study was approved by the Committee of Ethics of Hacettepe University, School of Medicine (Approval number: HEK 11/32-3).
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RESEARCH ARTICLE

Evaluation of Geriatric Patients Undergoing Hip Surgery: A Retrospective Study

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Abstract

Objective: Global improvement in the quality of life has led to a rapid expansion of the elderly population. A majority of patients undergoing hip or lower extremity surgery belong to the geriatric age group; in these patients, regional anaesthesia is generally preferred over general anaesthesia due to the common occurrence of concomitant conditions. In this study, we investigated the effect of the anaesthetic technique on mortality, morbidity, and clinical outcomes in geriatric patients undergoing hip surgery.

Methods: This study evaluated 700 patients over 65 years of age with an ASA status of III/IV who had undergone hip surgery between 2009 and 2013 at Fırat University Hospital. Based on a review of patient records, 114 patients were eligible for the study. The two groups were comparable in terms of age, ASA status, gender, anaesthesia duration, haemoglobin levels at baseline and discharge, complication rates, need for post-operative intensive care unit admission, concomitant conditions, need for volume replacement, mortality rate and need for blood and blood products.

Results: Patients were divided into the general (n = 76) and regional (n = 38) anaesthesia groups. Pre- and post-operative haemoglobin levels were not significantly different between the two groups($p>0.068$) Surgery duration (113.68 ± 34.73 min) and hospital stay length (11.42 ± 4.03 days) were statistically shorter in the regional anaesthesia group.

Conclusion: In geriatric patients undergoing hip surgery, regional anaesthesia is superior to general anaesthesia, as it results in reduced surgery duration, hospital stay length and need for blood transfusions.

Key words: Geriatrics, general anesthesia, regional anesthesia, arthroplasty, mortality rate

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Introduction

Global improvement in the quality of life has led to a rapid expansion of the elderly population. Individuals over 65 years of age are considered elderly and those over 80 years of age are considered advanced elderly. General improvements in the quality of health care and advances in anaesthetic and surgical techniques have led to an increase in the number of the elderly undergoing anaesthesia (Turkmen and Turgut,2007, Ogurlu et al,2007; Bettelli, 2010; Deiner and Silverstein, 2011).

More than half of geriatric patients have one or more concomitant conditions, such as chronic

obstructive pulmonary disease, diabetes mellitus, cardiac failure, or renal failure, which are associated with an increased risk of perioperative and post-operative complications (Chung et al, 1999, Aldwinckle and Montgomery, 2004,).

The majority of patients undergoing lower extremity surgery belong to older age groups. In this population, regional anaesthetic techniques is generally preferred to general anaesthesia to avoid complications due to co-existing conditions (Celik et al, 2010). Despite the absence of clear scientific evidence on the superiority of one technique over the other, discussions regarding the advantages of regional anaesthesia have been ongoing for many years (Takmaz, 2012; Seyedi et al, 2015).

This study aimed to investigate the effect of the anaesthetic technique on morbidity and clinical outcomes in geriatric patients undergoing hip surgery. In light of recent data, a discussion regarding the efficacy and advantages of both anaesthetic methods is provided.

Methods

The study protocol was approved by the Ethics Committee for Clinical Research, Firat University Medical Faculty (Date:01.11.2012/ Decision number:18-02). This article is derived from the Republic of Turkey, our thesis registered with expertise in the national thesis center number 388667.

Data used for retrospective analyses were retrieved from case files of patients who underwent hip surgery at Firat University Hospital. We evaluated 700 patients over 65 years of age with an ASA status of III/IV and who underwent hip surgery between 2009 and 2013 at Firat University Hospital. Of these, 114 patients were eligible for the study based on adequate data in patient files (i.e. age, sex, need for volume replacement, blood transfusion, post-operative intensive care, hospital stay length, complications, haemodynamic alterations, surgery type, concomitant conditions, ASA status and duration of anaesthesia and surgery). A total of 586 patients were excluded from the analyses due to reasons including coding errors or age below 65 years.

This study included 76 patients treated with general anaesthesia and 38 with regional anaesthesia. The two groups were compared in terms of age, sex, need for volume replacement, blood transfusion, post-operative intensive care, hospital stay length, complications, haemodynamic alterations, surgery type, concomitant conditions, ASA status and duration of anaesthesia and surgery.

Statistical analysis

Statistical analyses were performed using the SPSS 15.0 software package (The Statistical Package for the Social Sciences, Chicago, IL, USA; Licence number: Z-125-3301-14). Data were recorded as mean ± SD. Parametric data were compared using the student's t test, while chi-squared tests were used for the comparison of nonparametric data between groups. Quantitative data are expressed as mean and standard deviation minimum maximum values.A p-value of <0.05 was considered significant.

Results

The two study groups, i.e., general and regional anaesthesia groups, comprised 76 and 38 patients, respectively (Figure 1). No significant age differences were noted between the two groups (p =0.075). The youngest and eldest patients were 65 and 104 years of age in the general anaesthesia group and 68 and 92 years of age in the regional anaesthesia groups, respectively (Table 1).

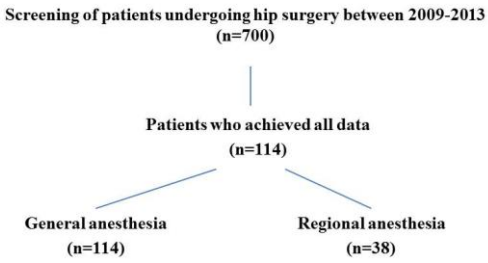

Figure 1. Patient Disposition

Table 1. Demographic data of patients

Group		Minimum	Maximum	Mean±SD	*P* value
General Anestesia (n=76)	Age	65	104	78,02±8,91	0.075
	ASA classification	3	4	3,38±0,48	0.056
	Duration of anesthesia	75	240	147,53±34,97	0.066
	Baseline hemoglobin (gr/dl)	9	17	12,42±1,82	0.071
	Hemoglobin at discarge	7	14	9,71±1,40	0.068
	Volume (ml)	1000	4000	2824,74±756,42	0.081
	*Lenght of hospital (day)	3	50	13,72±7,43	**0.031***
	*Duration of surgery (min)	60	210	127,17±35,48	**0.024***
	Gender (F/M:48/28)				
Regional Anesthesia (n=38)	Age	68	92	80,60±6,08	0.075
	ASA classification	3	4	3,44±,50	0.056
	Duration of anesthesia	60	240	138,82±37,99	0.066
	Baseline hemoglobin (gr/dl)	10	16	12,73±1,67	0.071
	Hemoglobin at discarge	7	14	10,23±1,54	0.068
	Volume (ml)	1000	4100	2952,63±830,08	0.081
	*Lenght of hospital (day)	3	22	11,42±4,031	**0.031***
	*Duration of surgery (min)	50	210	113,68±34,73	**0.024***
	Gender (F/M:20/18)				

(*):p<0.05 According to Student T test or Chi-Square test

Although pre- and post-operative haemoglobin levels were not significantly different between the two groups, post-operative haemoglobin levels were lower in both groups than pre-operative levels(p=0.068). However, there was a more marked decline in haemoglobin level among patients in the general anaesthesia group than among those in the regional anaesthesia group (Figure 2).

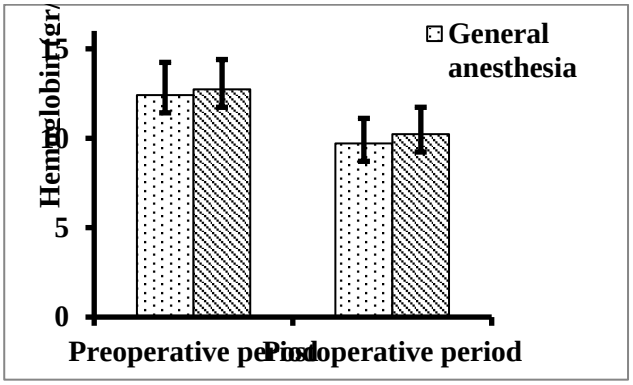

Figure 2. Comparison of pre- and post-operative haemoglobin levels in patient groups
* Right columns represent general anesthesia group, left columns represent regional anesthesia group.

The mean hospital stay lengths in the general and regional anaesthesia groups were 13.7 ± 7.43 and 11.4 ± 4.03 days, respectively (p=0.031) (Figure 3).

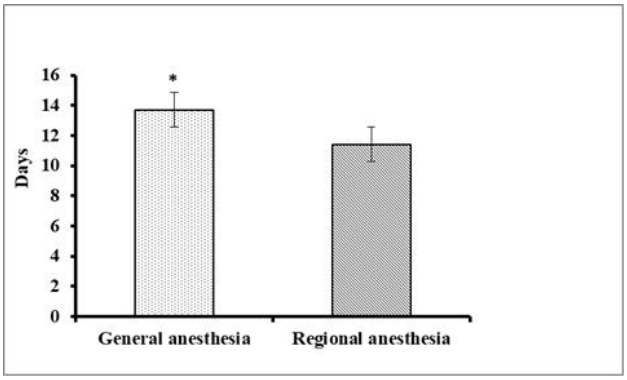

Figure 3: Comparison of hospital stay length of groups
* Right columns represent general anesthesia group, left column represent regional anesthesia group.

The mean surgery durations were 127 ± 35.47 and 113 ± 34.73 min and the mean anaesthesia duration were 147 ± 34.97 and 138 ± 37.99 min in the general and regional anaesthesia groups, respectively (Figure 4). (p=0.024,p=0.066 respectively)

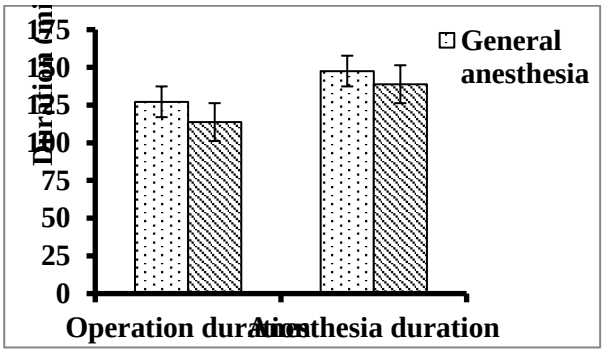

Figure 4. Comparison of duration of surgery and anaesthesia of groups

***** Right columns represent general anesthesia group, left columns represent regional anesthesia group

Discussion

In our study, we found that the length of hospital stay was shortened in the regional anesthesia group between the regional anesthesia group and the general anesthesia group. Similarly, we found that the duration of surgery was shortened in the regional anesthesia group. This is evidence that regional anesthesia is more advantageous than general anesthesia. Early discharge will also protect patients from thromboembolic events. Early discharge, returning to early daily life activities will also contribute to the national economy.

For study purposes, participants were classified in two groups: those undergoing regional anaesthesia and general anaesthesia. The two groups were examined and compared in terms of age, sex, need for volume replacement, blood transfusion, post-operative intensive care, hospital stay length, complications, haemodynamic alterations, surgery type, concomitant conditions, ASA risk score and duration of anaesthesia and surgery.

In the study by Polanczyk et al. (2001) which involved 4315 patients over 50 years of age undergoing elective non-cardiac surgical procedures between 1989 and 1994, the age-adjusted mortality and morbidity rates were reported as follows: mortality rate in individuals between 50–59, 60–69, 70–79 and >80 years of age were 3%, 5%, 9% and >26%, respectively. The corresponding figures for morbidity rate were 4.3%, 5.7%, 9.6% and 12.5%, respectively.

In our study of 114 patients over 65 years of age, 64.91% were over 75 years of age and 21.1% were over 85 years of age. The mean age in our patient group was lower than that in several previous reports involving geriatric patients with femoral fracture.

In a retrospective cohort analysis by Franzo et al. (2005) which involved 6629 patients undergoing surgery in different centres between 1996 and 2001, the in-hospital mortality rate was 5.4%, mortality rates at 6 and 12 months after discharge were 20.0% and 25.3%, respectively. In addition, there was a significant decline in mortality rates between 1996 and 2001, which was confirmed in a multivariate model. The authors propose that the single most important factor accounting for this decline is the reduced workload of surgical units.

Foss and Kehlet, (2005) in their meta-analysis on mortality in patients with hip fractures undergoing surgery in different European centres, found a 30-day mortality rate of 10% and a 1-year mortality rate of 25%. The mortality rate was 7.8% (9/114) in that study. In our study, the in-hospital mortality rate was 7.9%, consistent with that of the published data.

In a 1984 study, McKenzie et al (1984) reported a lower rate of post-operative mortality rate in a limited number of patients undergoing regional anaesthesia than in those undergoing general anaesthesia. In another study examining the association between the anaesthetic technique and mortality in elderly patients undergoing hip surgery, the mortality rate was 14.61% in general anesthesia group while it was 9.09% in regional anesthesia, and the relative and absolute risk of mortality was higher in the general anaesthesia group, whereas the causes of death (cardiovascular disease or infection) did not significantly differ (Melendez et al, 2009).

The comparison of mortality between regional and general anaesthesia group in our study showed a mortality rate of 7.9% in the regional anaesthesia group, with three cases of mortality in 38 patients. The corresponding mortality rate in the general anaesthesia group was 7.9%, with six cases of mortality in 76 patients. These results suggest that the anaesthetic technique does not affect mortality rates.

Meyer et al. (2009) found a significantly increased risk of mortality in patients with hip fracture who had low mental status scores, two or more concomitant conditions and a history of being unable to walk outside of the home before the fracture. No such increase was noted in patients without these risk factors.

Svensson et al. (1996) found an association between the 1-year post-operative mortality rate and concomitant conditions before surgery. Patients with no concomitant health conditions had no mortality, whereas those with one or two concomitant conditions had a mortality rate of 14% and those with three or four conditions had a mortality rate of 24%.

In this study on geriatric patients who underwent hip surgery in a 4-year period, in-hospital mortality rates were estimated. Fifteen of our 114 participants had no concomitant conditions. All nine patients who

died had at least one concomitant condition, eight had more than two conditions and one had only a single concomitant condition.

Previous studies suggest that epidural anaesthesia in patients undergoing total hip replacement could reduce blood loss and prevent intraoperative hypertension. It may also reduce the incidence of re-operation in those undergoing vascular surgery by providing adequate tissue perfusion. Such reported advantages support the utilisation of regional anaesthesia and analgesia in the elderly (Jin and Chung, 2001). Regional anaesthesia is considered to confer the lowest risk of post-operative hypoxaemia, consequently reducing pulmonary oedema and blood loss and allowing early diagnosis of mental status changes. Furthermore, the effect of spinal anaesthesia on lowering central venous pressure should be emphasised (Rodgers et al, 2000).

In this study, rates of post-operative reduction in haemoglobin levels were similar between the regional and general anaesthesia groups. The proportions of patients experiencing bleeding were also comparable. However, the reduction in haemoglobin levels was less marked in the regional anaesthesia group.

Maurer et al. (2007) reported significantly reduced surgical time, intra- and post-operative blood loss and need for transfusions in patients undergoing spinal anaesthesia, suggesting that spinal anaesthesia may be superior to general anaesthesia for patients undergoing unilateral hip surgery.

Neuman et al. (2014) divided patients undergoing hip surgery based on the type of anaesthetic technique used, i.e. regional and general anaesthesia groups. The two groups were compared with regard to 30-day mortality and hospital stay length. There was no significant difference in the former, whereas the latter was shorter among regional anaesthesia patients.

In a review by Liu Y. et al. (2017) They emphasized that anesthesia management in the elderly started with preoperative examination and multidispliner should be approached while making preoperative preparation. Perioperatively, they emphasized that it should be taken to surgery with equipment intended for multiorgan protection. For example, they emphasized that it would be better to plan the operation with advanced monitoring techniques.

Should we avoid general anesthesia in elderly patients? entitled of Strom et al. (2014) They stated that postoperative cognitive dysfunction is more common in regional anesthesia in general anesthesia. They emphasized that minimal sedation and regional anesthesia should be preferred in elderly patients whenever possible. If there is no contraindication in our clinic, the first choice is regional anesthesia in the elderly.

In a study by Patel et al., (2018) They compared general anesthesia and regional anesthesia techniques in elderly patients. They stated that they did not see any difference in terms of mortality and morbidity in patients receiving general anesthesia.

In a study by Chen et al., (2019) They compared different anesthesia techniques in terms of mortality and morbidity in hip fracture in elderly patients. In terms of 30-day mortality, they did not see any difference between the group receiving general and regional anesthesia. However, they observed that postoperative complications were higher in the group receiving general anesthesia.They observed that the frequency of complications such as postoperative respiratory failure, longer hospital stay, longer stay in intensive care unit was higher in the general anesthesia group. In our study, similarly, we detected fewer complications in patients undergoing regional anesthesia.

Similar to previous reports, patients in the regional anaesthesia group in our study required fewer blood transfusions and spent less time in the hospital compared with those in the general anaesthesia group.

The main results of our study include the following:

No difference between patients undergoing hip surgery with general or regional anaesthesia in terms of age, sex, ASA risk score, anaesthesia duration, volume replacement, complications and need for intensive care. The surgery duration was shorter among regional anaesthesia patients than among general anaesthesia patients. Despite the absence of a significant difference between pre- and post-operative haemoglobin values, the reduction was less marked in regional anaesthesia patients.The frequency of concomitant conditions was comparable across the study groups.Blood transfusion requirements were similar between the two groups, although patients in the regional anaesthesia group required less blood transfusion. The two groups were comparable in their need for intensive care.Patients in the regional anaesthesia group had a shorter hospital stay length.

Conclusion

No difference between patients undergoing hip surgery with general or regional anaesthesia in terms of age, sex, ASA risk score, anaesthesia duration, volume replacement, complications and need for intensive care. The surgery duration was shorter among regional anaesthesia patients than among generalanaesthesia patients. Despite the absence of a

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In the ligt of all these results, regional anaesthesia seems to offer certain advantages over general anaesthesia in elderly patients undergoing hip surgery with respect to hospital stay length, surgery duration and the need for blood transfusions.

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CASE REPORT

A rare Localization of Mixoma: Originating in the Right Atrial Septum

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Abstract
Myxoma is the most common bening cardiac tumourt. Approximately 75-80 % of cardiac myxomas are located in the left atrium. The most common non-specific symptoms are such as shortness of breath, syncope. A 74-year-old female patient was admitted to our outpatient clinic with shortness of breath and chest pain, in the echocardiography showed a mobile mass in the right atrium. The patient, whose diagnosis of myxoma was confirmed by trans esophageal echocardiography, underwent intracardiac mass excision. Because the right atrial myxomas are rare, we wanted to present our patient. An underlying cardiac pathology should be kept in mind in patients presenting with symptoms such as non-specific breathlessness
Key words: Right atrial myxoma, cardiac tumour, dyspnea

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Introduction

Myxoma is primary cardiac tumor wich is bening character and occurs in the left atrium in more than 75% of patients. As an atypical location, the right heart location is observed in about 10-15% of cases and its clinical presentation is not specific. Although it is rare in tumors located in the right heart, it is known that the incidence of pulmonary embolism increases. (Shapiro 2001; Lepillier et al, 2010; Kaya et al, 2014).

Myxomas can be seen in almost any age group, but it is known to be detected most frequently after the third decade. The symptoms and findings detected in patients vary according to the localization of the tumor. Left atrial myxomas may present with dyspnea, syncope with the movement due to mitral obstruction and systemic emboli. It may show symptoms of right heart failure in the right heart and

cause pulmonary embolism (Castillo and Silvay 2010; Veicki et al. 2010)

In patients with progressive shortness of breath with no underlying cause or embolic pathologies for which no possible cause can be found should be caution exercised in terms of the possibility of intracardiac tumor. We presented to a patient with right atrial mixomas which is rare who applied to different outpatient clinics for several months with shortness of breath.

Case

A 67-year-old female patient was brought directly to A 74-year-old female patient was admitted to our clinic with atypical chest pain and dyspnea for about a month. The patient's dyspnea was independent of effort and was more severe over the past week. She had previously known hypertensionwith- out atherosclerotic risk factors. On his physical examination, blood pressure and heart rate were 120/ 80 mmHg and 95 bpm, respectively. Heart and respiratory auscultation findings were normal except for 2/6 systolic murmur, which was heard maximally at the left parasternal region. Electrocardiogram showed sinus rhythm and right bundle branch block. Transthoracic echocardiography showed normal left ventricular systolic function (ejection fraction: 65%) and mass on the rigt atrial septum (Figure. A). For a more accurate assessment, we performed a transesophageal echocardiography, which showed a mobile 2.1 x 1, 2 cm mass origination in the right atrial septum with a handle. Because of its mobility and the risk of embolization, the mass was surgically (Figure. B) removed. The histological findings showed myxoma. The patient was discharged uneventfully after the operation.

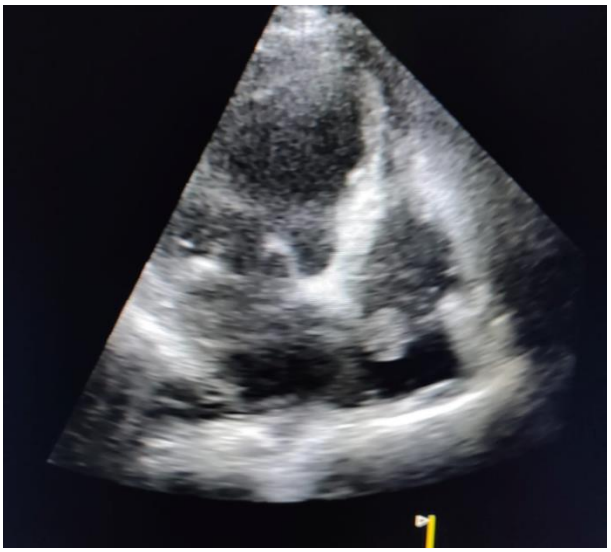

Figure A. Tranthoracic echo image of myxoma

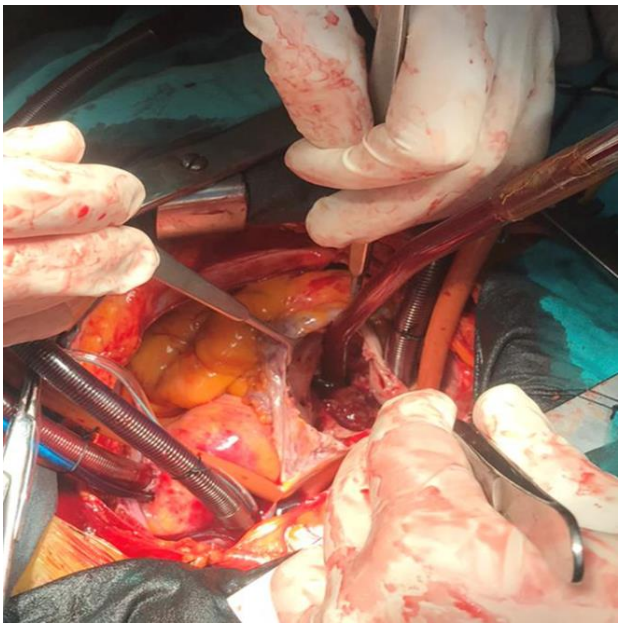

Figure B. Intraoperative view of Myxoma

Discussion

The myxoma is a primary benign cardiac tumor whose etiology is mostly unknown, adhering to the left side of the heart with a pedicle. Although it is suggested that myxomas develop from thrombus, these tumors are thought to originate from embryonal mesenchymal cells. Myxomas are divided into two as sporadic and familial form. Although it is the most common sporadic form, the family form has also been reported at a rate of 7%. (Sun and Wang 2008, Camm et al. 2009; Kaya et al. 2014;)

It is known that there is a correlation between myxoma size and symptoms. In addition to nonspecific symptoms such as fever, fatigue, and hemoptysis the most common symptom is with dyspnea and chest pain. Myxomas with right cardiac involvement may cause tricuspid insufficiency and right heart failure, depending on the location or deform the tricuspid valve. In addition, it has been reported that massive embolism may occur in these patients, and recurrent emboli may occur with small tumor fragments (Calejero et al. 2005, Beso and Cedo 2013).

Early diagnosis of myxoma is difficult because the symptoms of myxoma are frequently nonspecific. In patients with myxoma may hear diastolic murmur mixed with mitral stenosis during auscultation. (Camm et al, 2009). Diagnosis of myxoma is made by 2-dimensional transthoracic echocardiography in all cases. Transesophageal echocardiography gives detailed information about the localization and size of the tumor. Computed tomography and magnetic

resonance imaging techniques can also be used for diagnosis. (Kaya et al. 2014)

The treatment of myxoma is surgical excision of the mass completely and together with the intact around tissue. The point to be considered in the operation of the patient is that the vena inferior cannula should be placed after entering the pump when necessary to avoid intraoperative tumor embolization during cannulation. Surgical excision of myxoma results in complete recovery if performed carefully. In long-term follow-up, recurrence is very very rare in these patients. (Kuroczynski et al. 2009; Scrofani et al. 2020) Recurrence is generally observed in case of insufficient resection, tumor with several orgin and familial type. (Pedro, 2008)

Conclusion

Right atrial myxoma can form a severe status after admission with symptoms of shortness of breath. Therefore, in the patient with shortness of breath and progresses or systemic /pulmoner embolic phenomenon the phsicians should be carefully and cardiac tumors should be considered. In these patients, evaluation with transthoracic echocradiography, which is a noninvasive diagnostic method, is very important and it should be remembered that these patients should be evaluated very carefully. Surgical excision should be done at an early stage after diagnosis to prevent it.

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CASE REPORT

Sialolith of the Submandibular Gland: A Case Report

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Abstract
Sialolithiasis is described as the existence of calcified structures in ducts of salivary glands and is the most widespread disease of the salivary glands. 80-95 % of sialoliths occur at the submandibular salivary gland. Sialoliths with an average frequency of occurrence of 12: 1000 are approximately twice as common in men as in women. Sialoliths may be diagnosed with clinical examination, conventional radiography, computed tomography and ultrasonography. Common clinical signs in cases of sialoliths include painless swelling, large swelling often accompanied by trismus associated with eating, symptoms ranging from moderate discomfort to severe pain. In this case report clinical, radiological signs and surgical therapy of salivary stone in the submandibular gland is represented.
Key words: Sialolithiasis, Sialolith, Submandibular gland

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Introduction

Sialolithiasis is described as the existence of calcified structures in ducts of salivary glands and is the most widespread disease of the salivary glands (Angiero et al., 2008; Iqbal, Gupta et al. 2012). The size of sialoliths is generally 1-10 mm, they are seldom observed to be bigger than 15 mm (Fowell and MacBean, 2012; Sadıkhov et al., 2019). Although sialoliths are more common in the adult population, cases of sialolith have also been reported in children in the literature. Sialoliths with an average frequency of occurrence of 12: 1000 are approximately twice as common in men as in women (Iqbal et al., 2012). While 80-95% of salivary stones seen in the submandibular gland, are seen in the 5-20% parotid gland, 1-2% in the sublingual and minor salivary glands (Iqbal et al., 2012). Sialoliths are clinically usually characterized by pain and swelling. There are also symptoms such as reduced saliva flow in the mouth of the salivary gland ducts, restriction of the mouth opening and pus flow (Omezli et al., 2016).

While 80% of sialoliths cases can be detected by simple radiographic methods, it may be necessary to examine the other 20% by imaging techniques like computed tomography, magnetic resonance imaging (MRI), ultrasonography, sialography or sialendoscopy (Pastor-Ramos et al., 2014). Conservative methods can be applied for the treatment of small size sialoliths (Aiyekomogbon et al., 2018). Conservative treatment methods are antibiotics, anti-inflammatory drugs, local massage and heat application to the salivary gland, spontaneous passage from the salivary gland duct with saliva flow stimulants (Marchal and Dulguerov, 2003; Aiyekomogbon et al., 2018). When cannot achieved with conservative methods, recently interventional methods with minimally invasive techniques are applied. These are stone removal from the duct ostium with a blunt instrument, interventional sialography, therapeutic sialendoscopy, extracorporeal shock wave lithotripsy (ESWL), CO2, holmium and erbium: YAG laser application, intraductal lithotripsy and piezoelectric surgery (Angiero et al., 2008; Pastor-Ramos et al., 2014; Kondo et al., 2018; Guenzel et al., 2019).

In this case report clinical, radiological signs and surgical therapy of salivary stone in the submandibular gland is represented.

Case

A 40-year-old male patient was admitted to Ordu University, Faculty of Dentistry, Department of Oral and Maxillofacial Surgery for complaints of swelling and pain during eating in the left submandibular area. Also, he had swelling, tension and sensitivity in the left submandibular area. The patient had no significant systemic disease. Radiographic examination showed sialolith in the left submandibular area (Figure 1-2). After the informed consent obtained, Under the regional anesthesia sialolith was surgically removed with an intraoral approach. An incision was made on the submandibular gland duct where the sialolith is located. The sialolith was attentively removed from the base of the mouth, preserving the submandibular salivary gland by blunt dissection. Excised sialolith was 16 mm x 8 mm in size, hard structure and yellow in color (Figure 3). After the sialolith was removed, a drainage catheter was placed in the submandibular gland duct (Figure 4). Postoperatively, the patient was prescribed antibiotic (Amoxicillin clavulanate, 2000 mg / day), analgesic (Naproxen sodium) and Orohex mouthwash. The drainage catheter was removed after 48 hours. No complications were observed on the 7th postoperative day. A clear saliva flow was observed from the left submandibular gland duct. No recurrence was observed after 1 year of follow-up.

Figure 1. Preoperative panoramic radiography

Figure 2. Preoperative occlusal radiography

Figure 3. Excised sialolith

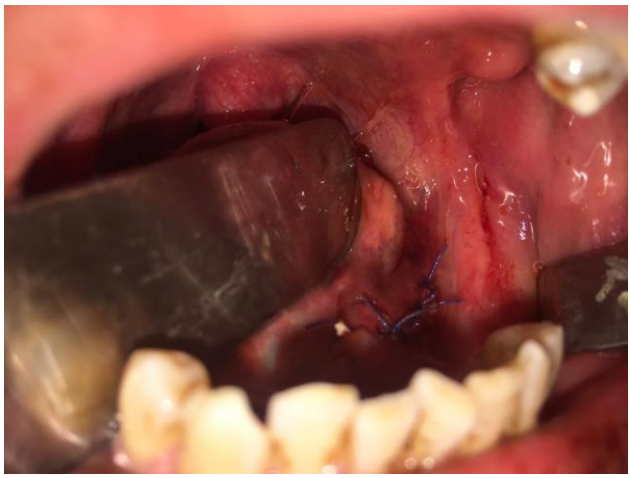

Figure 4. Postoperative intraoral view

Discussion

Sialolithiasis is described as the existence of calcified structures in ducts of salivary glands and is the most widespread disease of the salivary glands.(Angiero et al., 2008; Iqbal et al., 2012) It has also been shown that stagnation in saliva flow, infection of the salivary duct or gland, physical damage to the salivary duct or gland can predispose to stone genesis. (Sunder et al., 2014) Recently, effects of tobacco on saliva have also been examined and it has been shown that tobacco smoking increases the cytotoxic efficiency of saliva, decreases the polymorphonuclear phagocytic capability, reduces salivary amylase, peroxidase and these can cause stone formation.(Aiyekomogbon et al., 2018) A study has shown a relationship between sialolithiasis and nephrolithiasis however, it was stated that more researches are required verify this relationship.(Wu Hung et al., 2016) Sialoliths appear mostly in the submandibular gland.(Iqbal et al,. 2012) The higher alkali and calcium concentration of the saliva produced by the submandibular gland, the long and curved anatomical structure of the submandibular gland duct, the occurrence of saliva flow against gravity are effective in increasing the incidence of sialoliths in the submandibular gland.(Oliveira et al., 2016)

Sialoliths seen in the submandibular salivary gland may be easily diagnosed as they show evident clinical features, also they may remain completely asymptomatic.(Sunder et al., 2014) Common clinical signs in cases of sialoliths include painless swelling, large swelling often accompanied by trismus associated with eating, symptoms ranging from moderate discomfort to severe pain.(Sunder et al., 2014) The clinical symptoms observed in our case are consistent with the literature.

Ultrasonography is recommended as the first imaging option in cases suggesting the presence of sialolith clinically (Aydın et al., 2004). Advantages of ultrasonography include low cost, noninvasive technique and no radiation exposure to the patient. Other imaging techniques include panoramic and occlusal radiographs, computed tomography, ultrasonography, sialography, magnetic resonance imaging or sialendoscopy (Pastor-Ramos et al., 2014). Occlusal radiography is the most dependable technique for imaging submandibular sialolith. However, since the imaging area is up to the second molar tooth posteriorly, it is not reliable for the diagnosis of giant sialoliths occuring in the posterior area of the Wharton duct (Rai and Burman, 2009). In our case, diagnosis of sialolith was made by panoramic and occlusal radiographs. Digital sialography had arisen the susceptibility and specificity of the traditional sialography technique. The main benefit of this new technique is to obtain a clear view of the anatomical structures without superposition. It is a disadvantage that the conventional sialography method requires the use of contrast material. Contrast agents can expose the patient to radiation dangers, perforate the wall of the salivary gland duct, reason pain and contraindicated in case of acute infection (Sunder et al., 2014). The sialo-MRI is a non-invasive technique used in the evaluation of salivary gland diseases, a method introduced recently. Among the most important advantages of this technique are the absence of contrast agent injection, its ability to produce sialographic images without ionizing radiation and the unchanged structural anatomy of the salivary glands. But the main disadvantages are requiring long time, being expensive, lack of compliance in claustrophobic patients and the artifact formation in those with metallic dental prostheses (Andretta et al., 2005).

Treatment of sialolith depends on the duration of symptoms, the number of recurrences, the size and localization of the sialolith. Lustmann et al. reported that symptomatic sialoliths must be treated with an intraoral surgical approach (Lustmann et al., 1990; Ozdede et al., 2016). If there is no infection, sialoliths can be removed by hand manipulation, which are located near to the orifice of Wharton's duct. Surgical excision of sialoliths is suggested, if located on the distal side of the Wharton duct and in front of the lower first molar with respect to the duct. Recently, interventional radiological methods such as ESWL (Extracorporeal shortwave lithotripsy), which is a safe, effective, minimally invasive technique for salivary stones, are becoming increasingly popular

(Aiyekomogbon et al., 2018). Today, laser methods such as CO2 and Erbium: YAG are also used in sialolith treatment (Haas et al., 2018). Treatment methods such as ESWL and sialendoscopy are efficient alternatives to traditional surgical methods for small salivary stones. Methods like sialoadenectomy are invasive techniques and may damage many significant tissues, particularly the marginal mandibular, lingual nerve and hypoglossal nerve. The formation of new cells and easier proliferation of cells in laser applied tissues provides an increase in wound healing quality. Thanks to these features of the laser minimal swelling, bleeding and pain are observed after surgery (Angiero et al., 2008; Haas et al., 2018).

Piezoelectric surgery is used to remove sialoliths (Pastor-Ramos et al., 2014). Piezoelectric surgery technique is a minimally invasive technique that reduces damage to surrounding soft tissues (Pastor-Ramos et al., 2014) The limitation of this technique is that it is dependent on the accessibility of the stone (Pastor-Ramos et al., 2014).

Conclusion

In conclusion, sialoliths should be evaluated with preoperative history, clinical examination findings and accurate imaging methods. Localization of salivary stone is also important in diagnosis and treatment approaches. It should be distinguished from soft tissue calcifications such as calcified lymph nodes and vascular calcifications, bone lesions such as mandibular torus and osteoma.

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CASE REPORT

Nursing Care of a Patient Diagnosed with COVID-19: A Case Report According to Meleis' s Transition Theory

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Abstract

The transition theory developed by Afaf İbrahim Meleis is a nursing theory aimed at defining changes in individuals' lives and improving their health. Effects of such changes and transitions on individuals' health differ from one person to another. Nurses assist patients in these transition times by developing different intervention methods for them. Meleis' s transition theory is of importance because it is based on nursing profession and has contributed to the emergence of nursing science. A female patient presented to a private health institution with complaints of fever (38.2°C) and sore throat. The result of the 2019-nCov test performed was positive and she was quarantined in a socially isolated room of the hospital. Uncertainty and fear of death due to COVID-19, a global epidemic, bring about serious consequences for patients. In this case report, in line with Meleis' s transition theory, nursing care was planned for this 52-year-old woman diagnosed with 2019-nCov.

Key words: Coronavirus, 2019-nCov, pandemic, Meleis' s transition theory, Nursing care.

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Introduction

On the last day of December 2019, cases of pneumonia of unknown cause, believed to have emerged from a seafood market in Wuhan City, Hubei Province of China, were reported to the World Health Organization (WHO) (Lu et al., 2020). The investigation conducted in the region revealed that this situation was caused by the Wuhan corona virus. The clinical symptoms of the disease were fever and dyspnea, and bilateral pulmonary inflammation in the chest x-ray. The WHO named this disease '2019-nCov' and declared the case a "pandemic." As the virus spread rapidly around the world, countries took precautions accompanied by social restrictions implemented at various levels against the pandemic (Dunlop et al., 2020; EU, 2020). In our country, Turkey, since March 10, 2020, the cases of 2019-

nCov have started to appear (TUBITAK, 2020). This disease, which has been affecting the whole world since December 2019, causes uncertainty, fear and panic in individuals. In addition, the transition from a healthy life to an uncertainty and disease causes fear of death in individuals (WHO, 2020).

Changes in health and illness of individuals create a process of transition, and clients in transition tend to be more vulnerable to risks that may in turn affect their health. Uncovering these risks may be enhanced by understanding Meleis' s transition process. The concept of transition, as described in nursing, is complex and multidimensionally identified as awareness, engagement, change and difference, time span, critical points and events (Figure 1) (Meleis et al., 2000).

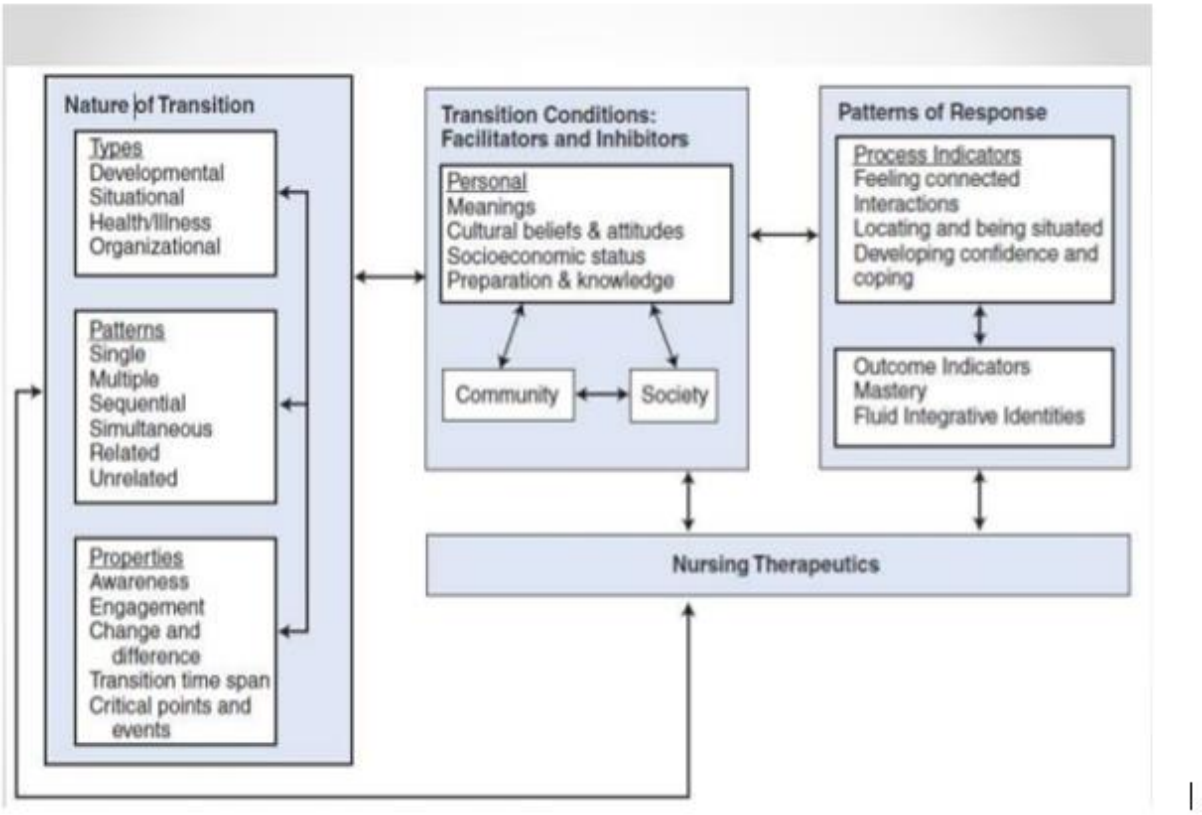

Figure 1. Middle-Range Transition Theory (Meleis AI, Sawyer LM, Im EO, Hilfinger Messias DK, Schumacher K. Experiencing transitions: an emerging middle-range theory. Adv nurs sci 2000;23(1):12–28.)

Awareness

Awareness is related to perception, knowledge, and recognition of a transition experience. Level of awareness is often reflected in the degree of congruency between what is known about processes and responses and what constitutes an expected set of months of responses and perceptions of individuals undergoing similar transitions (Meleis et al., 2000; Davies, 2010).

Engagement

Another property of transitions is the level of engagement in the process. Engagement is defined as the degree to which a person demonstrates involvement in the processes inherent in the transition. Examples of engagement are seeking out information, using role models, actively preparing, and proactively modifying activities (Meleis et al., 2000; Davies, 2010).

Changes and differences

Changes and differences are a property of transitions. Changes in identities, roles, relationships, abilities, and patterns of behavior are supposed to bring a sense of movement or direction to internal processes, as well as external processes (Meleis et al., 2000; Davies, 2010). Meleis et al. (2000) asserted that all transitions involve change, whereas not all change is related to transition. Then, they suggested that to fully understand a transition

process, it is necessary to uncover and describe the effects and meanings of the changes involved and the dimensions of changes (e.g., nature, temporality, perceived importance or severity, personal, familial, and societal norms and expectations). Differences are also suggested as a property of transitions. Meleis et al. (2000) believed that confronting differences could be exemplified by unmet or divergent expectations, feeling different, being perceived as different, or seeing the world and others in different ways, and suggested that it might be useful for nurses to consider a client's level of comfort and mastery in dealing with changes and differences.

Time Span

Time span is also a property of transitions and all transitions may be characterized as flowing and moving over time (Meleis et al., 2000; Davies, 2010). According to the assertion by Bridges (1991) in the middle range theory of transition, transition is defined as a span of time with an identifiable starting point, extending from the first signs of anticipation, perception, or demonstration of change; moving through a period of instability, confusion, and distress; to an eventual "ending" with a new beginning or period of stability. However, Meleis et al. (2000) also made the point that it might be difficult or impossible, and perhaps even counterproductive, to put boundaries on the time span of certain transition experiences.

Critical Points and Events

Some transitions are associated with an identifiable marker event; such as birth, death, the cessation of menstruation, or the diagnosis of an illness; whereas in other transitions, specific marker events are not as evident. The various studies involving multiple transitions provided evidence that most transition experiences involved critical turning points or events. In addition, there is final critical points, which were characterized by a sense of stabilization in new routines, skills, lifestyles, and selfcare activities. Each milestone requires the nurse's attention, knowledge and experience in different ways (Meleis et al., 2000; Davies, 2010).

In this case report, based on Meleis' s transition theory, nursing care was planned for a 52-year-old woman diagnosed with 2019-nCov. Our review of the literature demonstrated that no study in which nursing care was planned in line with Meleis' s transition theory for patients diagnosed with 2019-nCov was conducted. Thus, we expect that our case report would significantly contribute to the current literature.

Case

The study was carried out in line with the principles of the Helsinki Declaration. Approval was received for this study from the patient. The patient MA is a 52-year-old woman and married. She presented to a private health institution on April 1, 2020 with complaints of fever (38.2°C) and sore throat. The results of the routine biochemistry and hemogram tests indicated the following: AST = 88 UL (0-50 UL), ALT = 75 UL (0-50 UL), CRP = 120 mg / L (0-5mg / L), IG% = 3.7 (0-0), HCT = 36.4% (40-53%), RDW-S = 37.5 (0-0), P-LCR = 21 (0-0). The patient, who was diagnosed with tuberculosis (TBC) at the age of 17, underwent chest X-ray and computed tomography (CT) for the diagnosis. The diagnostic methods revealed no pathological findings. In the oropharyngeal swab sample of the patient, the result of the diagnosis test of 2019-nCovwas positive. Therefore, the anamnesis of the patient was obtained, which demonstrated that 2019-nCov was transmitted to her from her husband who shared the same house with her. In line with this result, the patient was quarantined in a hospital room where isolation measures were taken. The patient was intravenously administered moxifloxacin (3x400mg) and esomeprazole (2x40mg). The patient suffered intensive feelings of anxiety, hopelessness, obscurity and fear due to the diagnosis and treatment procedures and isolation measures she underwent. Therefore, nursing care was planned for her based on Meleis' s transition theory.

-In this period, the awareness phase of the transition theory, the patient was informed

about her illness, and treatment and isolation measure she was to undergo. Her fears and worries were resolved so that she could express herself. Her physiological and psychological needs were determined.

-At the stage of taking responsibility, she was encouraged to take part in her own physical

and spiritual care, which supported her to be aware of self-care.

-In the stage of change and differences, the patient, who was under quarantine and tried

to adapt to the difficult process, was enabled to cope with and adapt to this situation.

-At the time process stage, she was told the process of transition from disease to health

is like the transition period from health to disease and was given mental support that this situation would bring about new beginnings.

-In the stage of critical points and events, she was given information about new routines, lifestyles, and selfcare activities.

It is important for a nurse to provide nursing care to the patient by using his or her knowledge and skills during events such as illness, a turning point in a person's life. At this stage, nursing interventions to meet the patient's needs were planned. Her physical, psychological and spiritual needs were met by providing holistic, supportive and individual care to her.

Discussion

The number of people infected with 2019-nCov is increasing dramatically worldwide. The disease has led to a chain of infections representing the largest outbreak outside Asia to date (Spina et al., 2020). In Turkey, the first transmission from person to person was reported on March 10, 2020. As of April 14, 2020, In Turkey, the numbers of positive cases, deaths and survivors were reported as 65,111, 1,403 and 4,799 respectively ranging from hour to hour (TUBITAK, 2020).This outbreak of the disease causes uncertainty, fear and panic in individuals and the society due to the day-by-day increase in its severity (WHO, 2020).Nurses play a great role in the transition both from health to illness and from illness to health in this pandemic, since they are healthcare workers who care for both healthy and sick individuals in different situations such as health, illness, birth and death (Bekmezci et al., 2016; Lindmark et al., 2019). The transition theory developed by Afaf İbrahim Meleis is involved in the meaning that an individual attribute to the transition, and his or her expectations about the transition, knowledge and skill levels, and emotional and physical well-being (Davies, 2010; Bekmezci et al., 2016; Aydin and Kukulu, 2020). In case that the patient suffers from such feelings as fear of death and hopelessness when his or her diagnosis of COVID-19 is positive, nurses' answering the patient's questions, alleviating his or her fears and informing him or her about the disease are among the factors that facilitate the transition period. In our case, supportive care and education given to the patient increased her satisfaction, contributed to the improvement of her symptoms and her self-care, and improved her health and well-being. In this pandemic, maintaining the physical care of a patient and reducing his or her complications are among the responsibilities of the nurse. The patient who was provided nursing care in accordance with Meleis' s transition theory was discharged from the hospital on April 15, 2020 by taking the necessary protective measures after her symptoms and test results improved thanks to the treatment and care given to her, and the result of her COVID-19 diagnostic test was negative.

Conclusion

Nurses' putting theories into practice and disseminating and supporting them in the care process of COVID-19 epidemic disease are of great importance. In this transition from disease to health stage of this pandemic, using Meleis' s transition theory in nursing care will increase the effect and quality of the physical, psychological and spiritual care, and will provide a holistic support to the patient. This theory is a useful model for nurses to plan and implement nursing care for patients who are in the transition period.

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